SYNTHESIS OF CHLORINATED *N*-H PYRROLIDINES, TETRAHYDROTHIOPHENES, FURANS AND *N*-H PYRROLES BY Cu (I)-CATALYZED *5-EXO* OR *5-ENDO* HALOGEN ATOM TRANSFER RADICAL CYCLIZATION OF 2,2,2-TRICHLOROETHYL ALKENYL AMINES, SULPHIDES AND ETHERS

DHARMENDRA KUMAR GUPTA

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY DELHI

MARCH 2014

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by

DHARMENDRA KUMAR GUPTA

Department of Chemistry

Submitted

in fulfillment of the requirements of the degree of Doctor of Philosophy

to the

Indian Institute of Technology Delhi

March 2014

Dedicated to my parents

Certificate

This is to certify that the thesis entitled "**Synthesis of chlorinated *N*-H pyrrolidines, tetrahydrothiophenes, furans and *N*-H pyrroles by Cu (I)-catalyzed *5-exo* or *5-endo* halogen atom transfer radical cyclization of 2,2,2-trichloroethyl alkenyl amines, sulphides and ethers**", being submitted by **Mr. Dharmendra Kumar Gupta**, to the Indian Institute of Technology Delhi, for the award of the degree of "**Doctor of Philosophy**" in chemistry is a record of bonafide research carried out by him. Mr. Dharmendra Kumar Gupta has worked under my guidance and supervision, and has fulfilled the requirements for the submission of this thesis which to my knowledge has reached the requisite standard.

The results embodied in this dissertation have not been submitted in part or full, to any other University or Institute for the award of any degree or diploma.

Ram N. Ram
Thesis supervisor
Professor
Department of Chemistry
Indian Institute of technology Delhi
New Delhi-110016
India

I.I.T Delhi
March, 2014

ACKNOWLEDGEMENTS

I wish to express my deep sense of gratitude to my research supervisor ***Prof. R. N. Ram***, Professor, Department of Chemistry, Indian Institute of Technology, Delhi, for his guidance, interest and encouragement, which made this work possible.

I would like to thank the Head of the Department of Chemistry, Prof. A. Ramanan and the ex-Heads of the Department of Chemistry, Prof. A. K. Singh and Prof. B Jayaram for providing the essential facilities for carrying out my research.

I would like to express many thanks to my laboratory colleagues, Dr. Manoj T.P, Dr. Ram Kumar, Dr. Neeraj Kumar, Vineet Soni and Nisha Dawra for their fruitful advices, moral support and uninhibited help from time to time. It is my great pleasure to express many thanks to my friends particularly, Srinivas, Anjul, Nem singh, Dheeraj, Karunesh, Kesav, Srikanta Sahu, Rahul Siwach, Dhirendra Yadav, Anuj, Gyaneshwa Rao, Pradumn Singh, Amit Singh, Om prakash, Vineet Kumar, Rajesh Chhatra, Pramod Goswami, Aradhana Nayal, R. P. Verma, Sandhya Sadanandan, Appa Rao Sappala, Praveen Kumar, Bijesh, Parminder, Nagaraja, Arun, Arunava, Vivek, Jahangeer, Kapil, Atal and Raju for their well wishes and kind help in trying times during the course of the present work at IIT-D. I would like to express many thanks to all other friends and well wishers for their help and support. The help rendered by the technical staff of the department is duly appreciated.

Lastly and most importantly, I take this opportunity to express my heartfelt affection, love and thanks to my parents and other family members.

Dharmendra Kumar Gupta

ABSTRACT

Transition metal-catalyzed halogen atom transfer radical cyclization (HATRC) has emerged as an important synthetic tool for the synthesis of halogenated heterocycles. It has been used in total and formal synthesis of many natural and synthetic bioactive molecules. However, copper (I)-catalyzed *5-exo* HATRC of *sec*.-amides having unprotected NH group has been reported to be unsuccessful probably due to insoluble complex formation and deactivation of the catalyst. The Cu (I)-catalyzed HATRC of unprotected *sec*.-amines and protected or unprotected enamines has not been explored. This laboratory reported CuCl/bpy-catalyzed *5-exo* HATRC of 2,2,2-trichloroethyl allyl ethers but vinyl ethers have not been explored so far either for *5-endo* or *4-exo* cyclization. Sulphides as substrates have also been not investigated. In this case also a substrate S-copper interaction is expected, which might deactivate the catalyst. The present work describes successful accomplishment of Cu (I)-catalyzed HATRC of these difficult substrates.

Following an introductory chapter on Cu (I)-catalyzed HATRC, the thesis describes the present work on hitherto unknown applications of Cu (I)-catalyzed HATRC in the synthesis of several new chlorinated 5-member heterocycles over the next four chapters.

Chapter 2 describes a mild and highly regioselective CuCl/PMDETA-catalyzed chlorine atom transfer radical cyclization of unprotected 2,2,2-trichloroethyl allyl *sec*.-amines to furnish 3,3-dichloro-4-(α-chloroalkyl)-*N*-H pyrrolidines in good to high yields (76-87%) with 2,4-*trans* geometry almost exclusively in most of the cases. The cyclization of α,α'-unsubstituted 2,2,2-trichloroethyl allyl amines and α or α'-substituted (or side chain functionalized) 2,2,2-trichloroethyl allyl amines requires 40 mol% of the catalyst at reflux temperature and 40-60 mol% of the catalyst at 0 ˚C, respectively in acetonitrile. The usually observed inhibitory effect of the substrate NH-copper interaction on HATRC did not pose a problem here probably due to

steric hindrances by the α-substituents and/or the bulky CCl_3 group, to such an interaction. The highly basic PMDETA ligand might also be playing a role. The amine cyclization precursors were easily accessible by different methods such as by decarboxylative addition of trichloroacetic acid to aldimines and ketimines derived from allylic amines, alkylation of 2,2,2-trichloroethyl amine with allylic halides, condensation of anhydrous chloral with allylic amines followed by reduction of the imine with $NaBH_4$ and Michael addition of allylic amine to β-trichloromethyl substituted Michael acceptors. The diversity accessible in the synthesis of the acyclic precursors led to the synthesis of a variety of 3,3-dichloro-*N*-H pyrrolidines having no substituent or alkyl, aryl and heteroaryl substituents at the C-2 position as well as functional groups such as NO_2, CN, CO_2Me, COPh in the side chain at this position. The chlorinated and side chain functionalized *N*-H pyrrolidines are potential synthetic building blocks. An aspect of the synthetic applications of these pyrrolidines in the synthesis of *N*-H pyrroles was illustrated by aromatizing one of them by double dehydrochlorination-isomerization with DBU.

Chapter 3 describes a mild and highly regioselective cyclization of α-acetoxy-2,2,2-trichloroethylallylic sulphides and the side chain functionalized 2,2,2-trichloroethyl allylic sulphides with CuCl/PMDETA (1 equiv or 50 mol % at reflux) at room temperatures in acetonitrile to afford the chlorinated and functionalized tetrahydrothiophenes in good to high yields (52-83%). The crystal structures of the major diastereomer obtained at room temperature showed that the substituents at C-2 and C-4 were *cis* to each other whereas the crystal structure of a major product obtained at reflux showed it to be the 2,4-*trans* diastereomer. The sulphide precursors, α-acetoxy-2,2,2-trichloroethyl allylic sulphides and side chain functionalized 2,2,2-trichloroethyl allylic sulphides, were prepared from allylic sulphides by their reaction with chloral/bromal and Michael acceptors, respectively using known chemistry. The anticipated

inhibitory effect of substrate S-copper interaction on HATRC did not pose a problem probably due to the effect of the strong PMDETA ligand. Steric hindrance by the bulky CCl_3 group and the α-substituent to such an interaction might also contribute. The application of these tetrahydrothiophenes was demonstrated by converting an α-acetoxytetrahydrothiophene into a β-actoxydihydrothiophene by teatment with Zn/AcOH, which involved an interesting migration of the acetoxy group.

Chapter 4 describes a single step regioselective method involving CuCl/PMDETA (70 mol%)-catalyzed *5-endo-trig* chlorine atom transfer radical cyclization of NH-unprotected *N*-(2,2,2-trichloroethyl)enamines followed by aromatization by double dehydrochlorination for the synthesis of tri- and tetrasubstituted 2,3-difunctionalized 4-chloro-*N*-H pyrroles in good to high yields (63-84%) from readily accessible trichloroethyl amines in the presence of AIBN (1equiv) under milder conditions. The generally unfavorable, 5-*endo* cyclization appears to be facilitated by stabilization of the intermediate radical by capto-dative effect among other factors. Although a radical mechanism nicely explained the formation of the products, radical polar cross over mechanism through other routes including the oxidation of the captodative radical intermediate to a cation by Cu (II) could not be excluded. It allows the introduction of a variety of substituents, alkyl, aryl and heteroaryl substituent at the C-5 position and keto and ester groups at the C-2 and C-3 positions.

The chapter 5 describes a single step regioselective method involving CuCl/TMEDA/PMDETA (55-70 mol%)-catalyzed *5-endo-trig* chlorine atom transfer radical cyclization of 2,2,2-trichloroethyl vinyl ethers followed by aromatization by double dehydrochlorination for the synthesis of tri- and tetrasubstituted 2,3-difunctionalized 4-chlorofurans in good to high yields (58-83%) in benzene at reflux temperature. 2,2,2-

Trichloroethyl vinyl ethers were obtained easily by the reaction of trichloromethyl carbinols with DMAD or functionalized vinylic halides/pseudo halides. The success of the disfavored 5-*endo* cyclization was attributed to the formation of the captodatively stabilized radical intermediate in the cyclization step and relatively high reaction temperature. As in the case of enamine cyclization mentioned above, the involvement of a cation intermediate in the reaction could not be excluded. The present method of 4-chlorofuran synthesis is applicable to the synthesis of a variety of 4-chlorofurans with ester group at C-2 position and an ester or keto group at the C-3 position. The C-5 position may have an alkyl, aryl or heteroaryl substituent or may be kept unsubstituted. Furanonapthoquinones were also accessible by this methodology.

All the syntheses mentioned above are broad, economical and use mild reaction conditions. They are free of the wasteful protection and deprotection steps. The chlorinated and functionalized heterocycles prepared there from are difficult to access by other means. They may serve as versatile synthetic intermediates in advanced synthesis by virtue of their high functional density. The functional groups such as chlorine, keto, ester, acetoxy, *N*H and/or bivalent sulphur present in them are important functional groups where from most of the synthetically important organic reactions originate. Thus, a variety of aliphatic, aromatic and alicyclic compounds may be prepared. Many naturally occurring and pharmaceutically important *N*-H pyrrolidines and *N*-H pyrroles contain chloro, keto and/or ester functionalities. The present method may be useful for the synthesis of chloro-analogs of such pyrroles to study structure–activity relationships.

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LIST OF ABBREVIATIONS

%	percent
δ	chemical shift
°C	degree centigrade
Ac	acetyl
AIBN	2, 2′-azobisisobutyronitrile
aq.	aqueous
Ar	aryl
atm	atmosphere
boc	t-butyloxycarbonyl
bpy	2,2′-bipyridine
Bn	benzyl
br	broad singlet (spectral)
Bu	*n*-butyl
BuOH	butanol
cat.	catalytic
Cbz	carbobenzyloxy
conc.	concentrated
Cy	cyclohexyl
d	doublet
dd	doublet of a doublet
ddd	doublet of a doublet of a doublet
DABCO	1,4-diazabicyclo[2.2.2]octane

DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DEPT	Distortionless Enhancement by Polarization Transfer
dil	dilute
DMAD	dimethyl acetylenedicarboxylate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPPP	1,3-Bis(diphenylphosphino)propane
DQF COSY	Double Quantum Filtered Correlation Spectroscopy
ee	enatiomeric excess
e.g	for example
Et	ethyl
equiv	equivalent
EWG	Electron Withdrawing Group
g	gram
HOMO	Highest Occupied Molecular Orbital
h	hour
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
IPA	isopropyl alcohol
IR.	infrared

J	coupling constant
Lit.	Literature
LUMO	Lowest Unoccupied Molecular Orbital
m	medium in IR; multiplet in NMR
M^+	molecular ion
mcpba	metachloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
min	minutes
mL	millilitre
mmol	milli mole
mol	mole
mp	melting point
m/z	mass/charge
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NEt_3	triethylamine
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	Nuclear Overhauser and Exchange Spectroscopy
Ph	phenyl
PMDETA	*N*,*N'*,*N'*,*N''*,*N''*-Pentamethyldiethylenetriamine
ppm	parts per million

PTSA	*p*-toluenesulfonic acid
PMB	*p*-Methoxybenzyl
$^{13}C\{^{1}H\}$	proton-decoupled ^{13}C spectrum
n-Pr	*n*-propyl
q	quartet
s	strong in IR;singlet in NMR
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
Ts	tosyl
uW	microwave
w	weak

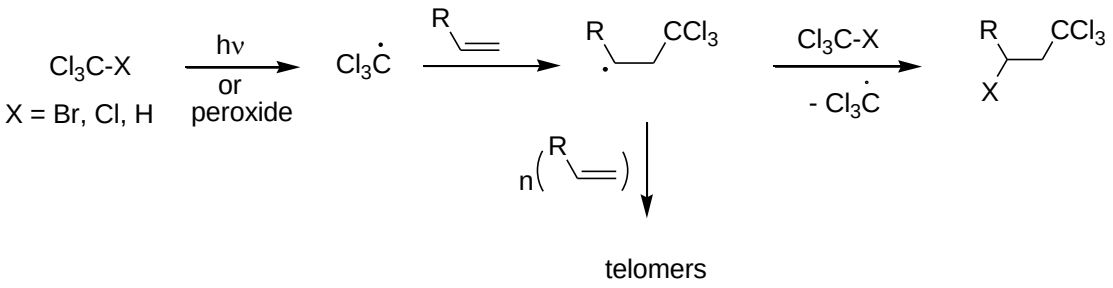
NOTES

1. All the melting points reported from the present work are uncorrected and were determined on an electrical melting point apparatus by taking the sample in a glass capillary sealed at one end.
2. The solvents were purified by routine methods and were distilled before use.
3. TLC was performed on silica gel plates using iodine for visualizing the spots.
4. Purification of the compounds was done by column chromatography on 60-120 mesh silica gel, neutral and basic alumina using suitable solvents.
5. The commercial nitrogen gas was used after passing successively through traps containing solutions of alkaline pyrogallol, conc. H_2SO_4 and KOH pellets.
6. IR spectra of the liquid sample were recorded by placing the liquid sample between KBr discs using a Nicolet Protégé 460 ES-P FTIR spectrometer. For solid samples, KBr pellets, made from a mixture of KBr and the sample, were used.
7. NMR spectra were recorded in $CDCl_3$with tetramethylsilane as internal standardor in DMSO (D_6) using a Bruker 300 MHz FT spectrometer.
8. ^{13}C DEPT NMR was used routinely to determine the number of hydrogen atoms linked to carbons.
9. Mass spectra were recorded on a high-resolution mass spectrometer, microTOF-Q II using ESI technique in positive-ion mode.

CHAPTER 1

Introduction: Some aspects of copper (I)-catalyzed halogen atom transfer radical cyclization

Free radical addition of an activated carbon-halogen bond such as that of poly halomethanes to alkenes and alkynes in the presence of light or a radical initiator is known as halogen atom transfer radical addition (HATRA) or simply atom transfer radical addition (ATRA). It is also known as Kharasch reaction in recognition of its discoverer, who published full details of the reaction in 1947.[1] Kharasch et al. observed that chloroform, tetrachloromethane and bromotrichloromethane on reaction with 1-decene, styrene and other alkenes in the presence of UV light or a radical initiator, such as diacetyl or dibenzoyl peroxide formed 1:1 adducts as the major products in most of the cases. They proposed a free radical chain mechanism for the reaction (**Scheme 1**) which is now well accepted. The reaction was performed by taking a few fold excess of the polyhalomethane which suppressed polymerization by chain transfer. Only relatively small reactant-dependent variable amounts of telomers and radical coupling products accompanied the 1:1 adduct. Chloroform reacted by addition of the C-H bond under these conditions. Amongst the polyhalomethanes, the following order was observed with regard to the rate of the reaction and product yield: $BrCCl_3$ > CCl_4 > $CHCl_3$ which, understandably, is in accordance with the ease of homolytic cleavage of the C-X bond **(**X = Br, Cl, H) (**Scheme 1**).

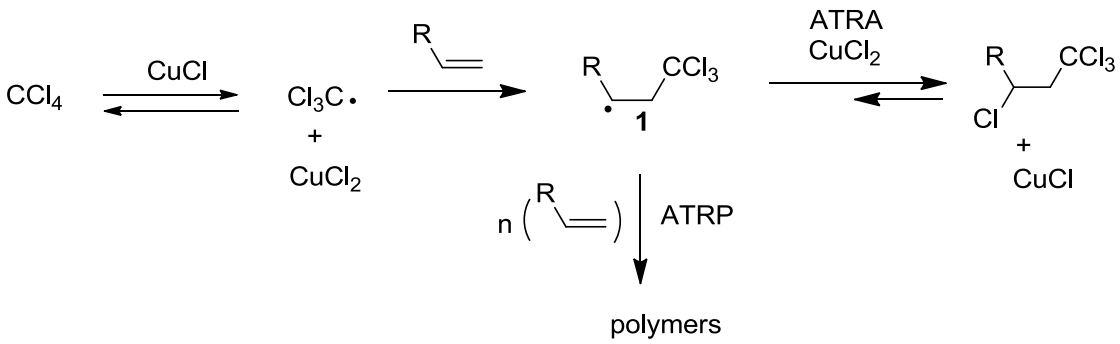


Scheme 1

However, in the case of the reaction of easily polymerizable vinyl monomers such as styrene, acrylates and acrylonitrile with less reactive polyhalomethanes, such as

chloroform and CCl_4, telomerization was a serious problem even under dilute conditions.

An important observation which solved the problem of telomerization and thus increased the synthetic value of Kharasch reaction was that it could be catalyzed by salts or complexes of many transition metals.[2] The proposed mechanism for CuCl-catalyzed HATRA, the finer details of which may be debatable, is illustrated in **Scheme 2** by taking the example of addition of CCl_4. Cuprous chloride abstracts a chlorine atom from CCl_4 by a reversible redox reaction to generate a trichloromethyl radical, which adds on the double bond of the alkene to form the radical adduct **1**. The oxidized copper salt, cupric chloride, formed in the first step, is a better chlorine atom donor than CCl_4 and transfers a chlorine atom to the radical adduct **1** efficiently to complete the addition and regenerate the CuCl catalyst to enter in the next catalytic cycle. The equilibrium concentration of the radical species remains very low and thus the polymerization is suppressed. However, in the presence of excess of the alkene, atom transfer radical polymerization[3] (ATRP) can be conducted in a controlled manner.



Scheme 2

Thus, by changing the concentration of the alkene either HATRA or ATRP can be performed.

Transition metal-catalyzed Kharasch reaction or HATRA is applicable not only to CCl_4 and other polyhalomethanes but also to higher trihalomethyl compounds.

Almost any type of trichloromethyl compound can add to unhindered alkenes in the presence of a suitable catalyst.[2] Salts or complexes of a large number of metals, such as Cu, Ru, Fe, Ni, Cr, Mo, etc. have been used as catalysts in the reaction.

1.1. Transition metal catalyzed halogen atom transfer radical cyclization

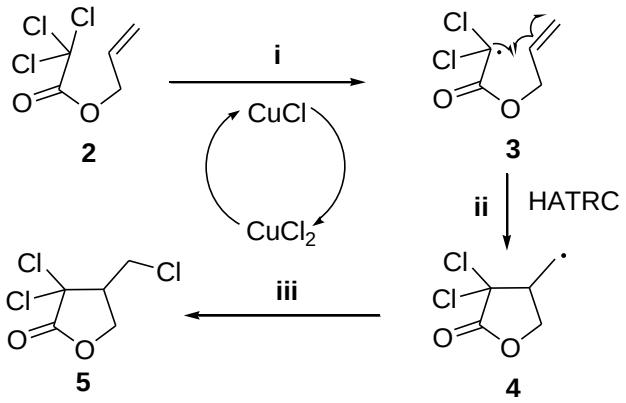
The intramolecular version of the transition metal-catalyzed ATRA leads to cyclization in which case the reaction is known as halogen atom transfer radical cyclization (HATRC) or simply atom transfer radical cyclization (ATRC).[4] Transition metal-catalyzed HATRC has emerged as a useful tool in organic synthesis. The reaction has several advantages over the classical Bu_3SnH-promoted radical cyclization. Transition metal-catalyzed HATRC is catalytic in nature whereas Bu_3SnH-promoted cyclization is not catalytic in tin hydride. Organotin hydride-promoted reaction is a reductive process in which the final cyclized radical is reduced. Thus, the synthetically valuable halogen functionality is not available for further elaboration but in the case of transition metal-catalyzed radical cyclization, all the halogens are preserved in the final product and can be used for further transformation. Transition metal-catalyzed cyclization can be performed at relatively higher concentrations. The Bu_3SnH-promoted cyclization is normally performed under dilute conditions to suppress the direct reduction of the starting halide before cyclization, which is a serious side reaction. Organotin hydride, such as Bu_3SnH is more expensive as compared to transition metal catalysts considering that the latter are required in only catalytic amounts. Bu_3SnH is not very stable and decomposes steadily even if carefully stored. Organotin reagents are toxic and removal of organotin residues from the reaction mixture is difficult whereas the transition metal salts are generally removed by filtration of the reaction mixture. Copper(I)[4] and Ru(II)[5] are the two most widely used catalysts

for the transition metal catalyzed HATRC of which the former is cheaper and the most popular. Therefore, some selected and relevant aspects of HATRC reactions catalyzed by copper (I) salts and complexes will be described here briefly.

1.1.1 Copper(I)-catalyzed halogen atom transfer radical cyclization

Cu(I)-catalyzed HATRC is a widely used radical reaction for the synthesis of useful synthetic intermediate such as lactones, lactams, tetrahydrofurans, pyrrolidines and carbocycles which may be transformed to naturally occurring compounds.[4]

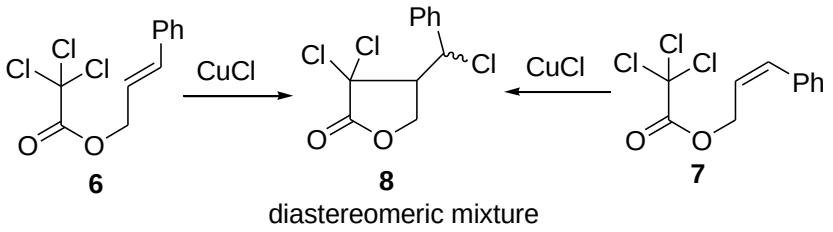
Trichloroacetates and trichloroacetamides derived from allylic alcohols and allylic amines, respectively have been the main substrates for Cu(I)-catalyzed HATRC. Nagashima et al.[6,7] have studied HATRC of activated allylic trichloroacetates in detail. Thus, the reaction of allyl trichloroacetates **2** (**Scheme 3**) with 30 mol % CuCl in CH_3CN at 140 °C in a pressure bottle for 1 h yielded the cyclized product **5**. The mechanism involved (i) generation of the initial radical **3** and $CuCl_2$, (ii) cyclization and formation of the new radical **4** (iii) abstraction of chlorine atom from $CuCl_2$ to form the cyclized product **5** and re-generate CuCl.



Scheme 3

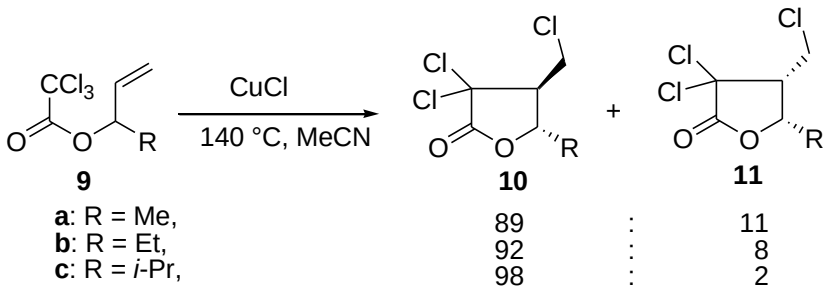
The cyclization occurred in CH_3CN solvent. Other solvents such as alcohols, benzene and DMF were found to be ineffective.

The regioselectivity of the CuCl-catalyzed HATRC of allylic trichloroacetates was excellent,[7] only γ-lactones were obtained as the main product via 5-*exo*-*trig* cyclization. No δ-lactones were formed except in one case where methallyl trichloroacetate was used, in which case the ratio of γ to δ-lactones was found to be 4:3 in a total yield of 70% of the cyclized products. The addition of carbon moiety and halogen to the olefinic bond was non-stereospecific as the reaction of the *trans*- and *cis*-cinnamyl trichloroacetates **6** and **7** respectively, provided the same mixture of diastereomers **8** (**Scheme 4**).



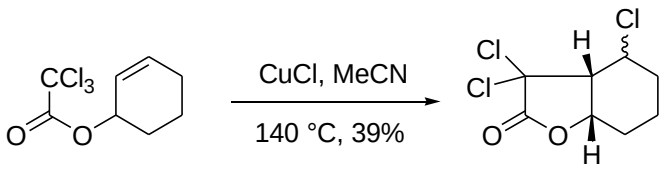
Scheme 4

The cyclization of the trichloroacetates **9** (**Scheme 5**) of secondary allylic alcohols was observed to be highly *trans*-stereoselective. The *trans* to *cis* ratio increased as the bulk of the substituent R increased from methyl to ethyl to isopropyl group.



Scheme 5

In contrast to the acyclic substrates, the reaction of the cyclic allylic trichloroacetate **12** (**Scheme 6**) yielded the *cis*-fused bicyclic lactone **13**.[8]

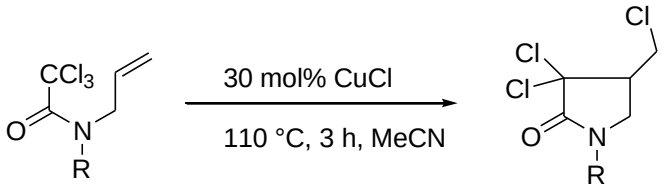


12 **13**

Scheme 6

Other copper salts such as Cu_2O, $Cu(NO_3)_2$ and Cu(CCPh) were also effective in catalyzing the cyclization of allyl trichloroacetate **2** at elevated temperature.[7]

The synthesis of γ-lactams[9] has also been accomplished by CuCl-catalyzed cyclization of *N*-allyl-2,2,2-trichloroacetamides in acetonitrile. Thus, the trichloroacetamide derivatives **14** (**Scheme 7**) on heating with 30 mol% CuCl in CH_3CN at 110 °C for 3 h afforded the corresponding γ-lactams **15** in good yields.



14

a: R = H
b: R = allyl

15

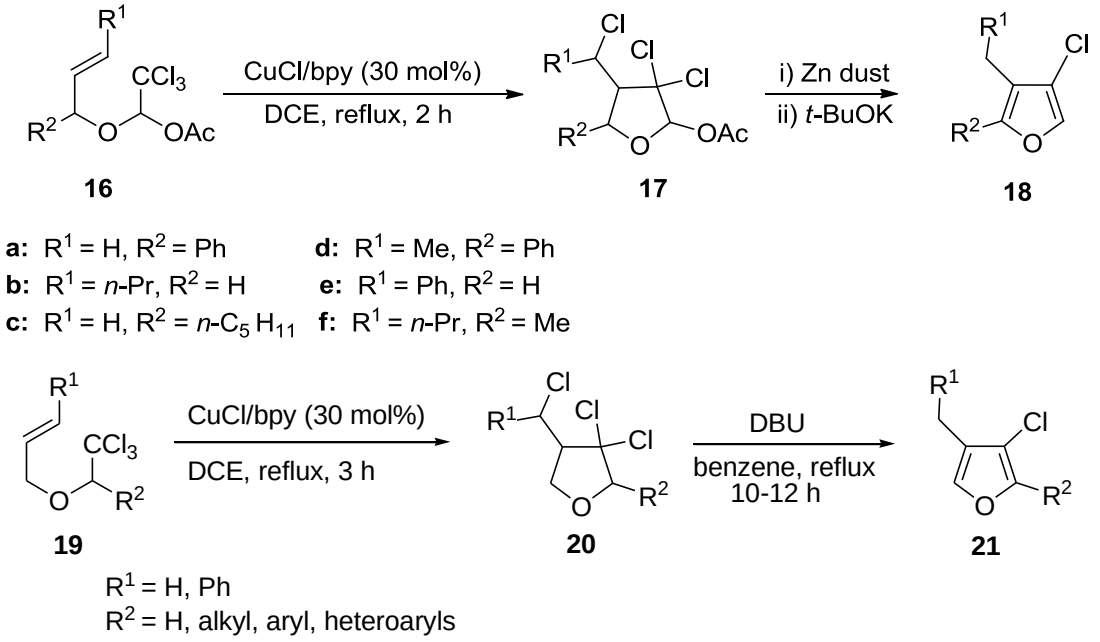
a: 57%
b: 87%

Scheme 7

The stereochemical and regiochemical courses of the above cyclizations were similar to that of Bu_3SnH-mediated free radical cyclizations.[8]

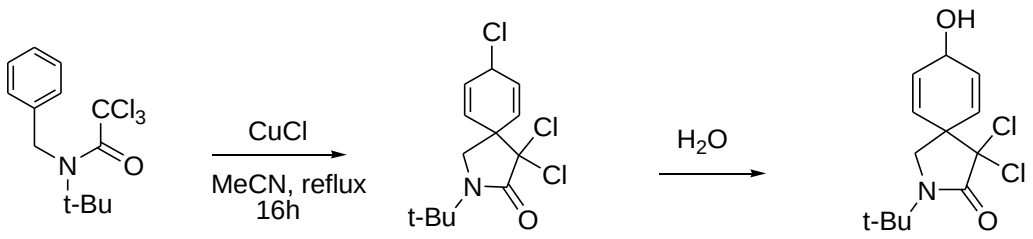
Ram. et al.[10] reported that chloral hemiacetals, prepared by simply mixing chloral with readily accessible allylic alcohols, after protection as 1-acetoxy-2,2,2-trichloroethyl allyl ethers **16**, (**Scheme 8**) underwent regioselective cyclization with 30

mol% CuCl–bpy in refluxing 1,2-dichloroethane (DCE) to afford the polychlorinated tetrahydrofurans **17**. Dechloroacetoxylation with Zn dust in THF followed by tandem dechlorination-aromatization with *t*-BuOK/18-crown-6 afforded the 4-chlorofurans **18** in good yield (51-74%).[10a] The 1-substituted 2,2,2-trichloroethyl allyl ethers **19**, prepared by allylation of trichloromethyl carbinols with easily available allylic bromides also underwent highly diastereoselective HATRC under similar conditions to afford the chlorinated tetrahydrofurans **20** in good to excellent yields (60-95%).[10b] The DBU-promoted dehydrochlorination and tandem isomerization in benzene at reflux afforded the 3-chlorofurans **21** in good yields (42-77%).



Scheme 8

Recently, Diaba et al.[11] reported CuCl-catalyzed spirocyclization of **22** (**Scheme 9**) in which the benzene ring worked as the radical trap to afford the dearomatized product **23**. The labile allylic chlorine atom in **23** was easily replaced by a hydroxyl group in aqueous medium to give the corresponding alcohol **24**.



22 **23** **24**

Scheme 9

1.2 Effects of ligands and substrate structure in Cu(I)-catalyzed HATRC

A ligand plays an important role in Cu(I)-catalyzed HATRC. Ligands may speed up the reaction either by solubilizing CuCl in the reaction mixture by forming a complex or by changing the redox potential of the catalyst system or by both the processes. Therefore, a number of ligands have been evaluated in such reactions.[4] Among the several screened ligands **(Fig. 1)**, by far the most successful ligands have been those based on 2,2'-bipyridine (bpy)**,** *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA)**,** *N*,*N'N'N''N''*-pentamethyldiethylenetriamine (PMDETA)**,** *N*,*N*,*N'*,*N'*,*N''*,*N''*-hexamethyltriethylenetetraamine (Me_6-tren)**,** *N*-alkyl-2-pyridylmethanimines (NPMIs) **L1**-**L7** and tris(2-pyridylmethyl)amine (TPA).

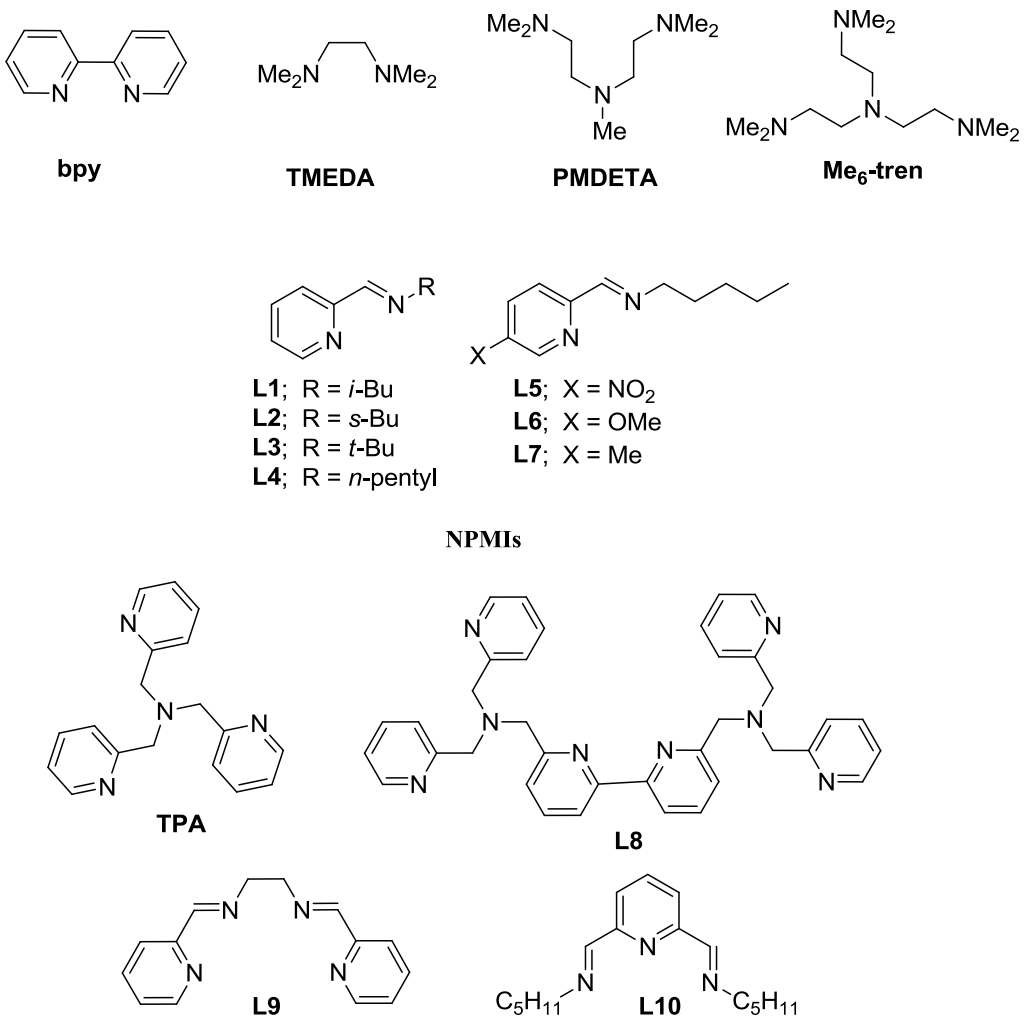
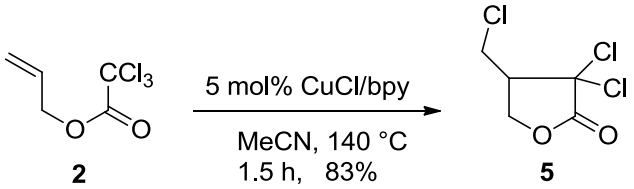


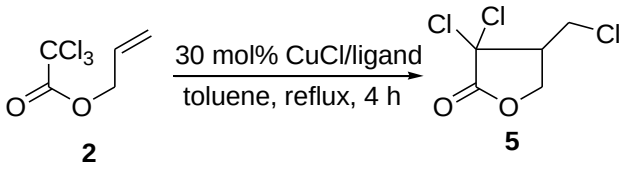
Fig. 1 Some important ligands used in Cu(I)-catalyzed HATRC

2,2'-Bipyridine has been the most popular ligand for copper(I)-catalyzed HATRC. Thus, the cyclization of allyl trichloroacetate **2** (**Scheme 3**) with 30 mol% of CuCl at 140 °C in MeCN in a sealed tube to the γ-lactone **5** was found to be accelerated four-fold when a 5 mol% each of CuCl and 2,2'-bipyridine were used in the place of CuCl[7] (**Scheme 10**).



Scheme 10

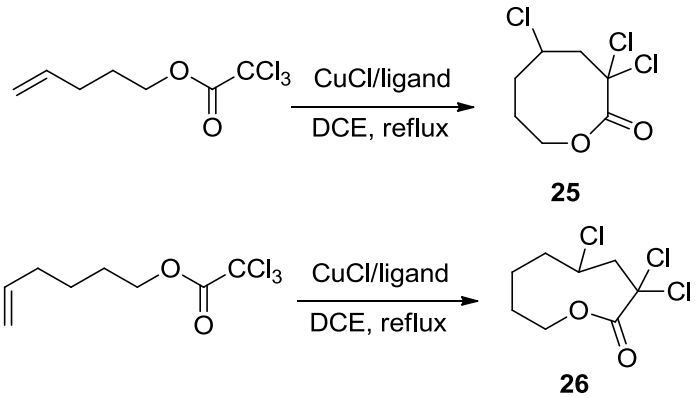
Clark et al.[12] have studied the effect of the *N*-alkyl substituted NPMI ligands **L1-L4** on the cyclization of allyl trichloroacetate **2**. They found that the CuCl-catalyzed cyclization of **2** using the NPMI ligand **L4** (**Fig 1**) proceeded faster than when 2,2'-bipyridine or TMEDA was used as the ligand as indicated by the reactant to product ratios shown in **Scheme 11**.



ligand	ratio of **2:5** after 4 h
L4	1:1
bpy	5:1
TMEDA	4:1

Scheme 11

Verlhac and coworkers[13,14] screened the ligands bpy**,** PMDETA, TPA and **L8** (**Fig. 1**) and observed that the ligands TPA and **L8** considerably improved the catalytic activity of the copper(I) in macrocyclization reactions. Using these ligands, they were able to prepare medium to large ring size lactones **25** and **26** in yields better than those obtained when bpy was used as the ligand (**Scheme 12**).

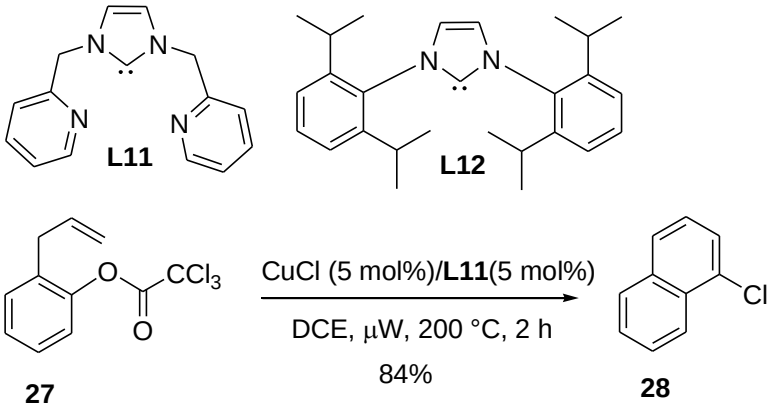


Ligand	Yield%
bpy	19
PMDETA	47
TPA	90
L8	99

Ligand	Yield%
bpy	4
L8	53

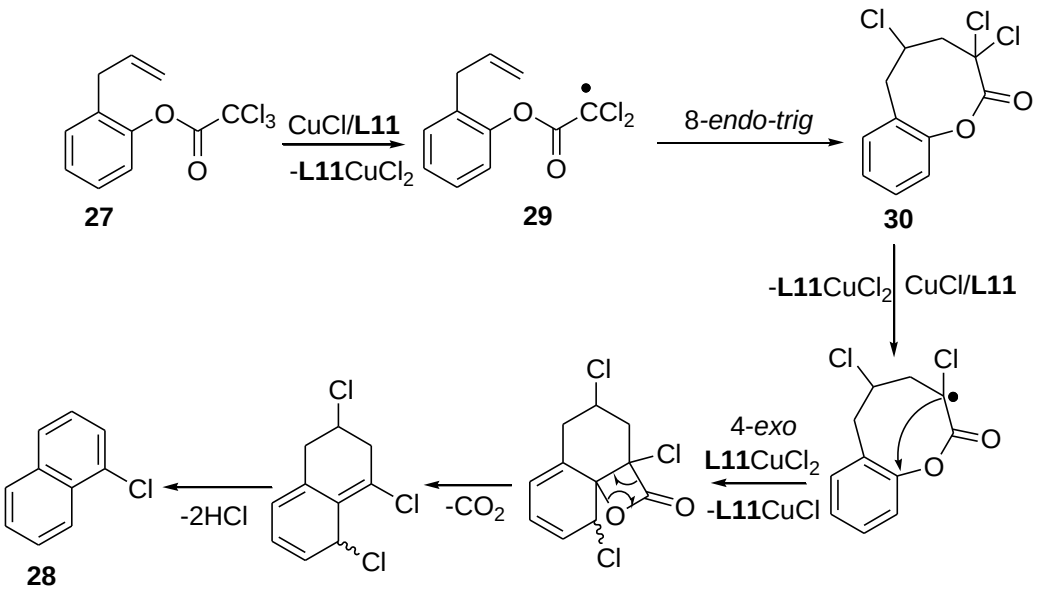
Scheme 12

Quayle and coworkers [15] reported the use of NHC (*N*-heterocyclic carbene)-based copper complexes **L11** and **L12** (**Scheme 13**) in catalytic amounts for an interesting benzannulation of 2-allylaryl trichloroacetates. Thus, benzannulation reaction of **27** in DCE containing the pre-formed copper(I)- **L11** complex (5 mol%) under microwave irradiation at 200 °C for 2 h afforded the chloroarene **28** in 84 % yield. However, refluxing the reaction mixture in toluene afforded **28** in only 23% yield.



Scheme 13

The proposed mechanism for the conversion of **27** to **28** is outlined in **Scheme 14** which involves initial formation of the expected 8-membered lactone **30**.

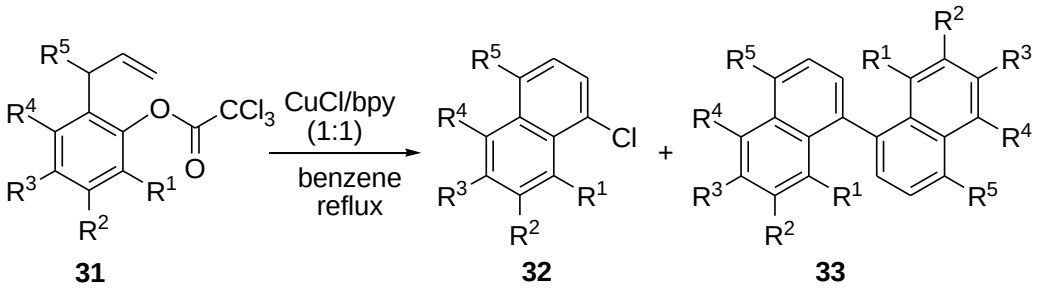


Scheme 14

These Cu(I)/NHC complexes also find application in catalyzing the HATRC of trichlorinated acetates and amides to give γ-lactams and lactones.[15b]

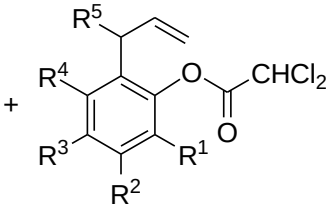
Ram et al.[16] reported an analogous benzannulation reaction of various 2-allylaryl trichloroacetates promoted by CuCl/bpy complex in refluxing benzene. However, the yields of the chloroarenes obtained by CuCl/bpy promoted benzannulation reaction were significantly lower (10-30%) compared to those obtained in the reaction catalyzed by the Cu(I)Cl complex with the NHC based ligands **L11** and **L12** (**Scheme 13**). They also observed the formation of the dimeric products **33** in 23-46% yields (**Scheme 15**). Under the heterogeneous reaction conditions, the transfer of chlorine atom from the sparingly soluble $CuCl_2$/bpy to the radical intermediate **30c** is a slower process than that under the homogeneous conditions used by Quayle and coworkers[15], thus allowing the dimerization of the radical intermediate **30c** to compete effectively with the chlorine atom transfer. With DCE as the reaction medium, reductive dechlorination of the starting material was the major reaction. A similar

mechanism as shown in **Scheme 14** was proposed for the formation of the products (**Scheme 16**).



31 **32** **33**

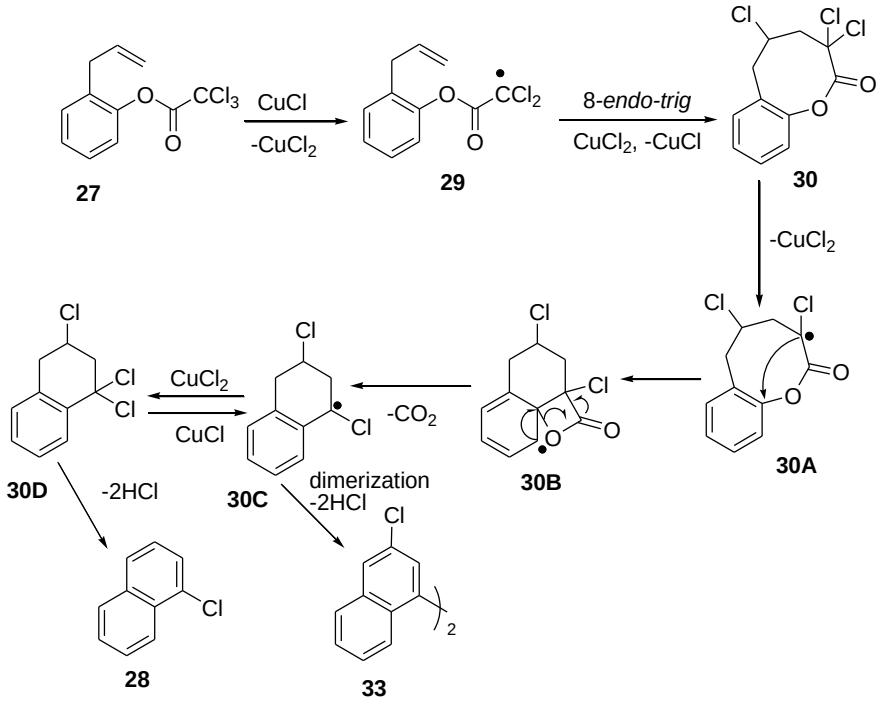
a, $R^1 = R^2 = R^5 = H$, $R^3 R^4 = CH=CH-CH=CH$
b, $R^1 R^2 = CH=CH-CH=CH$, $R^3 = R^4 = R^5 = H$
c, R^1= H, R^2 = H, R^3 = Cl, R^4 = H, R^5=H
d, R^1= H, R^2 = H, R^3 = Me, R^4 = H, R^5=H



34

	yields %		
	32	**33**	**34**
a	20	40	30
b	20	-	-
c	12	32	50
d	-	46	30

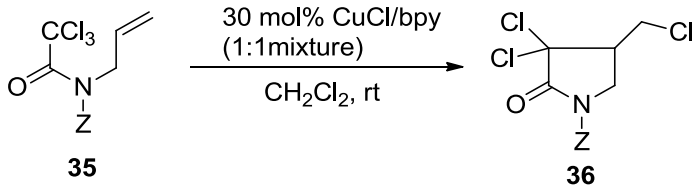
Scheme 15



27 **29** **30** **30A** **30B** **30C** **30D** **28** **33**

Scheme 16

Cyclization of the *N*-protected-*N*-allyltrichloroacetamides[8] **35** (**Scheme 17**) to the corresponding trichlorinated γ-lactams **36** proceeded much faster and at lower temperatures in the presence of 1:1 mixture of CuCl/bpy (30 mol% each) in DCM as compared to the reactions in the presence of 30 mol% CuCl alone in MeCN at 80 °C.



35 **36**

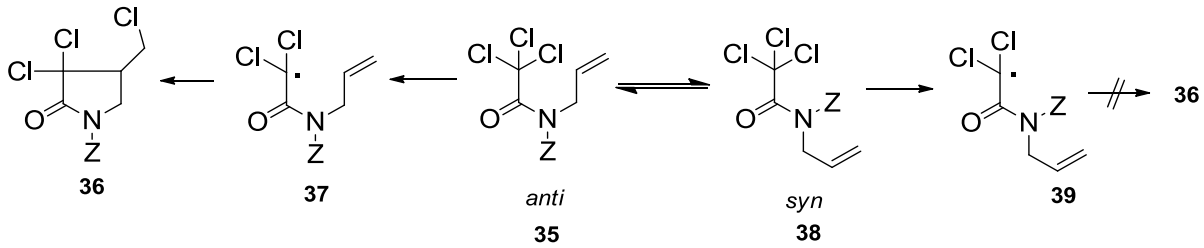
a: Z = Bn; **b**: Z = Ts; **c**: Z = Cbz

Substrate **35**	Catalyst (mol %)	Temp. °C	Time (h)	Yield(%) **36**
a	CuCl(30)	80	18	68
a	CuCl/bpy(30)	rt	1	98
b	CuCl(30)	rt	24	97
b	CuCl/bpy(5)	rt	0.2	91
b	CuCl/bpy(5)	-78	141	98
c	CuCl(30)	80	4	80
c	CuCl/bpy(30)	rt	2	78
c	CuCl/bpy(30)	-78	108	70

Dichloromethane was used as solvent in CuCl/bpy catalyzed reactions and CuCl-catalyzed reactions were performed in acetonitrile.

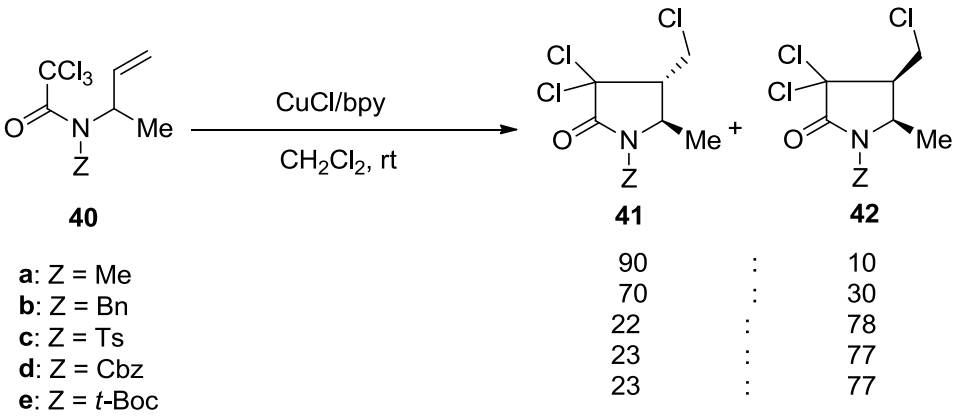
Scheme 17

The *N*-substituted-*N*-allyltrichloroacetamides **35** would cyclize only in the *anti* conformation **35** (**Scheme 18**). The nature of the *N*-substituent Z was observed to affect the conformer population. A bulky or electron withdrawing substituent (Z = Ts, Boc) favored cyclization by shifting the equilibrium towards the *anti* conformer **35.**



Scheme 18

The stereochemistry of the 5-*exo* atom transfer radical cyclization of the *N*-allylated trichloroacetamides was affected by the other substituent at the amide nitrogen.[8] Thus, the cyclization of the *N*-alkylamides **40a** and **40b** (**Scheme 19**) afforded the corresponding *trans* isomers **41** predominantly, whereas the cyclization of the *N*-tosyl, Cbz, or *t*-Boc derivatives **40c-e** produced the *cis* isomers **42** with good stereoselectivity.



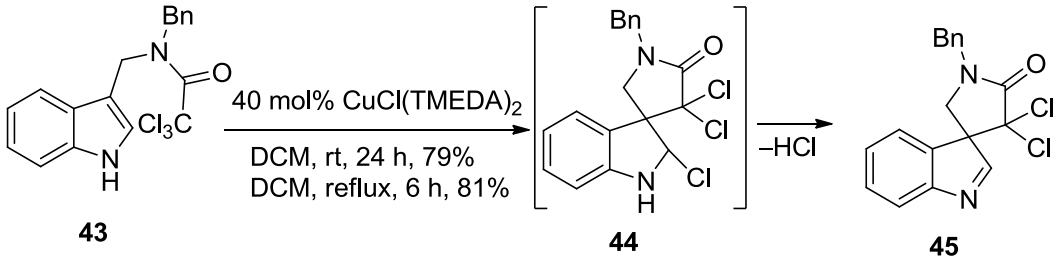
40

a: Z = Me
b: Z = Bn
c: Z = Ts
d: Z = Cbz
e: Z = *t*-Boc

41		**42**
90	:	10
70	:	30
22	:	78
23	:	77
23	:	77

Scheme 19

Stevens et al.[17] have shown the synthetic utility of TMEDA as a ligand in Cu(I)-catalyzed HATRC to synthesize spiro-indole derivatives. These spiro-indole derivatives resembled naturally occurring oxindole alkaloids which exhibit cell cycle inhibition activity. Thus, reaction of **43** (**Scheme 20**) with 40 mol% of CuCl and 80 mol% of TMEDA in DCM at room temperature furnished the spiro derivative **45** in 79% yield via 5-*exo*-*trig* cyclization. The initially formed spiro-indole intermediate **44** spontaneously lost HCl to form the spiro-indole **45**. The use of bpy as the ligand in the place of TMEDA led to the formation of the product in low yield (15%).



Scheme 20

The solid supported copper catalysts for HATRC are in demand due to their easy removal from reaction mixture and re-cyclability. Their reactivity can be tuned by changing the solid support. Therefore, the effect of various solid supported ligands derived from silica, polystyrene and JandaJel have been investigated in the HATRC of various trichloro-, dichloro- and monobromo substrates.[18,19] Some of the solid-supported ligands are shown in **Fig. 2.** The copper(I)- complexes derived from these ligands were effective in catalyzing 4-*exo*, 5-*exo* and 5-*endo* cyclizations. Reactions of alkynic substrates preferentially gave the cyclized products. Only small amounts of reductive dehalogenation products were formed.

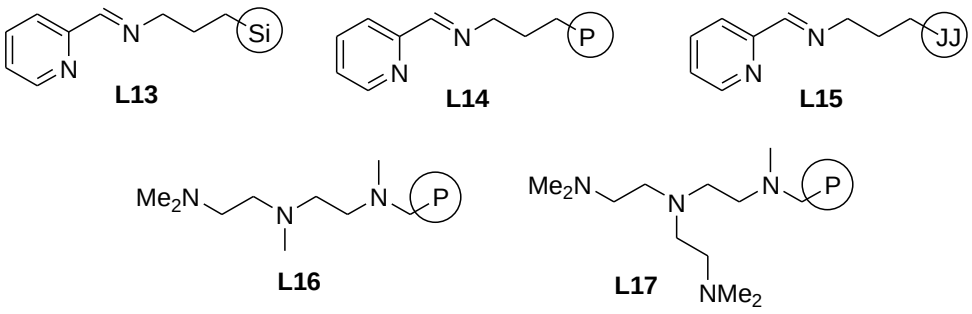
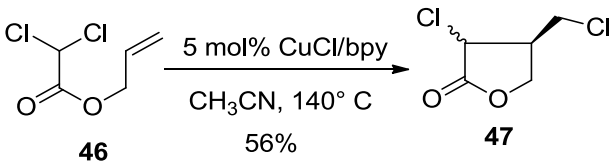


Fig. 2 Some solid-supported ligands used in Cu (I)-catalyzed HATRC

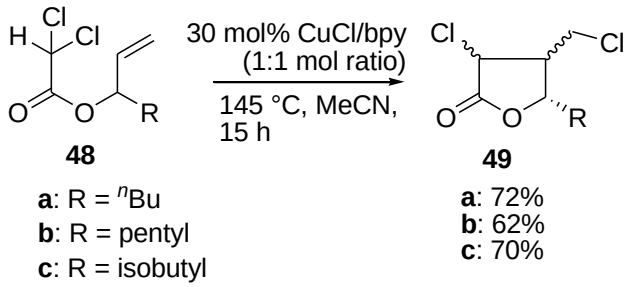
All the catalysts could be re-used. The catalysts retained their activity even after seven runs. However, these solid supported catalysts were found to be less active than their homogeneous counterparts. The diastereoselectivity of the reactions was similar to that observed under homogeneous catalysis. The selectivity and efficiency of the atom transfer process was mainly affected by the type of the ligand and less by the solid support on which it was immobilized.

The *gem*-dihalo compounds have higher energy LUMO as compared to that of the related trihalo compounds. Therefore these are generally less reactive than the trihalo compounds in copper(I)-catalyzed HATRC. Higher temperature and more active catalyst system are required for the reaction to be successful. For example, the allyl dichloroacetate **46** on heating with 30 mol% CuCl in acetonitrile in a sealed tube at 140 °C did not lead to its cyclization to **47**. However, 5 mol% of CuCl/bpy catalyst system successfully afforded the corresponding dichlorolactone **47** as a *trans*/*cis* mixture (4:1) in 56% yield under the same reaction conditions (**Scheme 21**).[7]



Scheme 21

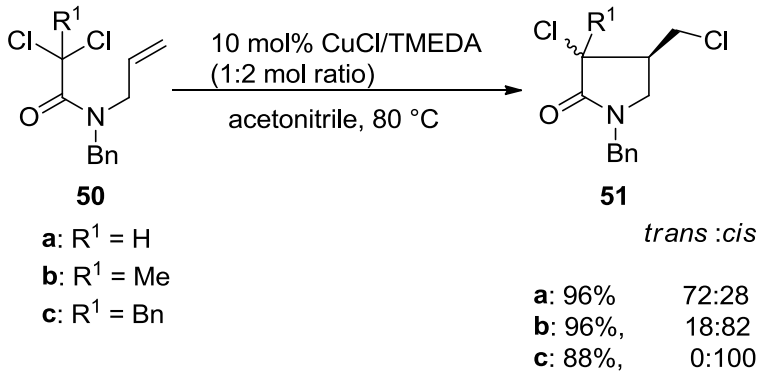
Similarly, the dichloroacetates **48** (**Scheme 22**) derived from secondary allylic alcohols cyclized to furnish the lactones **49** in good yields as inseparable mixtures of diastereomers on heating with 30 mol% CuCl/bpy in acetonitrile for 15 h at 145 ºC.[20]



Scheme 22

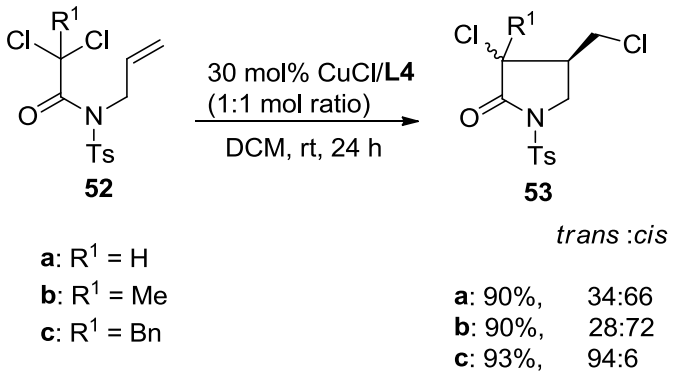
The high temperature and loading of excess amount of catalyst were due to lower reactivity of the dichloroacetates in HATRC.

Ghelfi and co-workers[21] reported the cyclization of *N*-benzyl-α,α-dichloroacetamides **50** with 10 mol% CuCl and 20 mol% TMEDA in acetonitrile at 80 °C (**Scheme 23**). The products **51** were obtained as mixtures of diastereomers.



Scheme 23

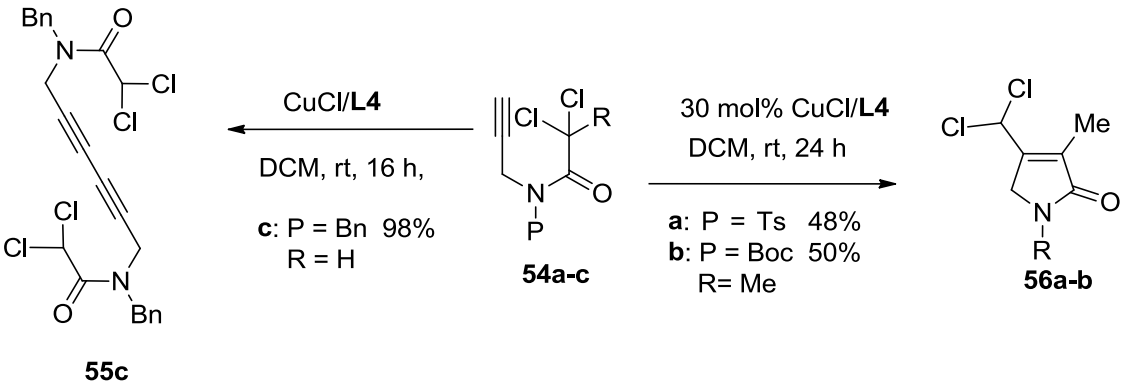
The reaction of the *N*-tosyldichloroamides **52** (**Scheme 24**) using 30 mol% CuCl and 30 mol% of the NPMI ligand **L4** (**Fig. 1**) in DCM occurred at room temperature.[12]



Scheme 24

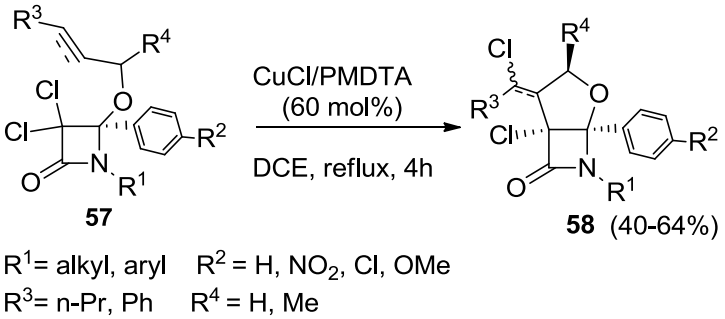
The cyclization of **52a** was catalyzed by 30 mol% CuCl/Me_6-tren in DCM at room temperature. The CuCl/**L4** catalyst failed to catalyze the cyclization of **52a**.[13] The effect of a range of NPMI ligands **L1-L4** of varying steric hindrance on the cyclization of **52** was also studied.[12] The results showed that as the size of the substituent on the nitrogen of NPMI ligand increased, the activity of the catalyst as well as the diastereoselectivity of the reaction decreased.

The reaction of the *N*-benzyldichloroacetamide derivative **54c** (**Scheme 25**) with one equivalent of CuCl/**L4** produced the acetylenic coupling product **55c** in 98% yield.[22] However, the electron withdrawing group such as Ts and Boc at the nitrogen atom as in **54a**,**b** promoted HATRC to **56a**,**b** by transfer of two chlorine atoms. In this case, only a catalytic amount of the catalyst (30 mol%) was required.



Scheme 25

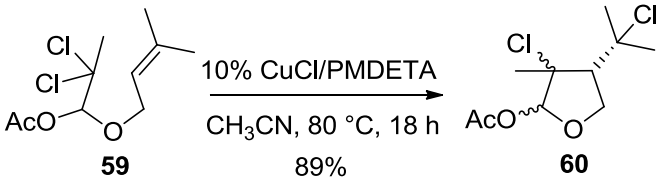
Recently, Ram et al.[23] used the dichloro-β-lactam **57** (**Scheme 26**) to prepare some bicyclic C-fused chlorinated tetrahydrofuro[3,2-c]azetidin-2-ones **58** by highly diastereoselective CuCl/PMDETA-catalyzed *5-exo*-trig/dig HATRC. The reaction was found to be influenced by the nature of the substituent at the lactam nitrogen and the nature of the ligand used. 2,2'- Bipyridine as ligand was ineffective, while TMEDA was effective in the case of the *N*-phenyl-β-lactam **57** (R^1 = Ph)). Only PMDETA was found to be a suitable ligand for the cyclization of both *N*-aryl and *N*-alkyl substituted **57**.



Scheme 26

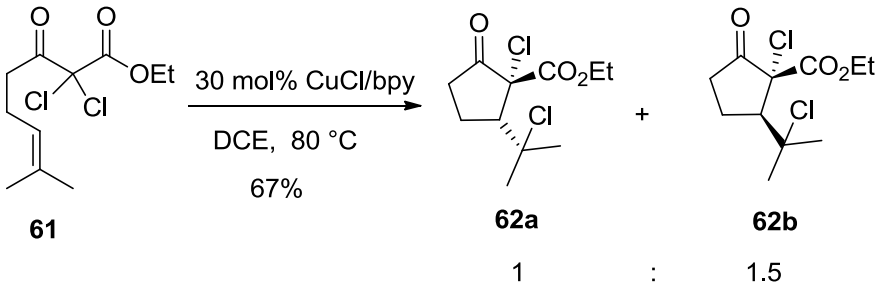
Recently, HATRC of *O*-allyl-2,2-dichloropropanal hemiacetal acetates have been reported.[24] For example, the HATRC of *O*-prenyl-2,2-dichloropropanal

hemiacetal acetate **59** to **60** (**Scheme 27**) has been realized by using 10 mol% CuCl/PMDETA as the catalyst in refluxing acetonitrile in 89% isolated yield. The classical CuCl/bpy catalyst failed to catalyze the cyclization whereas TMEDA was reported to give the cyclized product in poor yield (38%).



Scheme 27

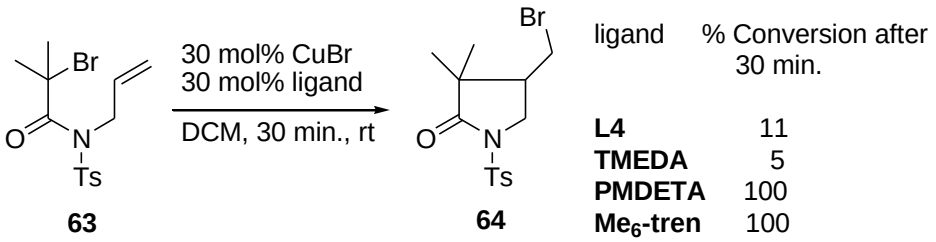
An electron withdrawing substituent lowers the LUMO of α,α–dichloroacetyl moiety and facilitates the abstraction of a chlorine atom by CuCl(I) complexes. For example, the HATRC of the unsaturated α,α-dichloro-β-ketoester **61** (**Scheme 28**) catalyzed by CuCl/bpy complex in DCE at 80 °C furnished a diastereomeric mixture of the carbo-cyclization products **62a** and **62b** in 67% yield.[25]



Scheme 28

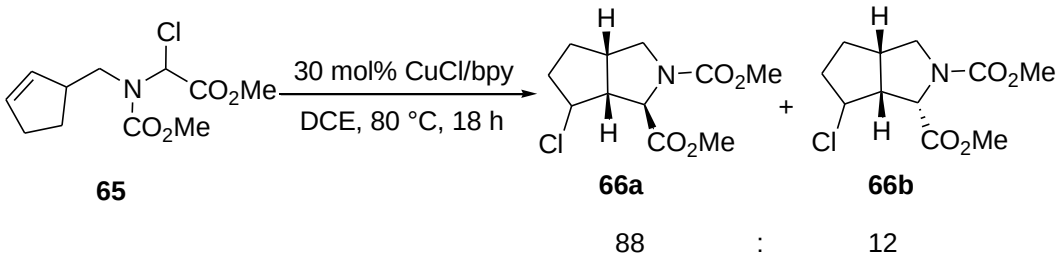
The HATRC of mono-bromo derivatives has been studied using some more reactive catalyst systems.[26] Thus, HATRC of the mono-bromo derivative **63** to **64** (**Scheme 29**) was found to be effectively catalyzed by 30 mol% CuBr/PMDETA or

CuBr/Me_6-tren complex in DCM at room temperature, whereas the complex of CuBr with NPMI ligand **L4** and TMEDA effected very less conversion of the starting material to the cyclic product **64**.



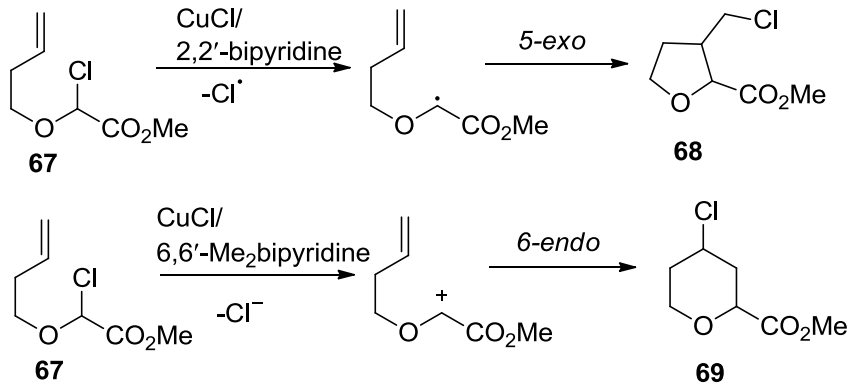
Scheme 29

The HATRC of less reactive mono-chloro[27] derivatives has also been reported. The reactivity of these substrates was enhanced by introduction of electron withdrawing group(s) to stabilize the radical intermediate formed after the abstraction of the halogen atom. Thus, the reaction of the mono-chloro derivative of glycine **65** (**Scheme 30**) with 30 mol% each of CuCl and bpy in DCE at 80 °C afforded the cyclized products **66** as a mixture of diastereomers **66a** and **66b**. The radical intermediate was stabilized by the captodative effect of the nitrogen atom and the ester group which were present at the radical center. In the absence of the ester group at the radical centre, no cyclized product was formed.[28]



Scheme 30

The choice of the ligand is important for the regiochemical and stereochemical outcome of the cyclization reaction.[28] A change in their structure can change even the nature of the incipient intermediates in the cyclization. Thus, the CuCl-catalyzed cyclization of methyl 2-(butyl-3-en-1-yloxy)-2-chloroacetate **67** (**Scheme 31**) with 2,2'-bipyridine as the ligand afforded the tetrahydrofuran derivative **68** via 5-*exo-trig* radical cyclization while with 6,6'-dimethyl-2,2'-bipyridine as the ligand only the 6-*endo* cyclization product **69** by a cationic mechanism was obtained.

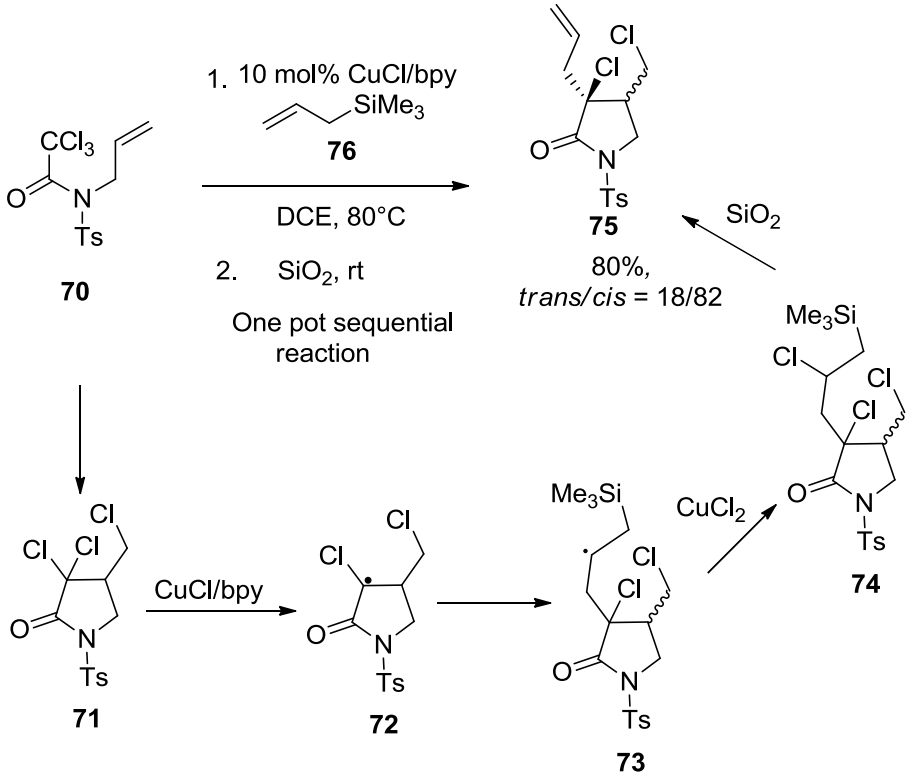


Scheme 31

1.3 Copper(I)-catalyzed sequential and tandem reactions

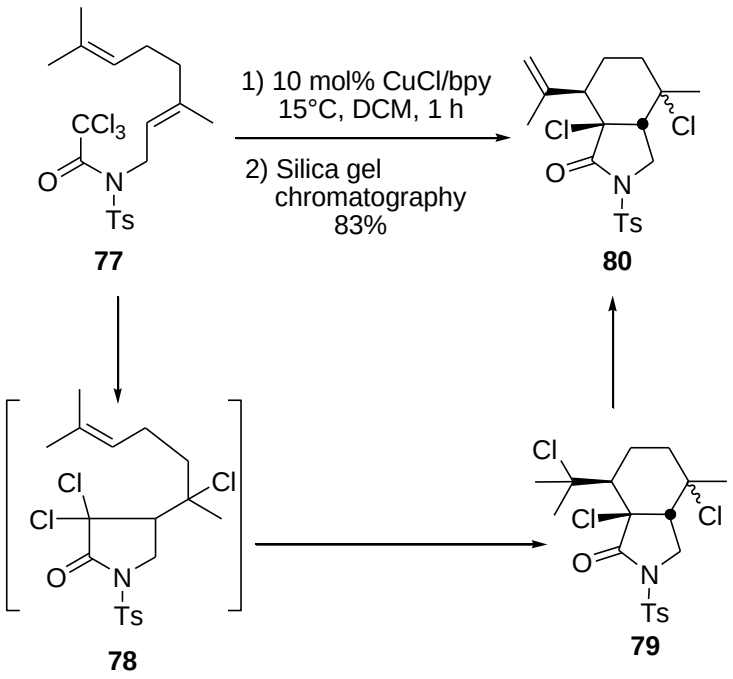
The utility of CuCl-complexes has also been demonstrated in sequential reactions. The intermolecular additions of polyhalo compounds to alkenes are generally slower than the intramolecular process. Therefore, these complexes were employed to catalyze cyclization and intermolecular[29]or intramolecular[30] addition in sequential manner. Thus, heating **70** (**Scheme 32**) with allyltrimethylsilane **76** in DCE in the presence of 10 mol% CuCl/bpy afforded the α-allylated γ-lactam **75** in 80% yield (*trans*/*cis* = 18/82).[29] The CuCl/bpy complex abstracts a chlorine atom from the activated *gem*-dichloro

group of **71** and generates a new radical **72.** This radical adds to the double bond of allyl trimethylsilyl **76** to generate the radical **73** which abstract a chlorine atom from $CuCl_2$/bpy to give the intermolecular addition product **74**. Compound **74** looses a chlorotrimethylsilane molecule to afford the final sequential cyclization and addition product **75**.



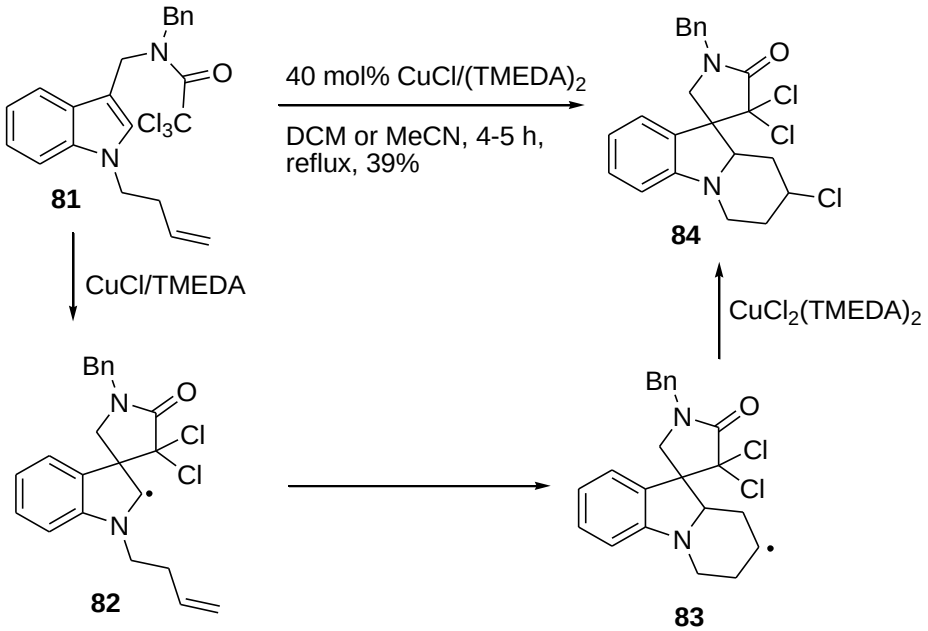
Scheme 32

Nagashima and co-workers[29] have exploited the application of these sequential reactions in intramolecular fashion to the synthesis of bicyclic lactams. Thus, reaction of **77** (**Scheme 33**) with 10 mol% CuCl/bpy at 15 °C in DCE for 1 h afforded the corresponding bicyclic lactams **79** as a mixture of two diastereomers in 2:1 ratio. Purification by silica gel chromatography was accompanied by elimination of an HCl molecule to furnish the bicyclic diastereomeric product **80**.



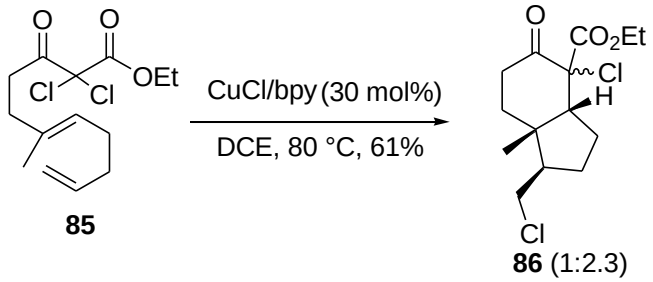
Scheme 33

Stevens et al.[30] used 40 mol% of the CuCl-TMEDA catalyst system for tandem radical cyclization of **81** (**Scheme 34**) in refluxing MeCN or DCM leading to the formation of the spiro compound **84** in 39% yield. The cyclization occurred via 5-*exo* and then 6-*endo* modes of cyclization.



Scheme 34

The cyclization of the α,α-dichloro-β-ketoester **85** (**Scheme 35**) with CuCl/bpy occurred in a tandem manner by 6-*endo* and then 5-*exo* cyclization to give a diastereomeric mixture of the *cis*-fused products **86**.[25]



85 **86** (1:2.3)

Scheme 35

1.4 Copper(I)-catalyzed enantioselective HATRC

Very few reports have been published[26, 31] on enantioselective Cu(I)-catalyzed HATRC. The enantioselectivity in these reactions were found to be poor. Clark et al.[31] have investigated the effect of chiral ligands **L18-L20** (**Fig. 3**) on the cyclization of *N*-allyl trichloroacetamides.

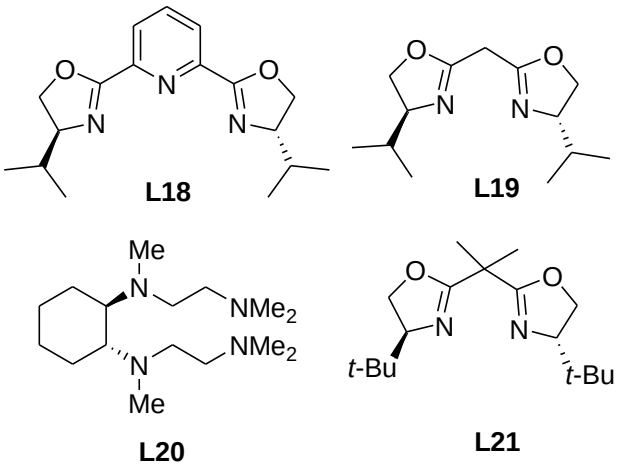
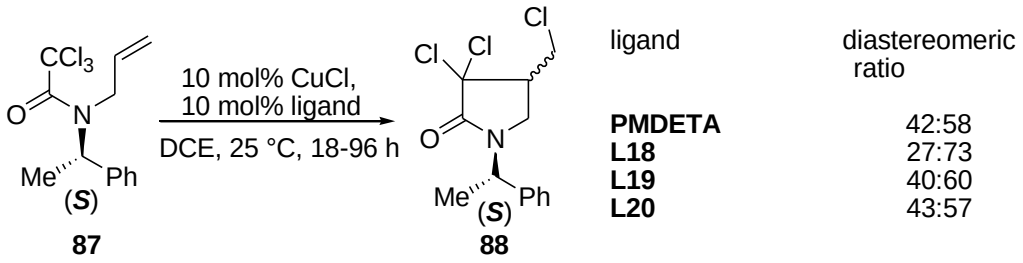


Fig. 3 Chiral ligands used in Cu(I)-catalyzed enantioselective HATRC

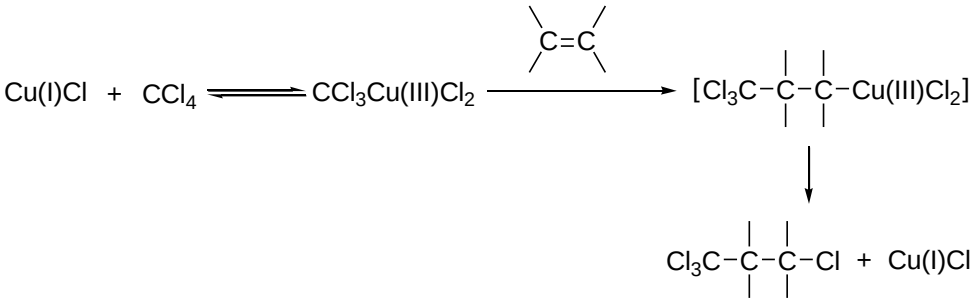
Thus, cyclization of the trichloroacetamide **87** (**Scheme 36**) was studied with 10 mol% of CuCl complex derived from the ligands **L18-L20** in DCE at reflux and at room temperature. The presence of chiral (*S*)-α-methylbenzylamine substituent had little influence on the diastereoselectivity of the cyclization. When the cyclization was performed at room temperature, it exhibited selectivity which was found to depend on the chirality of the ligand. This observation suggested the possibility of enantioselective HATRC by using chiral copper complexes. At higher temperature, the chirality of the ligands did not influence the diastereoselectivity and it was similar to that when non-chiral ligand was employed.



Scheme 36

Yang et al.[25] recently studied the HATRC of unsaturated α,α-dichloro-β-keto esters catalyzed by Cu(I) complexes with chiral bis(oxazoline) ligands **L18** and **L21**. Cyclization of **61** (**Scheme 28**) catalyzed by CuCl/**L21** as well as CuCl/**L18** in DCE at room temperature furnished the diastereomeric cyclization products **62a** and **62b** in 1:2.1 and 1:1.8 ratios, respectively. The same cyclized products were obtained in 1:1.5 ratio when the cyclization was catalyzed by CuCl/**L18** or CuCl/bpy in DCE at 80 °C. Thus, at higher temperature the diastereoselectivity was not found to depend on the chirality of the ligand. Moreover, the enantioselectivity of the reaction at room temperature using chiral ligands was found to be very low (below 10% *ee*).

Thus, by using chiral copper complexes in HATRC, it is possible to alter the diastereoselectivity of cyclization to some extent and also enantioselective cyclization may be designed. These findings also suggested that the radical involved in the Cu(I)-catalyzed cyclization was not completely free in nature and somehow copper complex was involved in the transition state for cyclization. Moreover, the facile co-addition of CO and CCl_4 to olefins catalyzed by palladium salts,[32] and binuclear metal carbonyls[33] and asymmetric addition of $BrCCl_3$ to styrene by chiral rhodium catalysts[34] can be explained by a redox mechanism which involves strong metal-radical interaction. By analogy, Bellus[35] had suggested that in copper-catalyzed reactions also the radicals remained coordinated to the copper during the entire course of the reaction as shown in **Scheme 37**.



Scheme 37

The radical species in these cases may be associated with the metal through non-covalent interactions at some or all the stages of the reaction- initial radical formation, radical addition and chain transfer (**Fig. 4**). However, close resemblance of chemo-, regio- and stereo selectivity and effects of additives on the Cu(I)-catalyzed reactions with those of the proven free radical reactions that involve unassociated free radicals (eg. Bu_3SnH-promoted, peroxide initiated) supported the possibility of favoring involvement of unassociated free radicals or radicals with only loose interaction with

the metal in the case of Cu(I)-catalyzed HATRC.[3,8,36] In the case of some other metals, such as Pd and Rh, the interaction may be quite strong to result in the formation of a covalent bond.[7]

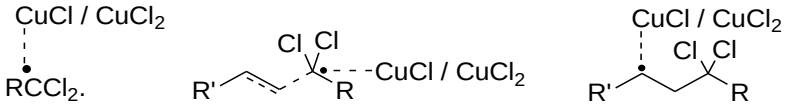
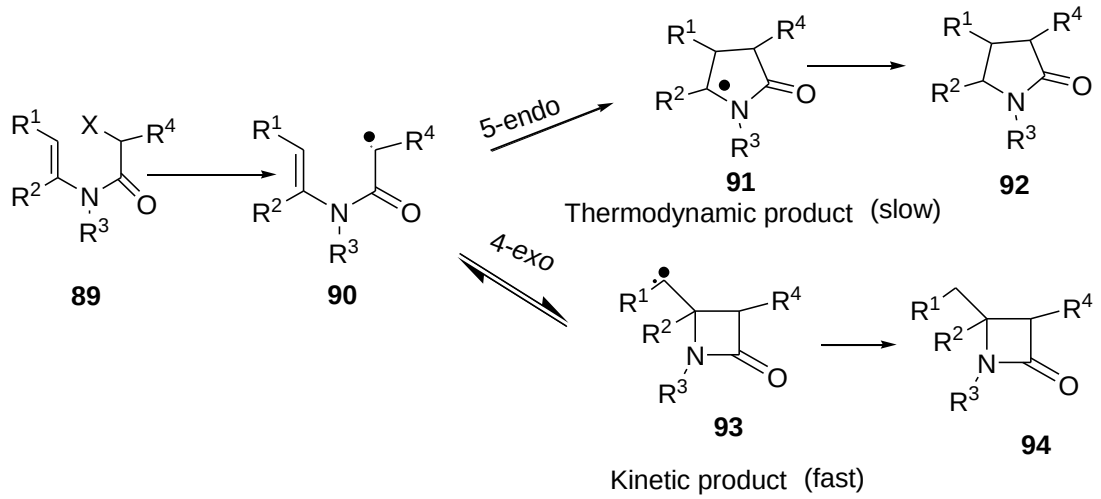


Fig. 4 Association of the radical intermediates with Cu(I)/Cu(II)

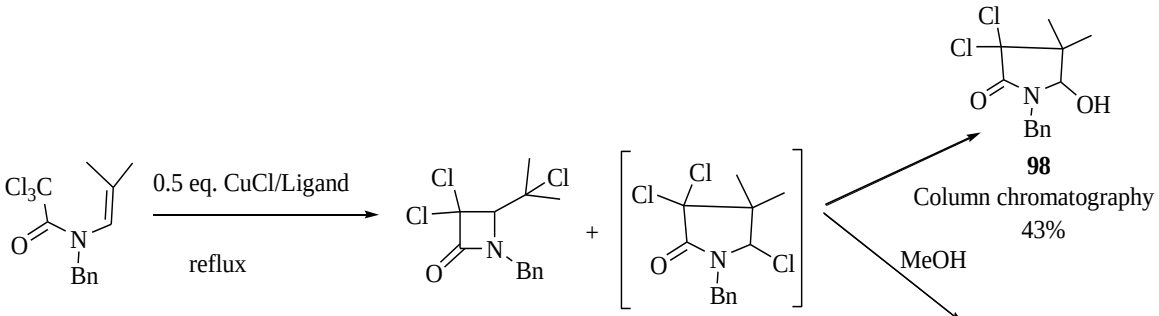
1.5. Copper(I)-catalyzed *5-endo* HATRC of haloenamides

Haloenamides **89** (**Scheme 38**) may, in principle, undergo *5-endo* cyclization to **91** and *4-exo* cyclization to **93**. Baldwin's empirical rules[37] predict *5-endo*-trig mode of radical cyclization to be "disfavored" process. Though the *4-exo* cyclization is allowed by these rules, it is, in general, a reversible process due to high strain in the cyclized four member ring system and easy opening of cyclic radical intermediate **93**, thereby shifting the equilibrium to the starting radicals **90**. Ikeda and coworkers[38] showed that *5-endo* or *4-exo* cyclization depended upon the electronic stability and/or the steric congestion of the cyclic radical intermediates **91** and **93** formed by ring closure of the carbamoylmethyl radical **90.** Therefore, both the modes of radical cyclization are usually not obsereved. These unusual cyclizations have been reported to occur in special cases where substituents in radical acceptor favor either the *4-exo* or *5-endo* mode of radical cyclization.[39] However using Bu_3SnH,[38] Ni/AcOH,[40] ceric ammonium nitrate(CAN),[41] $RuCl_2(PPh)_3$,[42] and $Mn(OAc)_3$[43] as reagents, several five-membered and four-membered nitrogen containing heterocycles **92** and **94** have been prepared through these mode of cyclizations.



Scheme 38

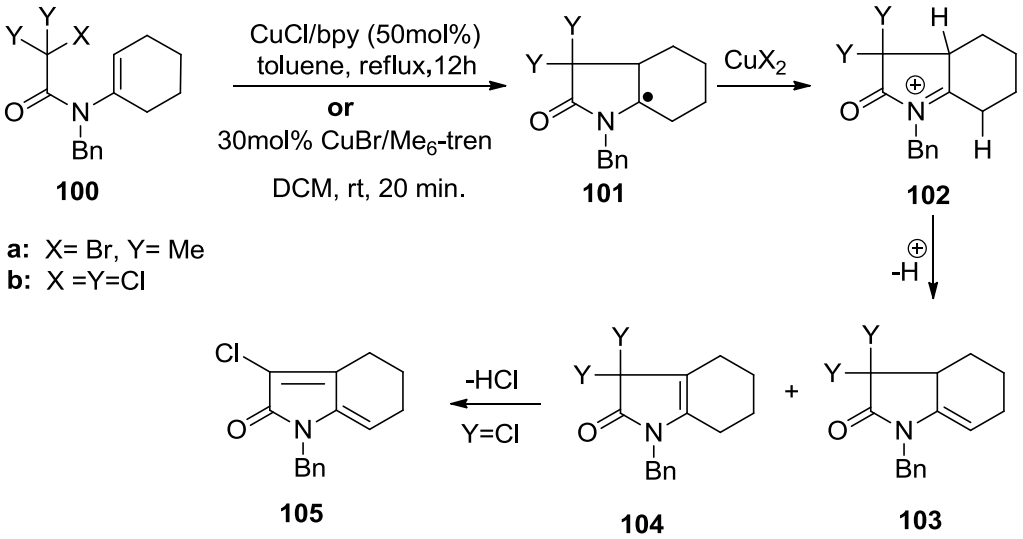
Cu(I)-complexes have also been employed in the 5-*endo* HATRC reactions of halo-enamide. Parsons and coworkers[42] reported that cyclization of the halo-enamide **95** (**Scheme 39**) using copper(I)chloride/bpy in boiling toluene gave α-chloro γ-lactam **97** as the major product by *5-endo* cyclization along with the β-lactam **96** by *4-exo* cyclization as the minor product. Purification of the crude product by column chromatography (on silica) resulted in hydrolysis of the α-chloro-γ-lactam **97** to give the α-hydroxy-γ-lactam **98**, while reaction with methanol gave the α-methoxy-γ-lactam **99.** The same reaction in acetonitrile gave the β-lactam **96** exclusively in 85% yield. This difference in regioseletivity was explained in terms of difference in solubility of CuCl complex in the two solvents. In acetonitrile the copper(II) complex was highly soluble and thus the initial kinetically favored *4-exo* cyclized radical was rapidly trapped by chlorine atom transfer from the $Cu(II)Cl_2$ complex, whereas in toluene the trapping of this radical was not fast due to the insolubility of the copper(II) complex. The reaction in toluene was therefore reversible leading to the formation of the thermodynamically more stable γ-lactam **97**.



Ligand	Solvent	yield	yield
bpy	Toluene	9%	86%
bpy/ TMEDA	CH_3CN	85% exclusively	not formed

Scheme 39

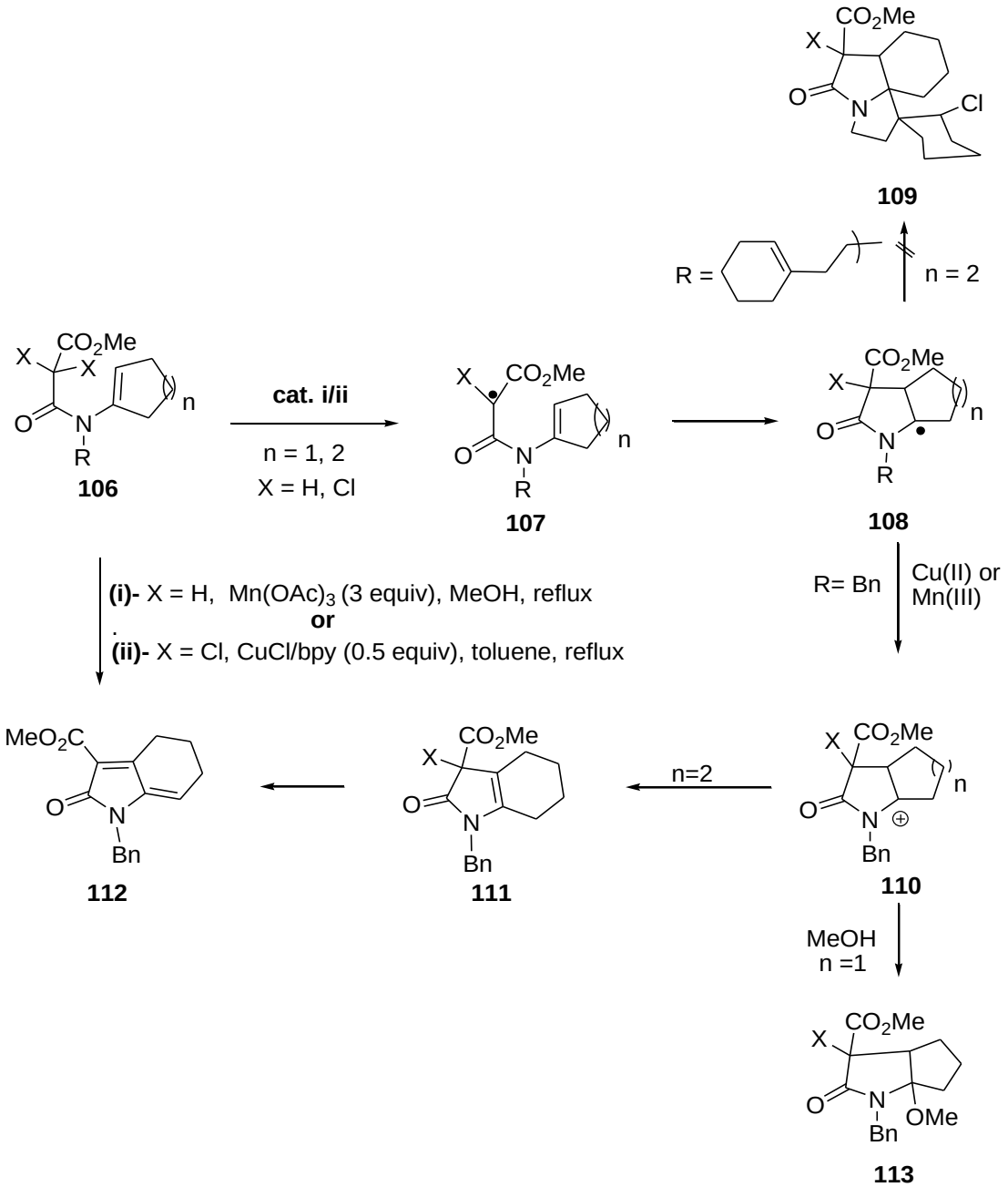
However, Parsons,[42] Clark[43] and coworkers observed that in the presence of hydrogen atom at the β-position of the enamide moiety **100** (**Scheme 40**), the cyclic radical **101** underwent Cu(II)-mediated oxidation to form the *N*-acyliminium ion intermediate **102**. The cationic intermediate adopted the radical-polar cross over mechanism and underwent deprotonation to form the unsaturated lactam **103** and **104**.



Scheme 40

Under the same reaction condition, these chlorinated lactams underwent further dehydrochlorination to form a doubly unsaturated lactam **105**. No *4-exo* products (β-lactams) were isolated from enamides **100**.

Parsons and Davies[44] compared manganese (III) acetate mediated and copper(I) chloride/bpy-catalyzed 5-*endo*-trig radical cyclization reaction of enamides **106** (**Scheme 41**) to produce functionalized pyrrolidinones **112**.

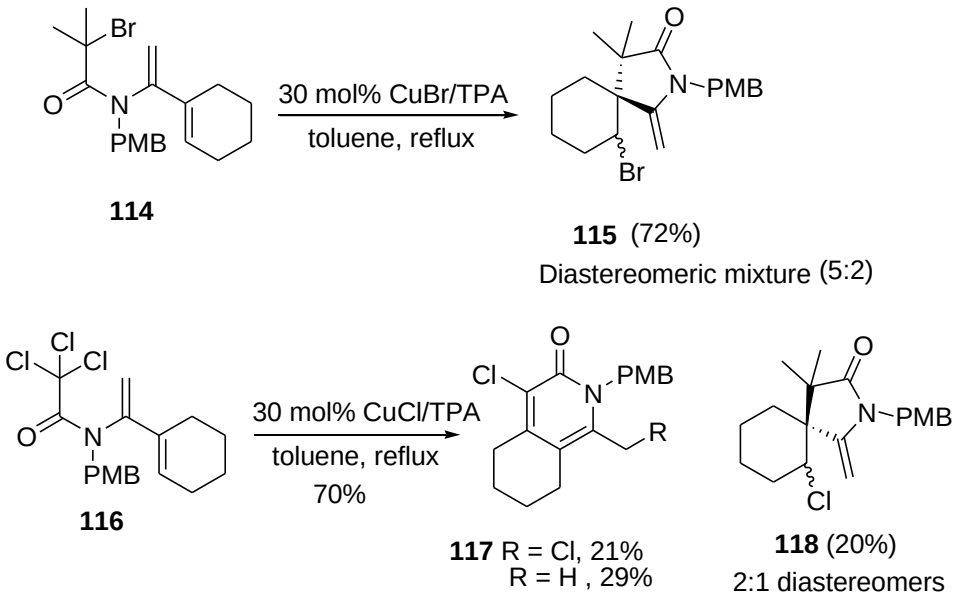


Scheme 41

They found that copper(I)Cl/bpy-catalyzed cyclization was very efficient and **112** could be isolated in 80% yield, while the corresponding manganese(III)-mediated reactions were generally more problematic, giving the product **112** in lower yields (35%). The best yield was obtained when 4 equiv. of manganese (III) acetate was used. No *4-exo* products (β-lactams) were isolated from enamides **106**. The *N*-homoallylic radical species **108** (R = cyclohex-1-enylethyl) had the option to undergo ring closure by either a *6-endo* or *5-exo* pathway by attack at the *N*-homoallylic double bond. However, attempts to trap the radical **108** (n = 2) intermediates by reaction with *N*-homomallylic double bond (in a tandem cyclization process) to obtain **109** were unsuccessful. Probably the rate of radical oxidation and cation deprotonation were faster than the radical or cationic cyclization onto the electron-rich *N*-homoallylic double bond. The tertiary radicals **108** were particularly susceptible to oxidation by reaction with a further equivalent of manganese(III) or copper(II). The resultant *N*-acyliminium ions **110** could then undergo deprotonation leading to the alkene **111**. In the presence of methanol, the methoxy derivatives **113** were isolated in an optimum yield of 39% as a single diastereomer. Thus, the intermediate *N*-acyliminium ion (of type **110**) reacted with methanol before deprotonation could occur. In all the cases, the reactions were proposed to proceed via oxidation of the tertiary radicals **108** to *N*-acyliminium ions **110**. Further oxidation of the alkene **111** (X = H) with manganese(III) acetate produced the diene **112**, while reaction of **111** (X = Cl) with copper(I)/bpy produced the diene **112** by further radical generation/oxidation or by dehydrochlorination (which could be mediated by bpy).[44]

Further, cyclization of the 2-substituted monobromo-dienamide **114** (**Scheme 42**) furnished the 5-*exo* cyclization product **115** as a 5:2 mixture of diastereomers in 72% yield under the same reaction conditions.[45] while, the cyclization of trichloro-

dienamide cyclization **116** afforded the 6-*endo* products **117** as the major product under the same reaction conditions. No *4-exo* products (β-lactams) were isolated from enamides **114** and **116**.

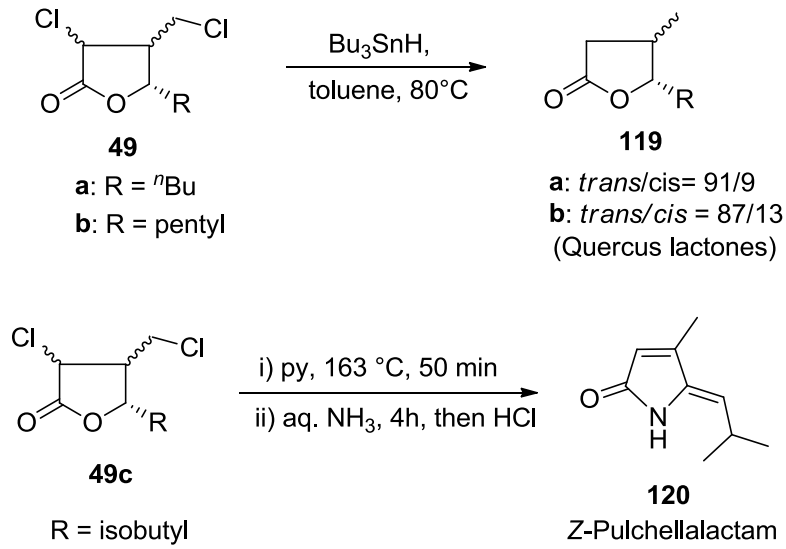


Scheme 42

1.6. Application of Cu(I)-catalyzed *5-exo* and *5-endo* HATRC in natural product synthesis

The Cu(I)-catalyzed HATRC has been employed to synthesize many biologically important natural products. For example, syntheses of some naturally occurring lactones and lactams such as Quercus lactones[20] **119** and (*Z*)-pulchellalactam[46]**120** (**Scheme 43**) have been accomplished successfully. In their syntheses, the compounds **49a** and **49b** (**Scheme 22**) obtained by CuCl/bpy-catalyzed HATRC were subjected to reductive dehalogenation by Bu_3SnH in toluene at 80°C to give racemic mixtures of the Quercus lactones **119a** and **119b** in good yields. Dehydrochlorination of **49c** and double bond isomerisation in pyridine at 160 °C

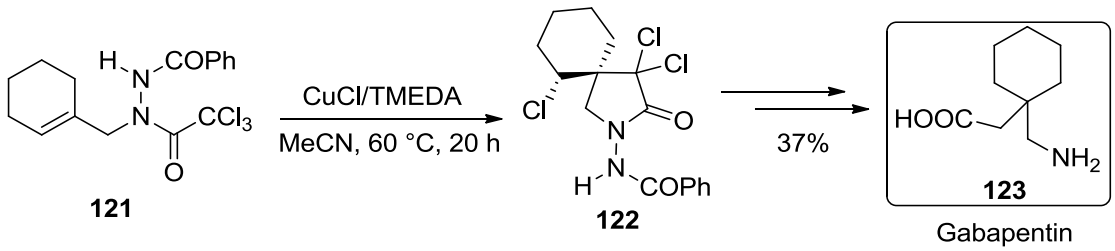
followed by treatment with aq. NH_3 and acidic workup furnished (*Z*)-pulchellalactam **120** in 22% overall yield. In another approach to synthesize (*Z*)-pulchellalactam, $RuCl_2(PPh_3)_3$-catalyzed HATRC of *N*-vinyl dichloroacetamides was used as the key step but it was not a good method due to poor (4%) overall yield of the product.[47]



Scheme 43

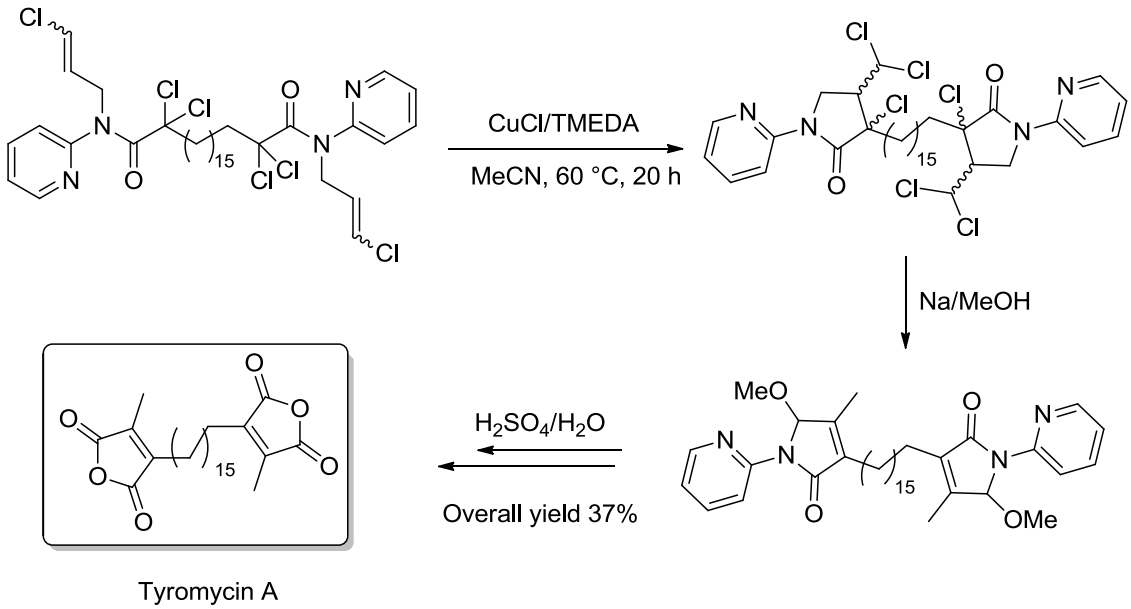
The wine, whisky and other alcoholic beverages contain these Quercus lactones and are responsible for their sensory effects. (Z)-Pulchellalalctum is a CD45 protein tyrosine phosphatase inhibitor and also a therapeutic agent for autoimmune and chronic anti-inflammatory diseases.

Likewise, gabapentin, **123** (**Scheme 44**) an anti-epileptic drug with extremely low toxicity, was synthesized in five steps in 37% overall yield involving $CuCl(TMEDA)_2$-catalyzed HATRC of **121** to **122** as the key step.[48]



Scheme 44

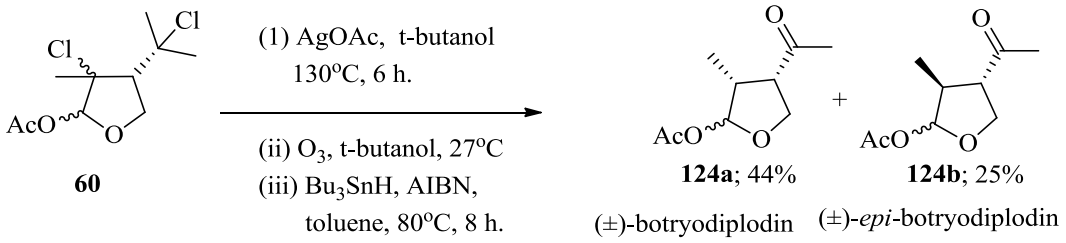
Tyromycin A, a naturally occurring metabolite inhibitor of the lecuine and cysteine mammalian APs (aminopeptidases) serves as an immunomodulating drug.[49] Synthesis of tyromycin A was accomplished by using CuCl/TMEDA-catalyzed HATRC as the key step (**Scheme 45**).



Scheme 45

(±)-Botryodiplodin **124a** and (±)-*epi*-botryodiplodin **124b** acetates (**Scheme 46**) have been synthesized from the chlorine atom transfer radical cyclization product **60**[24] (**Scheme 27**) through successive monodehydrochlorination, ozonolysis and

dechlorination. (–)-Botryodiplodin is a natural toxin and found to have antibacterial activity and cytostatic activity against neoplastic cells.



Scheme 46

Apart from these total syntheses of natural products, formal synthesis of many naturally occurring compounds have also been realized.

For example, the core units **125** and **126** (**Fig. 5**) of gilvocarcin antibiotics **127** were formally synthesized from the corresponding readily available *ortho*-allylaryl trichloroacetates using the Cu(I)-catalyzed benzannulation reaction described in **Scheme 13**.[15b]

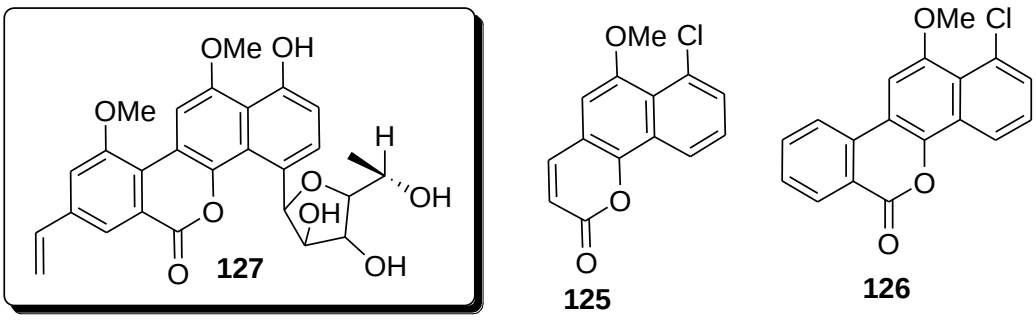
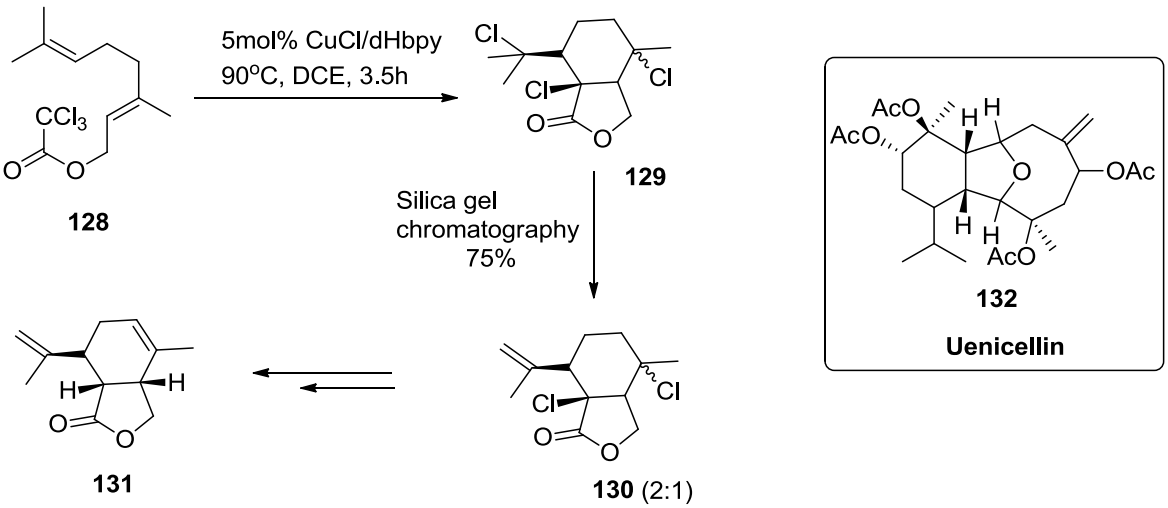


Fig. 5 Use of chlorobiaryls in the synthesis of Gilvocarcin

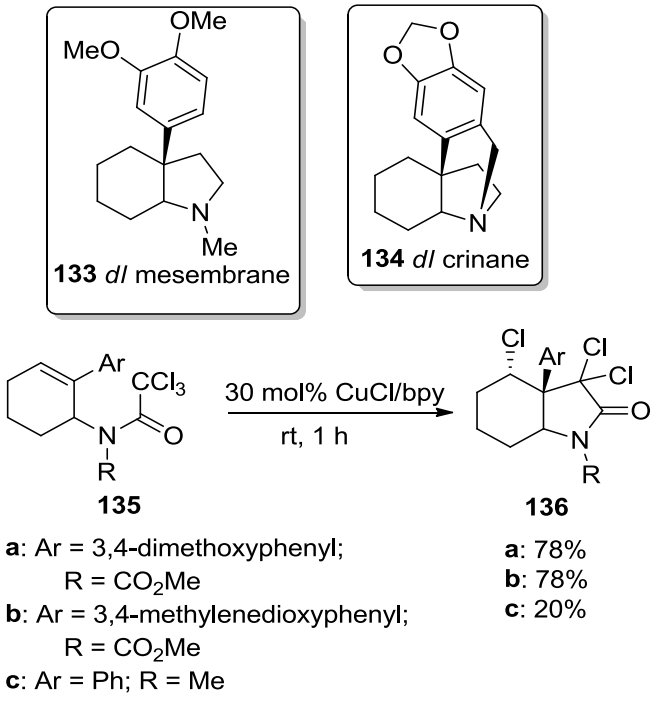
Through a sequential intramolecular HATRC, the formal bicyclic core unit **131** (**Scheme 47**) of eunicellin **132** was synthesized starting from the trichloroacetoxydiene **128**.[50] The tandem HATRC product **129** was converted to the bicyclic core **131** through standard reactions.



dHbpy = 4,4'-di-*n*-heptyl-2,2'-bipyridine

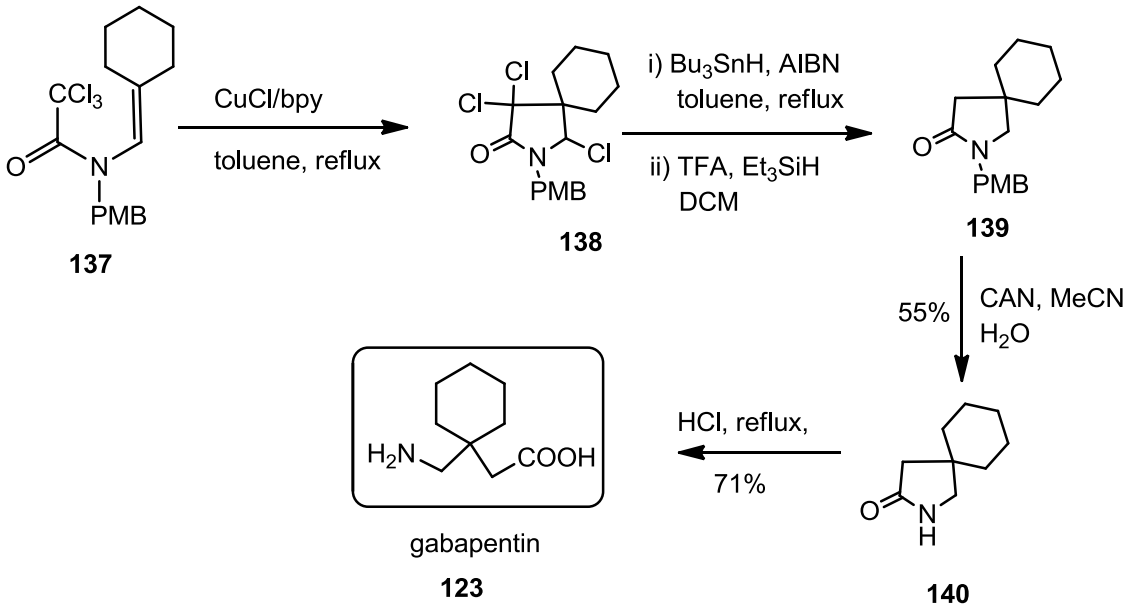
Scheme 47

The alkaloid mesembarane[51] **133** and crinane[52] **134** (**Scheme 48**) were formally synthesized by using CuCl/bpy-catalyzed HATRC of **135a** and **135b** respectively, as the key step.[53] Attempts to cyclize **135c** having a methyl group at the nitrogen under the same conditions produced the cyclization product only in very low yield due to higher population of the rotamers unfavorable to cyclization.



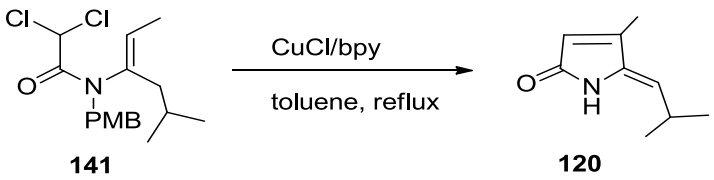
Scheme 48

Parsons and coworkers[47] used *5-endo* HATRC of halo-enamide **137** (**Scheme 49**) as a key step in the synthesis of gabapentin **123**. The enamide **137** when heated with copper(I)chloride/bpy in toluene at reflux condition gave the trichlorinated spirocycle **138**, which on reductive dechlorination and PMB-deprotection afforded **140.** The lactam **140** on acidic hydrolysis gave gabapentin **123** in good yield (71%). Gabapentin is an antiepileptic drug originally designed as a lipophilic GABA analogue, it has been shown that it does not interact with any of the enzymes on the GABA metabolic pathway.



Scheme 49

On heating with a copper(I)chloride/bpy in toluene at reflux condition, the *N*-protected enamide **141** (**Scheme 50**) underwent *5-endo* cyclization followed by dehydrochlorination to form the core ring system of pulchellalactam **120** in single step.[47]



Scheme 50

CHAPTER 2

Synthesis of chlorinated and functionalized *N*-H pyrrolidines by Cu (I)-catalyzed *5-exo* halogen atom transfer radical cyclization of 2,2,2-trichloroethyl allyl amines

2.1. Introduction

Pyrrolidines are present in many natural amino acids[54] for example in proline, hydroxyproline and kainic acid, etc., and alkaloids[55] such as hygrine and (-)-soienopsis fugax venoman,[55a] nonhygrine, ruspoline and cocaine,[55b] (-)-*trans* dendrochrycine,[55c] nicotine and (R)-cryspine A,[55d] etc. (**Fig**. **6**).

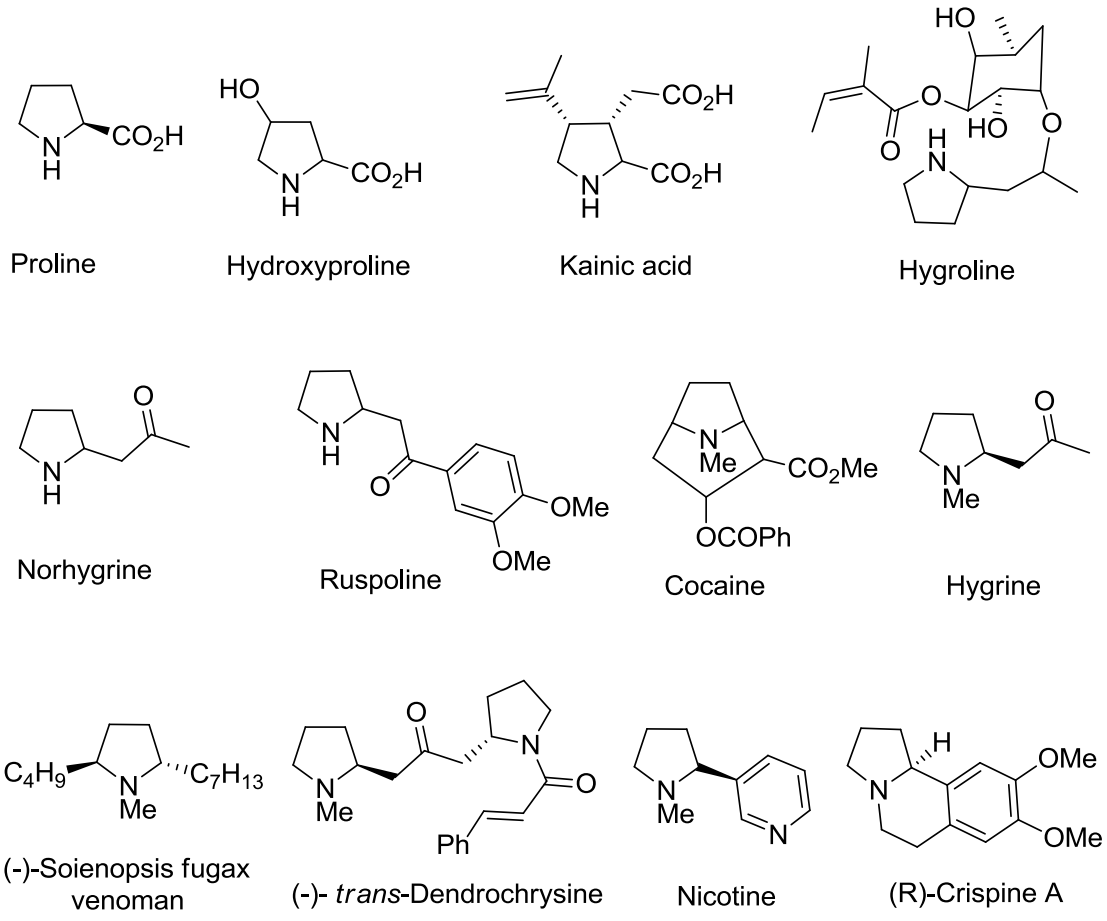
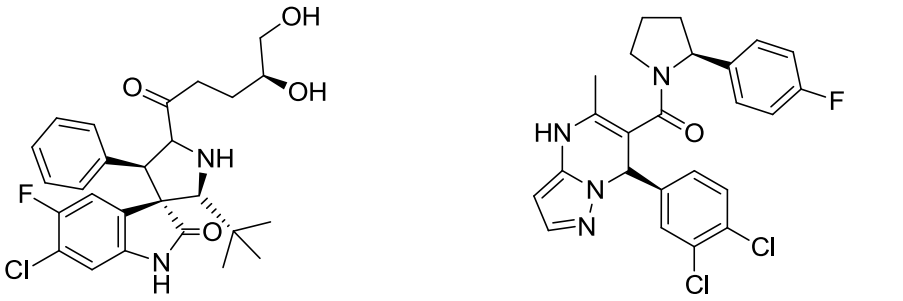


Fig. 6 Some naturally occurring pyrrolidine derivatives

A large number of pyrrolidines display a variety of physiological activities[56] such as the protease inhibitor aeruginosin,[56a] the novel glutamate receptor antagonist

kaitocephalin,[56b] the neuraminidase inhibitors A-315675,[56c,d] A-192558[56e] and antibiotic lemonomycin,[56f] etc.

Many synthetic pyrrolidines have found applications in pharmaceutical fields[57] such as MI-219 (antibacterial, cancer therepy)[57a] (**Fig**. **7**), BMS-394136 (selective Kv1.5 blocker),[57b] and others as β-amyloid cleaving enzyme-1 (BACE-1 inhibitors),[57c] gluconeogenesis inhibitor,[57d] antiviral activity,[57e] gastroprokinetic agent[57f] etc.



MI - 219 (Cancer therapy)

BMS - 394136 (selective Kv1.5 blocker)

Fig. 7 Examples of pharmaceutically important synthetic pyrrolidine derivatives

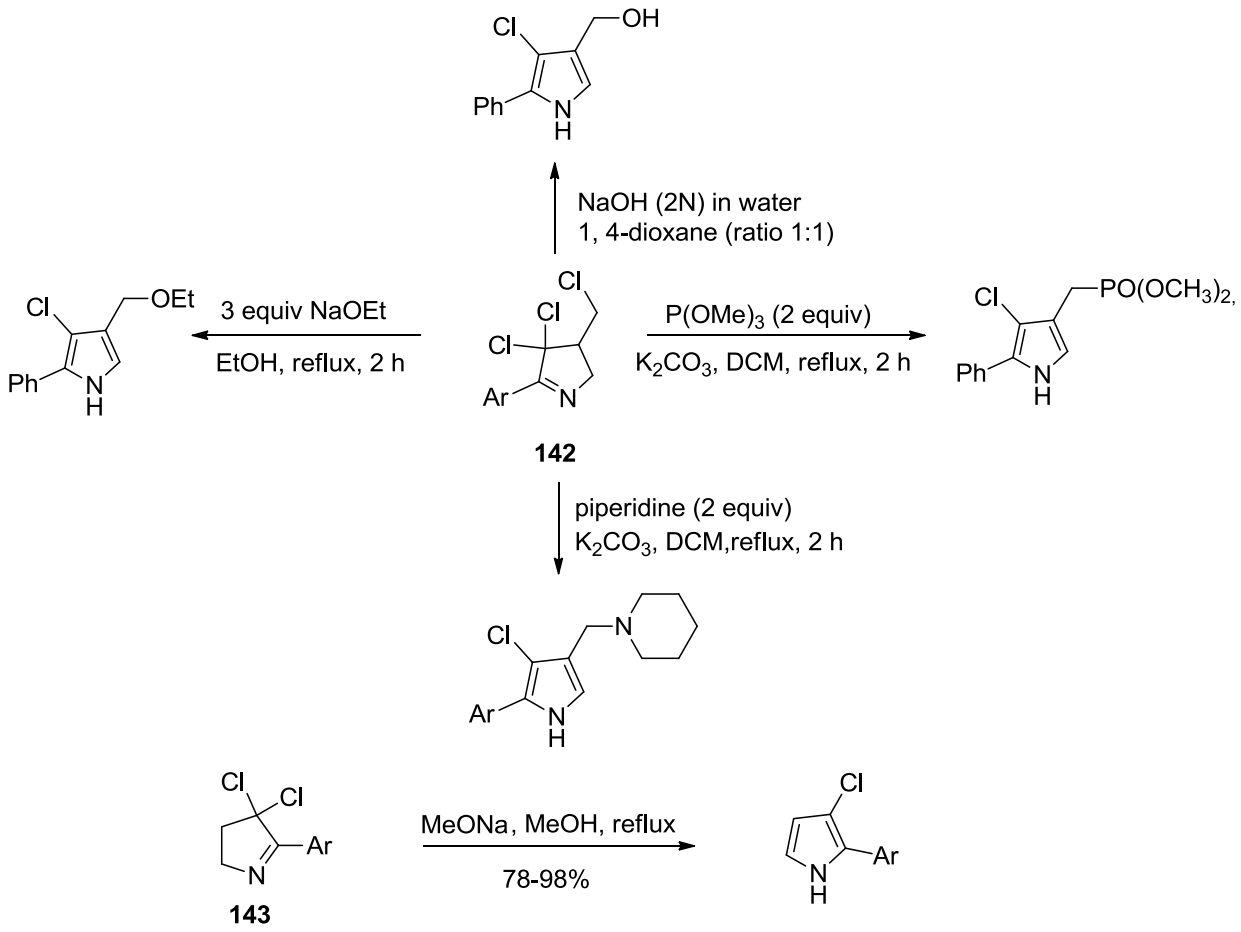
Many natural and pharmaceutically important pyrrolidines (**Fig. 6** and **7**) bear alkyl, aryl and heteroaryl substituents on the ring and ester or keto group in the side chain. Many reports describe the importance of halogen atom, the NH center and side chain functional groups of pyrrolidines which have been exploited for the construction of a variety of natural products[58] and potentially useful acyclic, alicyclic and aromatic compounds.[59] Functionalized *N*-H pyrrolidines have also been employed as chiral auxiliaries[60] and organocatalysts[61] in asymmetric synthesis. Therefore, synthesis of variously substituted *N*-H pyrrolidines continues to receive unabetted attention. Here, only synthetic importance and methods of preparation of pyrrolidines having chlorine, NH and

side chain functional group (keto, ester) (here in after referred to as chlorinated and functionalized *N*-H pyrrolidines), which are relevant to the present work, will be described briefly.

2.1.1. Synthetic importance of chlorine substituents in the pyrrolidine ring

The chlorine atoms present in many heterocycles were shown to be attractive substituents for useful synthetic transformation. Chlorine atom of heterocycles and carbocycles has been found to undergo selective reduction,[20,25] substitution,[62] elimination–aromatization[10] and tandem/sequential radical cyclization,[63] and thus has been used in assembling complex heterocycles and natural products.[58] Parsons and coworkers[47] employed Bu_3SnH as reducing agent in the synthesis of the anti-epileptic drug gabapentin (**Scheme 49**, **Chapter 1**) and the biologically active natural product pulchellalactam (**Scheme 43, Chapter 1**). Reductive dechlorination with Zn/acetic acid[64] has been used for preparing synthetically useful compounds and natural products such as Pilolactam. Ram et al.[10] demonstrated the utility of chlorine atom in base promoted elimination-aromatization of tetrahydrofurans and nucleophilic substitution of chlorine atom in the side-chain in a β-lactam-fused tetrahydrofuran by azide group.[23]

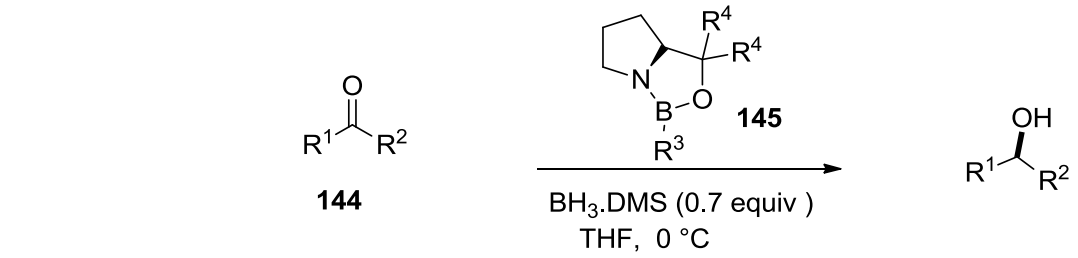
Kimpe and coworkers [65] reported aromatization of the chlorinated pyrrolines **142** and **143** (**Scheme 51**) by base-promoted dehydrochlorination. The chlorine atom present in the side chain of **142** was also substituted simultaneously by hydroxide, alkoxide, amines and phosphite.



Scheme 51

2.1.2. Synthetic importance of the NH group in the *N*-H pyrrolidines

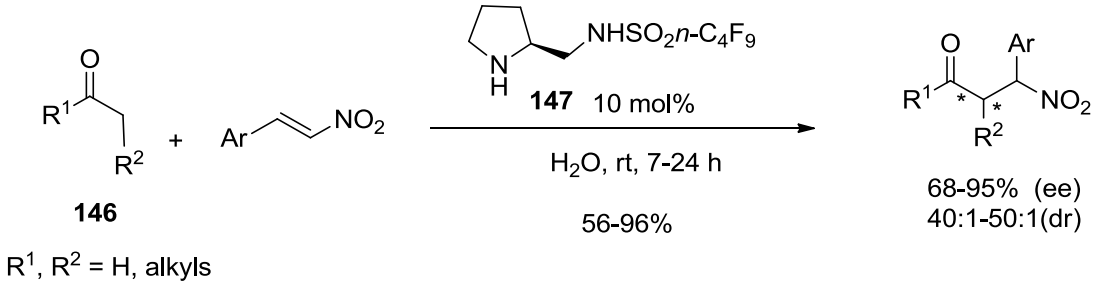
Jones et al.[66] employed *N*-H pyrrolidine derived substituted oxazaborolidine **145** (**Scheme 52**) in asymmetric reduction of ketones **144**. This protocol generally provided >93% (ee) of the desired enantiomer.



R^1 = alkyl, alicyclic R^2 = alicyclic,heteroaryl, aryls. R^3 = alkyl, aryl, R^4 = aryls

Scheme 52

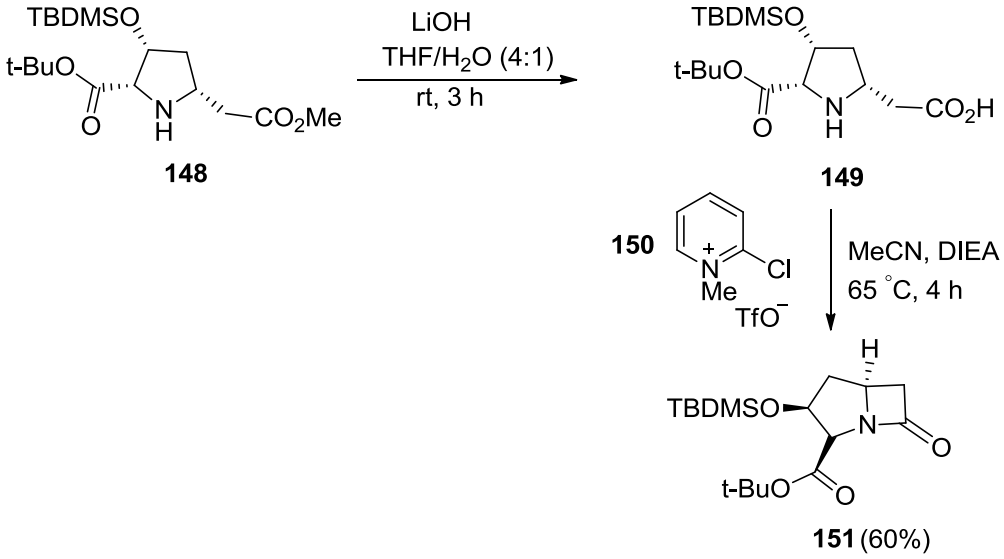
Wang and coworkers[67] employed a fluorous (S)-*N*-H pyrrolidine sulfonamide organocatalyst **147** (**Scheme 53**) to promote high enantio- and diastereoselective in Michael addition reactions of ketones and aldehydes **146** with nitroolefins in water.



R^1, R^2 = H, alkyls

Scheme 53

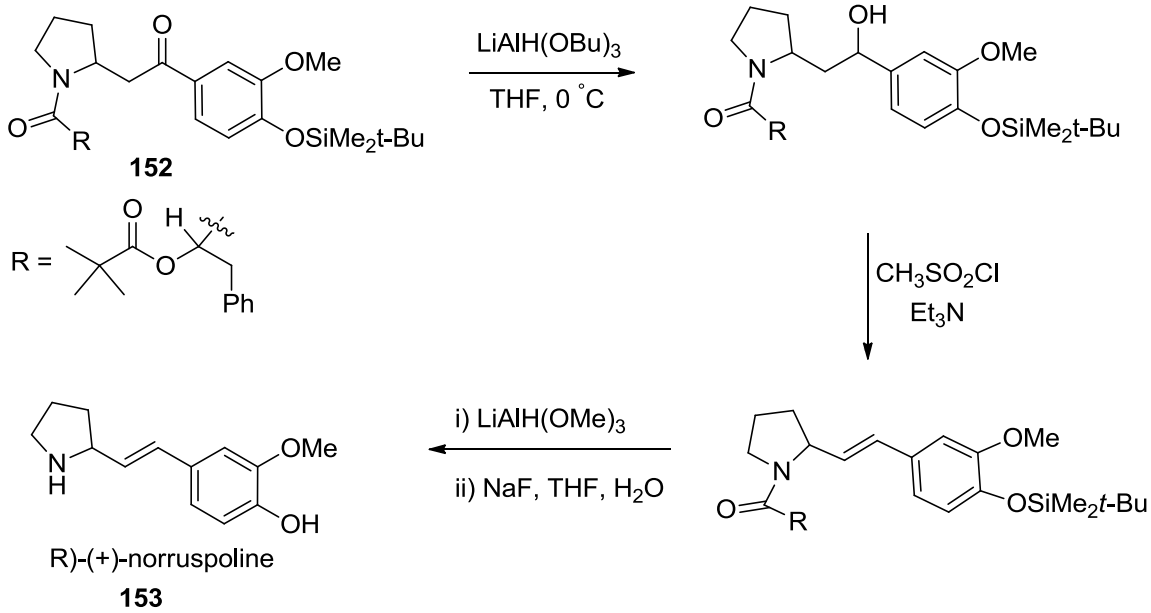
Rapoport and coworkers[58a] reported enantioselective synthesis of a functionalized carbapenam core **151** (**Scheme 54**) from the amino acid derived *N*-H pyrrolidine **148** for derivatization of antibacterial thienemycin. The synthetic strategy relied on synthesis of appropriately functionalized pyrrolidine **148** followed by its hydrolysis. Intramolecular formation of azetidone **151** from hydrolyzed product **149** was effected by utilizing a modified Mukiyama reagent **150**.



Scheme 54

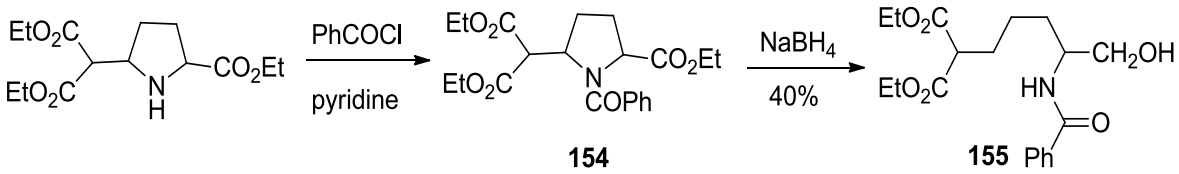
2.1.3. Synthetic importance of side chain functional group in pyrrolidines ring

The keto group of ketopyrrolidine **152** (**Scheme 55**) was used for the synthesis of the natural product (+)-norruspoline **153**, an alkaloid of the tropical plant *Ruspolia hypercraterformis.*[68]



Scheme 55

Side chain functionalized pyrrolidines have been used in the synthesis of functionalized acyclic compounds.[69] For example, Hussaini and Moloney[69a] reported reductive cleavage of the benzoylated pyrrolidine **154** (**Scheme 56**) to obtain the diversely functionalized product **155**.

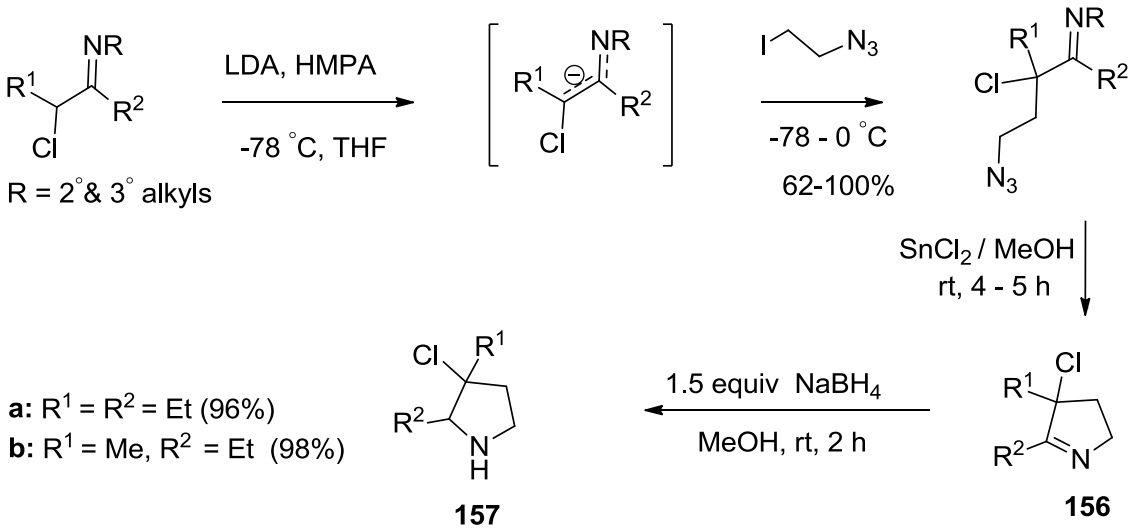


154 **155**

Scheme 56

2.1.4. Synthesis of chlorinated pyrrolidines

Despite the potential synthetic applications of chlorinated pyrrolidines, literature survey revealed that there are very few methods available for their synthesis. Furthermore, these methods have their own limitations with regard to yields, number of steps, the nature of substituent, the substitution pattern. For example, Kimpe and coworkers[65b] synthesized alkyl substituted β-chloropyrrolidine derivatives **157** by reducing the chlorinated cyclic imines **156** which in turn were obtained by a multistep approach as shown in **Scheme 57**.



157 **156**

Scheme 57

Similarly, Kimpe and coworkers[70] exploited the ring opening and rearrangement property of α-chloroazetidines **163** (**Scheme 58**) to synthesize the *N*-substituted β-chloropyrrolidines **165** by multistep approach. The chiral short-chain *R*-chloroaldehydes **159** were prepared from enantiomerically pure amino acids **158** in three steps. The aldehydes **159** and amines **160** were condensed to chiral imines which underwent stereoselective Staudinger reaction with acyl chlorides **161** to give the β-lactams (3*S*,4*S*)-4-[(1*S*)-1-chloroalkyl]azetidin-2-ones **162**. The azetidinone **162** on treatment with AlH_2Cl underwent reduction to azetidines **163**, which on heating underwent simultaneous ring opening and rearrangement to give the *N*-substituted β-chloropyrrolidines **164** in moderate yields.

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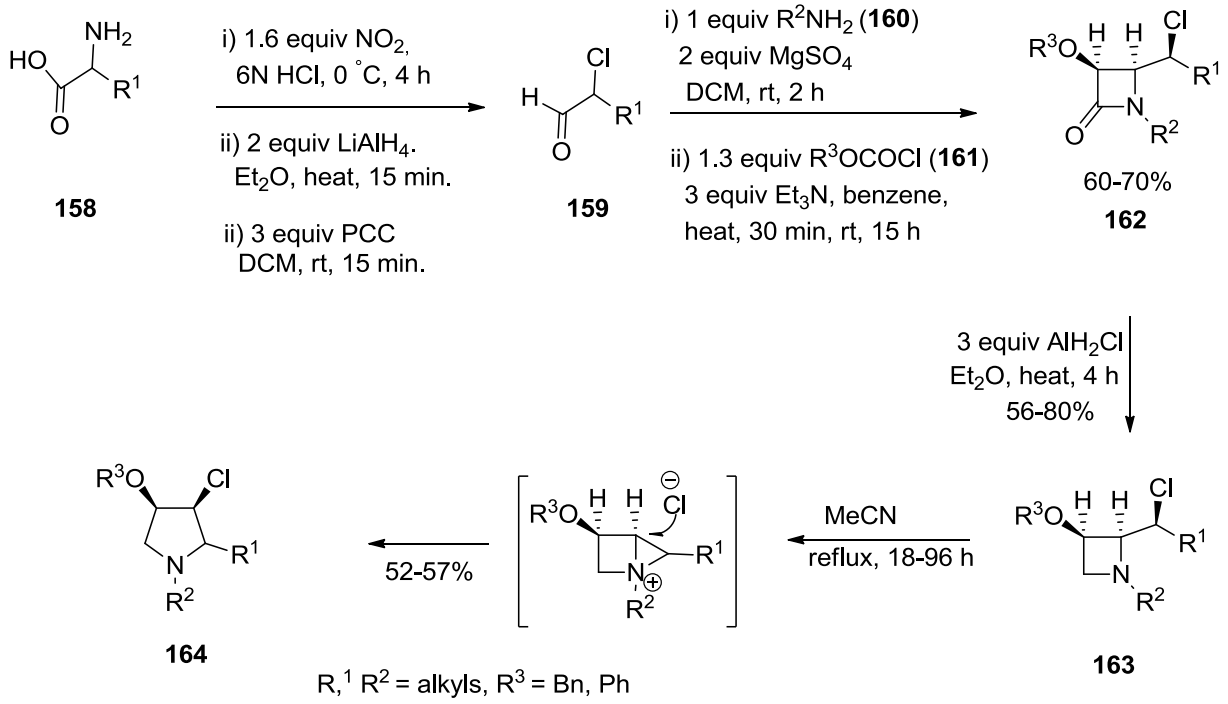


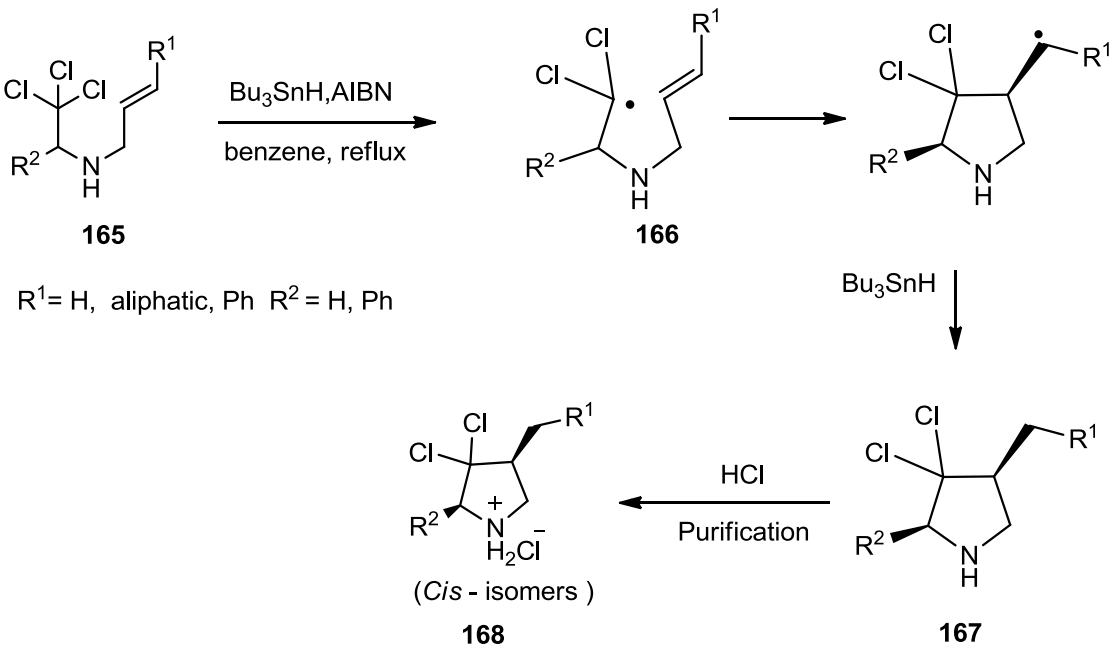
Scheme 58

Few other reports also employed ring opening and rearrangement property of α-chloro azetidines in the synthesis of *N*-substituted β-chloropyrrolidines.[71] Like the above methods, they are also multistep, giving *N*-substituted chloropyrrolidines in moderate yields.

2.1.5. Synthesis of chlorinated pyrrolidines by radical methods

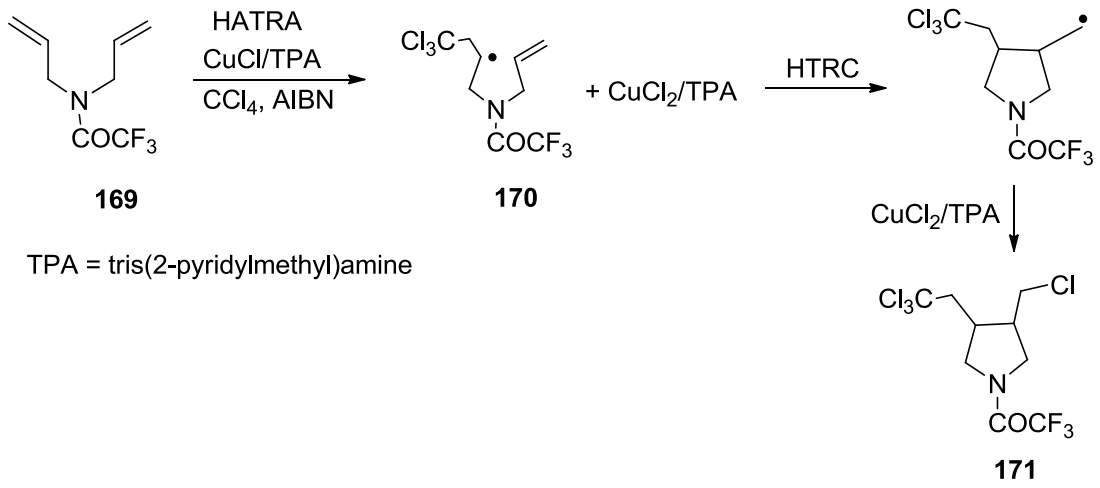
Literature survey on the radical protocols in the synthesis of nitrogen heterocycles revealed that few chlorinated pyrrolidines have been prepared by cyclization reactions of aminyl radicals and α and β carbon-centered radical.[72] In most of the cases, the nitrogen atom of the acyclic precursor was pre-protected to make the cyclization reactions regioselective. In one case where the nitrogen atom did not have the protecting group, the chlorinated *N*-H pyrrolidines were obtained but were purified as HCl salts.[73] Majority of the cyclization reactions used reductive cyclization protocols using Bu_3SnH. The acyclic precursors were prepared in many steps and had simple alkyl and aryl substituents only. Most of these methods deal with synthesis of *N*-substituted pyrrolidines having chlorine atom in the side chain.

Thus, Watanabe et al.[73] reported the preparation of cis-2,4-disubstituted-3,3-dichloro pyrrolidines **167** by cyclization of allyl(2,2,2-trichloroethyl)amines **165** (**Scheme 59**). The precursor **166** on treatment with Bu_3SnH/AIBN, generated β-amino alkyl radical intermediates **166**. These radical intermediates underwent *5-exo* cyclization followed by hydrogen atom abstraction to give the *cis*-2,4-disubstituted-3,3-dichloro pyrrolidines **167** exclusively. The *N*-H pyrrolidines were purified as HCl-salt **168** in high yields but the starting material had acid-resistant substituents such as alkyl and aryls mainly.



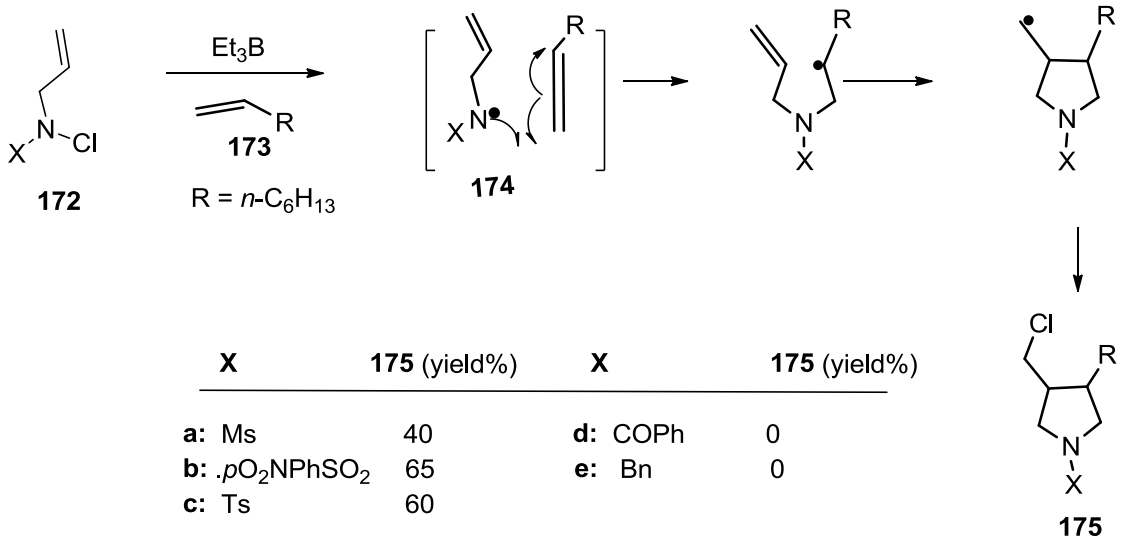
Scheme 59

Most of the other radical methods give the side chain chlorinated *N*-substituted pyrrolidines. For example, Ricardo and Pintauer[74] reported the synthesis of an *N*-protected pyrrolidine **171** (**Scheme 60**) bearing chlorine substituents in the side chains. CuCl/TPA-catalyzed intermolecular radical addition of CCl_4 to the C=C double bond of *N*,*N*-diallyl-2,2,2-trifluoroacetamide **169** followed by 5-*exo* cyclization of the β-aminoalkyl radical **170** produced and chlorine atom abstraction from $CuCl_2$ in high yield. The free-radical azo initiators such as AIBN were used as reducing agents to convert $CuCl_2$/TPA complex to CuCl/TPA so as to reduce the catalyst loading from usual 30 mol% to nearly 1 mol%.



Scheme 60

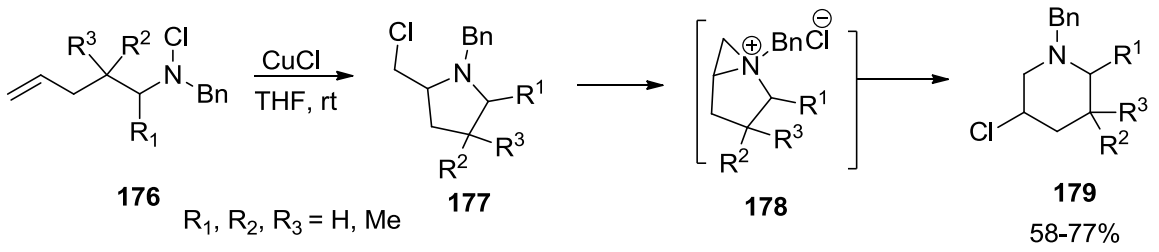
Similarly, Oshima and coworkers[75] reported a synthesis of *N*-protected pyrrolidines bearing chlorine substituents in side chain. The method involved radical [3+2] annulation reaction between the alkene **173** (**Scheme 61**) and *N*-centered radicals **174** generated from *N*-allyl-*N*-chlorosulfonamide **172** in the presence of Et_3B as a radical initiator. The success of the reaction and yields of the pyrrolidine products **175** depended on the nature of the *N*-protecting group. However, the stereoselectivity of the reaction was low.



X	**175** (yield%)	X	**175** (yield%)
a: Ms	40	**d:** COPh	0
b: .*p*O_2NPhSO_2	65	**e:** Bn	0
c: Ts	60		

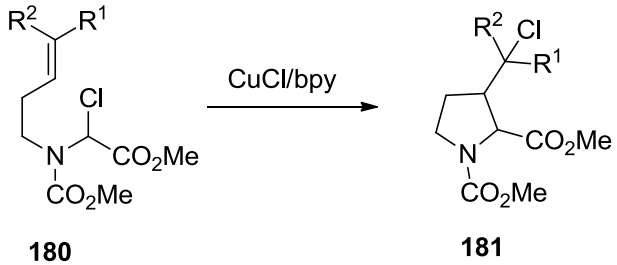
Scheme 61

The cyclization of aminyl radical by copper catalyst has not succeeded. Göttlich et al.[76] reported that Cu (I) complex-catalyzed intramolecular addition of *N*-chloramines **176** (**Scheme 62**) to carbon–carbon double bonds led to the formation of the chlorine substituted piperidines**179** as the sole product via a copper complexed-aminyl radical. The formation of **179** was due to a rearrangement of the unstable 2-chloromethyl-pyrrolidines **177** to the thermodynamically more stable 3-chloropiperidines **179** via aziridinium ion intermediate **178**.



Scheme 62

Speckamp and coworkers[27] described Cu(bpy)Cl-catalyzed HATRC of *N*-protected α-chloroglycine derivative **180** (**Scheme 63**) to 3-(1-chloro alkyl)-substituted proline ester **181**.



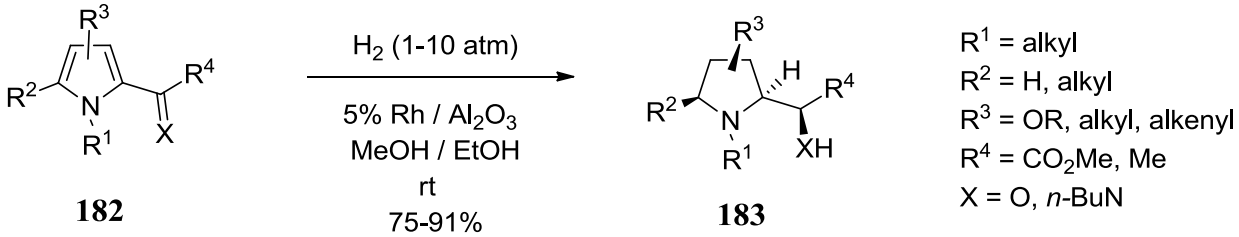
Scheme 63

This literature survey showed that radical cyclization protocols have not been as successful or widely explored in the synthesis of chlorinated pyrrolidines as for the tetrahydrofurans, lactones and lactams (**Chapter 1**).

2.1.6. Synthesis of pyrrolidines containing side chain functional groups

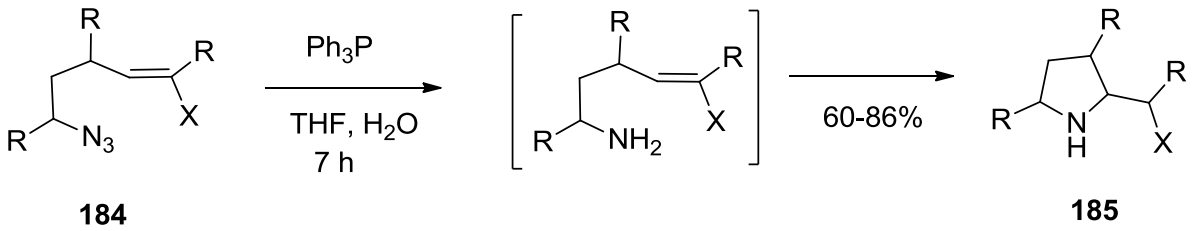
The functional groups in the side chain of pyrrolidine ring,[68-69] are important centers for chemical transformations as shown in **Scheme 54-56**. Such functionalized pyrrolidines were prepared mainly by reduction of the pyrrole ring[77] to pyrrolidine ring. A cyclization protocol of acyclic precursors has also been reported.[78]

The pyrrole derivatives are latent pyrrolidines.[77] The functionalized pyrroles **182** (**Scheme 64**) on metal-catalyzed hydrogenation afforded the functionalized pyrrolidines **183** having four new stereocentres with excellent diastereoselectivity.



Scheme 64

Knouzi and coworkers [78] reported a method for the preparation of the pyrrolidines **184** (**Scheme 65**) containing ester or cyano group in the side chain from the azides **185**.

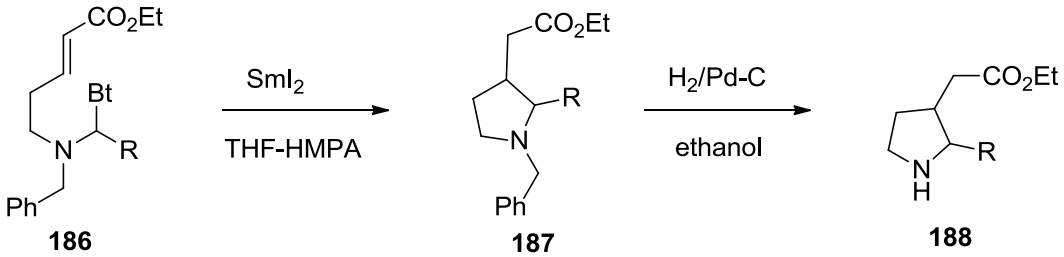


Scheme 65

The synthetic utility of these products might increase with incorporation of halogen as substituents in the ring, however to the best of our efforts, no such examples were found in the literature.

2.1.7. Synthesis of pyrrolidines containing side chain functional groups by radical methods

Due to synthetic utility of side chain functionalized pyrrolidines, several radical reactions for their synthesis have been employed. For example, Aurrecoechea et al.[79] reported the synthesis of 2,3-disubstituted *N*-H pyrrolidines **186** (**Scheme 66**) using SmI_2 mediated cyclization of carbon-centred nucleophilic α-aminoalkyl radicals generated from *N-(*α-benzotriazolylalkyl)alkenyl amines **186** to the electron deficient double bond substituted with an ester group. The removal of the *N*-benzyl group of **187** was effected by Pd-catalyzed hydrogenolysis to furnish the pyrrolidine **188**.



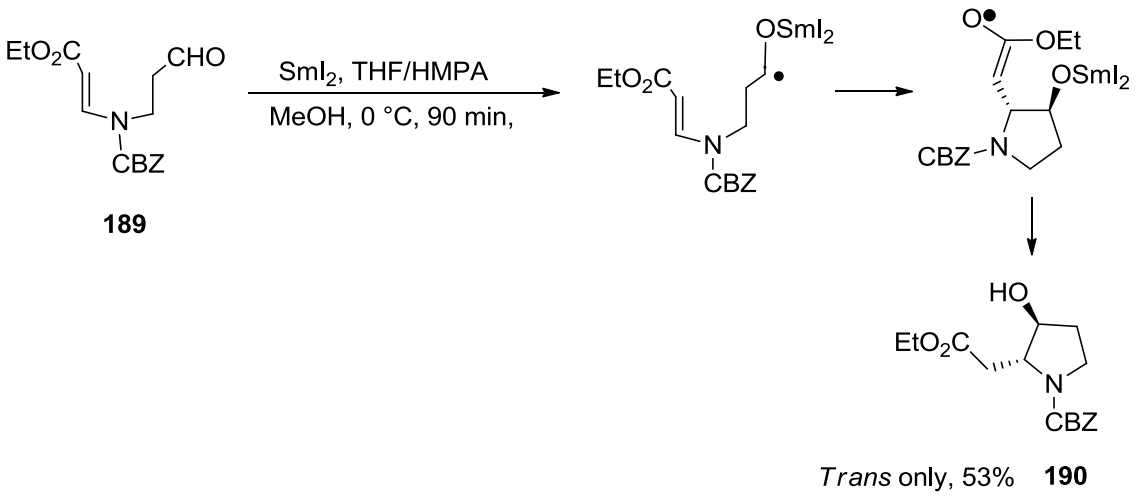
186 **187** **188**

R^1 = *i*-Pr, $(CH_2)_2CCH_3(OMe)_2$, $(CH_2)_4CO_2Et$

Scheme 66

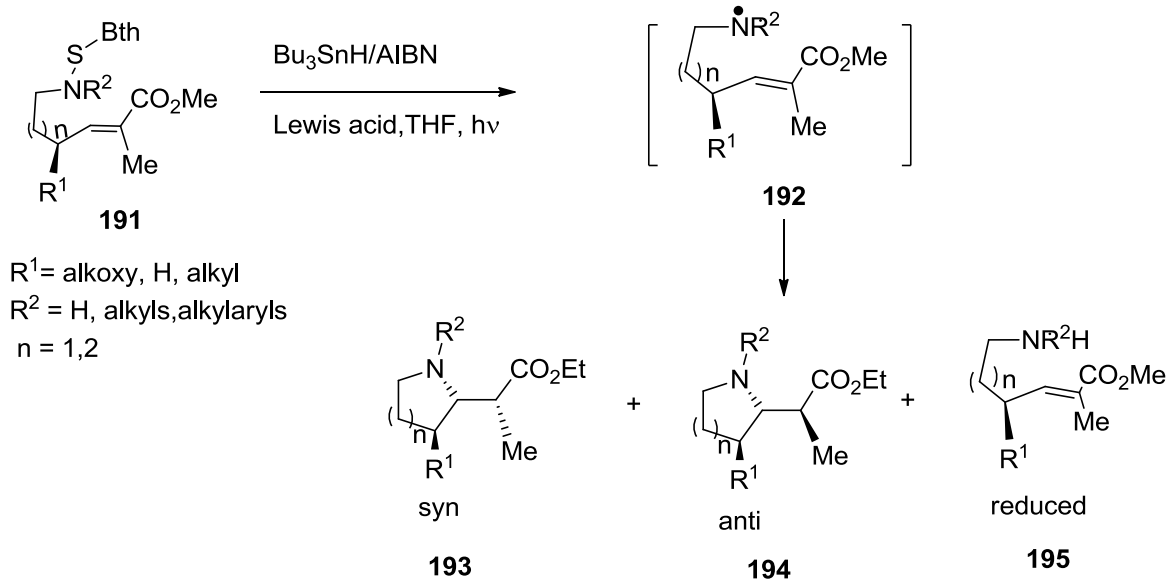
One important synthetic aspect of the pyrrolidine synthesis is the possibility of synthesis of *N*-unsubstituted pyrrolidines directly but most of the radical cyclization protocols give side chain functionalized *N*-substituted pyrrolidines. For example, Macdonald et al.[80] reported stereoselective synthesis of 2,3-disubstituted *trans*-pyrrolidine

190 (**Scheme 67**) by *5-exo-trig* cyclization of the γ-aminoalkyl radical generated by the reaction of the aldehydes **189** with SmI_2.



Scheme 67

Guindon et al.[81] reported that *N*-benzothiazolylsulfanylbenzylamines **191** (**Scheme 68**), on slow addition of Bu_3SnH generated the aminyl radicals **192** which underwent intramolecular addition to the alkene double bond followed by hydrogen atom abstraction to afford the 2,3-*trans*-disubstituted functionalized pyrrolidines **193** and **194** with *anti* or *syn* diastereoselectivity in 54-85% yields along with the reduced starting material **195.** The preferred *trans* diastereoselectivity originated from the minimization of allylic 1,3-strain imposed by the substituent R^1 and the methyl of the trisubstituted double bond during the cyclization of the intermediate **192.** In cases of **191** (R^2 = H), the crude mixture was treated with benzyl bromide and Et_3N in acetonitrile to separate the pyrrolidines as the benzylated products by flash column chromatography.



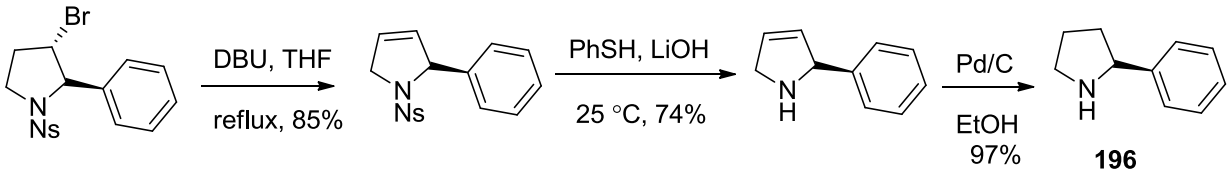
Scheme 68

These examples illustrated that radical methods have been widely used in the synthesis of pyrrolidines having functional groups in the side chain. But in most of the cases, the nitrogen atom was substituted. Deprotection was required to obtain the *N*-H pyrrolidines that too when the substituent was an easily removable protecting group.

2.1.8. Synthesis of pyrrolidines containing free NH

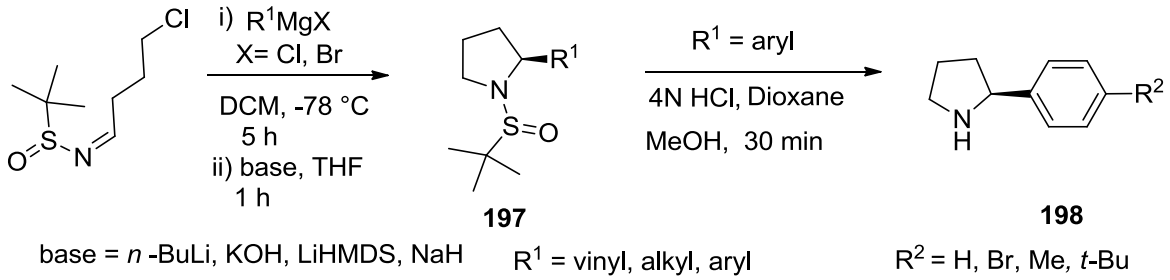
Due to additional synthetic advantages of free NH group, the synthesis of *N*-H pyrrolidines has been the main target of many approaches. Earlier sections have dealt with such pyrrolidines as far as possible. A few more relevant examples are given here under.

A number of reports have targeted at enantioselective synthesis of *N*-H pyrrolidines. However, most of these methods involved wasteful protection-deprotection methodology.[82,83] For example, Yeung and coworkers[83] synthesized the *N*-H pyrrolidine **196** (**Scheme 69**), an essential unit of a selective Kv1.5 blocker BMS-394136[57b] (**Fig. 7**), through a multistep route that required the deprotection of the sulphonamide group to amine.



Scheme 69

Similarly, Mahavir and Reddy[84] synthesized some analogous 2-substituted *N*-H pyrrolidines **198** (**Scheme 70**) enantioselectively. The methodology involved removal of the protecting group of **197** under strong acidic reaction conditions (4N HCl) which were viable only for acid resistant substituents such as alkyl and aryls.

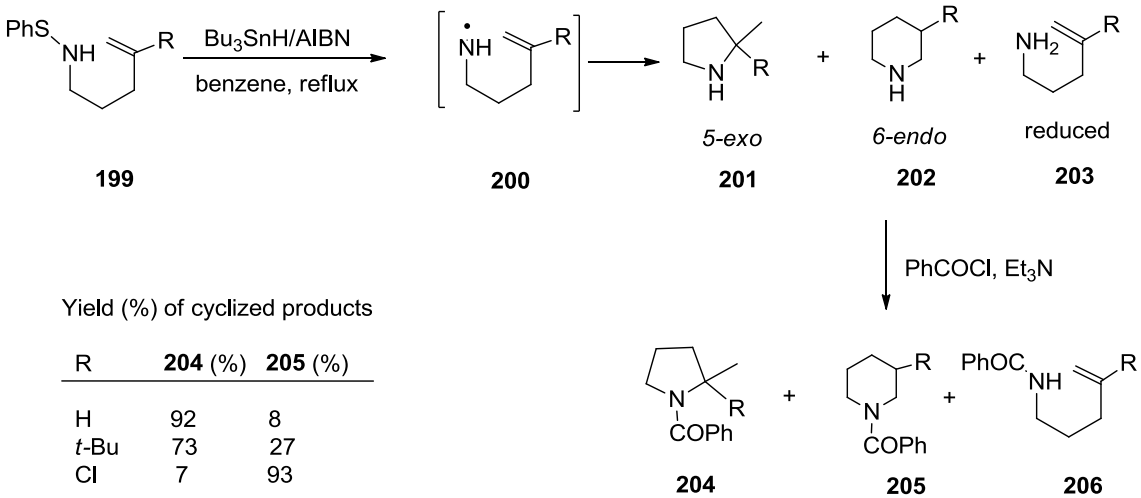


Scheme 70

2.1.9. Synthesis of *N*-H pyrrolidines by radical methods

Even though radical methods occur under mild and neutral conditions which can tolerate sensitive groups in general, the previous examples (**Section 2.1.5**.) showed that radical cyclization of either aminyl radicals or carbon-centred radicals gave pyrrolidines regioselectively when the nitrogen atom of acyclic precursor was substituted or protected.[72] Deprotection was needed to obtain the *N*-H pyrrolidines (**Scheme 66**). In cases, where the nitrogen was unsubstituted, the cyclization products were separated and purified by treatment of the crude product with HCl followed by recrystallization of the salt[73]or by benzylation of the crude mixture followed by flash column chromatography.[81]

In another case, the acylation of pyrrolidine products were necessary for separation and purification of the crude products and cyclization was non-regioselective. For example, Li et al.[85] reported that *N*-(benzenesulfenyl)pent-4-enylamines **199** (**Scheme 71**) on treatment with Bu_3SnH (1.5 equiv)/AIBN (0.2 equiv) in refluxing benzene gave the aminyl radicals **200**. These radicals underwent 5-*exo* and 6-*endo* cyclization to furnish the corresponding pyrrolidines **201** and piperidines **202** along with the reduced starting material **203**. The vinylic substituent R played an important role in controlling the regioselectivity of cyclization by radical stabilization. To facilitate separation and characterization, the resulting mixture of products **201, 202** and **203** were then treated with benzoyl chloride. The benzamides **204**, **205** and **206** were purified by column chromatography on silica gel. The cyclization products **204** and **205** were found in a combined 72% yield along with the direct reduction product **206** in 22% yields.



Scheme 71

Thus, these examples showed that direct, regioselective and diastereoselective synthesis of *N*-H pyrrolidines by radical methods is difficult. Non-radical methods used *N*-substituted

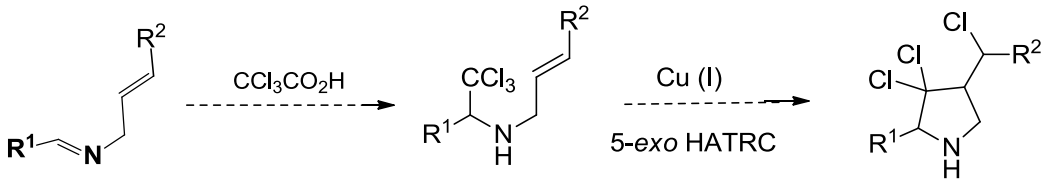
starting materials and the protecting groups were removed in the final stage for the synthesis of diastereoselective *N*-H pyrrolidines.

2.2. Statement of problems

From the foregoing it is clear that chlorinated pyrrolidines, side chain functionalized pyrrolidines and *N*-H pyrrolidines are potential building blocks for the synthesis of complex pyrrolidines and other natural and synthetic products. However, there are very few methods for the preparation of diversely substituted, chlorinated and/or side chain functionalized *N*-H pyrrolidines. These methods have their own limitations with regard to yields, number of steps, use of wasteful protection-deprotection methodology, nature of substituents and substitution pattern. In fact we could not find an example of a pyrrolidine with all the three attributes in the same molecule. However, an additional functional group would increase the synthetic value of chlorinated *N*-H pyrrolidines considerably. The chloro, N-H and the functional group reactive sites of such molecules provide multiple possibilities for further transformations through substitution, elimination, aromatization, cascade reactions functional group reactions and other inter and intramolecular reactions.

Radical reactions appear to be more promising for the synthesis of *N*-H pyrrolidines as they are generally less sensitive to the nature of substituents and do not necessarily require protection of sensitive groups. However, the reported radical reactions for direct synthesis of *N*-H pyrrolidines without taking recourse to protection-deprotection methodology suffered from the problem of regioseletivity, purification of the products and formation of side products such as reduced starting material. As seen in **chapter 1**, Cu (I)-catalyzed chlorine atom transfer radical cyclization has proven to be a versatile method for the synthesis of chlorinated heterocycles. However, Cu (I)-catalyzed HATRC of 2,2,2-

trichloroethyl amines (*N*-protected or unprotected) which could lead to the formation of chlorinated *N*-H pyrrolidines has not been reported so far. Therefore, it was considered worthwhile to attempt Cu (I)-catalyzed HATRC of 2,2,2-trichloroethyl allyl amines for the synthesis of chlorinated and functionalized *N*-H pyrrolidines directly without resorting to *N*-protection. The proposed strategy is sketched in **Scheme 72**.



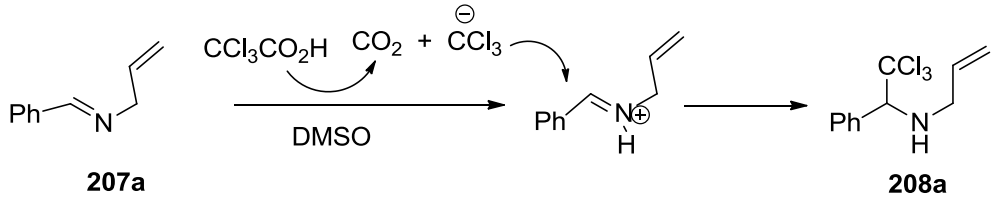
Scheme 72

2.3. Results and Discussion

2.3.1. Preparation and characterization of 1-phenyl-2,2,2-trichloroethyl allyl amine 208a

With this idea in view, first 1-phenyl-2,2,2-trichloroethyl allyl amine **208a** (**Scheme 73**) was prepared by slight modification of a method reported in the literature.[86] In the reported method some trihalogenoaminoethane derivatives were prepared by treating aromatic and aliphatic imines and ketimines with trihaloacetic acids in benzene or toluene at temperature ranging from 50-100 ˚C for aldimines to 25-75 ˚C for ketimines. In the reported method, the trihalogenoaminoethanes were isolated and purified as amine-HCl salts obtained by passing HCl, a process which could be unsuitable for acid-sensitive substituent such as furyl. Since trichloroacetic acid is known to undergo spontaneous decarboxylation at a lower temperature to form trichloromethyl anion in the presence of

polar solvents such as DMSO,[87] the reaction of aldimine **207a,** obtained by condensation allyl amine with benzaldehyde, was performed in this solvent instead of benzene or toluene by portion wise addition of a solution of two equivalents of trichloroacetic acid in DMSO into a solution of the aldimine **207a** in DMSO at 40 ˚C followed by stirring for 1 h at the same temperature. The lower reaction temperature in the present modifications prevented the side reactions and the trichloroethylallylamine **208a** was obtained in better yield (77%) after purification by column chromatography.



Scheme 73

The product **208a** was characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry.

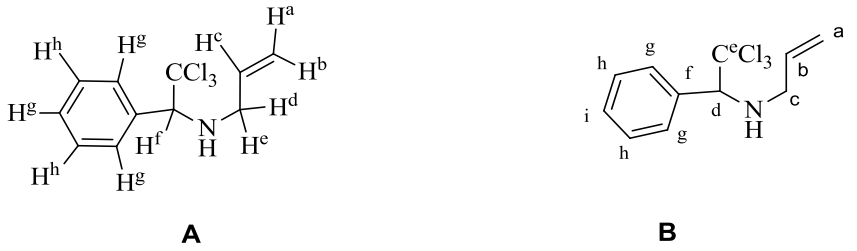


Fig. 8 ^{1}H NMR and ^{13}C NMR assignments for the structure 208a

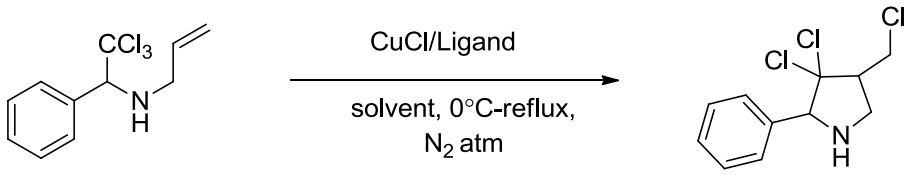
The ^{1}H NMR spectrum of **208a** (**Fig. 37**) showed a broad singlet at δ 1.70 ppm integrating for one proton. It disappeared on shaking the sample solution with D_2O. Thus it was assigned to the *N*-H proton. The doublet of a doublet at δ 3.11 ppm with coupling

constants of 14.5 and 6.9 Hz and the other doublet of a doublet at δ 3.39 ppm with coupling constants of 14.5 and 5.1 Hz integrating for one proton each were attributed to the two allylic diastereotopic CH_2 proton H^d and H^e (**Fig. 8**, **Structure A**). The singlet at δ 4.39 ppm integrating for one proton was attributed to the benzylic proton H^f. The multiplet at δ 5.10-5.16 ppm integrating for two protons was attributed to the geminal protons H^a and H^b of the olefinic bond. The multiplet at δ 5.79-5.93 ppm integrating for one proton was assigned to the olefinic CH proton H^c. The multiplet in the aromatic region at δ 7.37-7.39 ppm integrating for three protons was attributed to the *ortho* and *para* protons H^g. of the benzene ring The other multiplet at δ 7.51-7.54 ppm integrating for two protons was attributed to the *meta* protons H^h.

In proton-decoupled ^{13}C NMR spectrum of **208a** (**Fig. 38**), the three signals at δ 50.0, 76.4 and 102.9 ppm were assigned to the methylene carbon C^c, methine carbon C^d and the quaternary carbon C^e of the CCl_3 group (**Fig. 8. Structure B**), respectively. The signals at δ 116.9 and 135.8 ppm were assigned to the olefinic CH_2 and olifinic CH carbons C^a and C^b, respectively. The three signals at δ 127.9, 128.9 and 129.9 ppm were attributed to the CH carbons C^g, C^i and C^h, respectively of the benzene ring and the fourth at δ 135.9 ppm was assigned to the quaternary carbon C^f of the benzene ring. These assignments were also supported by DEPT-135 spectrum. The IR spectrum of the compound **208a** showed a medium intensity broad absorption at ν_{max} 3338 cm^{-1} due to N-H bond stretching. The HRMS spectrum of the compound **208a** showed $[M+H]^+$ peak at m/z 264.0108 exactly matching with the calculated value of 264.0108 for the molecular formula $C_{11}H_{12}Cl_3NH$.

2.3.2. Chlorine atom transfer radical cyclization of 1-phenyl-2,2,2-trichloroethyl allyl amine 208a: Optimization of reaction conditions

With the precursor **208a** for the cyclization in hand, the crucial HATRC of **208a** was investigated with varying amounts of CuCl in different solvents in the presence of some commercially available ligands such as bpy, TMEDA and PMDETA at different temperatures under a nitrogen atmosphere. With respect to CuCl, 2 equivalents of TMEDA or 1 equivalent of either bpy or the tridentate ligand PMDETA were used as per the normal practice in HATRC reactions. The progress of the reaction was monitored by TLC as well as ^{1}H NMR spectra of the aliquots taken from time to time. The reaction mixture was worked up by removing the solvent on a rotavapor under reduced pressure, taking the residual mass in ethyl acetate and washing with brine. The crude product obtained after evaporating ethyl acetate was purified by column chromatography. In all the cases, the reaction occurred to give the 5-*exo* cyclization product **209a** (**Scheme 74**). The yield of the product **209a**, amount of the catalyst used, reaction time and cleanliness of reaction were taken as significant parameters for the optimization. The results are compiled in **Table 1**.



208a **209a**

Scheme 74

Table 1. Copper(I)chloride/Ligand catalyzed 5-*exo* chlorine atom transfer radical cyclization of 1-phenyl-2,2,2-trichloroethyl allyl amine 208a under different conditions [a]

S. No.	CuCl mol%	CuCl/Ligand (mol ratio)	Solvent	Temp.	Time (h)	**209a** Yield (%)[b]	**208a** Recovered (%)[b]
1	100	CuCl/bpy (1:1)	DCE	reflux	6	35	55
2	100	CuCl/TMEDA (1:2)	DCE	reflux	4	71	-
3	40	CuCl/PMDETA (1:1)	DCE	reflux	3	74	-
4	40	CuCl/PMDETA (1:1)	DCE	0 ˚C	6	81	-
5	40	CuCl/PMDETA (1:1)	MeCN	0 ˚C	5	83	-
6	40	CuCl/PMDETA (1:1)	MeCN	-10 ˚C	12	65	25

[a] All the reactions were performed with 1 mmol of **208a** under a nitrogen atmosphere.

[b]Isolated yield after purification by column chromatography on basic alumina.

The literature precedents and the experience of this laboratory in HATRC reactions led us to use 40 mol% of CuCl to begin with the optimization of the reaction conditions for the HATRC of **208a**. Of the three ligands employed bpy, the most common ligand in Cu (I)-catalyzed HATRC in DCE was found to be not so effective. The reaction did not proceed to completion even with the stoichiometric amount of CuCl and bpy. Only 35% of the pyrrolidine **209a** and nearly 55% of the unreacted starting material **208a** (**S. No. 1**) were obtained after purification of the crude product by column chromatography. TMEDA was slightly better in terms of product yield (71%) (**S**. **No**. **2**) but in this case also, stoichiometric amounts of CuCl and TMEDA were required for the completion of the

reaction at reflux temperature. PMDETA was observed to be the most effective ligand in terms of the product yield (74%) (**S. No. 3**) and amount of the catalyst (40 mol %). It is probably due to its being a tridentate ligand whereas other two are bidentate ligands.[12] However, ^{1}H NMR of the crude products showed the presence of two isomers in about 90:10 ratio along with a small amount of side products.

In an attempt to minimize the occurrence of side reactions, the reaction was performed at 0 ˚C with 40 mol % CuCl/PMDETA. It was found to give encouraging results even though a longer reaction time (6 h) was required to complete the reaction. The product yield was raised to 81% (**S. No. 4**). The reaction was cleaner and the diastereoselectivity ratio was better as the ^{1}H NMR of the crude product obtained after simple work up showed almost a single isomer. Such increase in diastereoselectivity in copper catalyzed cyclization at lower temperatures has been noted earlier also.[8]

In order to explore the effect of solvent, the reaction was performed in acetonitrile at 0 ˚C with the same amount of catalyst (40 mol%). It was found to be slightly better than the reaction in DCE in terms of product yield (83%) (**S**. **No**. **5**) and reaction time (5 h). It might be due to higher solubility of the copper complex in acetonitrile.[12] Under similar conditions at -10 ˚C, the reaction could not proceed to completion even after a longer reaction time of 12 h. (**S**. **No**. **6**)

Thus, 40 mol% CuCl/PMDTA (1:1 mol ratio) in acetonitrile at 0 ˚C was found to be the best optimized reaction conditions for HATRC of **208a** in the terms of product yield, amount of the catalyst required, cleanliness of the reaction and diastereoselectivity.

The structure of the 3,3-dichloro-*N*-H pyrrolidine **209a** was supported by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and mass spectrometry.

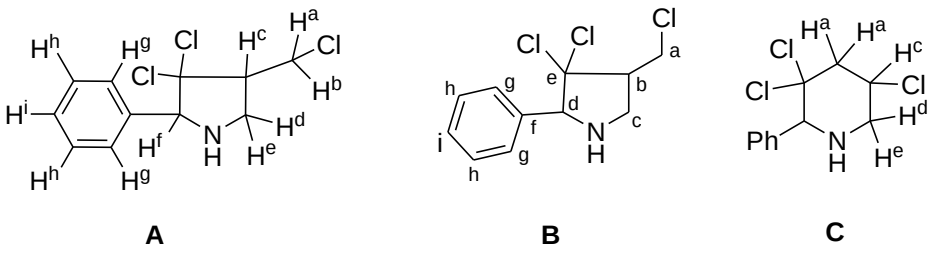


Fig. 9 ^{1}H NMR and ^{13}C NMR assignments for the structure 209a

Thus, the ^{1}H NMR spectrum of **209a** (**Fig. 71**) showed a broad D_2O-exchangeable singlet at δ 2.28 ppm integrating for one proton, which was assigned to the *N*H proton. The multiplet at δ 3.07-3.20 ppm, integrating for two protons, was assigned to the methine proton H^c and one of the diastereotopic methylene protons H^d or H^e of the pyrrolidine ring (**Fig. 9**, **Structure A**). The multiplet at δ 3.62-3.75 ppm integrating for two protons was assigned to one of the diastereotopic methylene proton H^a or H^b of the CH_2Cl group and the other diastereotopic proton H^e or H^d of the pyrrolidine ring methylene. The doublet of a doublet at δ 3.97 ppm with coupling constants of 10.8 and 3.6 Hz, integrating for one proton was assigned to the other diastereotopic proton H^b or H^a of the CH_2Cl group. The singlet at δ 4.60 ppm integrating for one proton was assigned to the benzylic proton H^f. In the aromatic region, a multiplet at δ 7.37-7.40 ppm integrating for three protons was assigned to the protons H^g and H^i at the *ortho* and *para* positions of the benzene ring. The multiplet at δ 7.44-7.46 ppm integrating for two protons was assigned to the protons H^h present at the *meta* position of the benzene ring.

The proton-decoupled ^{13}C NMR spectrum of **209a** (**Fig. 72**.) showed all the carbon atoms at the expected positions. The signals at δ 43.8 and 49.0 were assigned to the

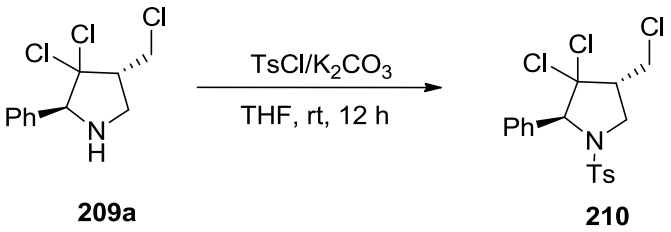
methylene carbons C^c and C^a (**Fig. 9, Structure B**), respectively. The methine carbons C^b and C^d appeared at δ 55.3 and 75.8 ppm, respectively. The signal at δ 94.3 ppm was attributed to the quaternary carbon C^e of the CCl_2 group. Four signals for the four different types of carbons of the benzene ring appeared in the aromatic region. The signals at δ 128.0, 128.1 and 128.4 ppm were assigned to the CH carbons C^g, C^i and C^h, respectively. The low intensity signal at δ 137.2 ppm was assigned to the quaternary carbon C^f of the benzene ring. These assignments were also supported by DEPT-135 spectrum. The IR spectrum of the compound **209a** showed medium and broad absorptions at ν_{max} 3368 cm^{-1} due to the *N*-H bond stretching. The HRMS spectrum of this compound showed $[M+H]^+$ peak at m/z 264.0108, which was within the acceptable limit of deviation from the calculated value of 264.0115 for the formula $C_{11}H_{13}Cl_3N$.

The interpretation of ^1H NMR and ^{13}C NMR was further supported by its HSQC spectrum (**Fig. 73**). The cross peaks revealed that the carbons C^a, C^b and C^c were correlated to the protons (H^a, H^b), H^c and (H^d, H^e), respectively. The protons H^a and H^b at C^a and H^d and H^e at C^c were well separated from each other. The methine proton H^c was most upfield CH proton.

For the alternate six membered ring structure **209a** (**Fig. 9**, **Strucure C**) which could arise by 6-*endo* cyclization, the chemical shift value for one of the methine protons H^c and carbon linked to it would be expected to be higher than the observed value. Also chemical shifts for the protons H^a and H^b and carbon linked to them would be expected to be lower than the observed values. The pyrrolidine structure of the product was finally confirmed by aromatization of an *N*-H pyrrolidine to the corresponding pyrrole (vide infra). Thus, the reaction occurred in a highly regioselective manner by 5-*exo*-*trig*

cyclization mode. No 6-*endo* cyclization product was isolated by column chromatography or detected by ^{1}H NMR of the crude product.

The reaction appeared to be highly diastereoselective because only one product was isolated by column chromatography. Determination of the stereochemistry of the product by NOE or NOESY ^{1}H NMR spectroscopy was not unambiguous because the relevant proton signals were not well separated. However, the single crystal X-ray diffraction spectroscopy of the tosylate **210** (**Scheme 75**) obtained by tosylation[88] of **209a** revealed a *trans* geometry for the product, assuming that no isomerization has occurred during the tosylation of **209a** under the mild condition employed. The ORTEP diagram of **210** is shown in **Fig. 10**.



209a **210**

Scheme 75

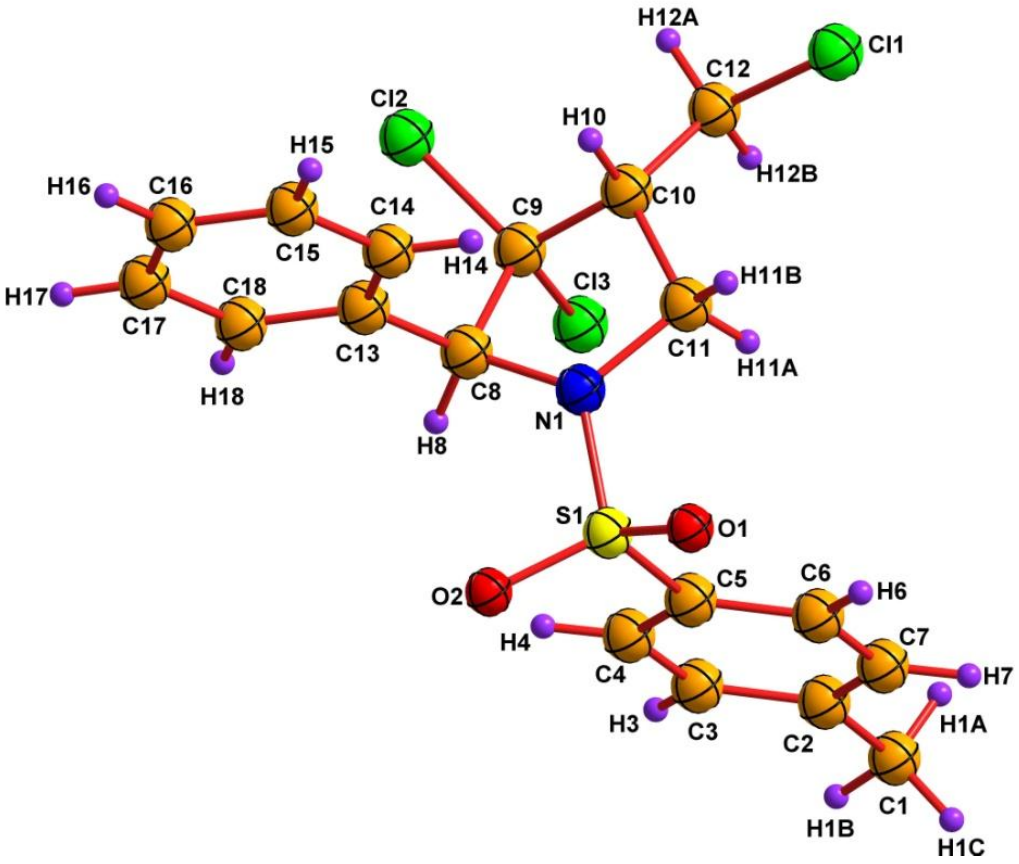
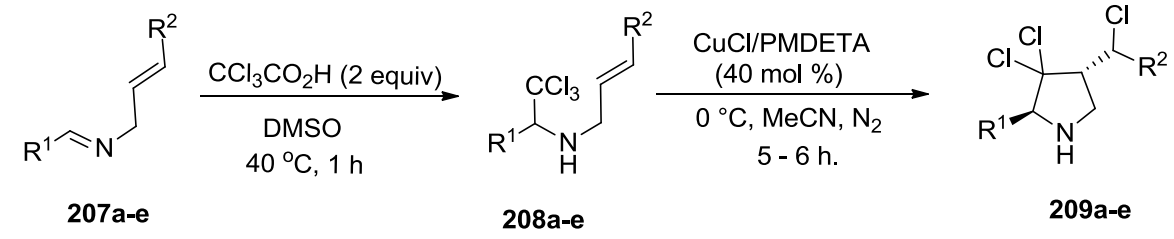


Fig. 10 ORTEP diagram of 3,3-dichloro-4-(chloromethyl)-2-phenyl-1-tosylpyrrolidine 210

2.3.3. Generalization of the scheme: Synthesis of other 2-substituted-3,3-dichloropyrrolidines 209

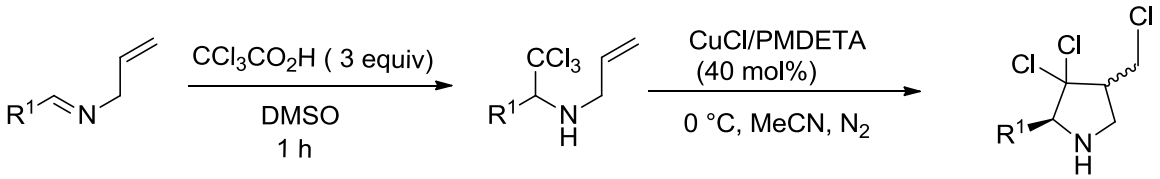
Next, the generality of the above approach to the synthesis of 2-substituted 3,3-dichloro-*N*-H pyrrolidines was demonstrated by preparing (1-alkyl/aryl/heteroaryl-2,2,2-trichloro)ethyl allyl amines **209b-g** (**Scheme 76**) by portion wise addition of 2 equivalents of CCl_3CO_2H in DMSO into a solution of the aldimines **208b-g** in DMSO at 40 ˚C (3 equiv for **208f** at 50 ˚C and for **208g** at 45 ˚C) and subjecting them to HATRC under the optimized conditions. In all these cases, the cyclization occurred smoothly in 5-*exo* mode.

The allyl amines **208a-e** furnished the pyrrolidines **209a-e** in high yields (80-84%). The results are shown in **Table 2**.



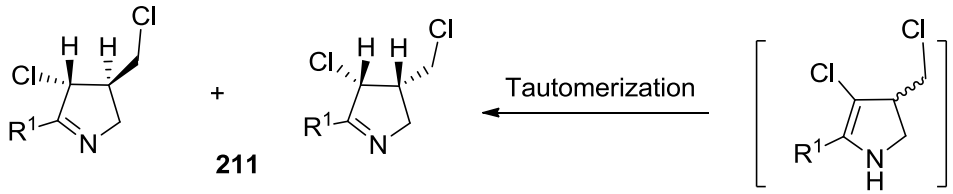
207a-e **208a-e** **209a-e**

a: R^1 = Ph, R^2 = H **c**: R^1 = Ph, R^2 = Ph; **e**: R^1 = *i*Pr, R^2 = H
b: R^1 = 4-$MeOC_6H_4$, R^2 = H **d**: R^1 = 2-furyl, R^2 = H;



207f,g	Temp (°C)	**208f,g**	Time (h)	**209f,g**
f: R^1 = 4-$O_2NC_4H_4$	50	52	5	89% (crude)
g: R^1 = 2-pyridyl	45	64	4	-

-HCl



211

	trans:*cis* ratio	yeild (%)
f:	100 : 00	79
g:	60 : 40	78

Scheme 76

Table. 2 Preparation of α-substituted 2,2,2-trichloroethyl allyl amines 208a-e and 2-substituted 3,3-dichloro-*N*-H pyrrolidines 209a-e

S. No.	R^1	R^2	**208** Isolated yield (%)[a]	**209** Time (h)	**209** Isolated yield (%)[b]
1	a: Ph	H	77	5	83
2	b: 4-$MeOC_4H_4$	H	80	5	84
3	c: Ph	Ph	76	5	80
4	d: 2-furyl	H	68	6	83
5	e: *i*-Pr	H	78	6	81

[a] The reactions were performed with 10 mmol of the aldimines **207**.

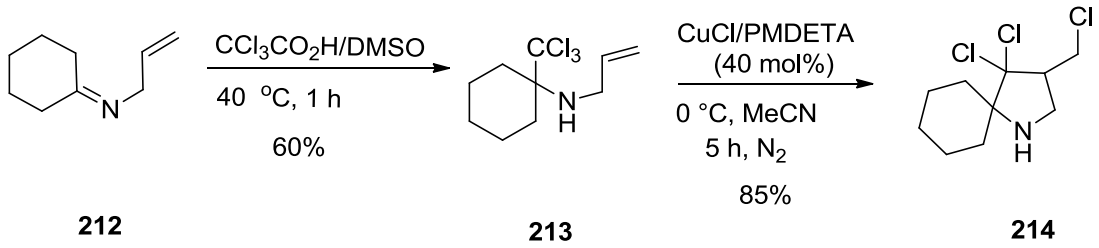
[b] The reactions were performed with 1 mmol of **208** in acetonitrile at 0˚C under a N_2 atmosphere.

The structures of **208b-f** and **209b-f** were compatible with their spectra, which had characteristics similar to those described for **208a**. The radical cyclization step was observed to be highly diastereoselective as revealed by ^{1}H NMR of the crude products. The other diastereomer was present only in traces at the best. The major diastereomer (arguably 2,4-*trans*) were separated easily in pure form by quick column chromatography.

All the pyrrolidines **209a-e** were found to be reasonably stable and could be stored for a long time (1 month). However, the 2-(4-nitrophenyl) derivative **209f** and the 2-(2-pyridyl) derivative **209g** (**Scheme 76**) were less stable. The ^{1}H NMR spectrum of the crude product obtained by cyclization of the allylamine **208f** revealed the formation of a single product **209f**. However, it was found to undergo dehydrochlorination followed by tautomerization to form pyrroline **211f** on standing for some time. Therefore, the crude

product was stirred with $NaHCO_3$ in chloroform at room temperature in order to completely convert it into the pyrroline. Purification by column chromatography furnished the pyrroline **211f** as a single diastereomer in 79% yield. The cyclization of the allyl amine **208g** furnished the pyrroline **211g** directly as a 3:2 mixture of diastereomers in 78% yield by 5-*exo* HATRC followed by complete dehydrochlorination and tautomerization. The pyrrolidine **209g** could not be isolated. In these cases, the higher acidity of the hydrogen at C-2 probably facilitated the base-promoted elimination of HCl in which the ligand might have acted as a base. In the case of HATRC of the pyridyl derivative **208g**, a considerable amount of the product was also recovered from the aqueous phase during work up by treating it with aqueous ammonia solution and extracting with ethyl acetate. The 2-pyridyl pyrroline **211g** is a bidentate ligand. Therefore it might have arguably interacted with copper complex and went into aqueous solution. The stereochemistry of these pyrrolines was determined unambiguously by ^{1}H NMR because the diagnostic proton at C-3 position appeared well separated in the spectra. In the ^{1}H NMR spectrum (**Fig. 84**) of the sole diastereomer **211f**, it appeared at 5.19 ppm as a singlet. The absence of its any perceptible vicinal coupling with the proton at C-4 position indicated a dihedral angle between these protons very close to 90 ˚C. This was possible when the two protons were *trans* to each other. Similarly, in the ^{1}H NMR spectrum of the mixture of diastereomers **211g** (**Fig. 86**), the C-2 proton of the major diastereomer appeared as a singlet at δ 5.43 ppm. This proton in the minor diastereomer however appeared as a doublet at δ 5.60 ppm with a vicinal coupling constant of 6.3 Hz. On the basis of these observations, the sole diastereomer **211f** and the major diastereomer in the mixture of **211g** were assigned the *trans* geometry. The minor diastereomer **211g** was accordingly assigned the *cis* geometry.

The scope of the above approach could be further extended to the synthesis of 2,2-disubstituted-3,3-dichloro-*N*-H pyrrolidine. It was demonstrated by synthesizing **213** (**Scheme 77**) and subjecting it to HATRC to obtain **214**. Thus, **213** was prepared in 60% yield by portionwise addition of a solution of 2 equivalents of CCl_3CO_2H in DMSO solution to a solution of ketimine **212** in DMSO at 40°C for 1 h. HATRC of **213** under the optimized reaction conditions for 5 h furnished the spiro-*N*-H pyrrolidine **214** uneventfully in high yield (85%).

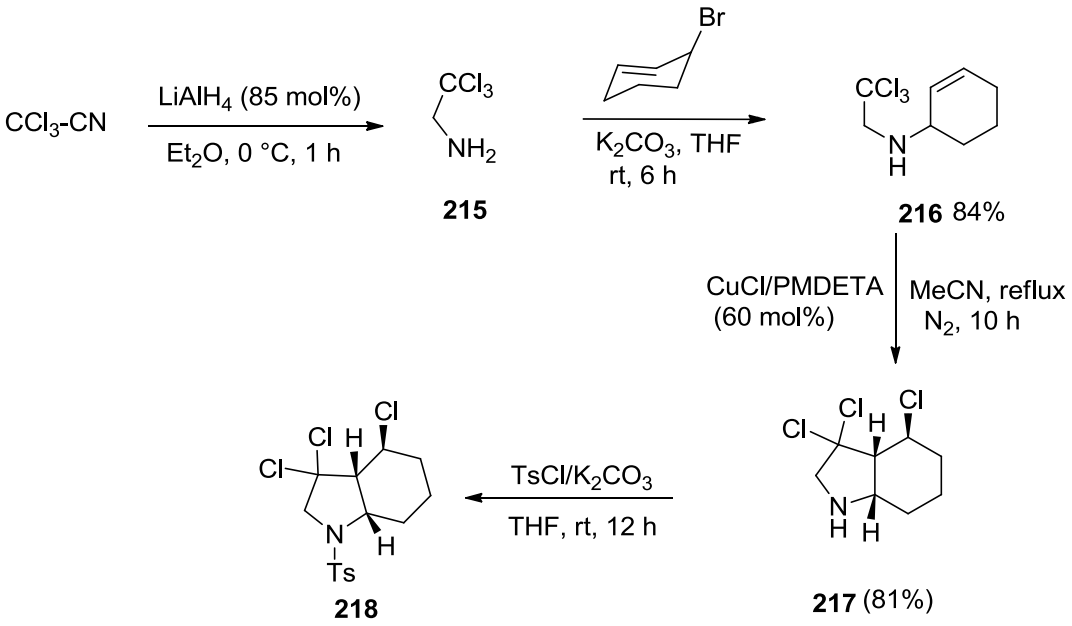


212 **213** **214**

Scheme 77

The 2,2,2-trichloroethyl allyl amine HATRC precursors can be obtained in other ways also and HATRC of these precursors appears to be highly facile. Therefore, the diversity accessible through the present methodology for the synthesis of 3,3-dichloro-*N*-H pyrrolidines is considerably high. For example, the 2,2,2-trichloroethyl allyl amines could also be obtained by allylation of previously known simple 1-unsubstituted 2,2,2-trichloroethyl amine. The latter could be easily prepared by reduction of trichloroacetonitrile with $LiAlH_4$ in diethyl ether as reported in the literature.[89] For an illustration, 2,2,2-trichloroethyl amine **215** (**Scheme 78**) was alkylated with cyclohexyl bromide in the presence of K_2CO_3 in THF with a view to explore the applicability of the methodology for the synthesis of fused *N*-H pyrrolidines. The *N*-(2,2,2-

trichloroethyl)cyclohex-2-enyl amine **216**, thus obtained underwent CuCl/PMDETA-catalyzed HATRC smoothly to afford the fused pyrrolidine **217** in 81% isolated yield after purification by column chromatography on a basic alumina column. However, in this case, the reaction required 60 mol % of CuCl/PMDETA and a longer time (10 h) for completion.



Scheme 78

The stereochemistry of the product **217** was determined by single crystal X-ray diffraction of the tosylation product **218**. The ORTEP diagram (**Fig. 11)** showed *cis* ring fusion. The chlorine atom on the cyclohexane ring occupied the convex face of the bicyclic ring skeleton, showing chlorine transfer from the less hindered side.

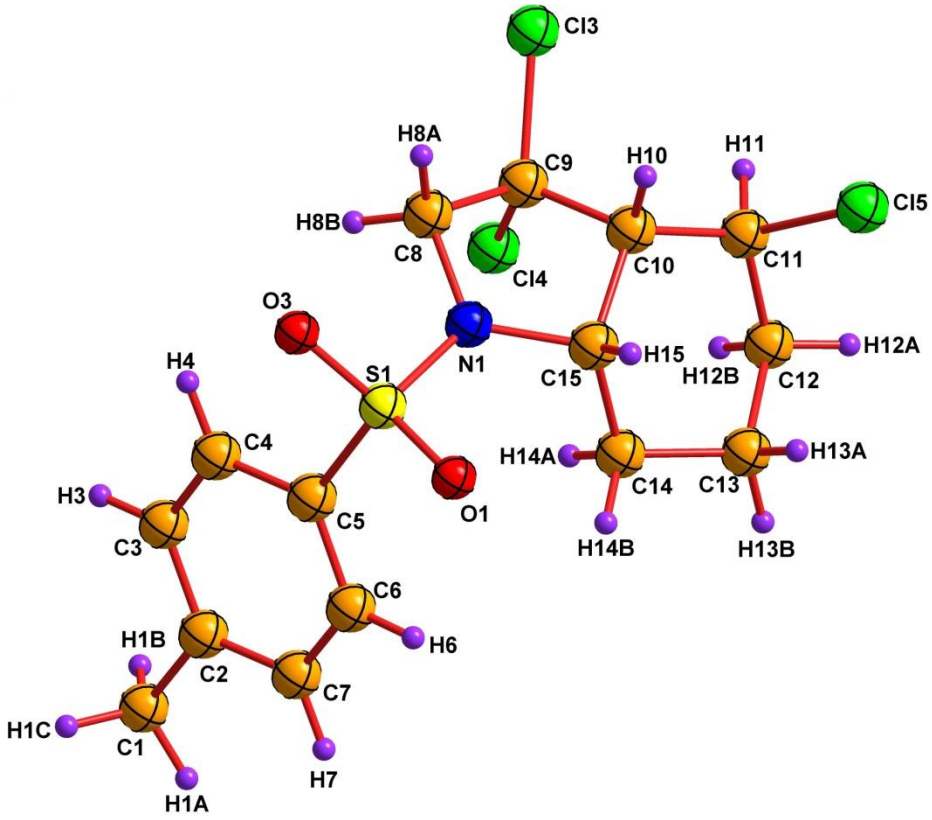
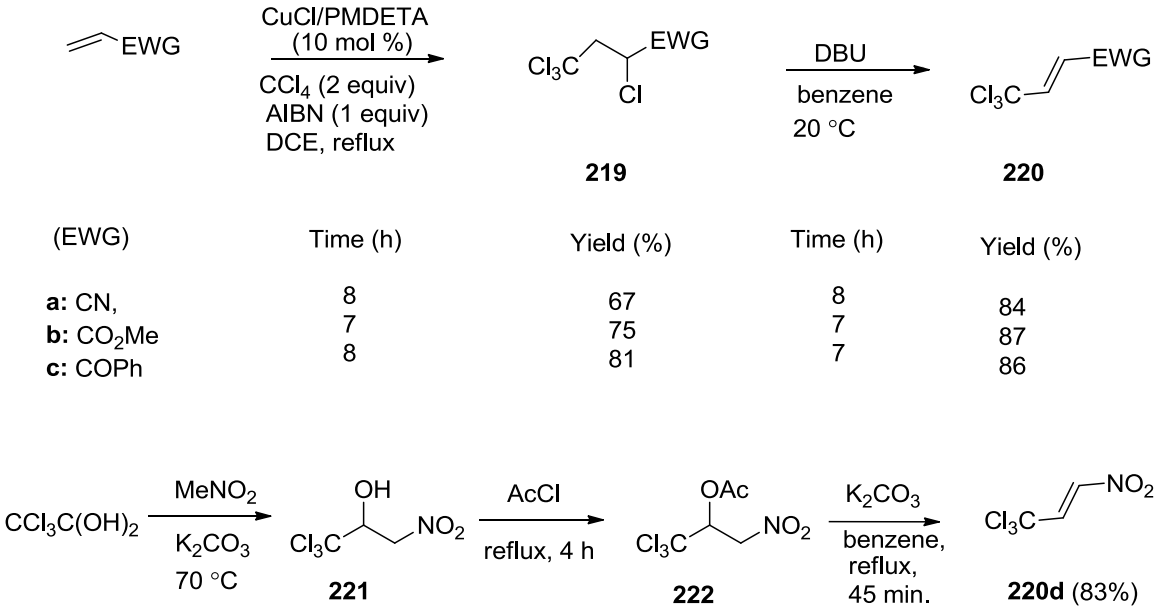


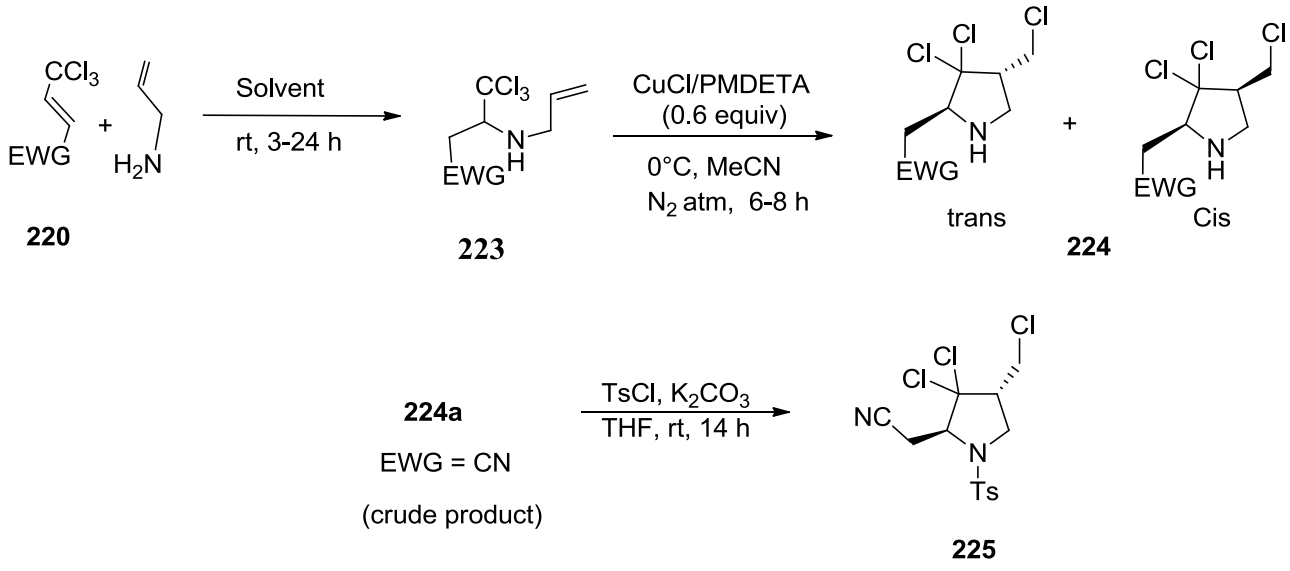
Fig. 11 ORTEP diagram of 3,3,4-trichloro-1-tosyl-octahydro-1H-indole 218

The scope of the present methodology for the synthesis of chlorinated *N*-H pyrrolidines was further extended to the synthesis of 3,3-dichloro-*N*-H pyrrolidines having a functional group in a side chain at C-2. For this purpose, the trichloromethyl substituted Michael acceptors **220a-c** (**Scheme 79**) were prepared by a method reported in the literature[90] with slight modifications that involved CuCl/PMDETA-catalyzed chlorine atom transfer radical addition (ATRA) of CCl_4 to the corresponding unsubstituted Michael acceptors in the presence of AIBN followed by dehydrohydrochlorination with DBU. The Michael acceptor **220d** was prepared by a reported method[91] involving Henry reaction of nitromethane with chloral hydrate, acetylation of the nitroalcohol thus obtained followed by dehydrodeacetoxylation with potassium carbonate.



Scheme 79

Reaction of equivalent amounts of trichloromethyl substituted Michael acceptors **220** and allyl amine furnished the functionalized cyclization precursors **223** (**Scheme 80**).



Scheme 80

The Michael addition with different Michael acceptors occurred under slightly different reaction conditions due to their differential reactivity.[92] The Michael acceptor **220c** and **220d** containing the keto and nitro group, respectively were found to react smoothly with allyl amine in THF solvent whereas the Michael acceptor **220b** containing the methyl ester group required a protic solvent methanol to occur. In contrast, the Michael acceptor **220a** bearing the cyano group did not react in any of these protic and aprotic solvents. It underwent the addition reaction in the presence of a catalytic amount of Et_3N in *t*-butanol. (**Table 3**)

Table 3. Synthesis of the cyclization precursors 223 and the chlorinated and functionalized *N*-H pyrrolidines 224

S. No.	**220** EWG	**223**[a]			**224**[b]		
		solvent	Time (h)	Isolated yield (%)	Time (h)	Yield (%)	Trans:Cis ratio
1	a: CN	*t*-BuOH[c]	24	76	7	87	100:0
2	b: CO_2Me	MeOH	4	83	8	82	100:0
3	c: COPh	THF	5	80	6	85	100:0
4	d: NO_2	THF	3	85	6	79	75:25[d]

[a] Reaction was done by taking 10 mmol of **220** and the products were purified by column chromatography.

[b] The reaction was done by taking 1 mmol of **223** and products were purified by column chromatography using basic alumina.

[c] Et_3N was used as a catalyst (30 mol%).

[d] Mixture of diastereomers, could not be separated by column chromatography.

Treatment of these 2,2,2-trichloroethyl allyl amine cyclization precursors **223** with CuCl/PMDETA at 0 ˚C for 6-8 h followed by purification by column chromatography on basic alumina column furnished the side chain functionalized 3,3,-dichloro-*N*-H pyrrolidines **224** (**Scheme 80)** in high isolated yields (79-87%) in a highly diastereoselective manner. However, these precursors were less reactive than **208** and required 60 ml% of the catalyst for completion in comparable duration of time. In all the cases, the minor isomers were present in too small amounts to be isolated by column chromatography. The results are compiled in **Table 3**.

The structures of these pyrrolidines were determined by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and HRMS. The gross NMR spectral features were similar to those of the others 1-substituted *N*-H pyrrolidines **209** and the substituent-dependent differences were as expected. However, the ^{1}H NMR spectra were more complex due to the presence of three pairs of diastereotopic methylene protons. Therefore, HSQC (**Fig. 94**) and COSY (**Fig. 95**) of a representative product **224a** were recorded for satisfactory interpretation. The 2,4-*trans* stereochemistry of the major products was indicated by single crystal X-ray diffraction spectroscopy of the tosylation product **225** of the pyrrolidine **224a**. The ORTEP diagram of **225** is shown in **Fig. 12**.

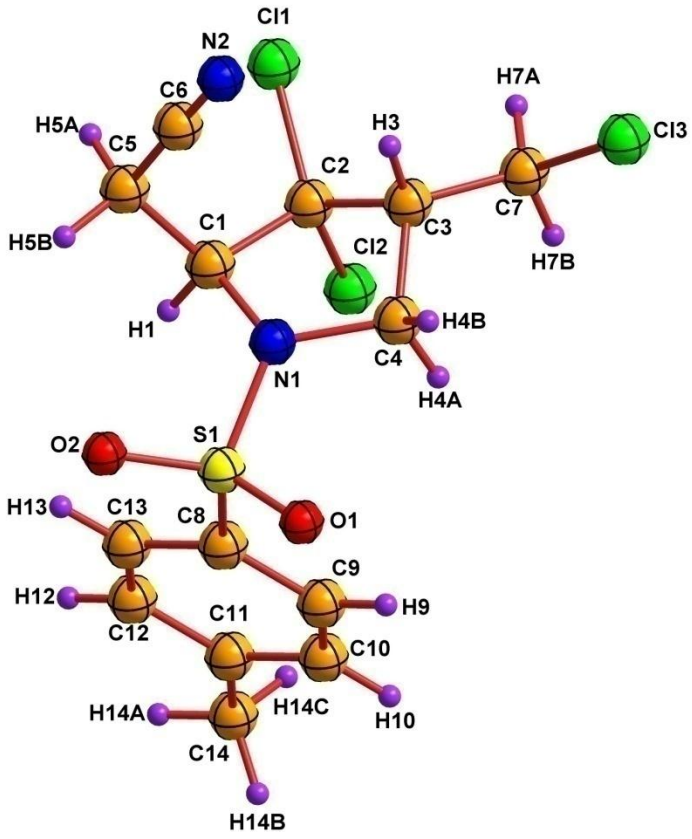
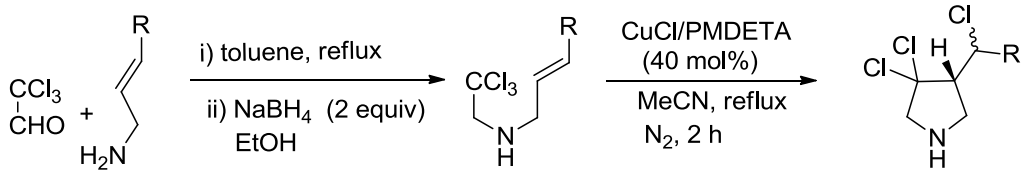


Fig. 12 ORTEP diagram of 2-(3,3-dichloro-4-(chloromethyl)-1-tosylpyrrolidin-2-yl) acetonitrile 225

The application of chloral in the preparation of HATRC precursors for the synthesis of tetrahydrofurans has been demonstrated by this laboratory.[10] A similar application of chloral in the synthesis of the HATRC precursors in the present context was envisaged. Thus, anhydrous chloral and allyl or cinnamyl amine on azeotropic condensation[93] followed by reduction[94] of the imine thus obtained with sodium borohydride afforded the 2,2,2-trichloroethyl allyl amines **226** (**Scheme 81**). These amines underwent 5-*exo* HATRC in the presence of 40 mol% CuCl/PMDTA (1:1 mol ratio) in acetonitrile. However, these reactions required heating at reflux for 2 h for completion. The crude products were almost pure and further purified by column chromatography using basic alumina to afford the 3,3-dichloro-4-(chloromethyl)-*N*-H pyrrolidines **227** in high yields

(76-81%). The product **227a** was a single diastereomer but the product **227b** was a 65:35 mixture of diastereomers. These were simpler pyrrolidines bearing no substituents at C-2(α) and C-5(α') positions. These reactions showed that the presence of a substituents at α and /or α' to the amine group in the cyclization precursor is not necessary for the success of the HATRC of the unprotected secondary trichloroethyl allyl amines, thus providing relief from our apprehensions that in such cases the reaction may be largely inhibited or may not occur at all due to deactivation of the catalyst by interaction with the unhindered *N*H group of the precursors or the products or both.[8] However, in these cases, the reactions were slower and did require 1 equivalent of the catalyst and longer reaction time (12 h) for the completion of the reaction at room temperature which might suggest some deactivation of the catalyst due to these interactions.[8,76,95]



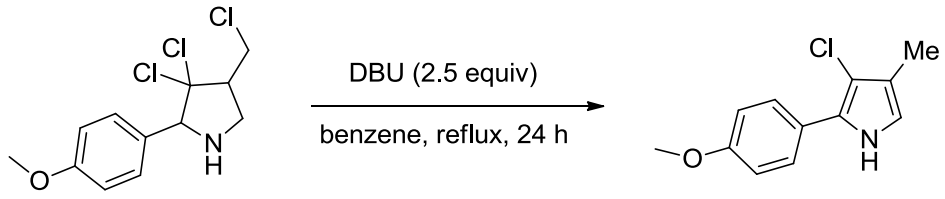
		226	**227**	
	Time	yield (%)	Yield (%)	Isomeric ratio
a: R = H	3	67	81	single
b: R = Ph	4	74	76	65 : 35

Scheme 81

2.3.4. Dehydrochlorination of the pyrrolidine 209b: Chloro-2-(4-methoxyphenyl)-4-methyl-1H-pyrrole 228

In order to demonstrate a synthetic application of the 2,2-dichloro- *N*-H pyrrollidines prepared in the present work in chloropyrrole synthesis, aromatization of the 2,2-dichloropyrrolidine **209b** was undertaken using a method reported by this laboratory

for base-mediated dehydrochlorination-isomerization of analogous chlorinated tetrahydrofurans.[10] Thus, a solution of the crude chlorinated pyrrolidine **209b** (1 mmol) and DBU (2.5 mmol) in dry benzene (30 mL) was heated at reflux temperature for 24 h. Simple work up and purification of the product by column chromatography on basic alumina column afforded the 3-chloropyrrole **228** (**Scheme 82**) in 46% yield.



209b **228**

Scheme 82

2.4. Conclusion

The present chapter describes a mild and highly regioselective CuCl/PMDETA-catalyzed chlorine atom transfer radical cyclization of 2,2,2-trichloroethyl allyl amines. These unprotected secondry amines cyclized to 3,3-dichloro-4-α-chloroalkyl-*N*-H pyrrolidines almost exclusively in 5-*exo*-*trig* mode to furnish diversely substittued 3,3-dichloro-*N*-H pyrrolidnes. The piperidine product of 6-*endo*-trig radical cyclization could not be obtained in any case. The radical cyclization was highly stereoselective, giving pyrrolidines with 2,4-*trans* geometry almost exclusively in most of the cases. The acyclic precursors were easily accessible by different methods such as by decarboxylative addition of trichloroacetic acid to aldimines and ketimines derived from allylic amines, alkylation of 2,2,2-trichloroethyl amine with allylic halides, condensation of anhydrous chloral with

allylic amines followed by reduction of the imine with $NaBH_4$ and Michael addition of allylic amine to β-trichloromethyl substituted Michael acceptors. High diversity accessible in the synthesis of the acyclic precursors led to the synthesis of a variety of 3,3-dichloro-*N*-H pyrrolidines having no substituent or alkyl, aryl and heteroaryl substituents at C-2 position a well as functional groups such as NO_2, CN, CO_2Me, COPh in the side chain at this position and a chlorine substituent at the α-position of an alkyl substituent at the C-4 position. The chlorinated and side chain functionalized *N*-H pyrrolidines are potential building blocks for the advanced synthesis due to the presence of such versatile functional groups as chloro, ester, cyano, nitro as well as the NH group of the ring. An aspect of the synthetic applications of these pyrrolidines in the synthesis of *N*-H pyrroles was illustrated by aromatizing one of them by double dehydrochlorination-isomerization with DBU.

2.5. Experimental Section

2.5.1 Preparation of the starting materials

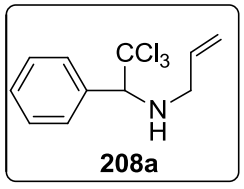
The aliphatic and aromatic aldimines **207** and the ketimine **212** were prepared by condensation of aldehydes or ketone with allylic amines following the procedures as reported in the literatures.[96] Chloral hydrate, trichloroacetonitrile and nitromethane were commercially available and were used as received.

2.5.1.1. Preparation of α-substituted 2,2,2-trichloroethyl allyl amines 208 and 213

General procedure. To a solution of aldimine **207** (10 mmol) or the ketimine **212** (10 mmol) in DMSO (10 mL) was added portion wise a solution of trichloroacetic acid (3.268

g, 20 mmol) at 40 ˚C (4.902 g, 30 mmol at 50 ˚C for **207f** and at 45 ˚C for **207g**) with stirring during 1 h. The stirring was continued at the same temperature and the progress of the reaction was monitored by TLC. After the disappearance of the imine as indicated by TLC (1 h), the solution was poured into ice-cold water and extracted with diethyl ether (for aliphatic products) or ethyl acetate/*n*-hexane mixture (50:50 v:v, for aromatic derivatives). The combined organic extract was washed with brine (2x50 mL), dried (Na_2SO_4) and filtered. The solvent of the filterate was evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography on neutral alumina using *n*-hexane and ethyl acetate-*n*-hexane mixture containing (0-3% ethyl acetate, v/v) as the solvent for elution to obtain 2,2,2-trichloroethyl allyl amines **208** and **213** in good to high yields (52-80%).

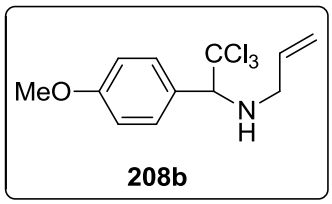
N-(2,2,2-Trichloro-1-phenylethyl)prop-2-en-1-amine ***208a****:*[73,86]



208a

Yellowish liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.70 (s, br, NH, D_2O exchangeable), 3.11 (dd, 1H, *J* = 14.5, 6.9 Hz, allylic CH), 3.39 (dd, 1H, *J* = 14.5, 5.1 Hz, allylic CH), 4.39 (s, 1H, benzylic CH), 5.10-5.16 (m, 2H, olefinic CH_2), 5.79-5.93 (m, 1H, olefinic CH), 7.37-7.39 (m, 3H, Hz, aryl CH), 7.51-7.54 (m, 2H, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.0 (CH_2), 76.4 (CH), 102.9 (C), 116.9 (CH_2), 127.9 (CH), 128.9 (CH), 129.9 (CH), 135.8 (CH), 135.9 (C) ppm; IR (KBr): ν_{max} 3338(m, br), 3069(m), 3031(m), 1643(w), 1459(s), 1417(w), 1340(s), 1195(w), 1114(m), 1080(s), 1021(m), 923(s), 790(s), 742(s), 700(s) cm^{-1}; HRMS(ESI+): m/z $[M + H]^+$ calcd for $C_{11}H_{12}Cl_3NH$ 264.0108, found 264.0108.

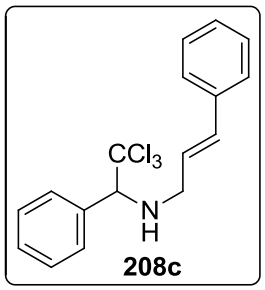
N-(2,2,2-Trichloro-1-(4-methoxyphenyl)ethyl)prop-2-en-1-amine ***208b****:*[73,86]



208b

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.22 (s, br, 1H, NH, D_2O-exchangeable), 3.09 (dd, 1H, *J* = 14.4, 6.9 Hz, allylic CH), 3.31 (dd, 1H, *J* = 14.1, 6.6 Hz, allylic CH), 3.83 (s, 3H, CH_3), 4.35 (s, 1H, CH), 5.10-5.16 (m, 2H, olefinic CH_2), 5.80-5.89 (m, 1H, CH), 6.91 (d, 2H, *J* = 8.4 Hz , CH), 7.45 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.0 (CH_2), 55.1 (CH_3), 75.8 (CH), 103.3 (C), 113.3 (CH_2), 116.8 (CH), 127.6 (C), 131.1 (CH), 135.8 (CH), 160.0 (C) ppm; IR (KBr): ν_{max} 3338(m, br), 3075(m), 3033(m), 2836(s), 1641(w), 1610(s), 1511(s), 1462(s), 1300(m), 1250(s), 1177(s), 1110(s), 1034(s), 924(m), 868(s), 799(s) cm^{-1}; HRMS (ESI+) : m/z $[M + H]^+$ calcd for $C_{12}H_{14}Cl_3NOH^+$ 294.0214, found 294.0214.

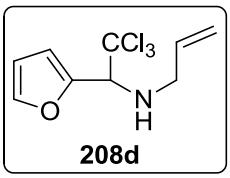
3-Phenyl-N-(2,2,2-trichloro-1-phenylethyl)prop-2-en-1-amine ***208c****:*[73,86]



208c

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.22 (s, br, 1H, NH, D_2O-exchangeable), 3.23 (dd, 1H, *J* = 14.1, 6.9 Hz, allylic CH_2), 3.42 (dd, 1H, *J* = 14.1, 4.8 Hz, allylic CH_2), 4.39 (s, 1H, benzylic CH), 6.15-6.23 (m, 1H, olefinic CH), 6.39 (d, 1H, *J* = 18.6 Hz, olefinic CH), 7.10-7.34 (m, 8H, aryl CH), 7.50 (s, br, 2H, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 49.6 (CH_2), 76.4 (CH), 102.9 (C), 126.2 (CH), 127.2 (CH), 127.4 (CH), 128.0 (CH), 128.4 (CH), 128.9 (CH), 129.8 (CH), 132.1 (CH), 135.9 (C), 136.6 (C) ppm; IR (KBr): ν_{max} 3335(m, br), 3029(s), 2920(w), 1591(w), 1492(s), 1456(s), 1300(w), 1194(w), 1122(s), 970(s), 791(s), 742(s), 697(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{17}H_{16}Cl_3NH$ 340.0422, found 340.0421.

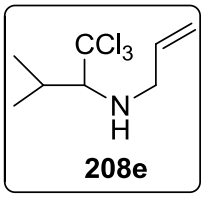
N-(2,2,2-Trichloro-1-(furan-2-yl)ethyl)prop-2-en-1-amine ***208d****:*



208d

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, br, 1H, NH, D_2O-exchangeable), 3.20 (dd, 1H, *J* = 14.1, 6.9 Hz, allylic CH), 3.42 (dd, 1H, *J* = 14.1, 5.1 Hz, allylic CH), 4.43 (s, 1H, CH), 5.13-5.22 (m, 2H, olefinic CH_2), 5.86-5.93 (m, 1H, olefinic CH), 6.42 (dd, 1H, *J* = 3.0, 1.8 Hz, furanyl CH), 6.49 (d, 1H, *J* = 2.4 Hz, furanyl CH), 7.46 (d, 1H, *J* = 1.5 Hz, furanyl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.4 (CH_2), 70.4 (CH), 101.5 (C), 110.4 (CH), 110.8 (CH), 117.4 (CH_2), 135.5 (CH), 142.7 (CH), 149.5 (C) ppm; IR (KBr): ν_{max} 3344(m, br), 3079 (w), 2924(m), 1642(w), 1496 (m), 1462(s), 1417(w), 1326(m), 1292(m), 1230(s), 1149(m), 1113(s), 1014(s), 925(s), 801(s), 742(s), 684(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_9H_{11}Cl_3NOH$ 253.9907, found 253.9901.

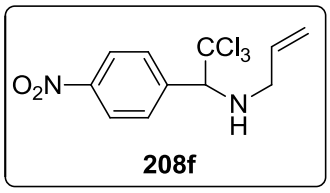
N-Allyl-1,1,1-trichloro-3-methylbutan-2-amine ***208e****:*



208e

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.07 (d, 3H, *J* = 7.0 Hz, CH_3), 1.09 (d, 3H, *J* = 7.0 Hz, CH_3), 1.80 (s, br, 1H, NH, D_2O-exchangeable), 2.50-2.62 (m, 1H, CH), 3.18 (s, 1H, CH), 3.52 (dd, 1H, *J* = 14.1, 5.7 Hz, allylic CH), 3.73 (dd, 1H, *J* = 14.1, 4.8 Hz, allylic CH), 5.10-5.23 (m, 2H, olefinic CH), 5.91-5.94 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.5 (CH_3), 23.5 (CH_3), 30.1 (CH), 53.8 (CH_2), 77.2 (CH), 106.6 (C), 116.1 (CH_2), 137.0 (CH) ppm; IR (KBr): ν_{max} 3398(m, br), 3080(w), 2965(s), 1644(w), 1465(s), 1367(w), 1159(m), 1108(m), 994(m), 921(s), 791(s), 756(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $H_8H_{15}Cl_3NH$ 230.0265, found 230.0265.

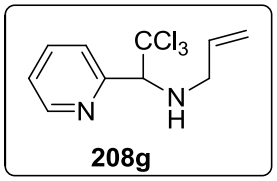
N-(2,2,2-Trichloro-1-(4-nitrophenyl)ethyl)prop-2-en-1-amine ***208f****:*



208f

Yellow crystals, mp 66 ˚C (*n*-hexane-DCM); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.25 (s, br, 1H, NH, D_2O-exchangeable), 3.08 (dd, 1H, *J* = 14.1, 6.9 Hz, allylic CH), 3.30 (dd 1H, *J* = 14.1, 4.8 Hz, allylic CH), 4.54 (s, 1H, benzylic CH), 5.09-5.15 (m, 2H, CH_2), 5.75-5.89 (m, 1H, CH), 7.76 (d, 2H, *J* = 8.7 Hz, aryl CH), 8.23 (d, 2H, *J* = 8.7 Hz, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.0 (CH_2), 75.7 (CH), 101.4 (C), 117.5 (CH_2), 123.1 (CH), 131.1 (CH), 135.2 (CH), 143.1 (C), 148.3 (C) ppm; IR (KBr): ν_{max} 3308(m, br), 3072(w), 2913(m), 1603(m), 1513(s), 1344(s), 1101(m), 1016(m), 922(w), 791(m), 743(w) cm^{-1}; HRMS (ESI+): m/z [M + Na]$^{+}$ calcd for $C_{11}H_{11}Cl_3N_2O_2Na$ 330.9784, found 330.9778.

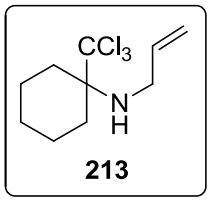
N-(2,2,2-Trichloro-1-(pyridin-2-yl)ethyl)prop-2-en-1-amine ***208g****:*



208g

Light red liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.13 (s, br, 1H, NH, D_2O-exchangeable merged with dd at δ 3.16), 3.16 (dd, 1H, *J* = 13.8, 6.3 Hz, allylic CH), 3.35 (dd, 1H, *J* = 13.8, 5.7 Hz, allylic CH), 4.41 (s, 1H, benzylic CH), 5.07-5.15 (m, 2H, allylic CH_2), 5.77-5.87 (m, 1H, allylic CH), 7.27 (t, 1H, *J* = 6.3 Hz, pyridyl CH), 7.48 (d, 1H, *J* = 7.8 Hz, pyridyl CH), 7.68 (t, 1H, *J* = 7.6 Hz, pyridyl CH), 8.62 (d, 1H, *J* = 4.2 Hz, pyridyl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz); δ 50.9 (CH_2), 75.9 (CH), 102.3 (C), 117.0 (CH_2), 123.5 (CH), 126.1 (CH), 135.8 (CH), 135.9 (CH), 149.0 (CH), 155.2 (C) ppm; IR (KBr): ν_{max} 3323(m, br), 3076(m), 2924(m), 1644(w), 1583(s), 1468(s), 1432(s), 1299(w), 1148(m), 1119(m), 995(s), 921(s), 799(s), 752(s) cm^{-1}; HRMS (ESI+): m/z [M + Na]$^{+}$ calcd for $C_{10}H_{11}Cl_3N_2Na$ 286.9875, found 286.9880.

*N-Allyl-1-(trichloromethy)cyclohexanamine **213**:*[73,86]

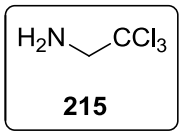


213

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09-1.99 {m, 11H, (10H, 5CH_2 and 1H, NH, D_2O-exchangeable)}, 3.51 (d, 2H, *J* = 5.4 Hz, NCH_2), 5.04-5.20 (m, 2H, olefinic CH_2), 5.84-5.97 (m, 1H, CH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6 (CH_2), 24.2 (CH_2), 30.1 (CH_2), 47.1 (CH_2), 73.0 (C), 106.3 (C), 120.0 (CH_2), 131.8 (CH) ppm; IR (KBr): ν_{max} 3389(m, br), 2932(s), 2856(s), 1643(m), 1452(s), 1347(w), 1292(s), 1179(s), 1108(m), 995(m), 918(s), 761(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{10}H_{16}Cl_3NH$ 256.0421, found 256.0421.

*2,2,2-Trichloroethyl amine **215**:*

This previously known amine was prepared by reduction of trichloroacetonitrile with $LiAlH_4$ according to a method reported in the literature.[89]

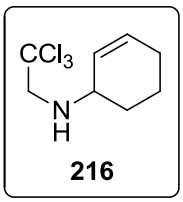


215

To a suspension of $LiAlH_4$ (3.225 g, 85 mmol) in dry diethyl ether (100 mL) at 0 ˚C, a solution of trichloroacetonitrile (14.439 g, 10.23 mL, 100 mmol) was added drop wise with stirring during 30 min. The reaction mixture was allowed to stir for another 30 min at the same temperature. Into the cooled solution, a saturated solution of brine (10 mL) was added drop wise till the effervescence stopped. It was diluted with diethyl ether (100 mL) and the suspension was stirred for 5 min. The stirring was stopped and the suspension was allowed to settle down, then it was decanted. The solvent was then washed with brine (2x25 mL), the organic layer was dried (Na_2SO_4), filtered and evaporated to obtain 2,2,2-trichloroethyl amine **215** as a yellow liquid in moderate yield (5.937g, 40%). The crude product was almost pure and was used as such in

the next step. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.96 (br, s, 2H, NH_2, D_2O-exchangeable), 3.47 (s, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.6 (CH_2), 102.7 (C) ppm; IR (KBr): ν_{max} 3440 (s, br), 3391(s, br), 2927(m), 1693(w), 1629(w), 1217(w), 769(s) cm^{-1}.

2.5.1. 2. Preparation of *N*-(2, 2, 2-trichloroethyl) cyclohex-2-enamine 216



216

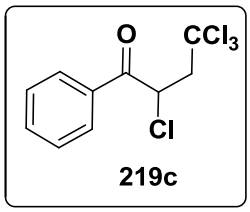
A mixture of 2,2,2-trichloroethylamine **215** (1.484 g, 10 mmol), cyclohexyl bromide (1.485 g, 10 mmol) and K_2CO_3 (2.073 g, 1.5 mmol) in THF (30 mL) was stirred at room temperature (25-30 ˚C). After completion of the reaction (6 h) as indicated by TLC monitoring, the solvent was removed under reduced pressure. The residual mass thus obtained was purified by column chromatography on basic alumina column using *n*-hexane as the eluent to obtain 2,2,2-trichloroethyl cyclohex-3-enyl amine **216** (1.919 g, 82%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23-1.89 {m, 7H, (6H, $3CH_2$ and 1H, NH, D_2O-exchangeable)], 3.35 (s, 1H, NCH), 3.45 (s, 2H, NCH_2), 5.59-5.72 (m, 2H, both vinylic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): 19.9 (CH_2), 25.1 (CH_2), 29.8 (CH_2), 53.0 (CH), 65.6 (CH_2) 100.7 (C), 129.3 (CH), 129.9 (CH) ppm; IR (KBr): ν_{max} 3371(m, br), 3022(s), 1648(w), 1456(s), 1310(w), 1140(s), 1028(m), 946(m), 800(s), 713(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_8H_{13}Cl_3NH$ 228.0103, found 228.0108.

2.5.1.3.1 Free radical addition of CCl_4 to Michael acceptors: Preparation of the adducts 219

These previously known (except **219c**) compounds were prepared according to a method reported in the literature[90] with some modifications.

General procedure: A flame-dried two-neck round-bottom flask was charged with CuCl (0.100 g, 2 mmol), PMDETA (0.4 ml, 0.346 g, 2 mmol) and degassed dichloroethelene (40 mL) under a N_2 atmosphere using Schlenk technique. Into this suspension, Michael acceptors (acrylonitrile/methyl acrylate/phenyl vinyl ketone) (20 mmol) and AIBN (3.28 g, 20 mmol) were added and the mixture was heated at reflux with stirring. The progress of the reaction was monitored by ^{1}H NMR in the case of **219a** and **219b** or by TLC in the case of **219c**. After completion of the reaction (7-8 h), the reaction mixture was cooled and diluted with diethyl ether and filtered. The filtrate was concentrated under reduced pressure and the residual mass was purified by column chromatography on a short pad of silica gel using ethyl acetate in *n*-hexane (5%, v:v) to give the adducts **219a** (1.387 g, 67%), **219b** (1.80 g, 75%) and **219c** (2.316 g, 81%) in good yields.

*2,4,4,4-Tetrachloro-1-phenylbutan-1-one **219c**:*



219c

Yellow liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.33 (d, 1H, *J* = 15.3, 2.7 Hz, CH_2), 4.17 (dd, 1H, *J* = 15.3, 6.9 Hz, CH_2), 5.49 (t, 1H, *J* = 6.9, 2.7 Hz, CH), 7.52 (t, 2H, *J* = 6.9 Hz, aryl CH), 7.63 (t, 1H, *J* = 7.1 Hz, aryl CH), 8.06 (d, 2H, *J* = 7.8 Hz, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.7 (CH_2), 56.7 (CH), 96.1 (C), 128.9 (CH), 129.1 (CH), 133.7 (C), 134.2 (CH), 190.9 (C) ppm; IR (KBr): ν_{max} 3063(w), 2938(m), 1695(s), 1591(m), 1449(m), 1419(w), 1367(w), 1312(m), 1245(m), 1179(m), 1046(m), 957(s), 850(s), 750(s), 692(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{10}H_8Cl_4ONa$ 306.9213, found 306.9221.

2.5.1.3.2. Preparation of trichloromethylated Michael acceptors 220

These previously known compounds[97] **220a-c** were prepared by slight modification of a method reported in the literature[90e] in which Et_3N was used as a base to dehydrochlorinate similar adducts in toluene at reflux.

General procedure: To a solution of the adduct **220a-c** (10 mmol) in benzene at 10 °C was added DBU (1.5 mL,1.522 g, 10 mmol) drop wise with stirring. The stirring was continued and the reaction mixture was allowed to warm up to 20 ˚C. The progress of the reaction was monitored by ^{1}H NMR in the cases of **220b** and **220c** or by TLC (in the case of **220c**). After the completion of the reaction (7-8 h), the reaction mixture was diluted with benzene (100 mL) and washed with water (2x20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography on a silica gel column using a mixture of ethyl acetate in *n*-hexane (1-5%, v:v) to obtain **220a** (1.440 g, 84 %), **220b** (1.774g, 87%) and **220c** (2.145, 86 %) in high yields.

The nitro derivative **220d** was prepared as indicated in the **Scheme 79** following a procedure reported in literature.[91c]

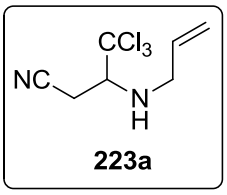
2.5.1.4. Preparation of the functionalized trichloroethyl allyl amines 223a-d

These previously unknown precursors were prepared by methods reported in the literature[96] for addition of aliphatic amines to some Michael acceptors bearing the same electron withdrawing groups, with some modifications.

General method. A solution of ally amine (0.78 mL, 0.57 g, 10 mmol) and the Michael acceptor **220c** or **220d** (10 mmol) in dry THF (or MeOH in the case of the ester derivative **220b**) (30 mL) was stirred at room temperature (25-30 ˚C). After completion of the reaction (**220b**: 4 h, **220c**: 5 h, **220d**: 3 h) as indicated by TLC, the solvent was removed on a rotavapor to obtain almost pure products in quantitative yields. The crude products were further purified by column chromatography on a small pad of basic alumina using a mixture of ethyl acetate in *n*-hexane (0-3%, v:v) as the solvent for elution to obtain the functionalized acyclic precursor **223b** (2.160 g, 83%), **223c** (2.453 g, 80 %) and **223d** (2.10 g, 85%)**.**

The cyano derivative **223a** was prepared as above by taking *t*-butanol (30 mL) as the solvent and triethyl amine (0.42 mL, 0.336 g, 3 mmol) as the catalyst and stirring the solution at room temperature (25-30 ˚C) for 24 h. It was obtained as a colorless liquid in high yield (1.730 g, 76 %).

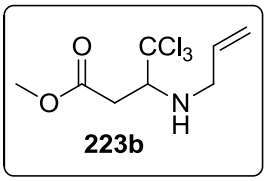
*3-(Allylamino)-4,4,4-trichlorobutanenitrile **223a**:*



223a

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.82 (s, br, 1H, NH, D_2O-exchangeable), 2.71 (dd, 1H, *J* = 17.1, 9.0 Hz, CH_2CN), 3.52-3.65 {m, 3H, (1H, NCH and 2H, allylic CH_2)}, 5.07-5.24 (m, 2H, olefinic CH_2), 5.78-6.0 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.9 (CH_2), 51.2 (CH_2), 68.7 (CH), 103.0 (C), 116.6 (C), 117.0 (CH_2), 135.5 (CH) ppm; IR (KBr): ν_{max} 3369(br, s), 2923(m), 2252(m), 1643(m), 1471(s), 1418(s), 1335(w), 1158(s), 997(s), 926(s), 783(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_7H_{10}Cl_3N_2H$ 226.9912, found 226.9904.

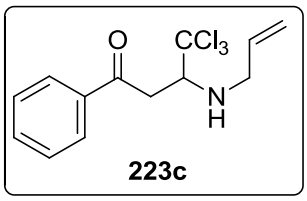
*Methyl 3-(allylamino)-4,4,4-trichlorobutanoate **223b**:*



223b

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.76 (s, br, 1H, NH, D_2O-exchangeable), 2.55 (dd, 1H, *J* = 15.6, 9.6 Hz, CH_2CO), 3.08 (dd, 1H, *J* = 15.6, 3.3 Hz, CH_2CO), 3.48 (dd, 1H, *J* = 14.1, 6.0 Hz, allylic CH_2), 3.58 (dd, 1H, *J* = 14.1, 5.7 Hz, allylic CH_2), 3.69 (s, 3H, OCH_3), 3.82 (dd, 1H, *J* = 9.6, 3.3 Hz, CH). 5.03-5.23 (m, 2H, olefinic CH_2), 5.73-5.86 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.2 (CH_2), 51.8 (CH_2), 52.0 (CH_3), 70.3 (CH), 104.7 (C), 116.2 (CH_2), 136.3 (CH), 170.8 (C) ppm; IR (KBr): ν_{max} 3377(m, br), 3080(w), 2952(m), 1740(s), 1644(w), 1439(m), 1358(m), 1274(s), 1175(s), 1024(m), 923(m), 795(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_8H_{12}Cl_3NO_2H$ 260.0006, found 260.0006.

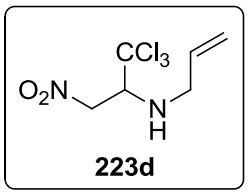
*3-(Allylamino)-4,4,4-trichloro-1-phenylbutan-1-one **223c**:*



223c

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.93 (s, br, 1H, NH, D_2O-exchangeable), 3.26 (dd, 1H, *J* = 18.0, 9.0 Hz, allylic CH_2), 3.49-3.63 {m, 2H, (1H, NCH and 1H, allylic CH_2)}, 3.76 (dd, 1H, *J* = 18.0, 3.0 Hz, $COCH_2$), 4.13 (dd, 1H, *J* = 18.0, 3.0 Hz, $COCH_2$), 4.99-5.15 (m, 2H, olefinic CH_2), 5.74-5.87 (m, 1H, olefinic CH), 7.51 (t, 2H, *J* = 7.5 Hz, aryl CH), 7.62 (t, 1H, *J* = 7.5 Hz, CH), 7.96 (d, 2H, *J* = 6.0 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.4 (CH_2), 52.0 (CH_2), 69.6 (CH), 105.4 (C), 116.3 (CH_2), 128.2 (CH), 128.7 (CH), 133.5 (CH), 136.2 (CH), 136.4 (C), 196.39 (C) ppm; IR (KBr): ν_{max} 3397(m, br), 3071(w), 2921(m), 1685(s), 1590(w), 1449(w), 1352(w), 1272(m), 993(m), 795(m), 755(m) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{13}H_{14}C_{l3}NONa$ 328.0020, found 328.0033.

N-(1,1,1-Trichloro-3-nitropropan-2-yl)prop-2-en-1-amine ***223d****:*



223d

Light yellow liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.82 (s, br, 1H, NH, D_2O-exchangeable), 3.53 (dd, 1H, *J* = 14.1, 6.0 Hz, allylic CH), 3.70 (dd, 1H, *J* = 14.1, 5.7 Hz, CH), 4.26 (dd, 1H, *J* = 9.6, 3.3 Hz, CHN), 4.51 (dd, 1H, *J* = 13.2, 9.6 Hz, CH_2NO_2), 5.06 (dd. 1H, *J* = 13.2, 3.3 Hz, $CHNO_2$ partially overlapped multiplet at δ 5.11-5.24), 5.11-5.24 (m, 2H, olefinic CH_2), 5.72-5.85 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.9 (CH_2), 51.2 (CH_2), 68.7 (CH), 103.0 (C), 117.0 (CH_2), 135.5 (CH) ppm; IR (KBr): ν_{max} 3382(m, br), 3081(w), 2926(m), 1643(w), 1561(s), 1472(w), 1425(m), 1379(s), 1162(m), 996(m), 926(m), 802(m), 636(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_6 H_9 Cl_3N_2 O_2H$ 246.9808, found 246.9802.

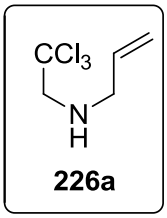
2.5.1.5. Preparation of α,α′-(unsubstituted *N*-2,2,2-trichloroethyl) allylic amines 226

These were prepared by azeotropic condensation[93] of chloral with allylic amines followed by reduction[94] according to the methods reported in the literatures with slight modifications.

General method. A solution of chloral (0.98 mL, 1.47 g, 10 mmol) and allyl amine (0.75 mL, 0.570 g, 10 mmol) or cinnamyl amine (1.33 g, 10 mmol) in the benzene was heated at reflux in a Dean Stark apparatus for 3 or 4 h, respectively. Benzene was removed under reduced pressure to obtain the Schiffs bases as orange viscous liquids which were used as such in the next step. To the solution of the Schiffs base in absolute ethanol (30 mL), $NaBH_4$ (0.756 g, 20 mmol) was added portion wise at 10 °C and the reaction mixture

stirred till completion of the reaction as indicated by TLC monitoring (2 h). The ethanol was removed on rotavapor, the residue was taken up in water (10 mL) and extracted with diethyl ether (3×50 mL). The combined organic extract was dried (Na_2SO_4), filtered and evaporated. The residual mass was purified by column chromatography on a basic alumina column using *n*-hexane as eluent to obtain the pure products **226a** (1.265 g, 67%) and **226b** (1.950 g, 74%) as colorless liquids.

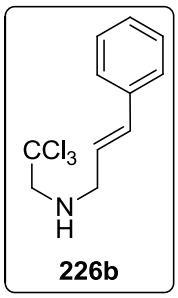
*N-(2,2,2-Trichloroethyl)prop-2-en-1-amine **226a**:*



226a

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.98 (s, br, 1H, NH, D_2O-exchangeable), 3.53 (d, br, 2H, *J* = 6.0 Hz, allylic CH_2), 3.55 (s, 2H, CH_2CCl_3), 5.14-5.27 (m, 2H, olefinic CH_2), 5.76-5.89 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.7 (CH_2), 67.1 (CH_2), 100.3 (C), 116.6 (CH_2), 136.1 (CH) ppm; IR (KBr): ν_{max} 3363(s, br), 3080(m), 1679(s), 1462(s), 1419(m), 1153(m), 992(m), 799(s), 712(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_5H_8Cl_3NH$ 187.9792, found 187.9795.

*3-Phenyl-N-(2,2,2-trichloroethyl)prop-2-en-1-amine **226b**:*



226b

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90 (s, br, 1H, NH, D_2O-exchangeable), 3.72 (s, 2H, CH_2CCl_3), 3.81 (d, 2H, *J* = 6.0 Hz, allylic CH_2), 6.39-3.40 (m, 1H, olefinic CH), 6.69 (d, 1H, *J* = 15.6 Hz, olefinic CH), 7.40-7.52 (m, 5H, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.2 (CH_2), 67.3 (CH_2), 100.4 (C), 126.3 (CH), 127.6 (CH), 127.7 (CH), 128.5 (CH), 131.9 (CH), 136.7 (C) ppm; IR (KBr): ν_{max} 3376(m, br), 3027(s), 2915(s), 1599(m), 1491(m), 1456(s), 1345(m), 1143(s), 968(s), 794(s), 741(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{11}H_{12}Cl_3NH$ 264.0102, found 264.0108.

2.5.2. Chlorine atom transfer radical cyclization of 2,2,2-trichloroethyl allyl amines 208, 213, 216, 223 and 226: Preparation of the chlorinated α-substituted *N*-H pyrrolidines 209, 214, 217, 224 and 227

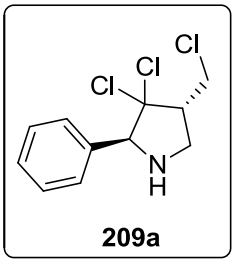
A flame-dried two-neck round-bottom flask was charged with CuCl (40 mg, 40 mol%) and degassed acetonitrile (20 mL) under a N_2 atmosphere using Schlenk technique. The suspension was cooled to 0 ˚C and PMDETA (0.070 g, 0.8 mL, 0.4 mmol) was injected into it. The mixture was stirred for 10 minutes at the same temperature. *N*-(2,2,2-trichloroethyl)prop-2-en-1-amine **208** or **213** (1 mmol) was added to this mixture and stirring was continued further at the same temperature. After the disappearance of the starting material as indicated by TLC monitoring and confirmed by ^{1}H NMR (4-6 h), the solvent was removed under reduced pressure. Diethyl ether or ethyl acetate (100 mL) was added to the residual mass. The organic phase was washed with brine (3x25 mL) to discharge the color of the solution. The aqueous phase was treated with aqueous ammonia and extracted with organic solvent to ensure maximum possible recovery of the pyrrolidine product lest there was any pyrrolidine in the aqueous phase, presumably due to the coordination with copper ions. The combined organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on a small basic alumina column using different mixture of ethyl acetate in *n*-hexane (10-40%, v:v) as the solvent for elution. The substituted pyrrolidines **209a-e** and **214** obtained in good to high yields (81-85%).

The fused pyrrolidine **217** and the side chain functionalized pyrrolidines **224** were prepared from the corresponding amines **216** and **223** and purified as above, except that 60

mol% each of CuCl and PMDETA were taken and the reaction mixture was stirred at 0˚C for 6-10 h.

The unsubstituted pyrrolidines **227a** and **227b** were prepared from the corresponding amines **226a** and **226b** and purified as above except that 40 mol% each of CuCl and PMDETA were taken and the reaction mixture was heated under reflux condition for 2 h.

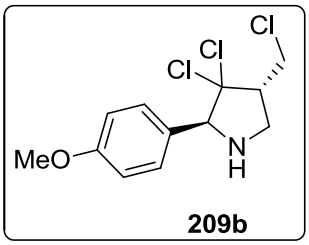
*3,3-Dichloro-4-(chloromethyl)-2-phenylpyrrolidine **209a**:*



209a

Light yellow liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (s, br, 1H, NH, D_2O-exchangeable), 3.07-3.20 [m, 2H, (1H, C<u>H</u>CH_2 and 1H, NCH_2) overlapped signals], 3.62-3.75 [m, 2H, (1H, CH_2Cl and 1H, CH_2N) overlapped signals], 3.97 (dd, 1H, *J* = 10.8, 3.6 Hz, CH_2Cl), 4.60 (s, 1H, CHN), 7.37-7.40 (m, 3H, CH), 7.44-7.46 (m, 2H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.8 (CH_2), 49.0 (CH_2), 55.3 (CH), 75.8 (CH), 94.3 (C), 128.0 (CH), 128.1 (CH), 128.4 (CH), 137.2 (C) ppm; IR (KBr): ν_{max} 3368(m, br), 3062(m), 3033(s), 2960(m), 1605(w), 1495(m), 1451(s), 1347(m), 1260(s), 1073(s), 1029(s), 921(s), 859(s), 787(s), 700(s), 672(m) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{11}H_{12}Cl_3NH$ 264.0115, found 264.0108.

*3,3-Dichloro-4-(chloromethyl)-2-(4-methoxyphenyl)pyrrolidine **209b**:*

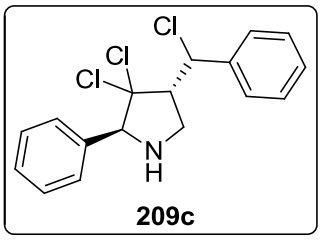


209b

Yellow solid, mp 81 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.25 (s, br, 1H, NH, D_2O-exchangeable), 3.08-3.15 [m, 2H (1H, methine CH and 1H, NCH_2)], 3.63-3.67 [m, 2H, (1H, CH_2Cl and 1H, NCH_2)], 3.80 (s, 3H, CH_3), 3.96 (dd, 1H, *J* = 10.5, 3.3 Hz, CH_2Cl), 4.53 (s, 1H, CHN), 6.90 (d, 2H, *J* = 8.4 Hz, CH), 7.36 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR

($CDCl_3$, 75 MHz): δ 43.8 (CH_2), 48.5 (CH_2), 55.1 (CH, CH_3), 75.0 (CH), 94.2 (C), 113.3 (CH), 128.4 (C), 129.1 (CH), 159.8 (C) ppm; IR (KBr): ν_{max} 3377(m, br), 2958 (m), 1612(m), 1515(s), 1440(m), 1253(s), 1180(m), 1033(m), 933(m), 830(m), 747(m) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{12}H_{14}Cl_3NOH$ 294.0219, found 294.0214.

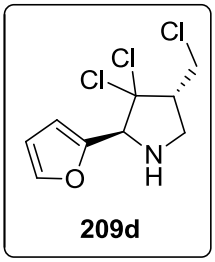
3,3-Dichloro-4-{(chloro)(phenyl)methyl}-2-phenylpyrrolidine ***209c****:*



209c

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.12 (s, br, 1H, NH, D_2O-exchangeable), 3.44-3.51 {m, 2H (1H, NCH_2 and 1H, methine CH)}, 3.75 (dd, 1H, *J* = 14.7, 12.0 Hz, NCH_2), 4.73 (s, 1H, benzyl CH), 5.42 (d, 1H, *J* = 6.3 Hz, CHN), 7.31-7.36 (m, br, 5H, aryl CH), 7.43 (d, 5H, *J* = 6.3 Hz, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 49.2 (CH_2), 59.5 (CH), 63.7 (CH), 77.4 (CH), 94.2 (C), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 137.6 (C) 139.3 (C) ppm; IR (KBr): ν_{max} 3369 (m, br), 3064(m), 1597(w), 1494(m), 1452(s), 1199(m), 1032(m), 881(m), 799(m), 757(s), 701(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{17}H_{16}Cl_3NH$ 340.0421, found, 340.0421.

3,3-Dichloro-4-(chloromethyl)-2-(furan-2-yl)pyrrolidine ***209d****:*

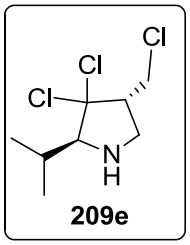


209d

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.74 (s, br, 1H, NH, D_2O-exchangeable), 3.12 (dd, 1H, *J* = 10.8, 8.4 Hz, NCH_2), 3.17-3.27 (m, 1H, methine CH), 3.62-3.72 {m, 2H, (1H, CH_2N and 1H, CH_2Cl)}, 3.96 (dd, 1H, *J* = 11.1, 3.9 Hz, CH_2Cl), 4.71 (s, 1H, CH), 6.37-6.40 (m, 2H, furanyl CH), 7.42-7.43 (m, 1H, furyl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.2 (CH_2), 48.8 (CH_2), 54.8 (CH), 71.0 (CH), 93.3 (C), 109.2 (CH), 110.3 (CH), 142.6 (CH), 151.0 (C) ppm; IR (KBr): ν_{max} 3373(m, br, NH), 2958(s), 1624(m), 1500(w), 1439(s),

1252(m), 1151(s), 1070(m), 1011(s), 927(m), 880(m), 841(s), 810(m), 743(s) cm $^{-1}$; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_9H_{10}Cl_3NOH$ 253.9902, found 253.9901.

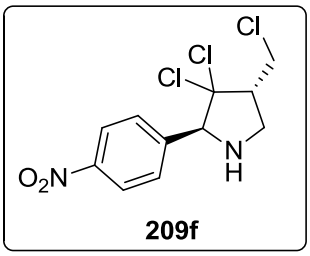
*3,3-Dichloro-4-(chloromethyl)-2-isopropylpyrrolidine **209e**:*



209e

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (d, 3H, *J* = 6.9 Hz, CH_3), 1.16 (d, 3H, *J* = 6.9 Hz, CH_3), 1.98-2.06 (m, 1H, isopropyl CH), 2.11 (s, br, 1H, NH, D_2O-exchangeable), 2.92 (dd, H, *J* = 11.4, 6.9 Hz, CH_2N), 2.97-3.07 [m, 2H, (1H, methine CH and 1H, CH_2N], 3.45-3.54 [m, 2H, (1H, NCH and 1H, CH_2Cl)], 3.94 (dd, 1H, *J* = 10.8, 4.2 Hz, CH_2Cl) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4 (CH_3), 20.6 (CH_3), 30.7 (CH), 44.4 (CH_2), 48.6 (CH_2), 58.3 (CH), 77.8 (CH), 94.6 (C) ppm; IR (KBr): ν_{max} 3307(m, br), 2963(s), 1466(s), 1391(m), 1284(m), 1081(s), 826(s), 726(m) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_8H_{14}Cl_3NH$ 230.0263, found 230.0265.

*3,3-Dichloro-4-(chloromethyl)-2-(4-nitrophenyl)pyrrolidine **209f**:*

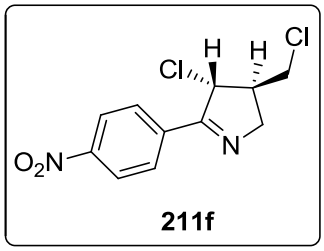


209f

It was obtained by general procedure described under **section 2.5.2**, the crude product **209f** was obtained as light yellow viscous liquid in (0.275 g, 89%) yield. The ^{1}H NMR of crude product, taken immediately after the work up showed pyrrolidine **209f** was almost intact and was a single isomer. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.083.13 [m, 2H, (1H, NH, D_2O-exchangeable and 1H, C<u>H</u>CH_2) partially overlapping a multiplet at δ 3.21-3.27], 3.21-3.27 (m, 1H, NCH_2), 3.67-3.77 [m, 2H, (1H, CH_2Cl and 1H, NCH_2)], 3.96 (dd, 1H, *J* = 11.1, 3.9 Hz, CH_2Cl), 4.80 (s, 1H, CH), 7.61 (d, 2H, *J* = 8.7 Hz, CH), 8.15 (d, 2H, *J* = 8.7 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.3 (CH_2), 48.7 (CH_2), 55.3 (CH), 74.8 (CH), 92.9 (C), 123.2 (CH), 129.3 (CH), 144.0

(C), 148.0 (C) ppm; IR (KBr): ν_{max} 3373 (m, br), 2923(s), 1601(m), 1522(s), 1347(s), 1107(m), 853(m), 739(s) cm^{-1} ; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{11}H_{11}Cl_3N_2O_2Na$ 330.9771, found 330.9778.

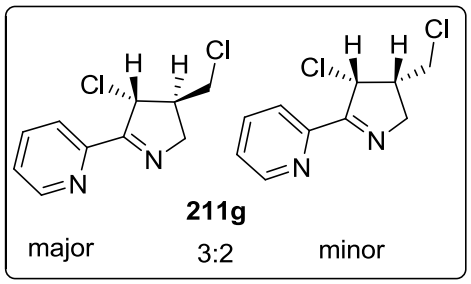
*4-Chloro-3-(chloromethyl)-5-(4-nitrophenyl)-3,4-dihydro-2H-pyrrole **211f**:*



211f

With passage of time, the physical state of the crude product **209f** appeared to change from liquid to solid. ^{1}H NMR of this compound showed a new downfield signal due to the formation of the elimination-tautomerization product **211f**. Chloroform (40 mL) was added to the crude product. $NaHCO_3$ (1.5 equivalent) was added to the solution and the mixture was stirred until the TLC showed complete disappearance of the pyrrolidine **209f**. It was further confirmed by taking ^{1}H NMR of the solution. The excess solid $NaHCO_3$ was filtered out. The organic layer was evaporated under reduced pressure and the crude product was purified by column chromatography on a short neutral alumina column using a mixture of ethyl acetate in *n*-hexane (10%, v:v) as the eluent. The pyrroline **211f** was obtained in good isolated yields (0.215 g, 79%) as a yellow solid, mp 84 ˚C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.09-3.11 (m, 1H, methine CH), 3.51 (dd, 1H, *J* = 11.4, 7.5 Hz, NCH_2), 3.71 (dd, 1H, *J* = 11.4, 5.4 Hz, NCH_2), 4.07 (dd, 1H, *J* = 17.7, 2.1 Hz, CH_2Cl), 4.45 (dd, 1H, 17.7, 7.2 Hz, CH_2Cl), 5.19 (s, 1H, CHCl), 8.09 (d, 2H, *J* = 8.4 Hz, aromatic CH), 8.28 (d, 2H, *J* = 8.4 Hz, aromatic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz); δ 44.8 (CH_2), 50.4 (CH), 61.1 (CH), 63.1 (CH_2), 123.7 (CH), 129.2 (CH), 137.0 (C), 149.1 (C), 168.2 (C) ppm; IR (KBr): ν_{max} 2962(w), 1591(m), 1521(s), 1441(w), 1347(s), 1108(w), 1012(m), 973(w), 864(m), 844(w), 713(m), 713(m) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_2O_2H$ 273.0196.

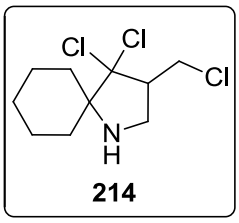
*2-(3-Chloro-4-(chloromethyl)-4,5-dihydro-3H-pyrrol-2-yl)pyridine **211g**:*



It was obtained by the general procedure described under **Section 2.5.2**. After completion of the reaction (4 h), the solvent of the reaction mixture was removed under reduced pressure and ethyl acetate (100 mL) was added to the residue. The organic phase was washed with water (3x25 mL). To the combined aqueous layer, aqueous ammonia (2x10 mL) was added and the solution was stirred for 10 minutes. It was extracted with ethyl acetate (2x25 mL). All the ethyl acetate extracts were combined and washed with brine (20 mL), dried (Na_2SO_4), filtered and evaporated. The crude product thus obtained was further purified by column chromatography on a small pad of basic alumina using a mixture of ethyl acetate in *n*-hexane (30%, v:v) as the solvent for elution. The diastereomeric mixture of pyrrolines **211g** (0.207g, 78%) was obtained as a light red liquid. The ^{1}H NMR revealed it to be a 3:2 mixture of the two diastereomers, *Trans* being the major isomer. ^{1}H NMR ($CDCl_3$, 300 MHz): δ [2.92-2.97 (m) (minor isomer) + 3.05-3.11 (m) (major isomer), 1H, C<u>H</u>CH_2], [3.41 (dd, *J* = 11.1, 7.5 Hz) (minor isomer) + 3.53 (dd, *J* = 11.1, 6.6 Hz)(major isomer), 1H, NCH_2], [3.69-3.80 (m) (major isomer + minor isomer), 1H, NCH_2], [3.87 (dd, *J* = 10.8, 8.4 Hz) (minor isomer) + 4.05 (d, *J* = 17.7 Hz)(major isomer), 1H, CH_2Cl], 4.27-4.42 [(m)(minor isomer)(major isomer), 1H, CH_2Cl,], [5.43 (s) (major isomer) + 5.60 (d, *J* = 6.3 Hz) (minor isomer), 1H, CHCl], 7.32 (t, 1H, *J* = 4.8 Hz, CH), 7.73 (t, 1H, *J* = 7.5 Hz, CH), 8.16 (d, 1H, *J* = 6.6 Hz, CH), 8.64 (d, 1H, *J* = 4.2 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.1 (CH_2), 45.0 (CH_2), 46.9 (CH), 50.1 (CH), 60.6 (CH), 61.1 (CH), 62.8 (CH_2), 63.5 (CH_2), 122.6 (CH), 122.9 (CH), 125.3 (CH), 125.4 (CH), 136.59 (CH), 136.62 (CH),

149.3 (CH), 149.4 (CH), 150.4 (C), 171.4 (C), 173.0 (C) ppm. IR (KBr): ν_{max} 3064(m), 2953(s), 2855(s), 1620(s), 1579(s), 1467(s), 1440(s), 1344(s), 1294(m), 1042(m), 981(m), 987(m), 799(s), 742(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{10}H_{10}Cl_2N_2H$ 229.0294, found 229.0294

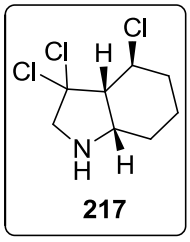
*3,3-Dichloro-4-(chloromethyl)-2-spirocyclohexyl-pyrrolidine **214**:*



214

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.2-1.91 [m, 11H, (10 H, 5CH_2 and 1H, NH, D_2O-exchangeable)], 2.88 (dd, 1H, *J* = 12.0, 8.4 Hz, NCH_2), 3.08-3.15 (m, 1H, methine CH), 3.32 (dd, 1H, *J* = 12.0, 9.0 Hz, NCH_2), 3.74 (t, 1H, *J* = 10.4 Hz, CH_2Cl), 4.03 (dd, 1H, *J* = 10.4, 3.9 Hz, CH_2Cl) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.2 (CH_2), 22.7 (CH_2), 25.7 (CH_2), 31.2 (CH_2), 44.1 (CH_2), 47.0 (CH_2), 54.4 (CH), 71.0 (C), 101.2 (C) ppm; IR (KBr): ν_{max} 3337(m, br), 2933(s), 2857(s), 1425(s), 1360(m), 1291(m), 1053(s), 905(m), 828(s), 787(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{10}H_{17}Cl_3NH$ 256.0421, found 256.0421.

*3,3,4-trichloro-octahydro-1H-indole **217**:*

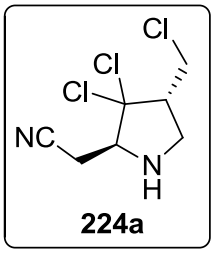


217

Colorless solid, mp 60 ˚C (*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33–1.47 (m, 1H, CH_2), 1.62 (pent, 2H, *J* = 6.6 Hz, CH_2), 172-1.84 (m, 2H, CH_2), 2.05 (br, s, 1H, NH, D_2O-exchangeable), 2.11-2.21 (m, 1H, CH_2)], 2.80 (t, 1H, *J* = 7.5 Hz, C<u>H</u>CCl_2), 3.41 (d, 1H, *J* = 13.2 Hz, NCH_2), 3.53 (d, 1H, *J* = 13.2 Hz, NCH_2), 3.58-3.68 (m, 1H, NCH), 4.37 (q, 1H, *J* = 6.2 Hz, CHCl) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.2 (CH_2), 28.2 (CH_2), 32.5 (CH_2), 56.2 (CH), 56.3 (CH), 60.5 (CH), 65.2 (CH_2), 90.7 (C) ppm; IR (KBr): ν_{max} 3295(s, br), 2939(s), 2870(s),

1656(m), 1447(s), 1367(m), 1265(m), 1084(m), 914(s), 839(s), 763(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_8H_{12}Cl_3NH$ 228.0108, found 228.0108.

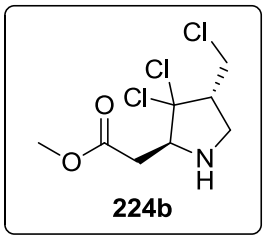
2-(3,3-Dichloro-4-(chloromethyl)pyrrolidin-2-yl)acetonitrile ***224a***:



224a

Light yellow liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.20 (s, br, 1H, NH, D_2O-exchangeable), 2.63 (dd, 1H, *J* = 16.8, 8.4 Hz, CH_2CN), 2.85 (dd, 1H, *J* = 16.8, 4.5 Hz, CH_2CN), [3.01-3.11{m, 2H, (1H, C<u>H</u>CH_2 and 1H, NCH_2)}], 3.53 (dd, 1H, *J* = 14.4, 10.8 Hz, NCH_2 overlapped with dd at δ 3.60), 3.60 (dd, 1H, *J* = 11.1, 8.4 Hz, CH_2Cl), 3.81 (dd, 1H, *J* = 8.4, 4.5 Hz, NCH), 3.91 (dd, 1H, *J* = 11.1, 3.9 Hz, CH_2Cl) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.6 (CH_2), 43.1 (CH_2), 48.4 (CH_2), 55.0 (CH), 68.6 (CH), 92.6 (C), 117.0 (C) ppm; IR (KBr): ν_{max} 3358 (s, br), 2961(s), 2253(s), 1633(w), 1441(s), 1415(s), 1263(m), 1215(m), 990(m), 924(s), 796(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_7H_9Cl_3N_2Na$ 248.9729, found 248.9724.

Methyl 2-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)acetate ***224b****:*

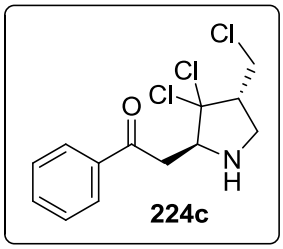


224b

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.99 (s, br, 1H, NH, D_2O-exchangeable), 2.51 (dd, 1H, *J* = 15.9, 9.3 Hz, $COCH_2$), 2.89 (dd, 1H, *J* = 15.9, 3.0 Hz, $COCH_2$), [2.97-3.08 {m, 2H, (1H, NCH_2 and 1H, C<u>H</u>CH_2}], [3.42-3.54 {m, 2H, (1H, CH_2N + 1H, CH_2Cl)}], 3.72 (s, 3H, OCH_3), 3.80 (dd, 1H, *J* = 9.3, 2.7 Hz, NCH), 3.92 (dd, 1H, *J* = 11.4, 3.3 Hz, CH_2Cl) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.2 (CH_2), 44.2 (CH_2), 48.7 (CH_2), 52.1 (CH), 55.6 (CH_3), 68.6 (CH), 93.9 (C), 171.3 (C) ppm; IR (KBr): ν_{max} 3355(m, br), 2954(s), 1738(s), 1601(m), 1440(s), 1376(m), 1300(s), 1263(s), 1198(s), 1027(s), 903(m),

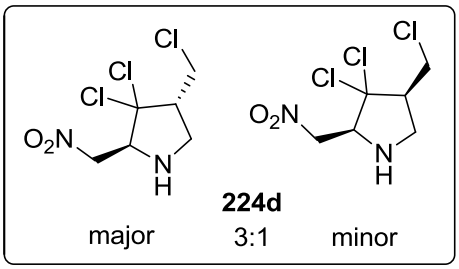
806(s) cm^{-1} ; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_8H_{12}Cl_3NO_2Na$ 281.9832, found 281.9826.

2-(3,3-Dichloro-4-(chloromethyl)pyrrolidin-2-yl)-1-phenylethanone ***224c****:*



Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.24 (s, br, 1H, NH, D_2O-exchangeable), 2.92 (d, 1H, *J* = 10.5 ,9.6 Hz, $COCH_2$), 3.07-3.13 (m, 1H, C<u>H</u>CH_2), 3.20-3.32 (m, 1H, $COCH_2$), 3.48-3.60 (m, 2H, NCH_2)], 3.68 (t, 1H, *J* = 10.4 Hz, CH_2Cl), 4.01 (dd, 1H, *J* = 11.1, 4.2 Hz, CHCl), 4.11 (dd, 1H , *J* = 9.6, 1.8 Hz, CHN), 7.49 (t, 2H, *J* = 7.5 Hz, aryl CH), 7.60 (t, 1H, *J* = 7.5 Hz, aryl CH), 8.00 (d, 2H, *J* = 7.2 Hz, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.3 (CH_2), 42.4 (CH_2), 47.9 (CH_2), 56.1 (CH), 67.7 (CH), 93.2 (C), 128.1 (CH), 128.2 (CH), 133.5 (CH), 136.3 (C), 197.3 (C) ppm; IR (KBr): ν_{max} 3326 (m, br), 2924(s), 2854(s), 1682(s), 1627(s), 1580(s), 1398(s), 1283(s), 1072(s), 1005(m), 827(s), 756(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{13}H_{14}Cl_3NONa$ 328.0038, found 328.0033.

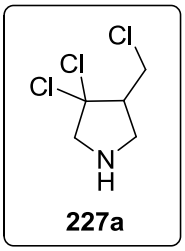
3,3-Dichloro-4-(chloromethyl)-2-(nitromethyl)pyrrolidine ***224d****:*



Reddish liquid; mixture of diastereomers (3:1); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.08 (s, br, 1H, NH, D_2O-exchangeable), 2.97-3.13 [m, 2H, (1H, C<u>H</u>CH_2 and 1H, NCH_2)}], 3.49-3.68 (m, 2H, (1H, NCH_2 and 1H, CH_2Cl), 3.95 (m, 1H, CH_2Cl), 4.29-4.47 (m, 1H, NCH), [4.38-4.46 (m)(minor isomer, overlapped with multiplet at δ 4.29-4.47) + 4.56 (dd, 1H, *J* = 13.5, 9.3 Hz)(major isomer), 1H, CH_2NO_2)], [4.82 (d, *J* = 12.9 Hz)(minor isomer) + 4.88 (d, *J* = 14.4 Hz)(major isomer), 1H, CH_2NO_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 41.5 (CH_2), 42.8 (CH_2), 48.1

(CH_2), 48.3 (CH_2), 55.3 (CH), 56.4 (CH), 68.7 (CH), 69.2 (CH), 76.1 (CH_2), 77.1 (CH_2), 90.1 (C), 90.9 (C) ppm; IR (KBr): ν_{max} 3367 (m, br), 2923(m), 1558(s), 1421(m), 1377(s), 921(s), 832(s), 764(m) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_6H_9Cl_3N_2O_2H$ 246.9794, found 246.9806.

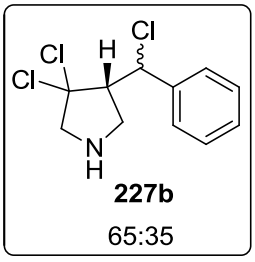
*3,3-Dichloro-4-(chloromethyl)pyrrolidine **227a**:*



227a

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.87 (s, br, 1H, NH, D_2O-exchangeable), 2.81-2.97 [m, 2H, (1H, C<u>H</u>CH_2 and 1H NC<u>H_2</u>CH)], 3.38-3.56 [m, 4H, (1H, CH_2Cl, 1H, NC<u>H_2</u>CH and 2H, CH_2CCl_2)], 3.91 (dd, 1H, *J* = 10.8, 4.2 Hz, CH_2Cl) ppm; ^{13}CNMR ($CDCl_3$, 75 MHz): δ 43.0 (CH_2), 49.8 (CH_2), 56.2 (CH), 66.1 (CH_2), 90.6 (C) ppm; IR (KBr): ν_{max} 3280 (m, br), 2957(s), 2878(s), 1657(s), 1439(s), 1260(m), 1082(m), 915(s), 801(s), 739(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_5H_8Cl_3NH$ 187.9798, found 187.9795.

*3, 3-Dichloro-4-(chloro (phenyl) methyl) pyrrolidine **227b**:*

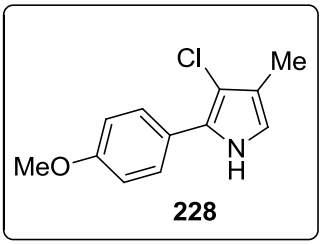


227b
65:35

Colorless liquid, diastereomeric mixture (65:35); ^1H NMR ($CDCl_3$, 300 MHz): δ [1.87 (s, br) and 2.26 (s, br) 1H, NH, D_2O-exchangeable)], 3.17-3.56 [m, br, 5H, (1H, $CHCCl_2$, 2H, 2C<u>H_2</u>CH and 2H, CH_2CCl_2], [5.00 (d, *J* = 10.2 Hz) (minor isomer) + 5.10 (d, *J* = 9 Hz) (major isomer), 1H, CHCl)], 7.30-7.43 (m, 5H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.2 (CH_2), 50.8 (CH_2), 59.5 (CH), 59.7 (CH), 61.6 (CH), 63.6 (CH), 67.4 (CH_2), 67.6 (CH_2), 89.9 (C), 91.1 (C), 127.1 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 128 (CH), 138.9 (C), 139.5 (C) ppm; IR (KBr): ν_{max} 3359(m, br), 2925(s), 1666(s), 1452(s), 1226(m), 1069(m), 921(s), 806(s), 702(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{11}H_{12}Cl_3NH$ 264.0100, found 264.0108.

2.5.3. Dehydrochlorination of the pyrrolidine 209b: Chloro-2-(4-methoxyphenyl)-4-methyl-1H-pyrrole 228

The reaction of 3,3-dichloropyrrolidine to 3-chloropyrrole was performed by following a method reported by this laboratory in which 3,3-dichloro-4-chloromethyl-tetrahydrofurans were aromatized by DBU.[10]



228

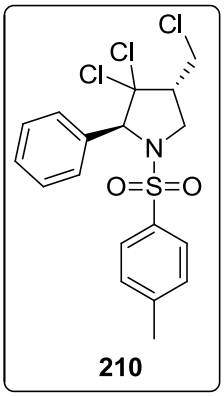
A solution of the chlorinated pyrrolidine **209b** (0.195 g, 1mmol) and DBU (0.38 mL, 2.5 mmol) in dry benzene (30 mL) was heated at reflux. After completion of the reaction as indicated by disappearance of the starting material **209b** on TLC monitoring (24 h), ethyl acetate (100 mL) was added to the reaction mixture. The solution was washed successively with saturated solution of NH_4Cl (2x20 mL) and with brine (20 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to obtain the crude product. The purification of the crude product by column chromatography on a neutral alumina column using a mixture of ethyl acetate in *n*-hexane (10-20%, v:v) as the mobile phase gave the pure product **228** (0.103 g, 46%) as a yellow solid, mp 89˚C (*n*-hexane: DCM), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s. 3H, CH_3), 3.84 (s, 3H, CH_3), 6.57 (s, 1H, CH), 6.96 (d, 2H, *J* = 8.7 Hz, CH), 7.57 (d, 2H, *J* = 8.7 Hz, CH), 7.97 (br, s, 1H, NH, D_2O-exchangeable) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.9 (CH_3), 55.3 (CH_3), 109.8 (C), 114.2 (CH), 114.6 (C), 118.7 (CH), 124.4 (C), 126.7 (C), 127.3 (CH), 158.5 (C) ppm; IR (KBr): ν_{max} 3363(s, br), 2927(m), 1697(s), 1576(m), 1526(s), 1451(s), 1248(s), 1097(m), 1027(s), 830(s), 723(m) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{12}H_{12}Cl_1N_1OH$ 222.0673, found 222.0680.

2.5.4. Tosylation products 210, 218 and 225 of pyrrolidines 209a, 217 and 224a

These were prepared using a method reported in the literature[88] for tosylation of 2-substituted pyrrolidines.

General method. A mixture of the *N*-H pyrrolidine **209a**, **217** or **224a** (1 mmol), tosyl chloride (0.190 g, 1mmol) and K_2CO_3 (2.073g, 15 mmol) in dry THF was stirred at room temperature (25-30 ˚C). After the disappearance of the starting material as indicated by TLC (12 h for **209a** and **217**, 14 h for **224a**), the reaction mixture was concentrated on a rotavapor and diluted with ethyl acetate. It was washed with brine (2x20 mL), dried (Na_2SO_4) and filtered. The filtrate was evaporated and the crude solid thus obtained was recrystallized from DCM/*n*-hexane to obtain the tosylated products **210** (0.317 g, 76%), **218** (0.313, 81%) and **225** (0.260 g, 68%).

*3,3-Dichloro-4-(chloromethyl)-2-phenyl-1-tosylpyrrolidine **210***:



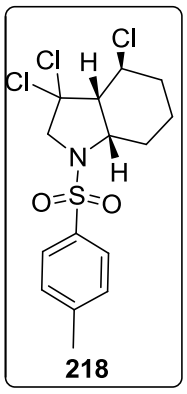
210

Colorless crystals, mp 127 ˚C (DCM:*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.45 (s, 3H, CH_3), 3.06-3.10 (m, 1H, C<u>H</u>CH_2), 3.38 (t, 1H, *J* = 9.9 Hz, NCH_2), 3.59 (t, 1H, *J* = 10.7 Hz, CH_2Cl), 3.83 (dd, 1H, *J* = 11.1, 3.3 Hz, 1H, NCH_2), 4.14 (dd, 1H, *J* = 8.8, 6.9 Hz, CH_2Cl), 5.28 (s, 1H, NCH), 7.28-7.37 (m, 7H, CH), 7.69 (d, 2H, *J* = 8.1 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.6 (CH_3), 40.7 (CH_2), 50.2 (CH_2), 52.7 (CH), 76.6 (CH), 90.9 (C), 127.7 (CH), 128.1 (CH), 128.3 (CH), 129.0 (CH), 129.6 (CH), 134.1 (C), 137.3 (C), 144.1 (C) ppm; IR (KBr): ν_{max} 3037(w), 2925(m), 1752(s), 1449(m), 1353(s), 1211(m), 1164(s), 1103(m), 1026(s), 756(m), 693(m) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{18}H_{18}Cl_3NO_2SNa$ 440.0030, found 440.0016.

X-ray crystal structure data of 210

Formula sum: $C_{18}H_{18}Cl_3NO_2S$, Formula weight: 418.75 g/mol; Crystal system: triclinic; Space group: P -1 (2); Unit cell dimensions: a = 6.559(2) Å b = 8.176(3) Å c = 18.176(6) Å α = 83.005(6)° β = 86.387(7)° γ = 87.751(7)°; Cell volume = 965.04(50) Å^3, Z = 2; Density calculated = 1.44099 g/cm^3; R_{All} = 0.094. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989262).

3,3,4-Trichloro-1-tosyloctahydro-1H-indole ***218****:*



218

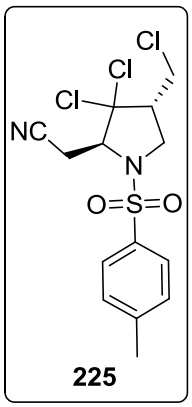
White crystals, mp 113 ˚C (DCM: *n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.61-2.36 (m, 6H, CH_2), 2.46 (s, 3H, CH_3), 2.74 (dd, 1H, *J* = 8.7, 3.0 Hz, $CHCCl_2$), 3.76 (d, 1H, *J* = 11.4 Hz, CH_2N), 4.0-4.20 (m, 1H, CHN), 4.16 (d, 1H, *J* = 11.4 Hz , NCH_2), 4.52 (q, 1H, *J* = 3.9, CHCl), 7.36 (d, 2H, *J* = 8.1 Hz, CH), 7.30 (d, 2H, *J* = 8.1 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): 17.3 (CH_2), 21.6 (CH_3), 28.9 (CH_2), 31.7 (CH_2), 55.2 (CH), 56.9 (CH), 59.3 (CH), 65.5 (CH_2), 85.0 (C), 127.5 (CH), 130 (CH), 133.3 (C), 144 (C) ppm; IR (KBr): ν_{max} 2950(s), 1597(m), 1444(s), 1340 (s), 1260(s), 1558(s), 1121(s), 1064(s), 1030(s), 842(s), 812(s), 693(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{15}H_{18}Cl_3NO_2SNa$ 404.0017, found 404.0016.

X-ray crystal structure data of 218

Formula sum: $C_{15}H_{18}Cl_3NO_2S$, Formula weight: 110.54 g/mol; Crystal system: monoclinic; Space group: P 1 21/c 1 (14); Unit cell dimensions: a = 12.881(4) Å b = 12.035(4) Å c = 12.685(4) Å, α = 90.00(0)°, β = 118.539(6)°, γ = 90.00(0)°; Cell volume = 1727.52(90) Å^3, Z = 17; Density calculated = 1.80621 g/cm^3; R_{All} = 0.2262. Detailed X-ray crystallographic

data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989286).

*2-(3,3-Dichloro-4-(chloromethyl)-1-tosylpyrrolidin-2-yl)acetonitrile **225**:*



225

White crystals, mp 78 ˚C (DCM: *n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.45 (s, 3H, CH_3), [3.02-3.13 {m, 3H, (1H, C̲HCH$_2$ and 2H, CH_2CN) overlapped signals}], 3.37-3.44 (m, 1H, CH_2N), 3.49 (t, 1H, *J* = 10.4 Hz, CH_2Cl), 3.85 (dd, 1H, *J* = 10.8, 3.3 Hz, CH_2N), 4.05 (dd, 1H, *J* = 9.3, 6.9 Hz, CH_2Cl), 4.34 (dd, 1H, *J* = 5.7, 3.0 Hz , NCH), 7.36 (d, 2H, *J* = 8.1 Hz, CH), 7.30 (d, 2H, *J* = 8.1 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): 21.6 (CH_3), 24.9 (CH_2), 40.1 (CH_2), 50.1 (CH_2), 53.3 (CH), 70.5 (CH), 89.2 (C), 116.2 (C), 127.9 (CH), 130.0 (CH), 131.9 (C), 145.0 (C) ppm; IR (KBr): ν_{max} 2972(m), 2254(C), 1596(m), 1413(m), 1340 (s), 1260(s), 1350(s), 1166(s), 1101(s), 1014(m), 933(m), 842(s), 740(m), (s), 662(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{14}H_{15}Cl_3N_2O_2SNa$ 402.9798, found 402.9812.

X-ray crystal structure data of 225

Formula sum: $C_{14}H_{15}Cl_3N_2O_2S$, Formula weight: 110.54 g/mol; Crystal system: monoclinic; Space group: P 1 21/c 1 (14); Unit cell dimensions: a = 8.656(5) Å b = 6.640(9) Å c = 12.436(6) Å, α = 90.00(0) °, β = 95.015(10) °, γ = 90.00(0) °; Cell volume = 1784.37(160) Å^3, Z = 17; Density calculated = 1.74866 g/cm^3; R_{All} = 0.0836. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989264).

Chapter 3

Synthesis of chlorinated and functionalized tetrahydrothiophenes by Cu (I)-promoted 5-*exo* halogen atom transfer radical cyclization of 2,2,2-trichloroethyl allyl sulphides

3.1. Introduction

Tetrahydrothiophenes (herein after referred to as THTs) have attracted considerable attention because of their widespread occurrence[98] in natural products which display a broad range of biological[99] and medicinal[100] activities. For example, the essential coenzyme biotin **229** (**Fig. 13**) is a water-soluble vitamin[98a-c] and salacinol **230** [98d-f] and kotalanol **231**[98g] are α-glucosidase inhibitors which were isolated from several *salacia* plant species.

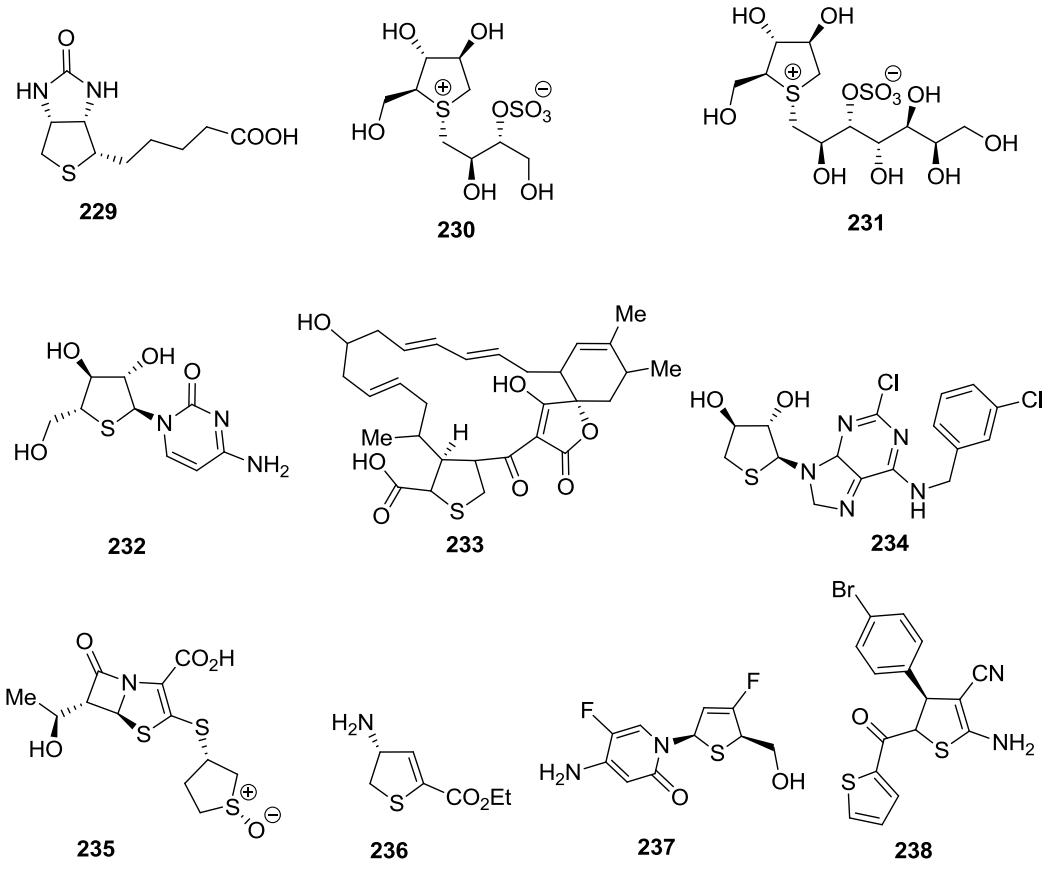


Fig. 13 Some naturally occurring and pharmaceutically important tetrahydrothiophenes

Many synthetic THTs show interesting biological activities[99] such as leukotriene antagonism,[99a] antioxidant activities,[99b] inhibition of copper amine oxidases,[99c] and plant growth regulation.[99d] They also constitute important pharmaceuticals.[100] For example, 4′-thioadenosine derivative **232** (**Fig**. **13**) is a highly potent and selective A3 adenosine receptor antagonist,[100a] the 4′-thiocytidine nucleoside **233** is active against HSV-1 and HSV-2,[100b] the tetronothiodin **234**[100c] is a cholecystokinin type-B receptor antagonist and the Sulopenem **235** is a potent antibacterial.[100d]

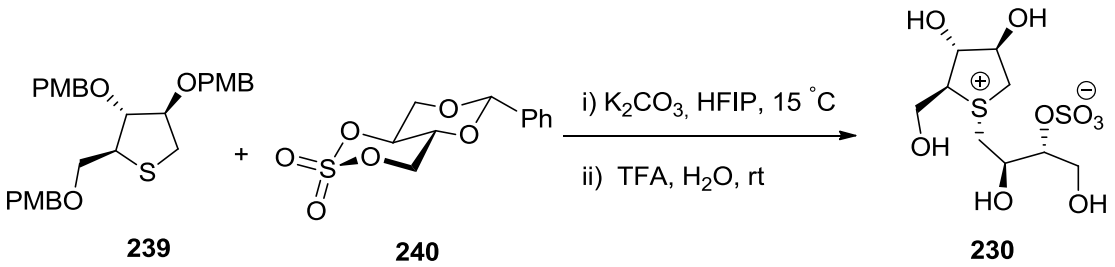
The dihydrothiophene ring is also present in many bioactive compounds and show medicinal properties.[101] (S)-Ethyl 4-amino-4,5-dihydrothiophene-2-carboxylate **236** (**Fig. 13**) inhibits copper amine oxidases (CAOs),[101a] the synthetic L-nucleoside **237** displays potent anti-HIV activity without significant toxicity[101b] and 4,5-dihydrothiophene-3-carbonitrile **238** exhibits antibacterial and antifungal properties.[101c]

A variety of chiral acyclic molecules,[102] aromatic thiophenes[103] and natural products[98d-f] have been prepared by using the nucleus of synthetic tetrahydrothiophenes, its substituents and functional groups by their chemical transformations. Many synthetic THTs act as building blocks for new chiral ligands in asymmetric metal catalysis,[104] organocatalysis[105] and self-assembled monolayer (SAMs).[106] Similarly, THTs or their sulfoxide or sulfonium analogues, have been prepared as mimics of natural and synthetic ligands for pharmacologically important targets.[107] Therefore, synthesis of highly substituted and functionalized THTs continues to receive unabated attention.[108] Here under, the synthetic importance and preparative methods of some halogenated and functionalized THTs with relevance to the present work will be illustrated briefly with the help of some recent examples.

3.1.1. Synthetic importance of sulphur atom of the tetrahydrothiophene ring and synthesis of tetrahydrothiophenes from chlorinated acyclic precursors

The sulphur atom of the tetrahydrothiophene nucleus is valuable centre for chemical transformations to produce natural products, chiral molecules and drugs. Many of these molecules containing THT ring have been prepared using chlorinated substrates.

Mohan and Pinto[109] reported a synthesis of the natural product salacinol **230** (**Scheme 83**) by forming a sulphonium salt of the substituted THT **230**. The *p*-methoxybenzyl-protected derivative **239** and the enantiopure cyclic sulfate **240** in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) reacted via regioselective S-alkylation and the product thus obtained on subsequent removal of the protecting groups furnished the salacinol **230** in 75 % overall yield.

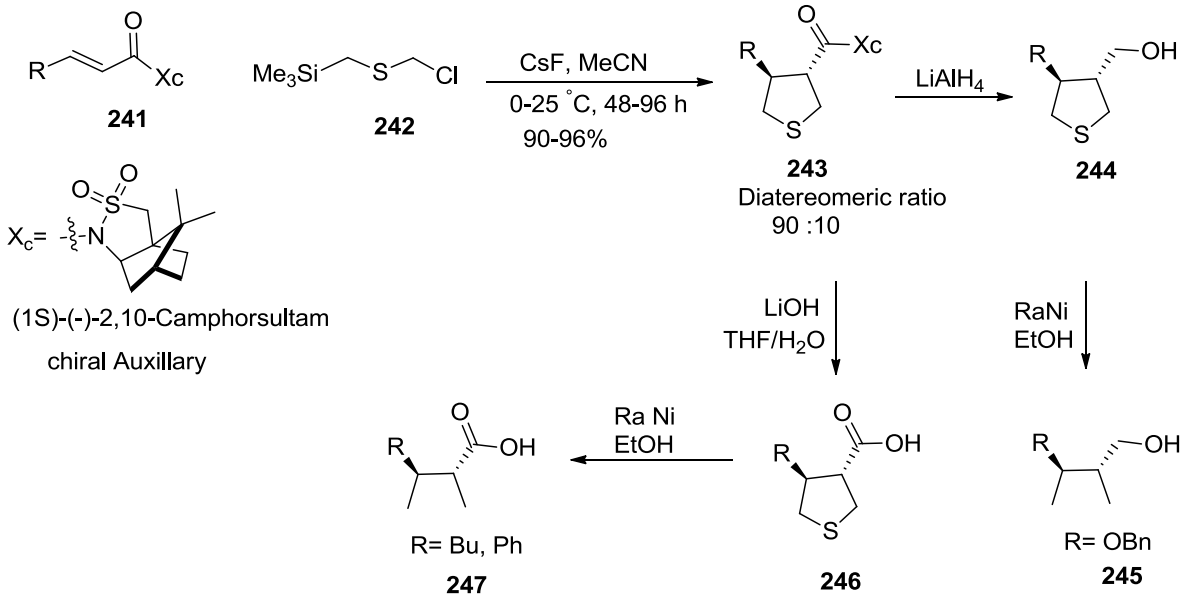


239 **240** **230**

Scheme 83

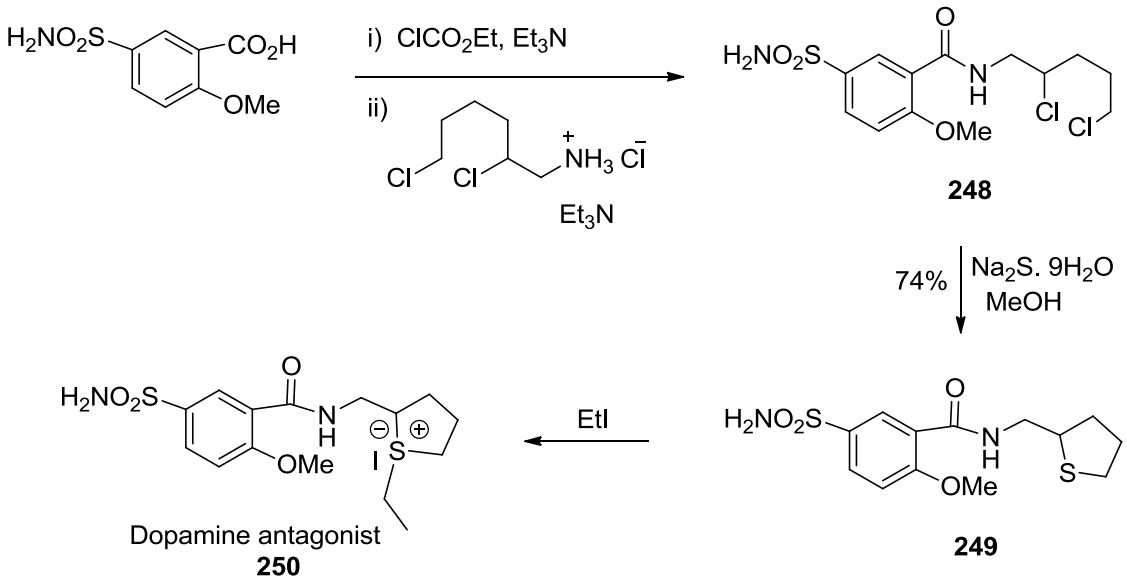
Hogberg and coworkers[110] employed Raney Ni-catalyzed desulphurization of functionalized THTs in the synthesis of the enantiomerically pure alcohols **245** or carboxylic acids **247** (**Scheme 84**). The α,*β*-Unsaturated camphorsultam amides **241** and the 1,3-dipole precursor **242** underwent asymmetric 1,3-dipolar cycloaddition in the

presence of CsF to furnish the *trans*-3,4-disubstituted tetrahydrothiophenes **243** in high diastereomeric ratios (up to 90:10) and high yields. Chromatographic removal of the minor *cis* diastereomer followed by reduction and cleavage of the chiral auxiliary of the major diastereomer **243** furnished **244** and **246**, respectively. The desulphurization of these functionalized THTs afforded enantiomerically pure **245** and **247**.



Scheme 84

Tetrahydrothiophene ring is generally constructed by condensation of 1,4-halobutanes with sodium sulphide. For example, Millar and coworkers[111] synthesized the functionalized THT **249** (**Scheme 85**) by treatment of the dichloro benzamide **248** with 5 fold excess of sodium sulfide nonahydrate which resulted in the formation of the **249**. Treatment of **249** with iodoethane furnished the dopamine antagonist tetrahydrothiophenium iodide **250**.

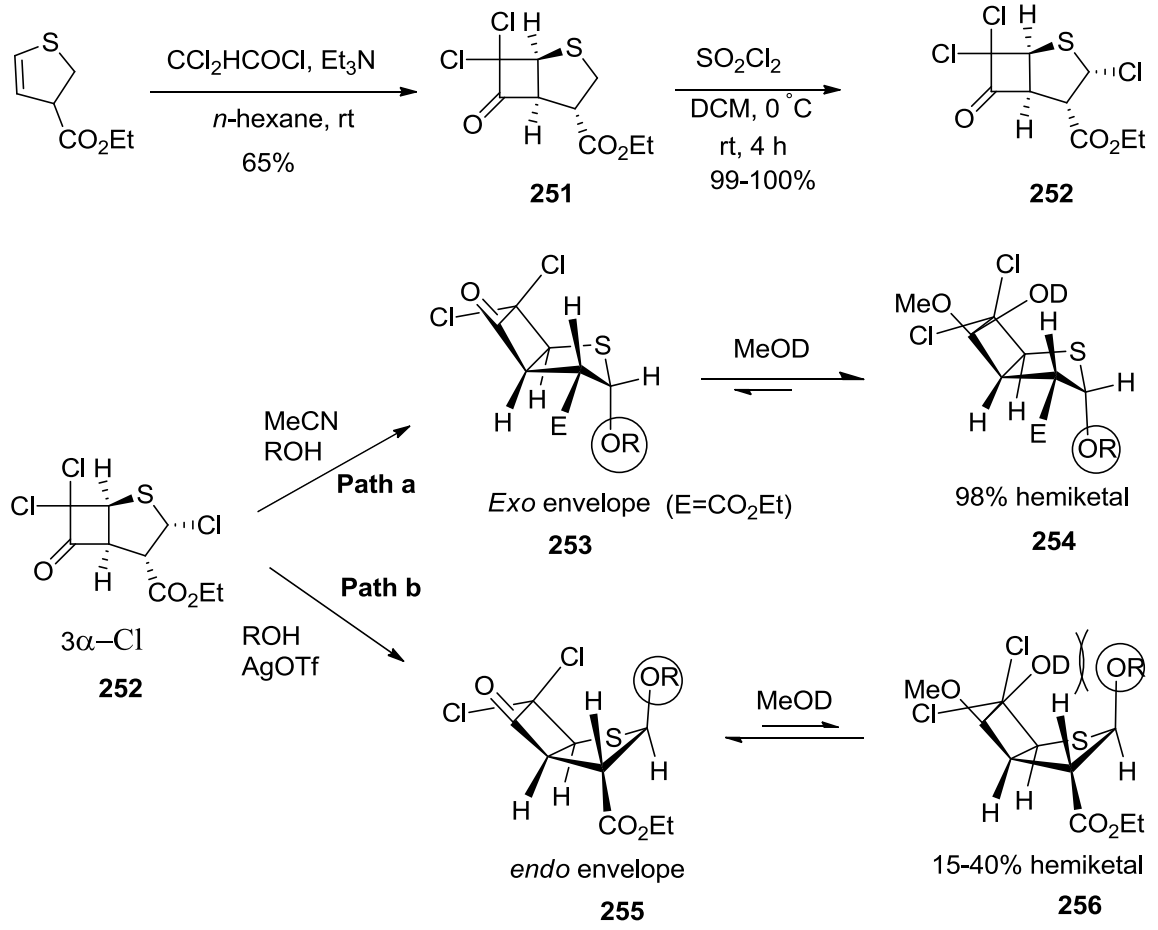


Scheme 85

3.1.2. Synthetic application and methods of preparation of halogenated tetrahydrothiophenes

Dmitrienko and coworkers[62a] synthesized the chlorinated fused tetrahydrothiophene **252** (**Scheme 86**) by stereoselective chlorination of the fused tetrahydrothiophene ring **251** with sulfuryl chloride as mimics of naturally occurring penicillin. The chlorinated tetrahydrothiophene **252** was converted to the 2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylates **253** and **255** with alkoxy functionality at C-3 by two complementary diastereoselective substitution reactions (**path a** & **b**). They found the tendency of the carbocyclic analogues of penicillins **253** and **255** to form the hemiketals **254** and **256**, respectively which were central to their ability to function as *β*-lactamase inhibitors. The carbocyclic analogues with 3-β-substituents favored an *endo*-envelope conformation **255** whereas those with 3-α substituents adopted an *exo*-envelope conformation **253.** The

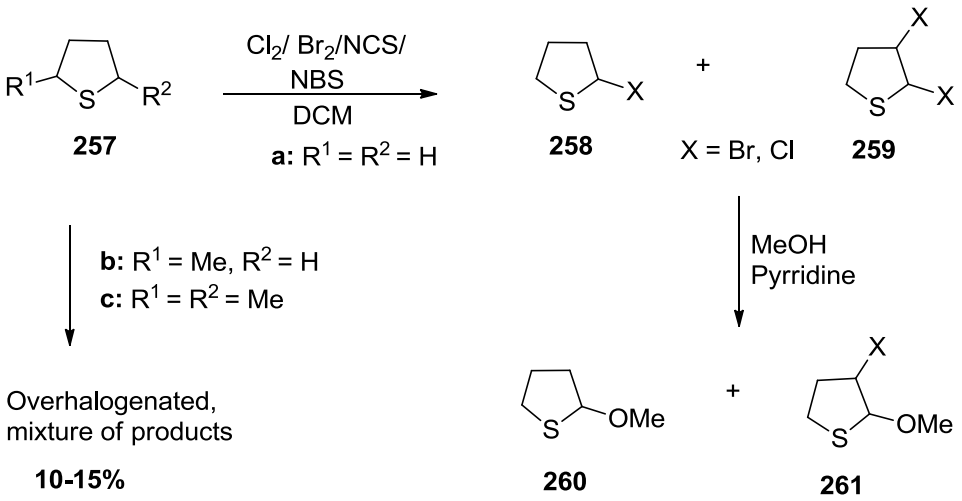
anomeric effect contributed to the large conformational preference favoring axial orientation of the C-3 substituent in **254**.



Scheme 86

A literature survey on the synthesis of chlorinated and brominated THTs revealed that such THTs were prepared mainly via halogenation of existing THTs via Pummerer reaction, using halogenating reagents NCS, PCl_5, SO_2Cl_2, Cl_2, Br_2 etc.[112] However, these methods have their own limitations with regard to yields, the nature of substituent and the substitution pattern. For example, reaction of the unsubstituted tetrahydrothiophenes **257a**

(**Scheme 87**) with molecular chlorine, sulphuryl chloride, phosphorus pentachloride, *N*-chlorosuccininide (NCS) gave unstable 2-chloro and 2,3-dichlorotetrahydrothiophenes **258** and **259**. These products were estimated by their reaction with methanol to give the 2-methoxytetrahydrothiophane **260** and *trans*-3-chloro-2-methoxythiophane **261** in a ratio of 2.4: 1.[112a]

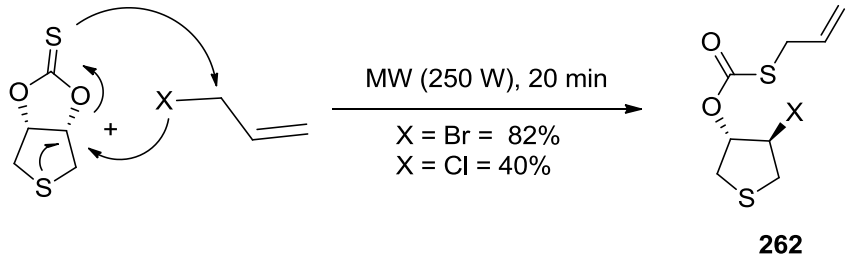


Scheme 87

These halogenation reactions are also affected by solvent and substituents of the THT ring.[112b-c] For the halogenations of the unsubstituted THT **257a** with one equivalent of NCS, more polar the solvent the greater the amount of 2,3-dichloroTHT **259** formed in comparison to 2-chloroTHT **258**. For example, on changing the solvent from benzene to chloroform, the ratio of 2-chloroTHT **258** to 2,3-dichloroTHT **259** changed from 80:20 to 5:95. The formation of **259** also accompanied with the formation of aromatic thiophene derivative as a side product. Reaction of NCS with either 2-methyl or 2,5-dimethyltetrahydrothiophene **257b** or **257c** in DCM led to the formation of 6-7 types of chlorinated products, mostly the dichlorinated products, whatever the polarity of the

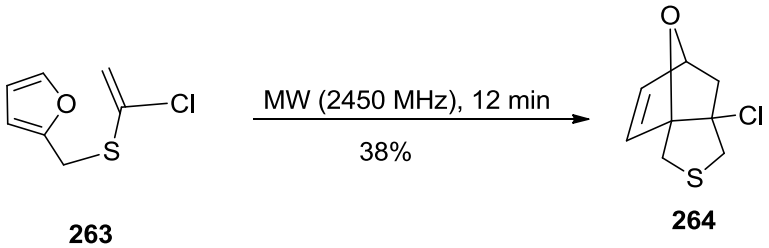
solvent. Distillation of these reaction mixtures gave 3-chloro-2-methyl-4,5-dihydrothiophen and 3-chloro-2,5-dimethyl-4,5-dihydrothiophene in 10-15% yields.

Two examples for the synthesis of β-halo tetrahydrothiophenes via substitution reaction at β-carbon were also found but ring contraction to four member rings was also reported as a side reaction.[113] Benazza et al.[113] reported formation of the β-halotetahydrothiophene **262** (**Scheme 88**) by reaction of 2,3-thiocarbonylthioanhydroerythritol with nearly 25 times excess of allyl halides under microwave irradiation. However, the chloro derivative was obtained in low yield.



Scheme 88

The fused β-chlorotetrahydrothiophene **264** (**Scheme 89**) was prepared by intramolecular furan Diels-Alder reaction of the chlorovinyl thioether **263** on microwave irradiation under solvent-free condition.[114]



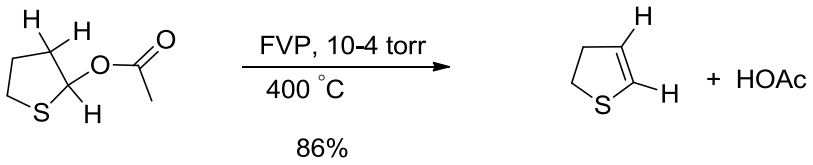
Scheme 89

The synthesis of THTs by substitution reaction of 1.4-dihaloalkanes (**Scheme 83-84)** with sulphides such as NaSH or Na_2S, KSCN, etc, is general, but these reactions are not suitable for the synthesis of halogenated THTs due to the possibility of elimination and/or substitution reactions of the halogenated products.[115]

There are many other routes for the synthesis of variously substituted THTs, such as nucleophilic epoxide and episulfide ring opening[116] (**Scheme 98**), intramolecular cyclization of dithio or monothioacetals,[117] ring contraction and expansion reactions,[104a,118] transition metal (Au, Ti, Cr, Cu, Rh etc.) assisted cyclothiotherification,[119] organocatalytic domino reactions[120] etc. But these methods are also not suitable for the synthesis of halogenated THTs because they used sulphur nucleophiles and/or basic conditions under which the halogen substituent in halogenated THTs might not survive.[121]

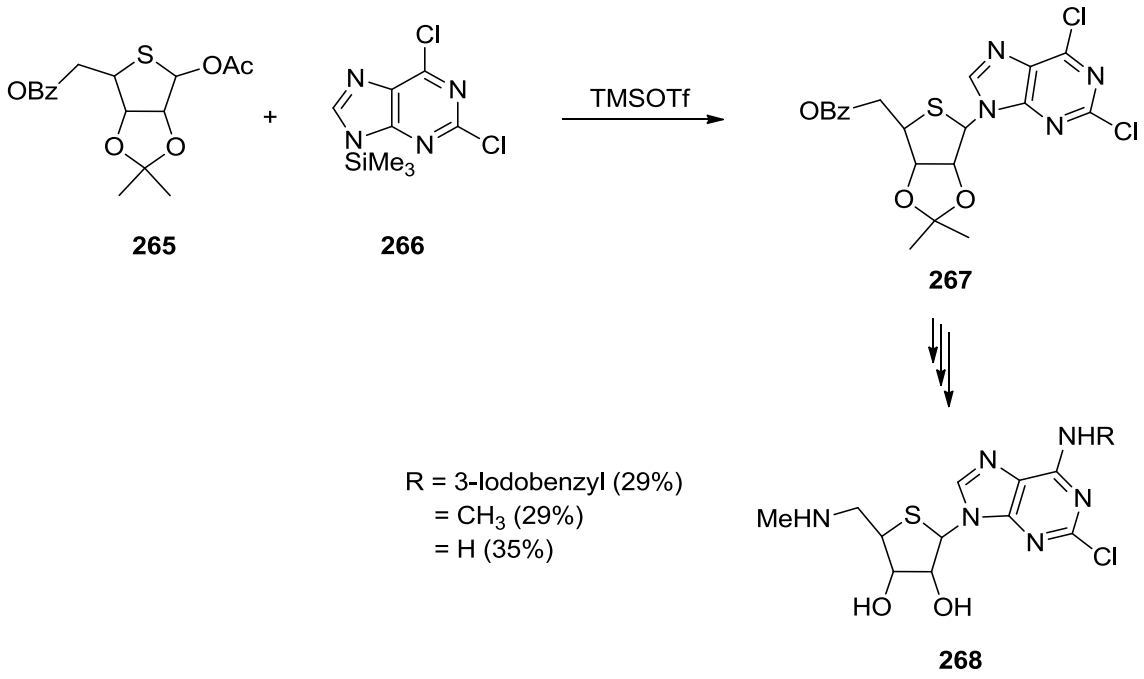
3.1.3. Synthetic applications and methods of preparation of 2-acetoxytetrahydrothiophenes

Trahanovsky and coworkers[122] reported dehydroacetoxylation of simple 2-acetoxy tetrahydrothiophene by flash vacuum pyrolysis (FVP) at 400 ˚C to give the 2,3-dihydrothiophene in high yield (86%) (**Scheme 90**).



Scheme 90

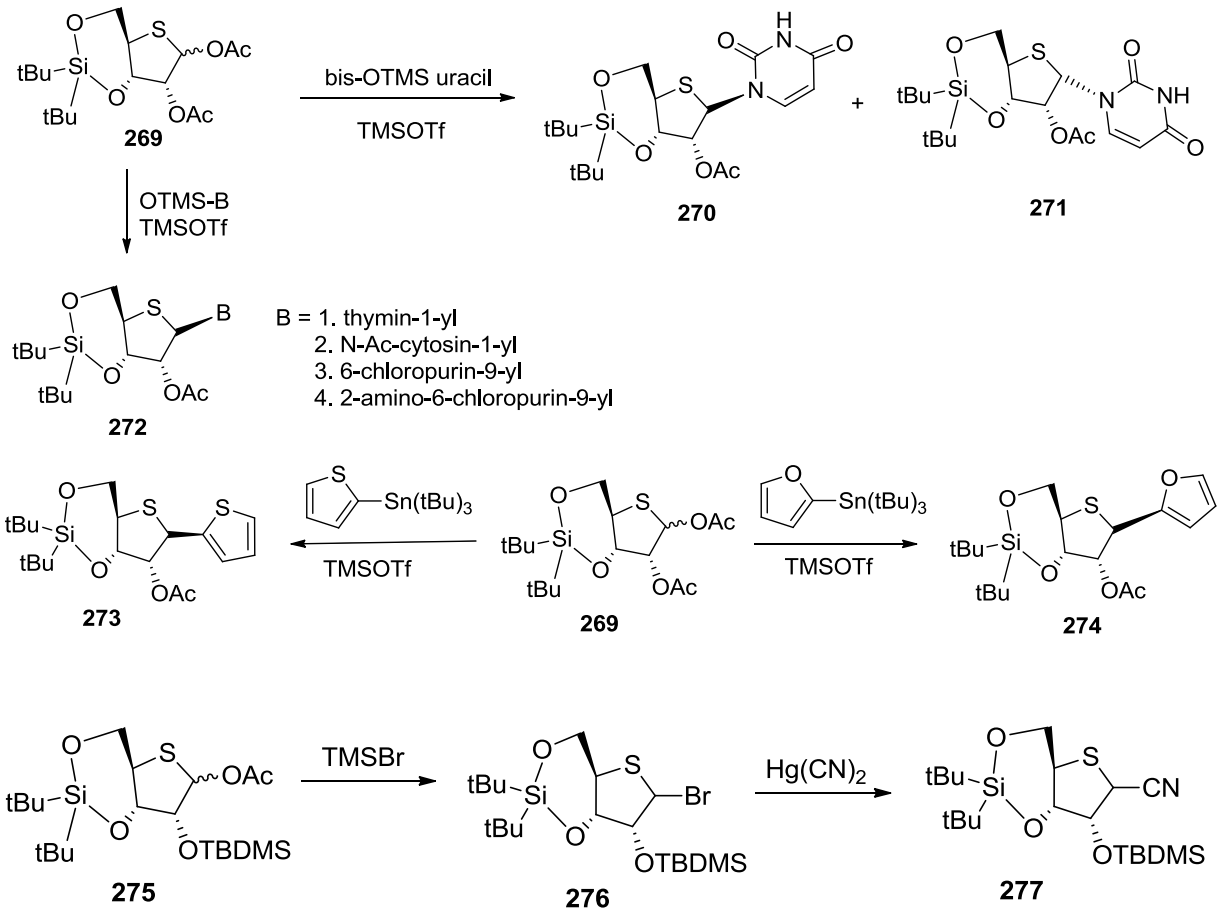
Jeong et al.[123] reported the synthesis of N^6-substituted D-4'-thiodenosine-5'-methyluronamides **268** (**Scheme 91**) as selective agonists of human A_3 adenosine receptors. The acetoxy group of the glycosyl THT **265** was substituted with silylated 2,6-dichloropurine **266** in the presence of TMSOTf to give the 2-chloro N^6-substituted 4'-thiopurine nucleoside **267** as a synthetic intermediate for the desired antagonist **268**.



Scheme 91

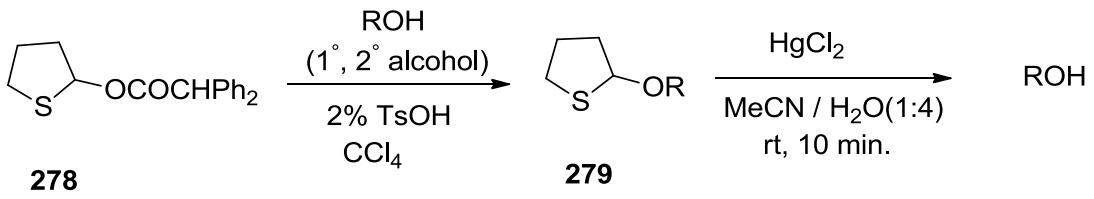
Haraguchi et al.[124] reported an extensive application of α-acetoxy group of highly substituted tetrahydrothiophenes. The thiosugar **269** (**Scheme 92**) was found to be useful glycosyl donor for the synthesis of β-anomers of 4'-thioribonucleosides **270, 271** and **272**. C-Glycosidation of thiosugar **269** proceeded with β-selectivity to furnish the 4'-thio-C-nucleosides **273** and **274**. The 2-acetoxy substituted THT **275** on treatment with TMSBr underwent substitution reaction to give the corresponding bromo derivative **276** which was

further substituted to obtain the cyano derivative **277**, the expected precursor for synthesis of 4'-thiotiazofurin.



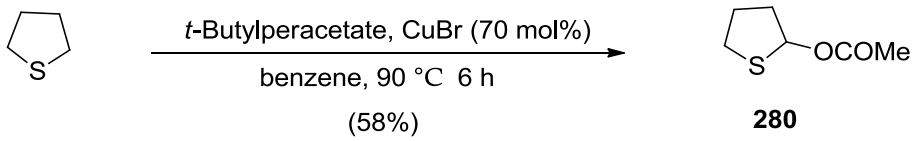
Scheme 92

Van der Gen and coworkers[125] employed 2-acyloxy group of THT **278** (**Scheme 93**) as a protecting group for alcohols. Primary and secondary alcohols were converted to their 2-tetrahydrothienyl ethers **279** by an acid-catalyzed exchange reaction with 2-tetrahydrothienyl diphenylacetate. The THT group was removed with mercuric chloride (1.5 equiv) under mild condition.



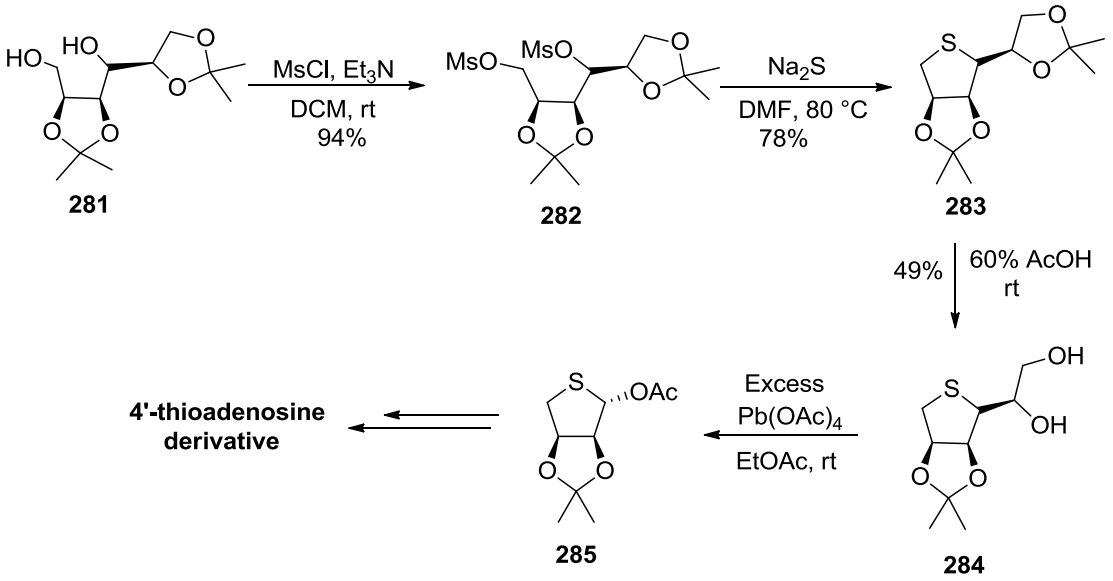
Scheme 93

Thus, the acetoxy group at 2-position of tetrahydrothiophenes is an important substituent used in the preparation of many natural products and synthetic compounds.[126] These 2-acetoxy THTs were prepared from THTs by Pummerer reaction with peracids and acetylation of thiolactols. For example, tetrahydrothiophene (**Scheme 94**) reacted rapidly at 90 ˚C with *t*-butyl peracetate in the presence of cuprous bromide to give the 2-acetoxy tetrahydrothiophene **280** in moderate yeld.[127]



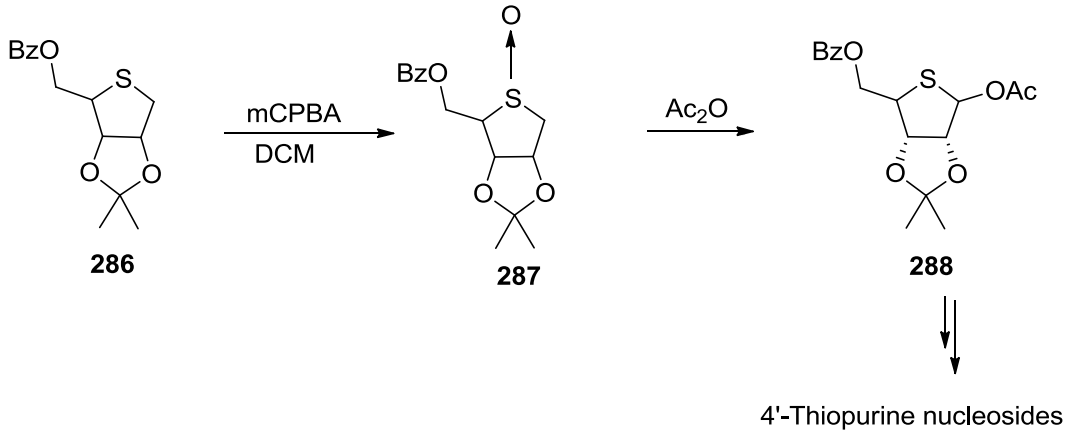
Scheme 94

The 2-acetoxy THT **285** (**Scheme 95**)**,** which has found an application in the synthesis of D-40-thionucleosides, was prepared by a multistep transformation.[128] D-Mannose was converted into the protected diol **281** by standard chemistry. It was mesylated to **282** and cyclized to tetrahydrothiophene **283** in the presence of sodium sulfide. Selective hydrolysis of the 5,6-acetonide residue and oxidative cleavage of the resulting diol **284** gave access to the acetate **285** via successive oxidative diol cleavage, oxidation of the resulting aldehyde to acid and then oxidative decarboxylation of the acid.[129]



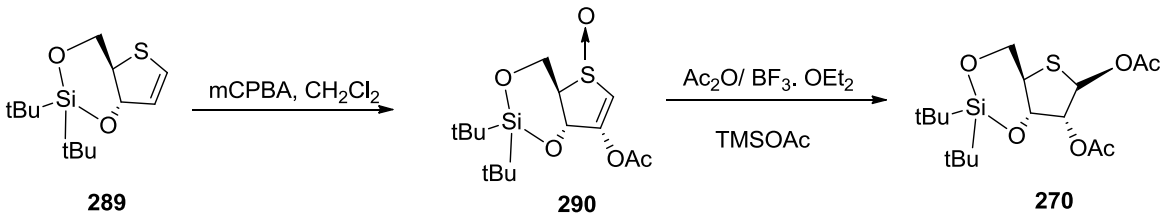
Scheme 95

The 2-acetoxy THT **288** (**Scheme 96**) as glycosyl donor was also prepared by oxidation of benzoate **286** with *m*CPBA followed by heating of the sulfoxide **287** with acetic anhydride. The intermediate **288** was utilized for the synthesis of 2-chloro N^6-substituted 4'-thiopurine nucleosides.[123]



Scheme 96

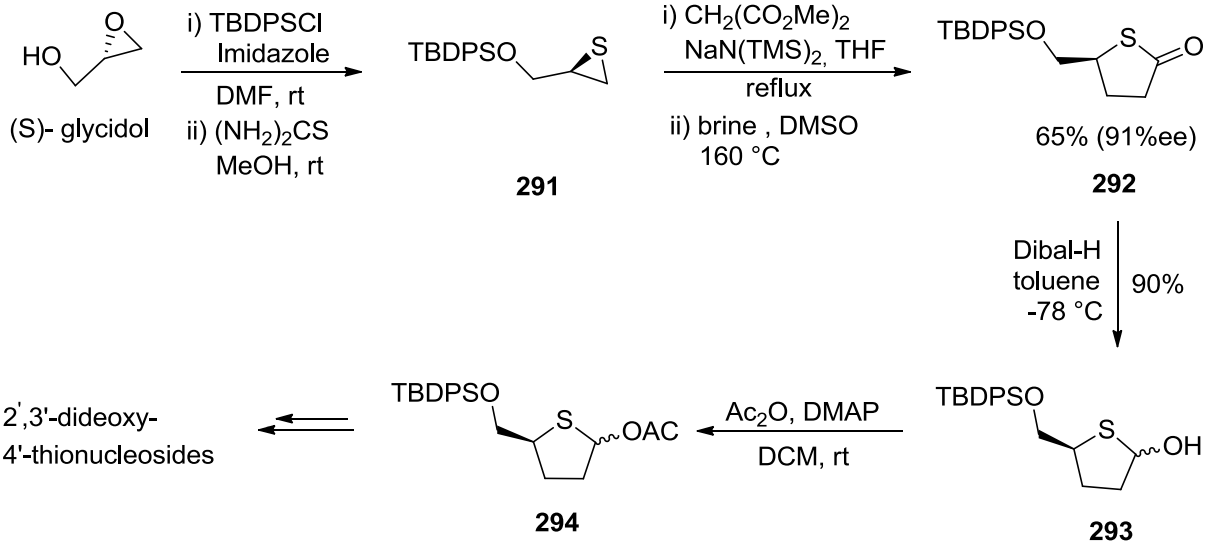
Similarly, Haraguchi et al.[124] reported the oxidation of the dihydrothiophene **289** (**Scheme 97**) with mCPBA followed by additive Pummerer reaction of S-oxide **290** with AC_2O/ $BF_3.OEt_2$/TMSOAc to obtain the 2-acetoxy THT **270** in 62 % yield.



289 290 270

Scheme 97

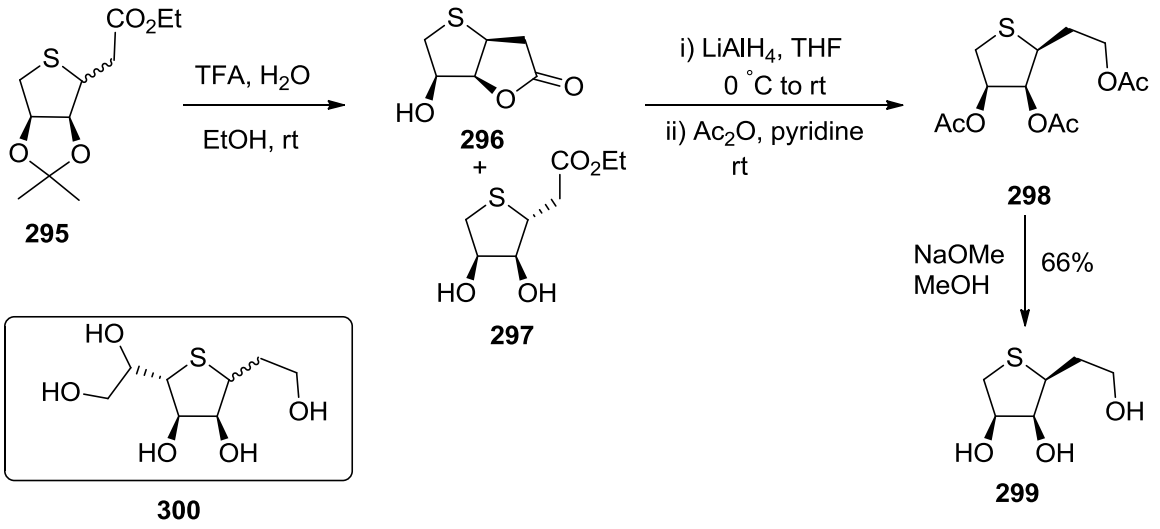
(S)-Glycidol was converted into tert-butyldiphenylsilyl (TBDPS) ether and then treated with thiourea to give the (R)-thiirane **291** (**Scheme 98**). Its reaction with dimethyl malonate anion in refluxing THF followed by Krapcho demethoxycarbonylation provided thiolactone **292.** It was reduced to thiolactol **293** and then acetylated to corresponding thiolactol acetate **294**. The thiolactol acetate **294** was employed as a synthetic precursor to prepare a wide range of 2',3'-dideoxy-4'-thionucleosides and their uridine derivative for antiviral testing.[116]



Scheme 98

3.1.4. Synthetic importance and synthesis of tetrahydrothiophenes having functional groups in side chains

Robina and coworkers[130] reported a synthesis of polyhydroxylated chiral thiolanes **299** (**Scheme 99**) as potential enzyme inhibitors. The side chain functionalized THT mixture **295** on treatment with aqueous trifluoroacetic acid (TFA) furnished lactone **296** along with unprotected thiolane **297**. A two-step reduction-acetylation sequence allowed the conversion of **296** into the triacetate **298** (52% yield), which was eventually transformed into trihydroxylated thiolane **299** on treatment with NaOMe/MeOH.

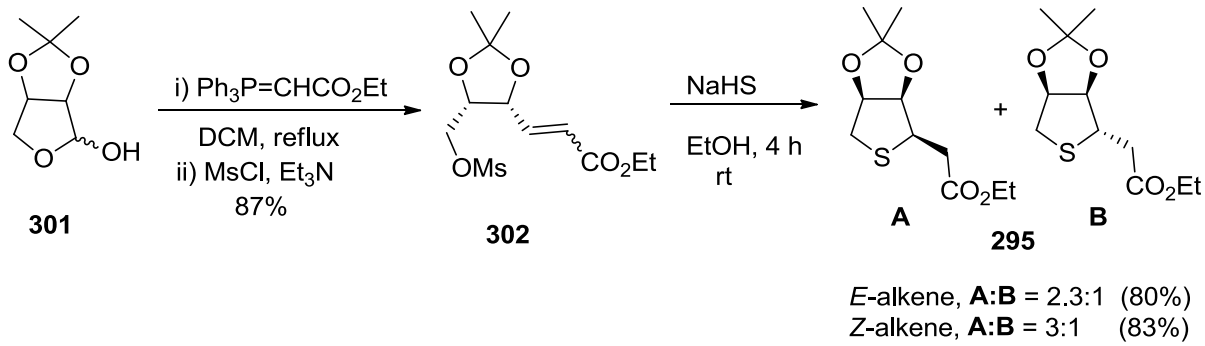


Scheme 99

Similar synthetic sequence was conveniently applied to prepare thiolanes **300** derived from mesitylated 2,3,5,6-di-*O*-isopropylidene-D-mannofuranose.[130]

The precursors **295 (Scheme 100**), were prepared as follows.[130] Wittig reaction of 2,3-*O*-isopropylidene-L-erythrose **301** with (carbethoxymethylene)triphenylphosphorane followed by mesitylation furnished the acyclic precursor **302** as *Z*:*E* mixture. The reaction of the *Z*-alkene with NaSH in dry ethanol gave a mixture of the thiolanes **295A** and **295B**

in 83% yield and in a 3:1 ratio whereas under identical conditions, the *E*-alkene gave the same products in 80% yield and in 2.3:1 ratio.



Scheme 100

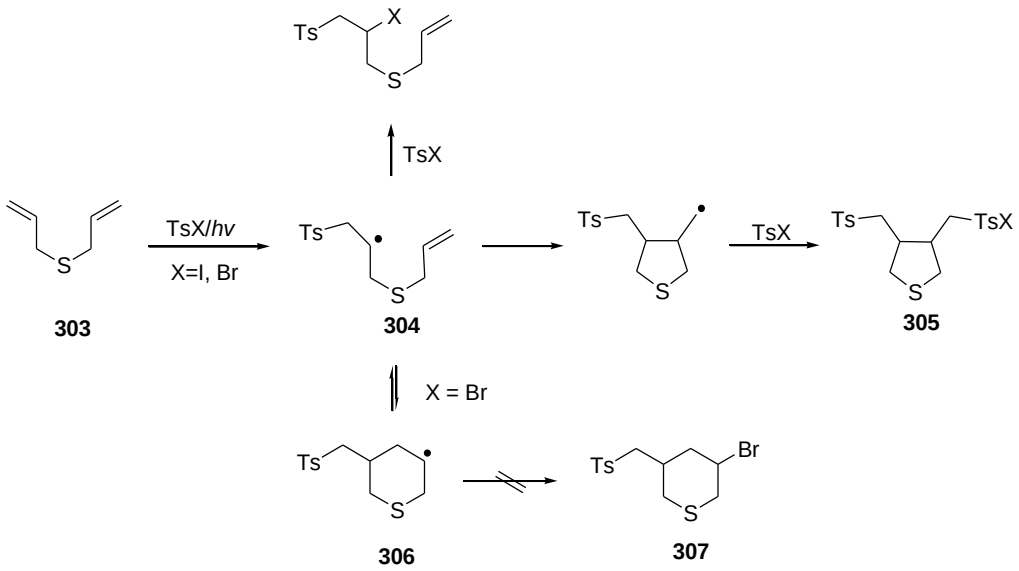
These reactions showed that the acetoxy group in the tetrahydrothiophenes at C-2 and functional group in the side chain also at C-2 position were valuable substituents. No such example containing the halogen atoms was found which could enhance their synthetic utility further, perhaps due to basic nucleophilic reaction conditions and reagents used for their preparation through acyclic routes.

3.1.5. Preparation of tetrahydrothiophenes by radical cyclization

Inspite of realisation of the merits of Cu (I)-catalyzed HATRC, a majority of radical cyclization methods for synthesis of THTs are still carried out by using tributyltin hydride (Bu_3SnH). The C-C bond forming cyclization of sulphides occur through α, β and γ-centred carbon radicals. The cyclization of β and γ-centred radicals have been found to be more regioselective than that of the cyclization of the α-centred radicals.[72,131] These

methods have their own limitations with regard to low yields,[132] regioselectivity,[133] rearrangement,[134] nature of substituents and substitution pattern.[135-136]

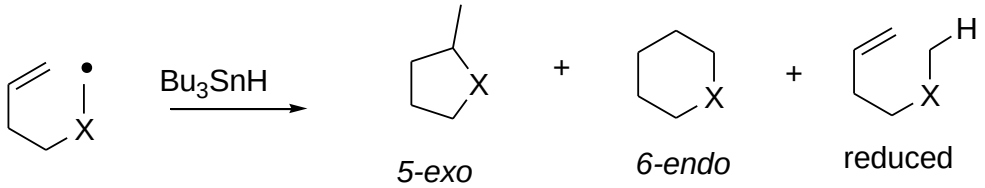
Corrk and coworkers[132] first described the light induced reversible radical additions of tosyl iodide and tosyl bromide to some diallyl sulphides **303** (**Scheme 101**) and observed the cyclization of β-carbon radical **304** to produce **305** in very low yields (11%) along with side addition product.



Scheme 101

The reluctance of the intermediate radical **304** to undergo cyclization could be due to the bigger size of the sulphur as compared to oxygen in which case such cyclizations occur easily. The presence of iodine and bromine in the reaction mixture may also cause complications due to the formation of sulfonium ions. Dell and Graney[133] reported that β-carbon radical **304** was formed reversibly with **306** although the 6-*endo* product **307** was not observed.

Dell and Graney[133] reported irreversible cyclization of α-sulfenyl- α-sulfinyl- and α-sulfonyl-5-hexenyl radicals. They found that α-S-**308a** (**Scheme 102**) and α-SO_2-5-hexenyl radicals **308c** gave measurable quantities of 6-*endo* product **310**. The α-SO-species **308b** cyclized to **309** with high selectivity (95.5:4.5) via a *5-exo* mode along with reduced starting material **311**.



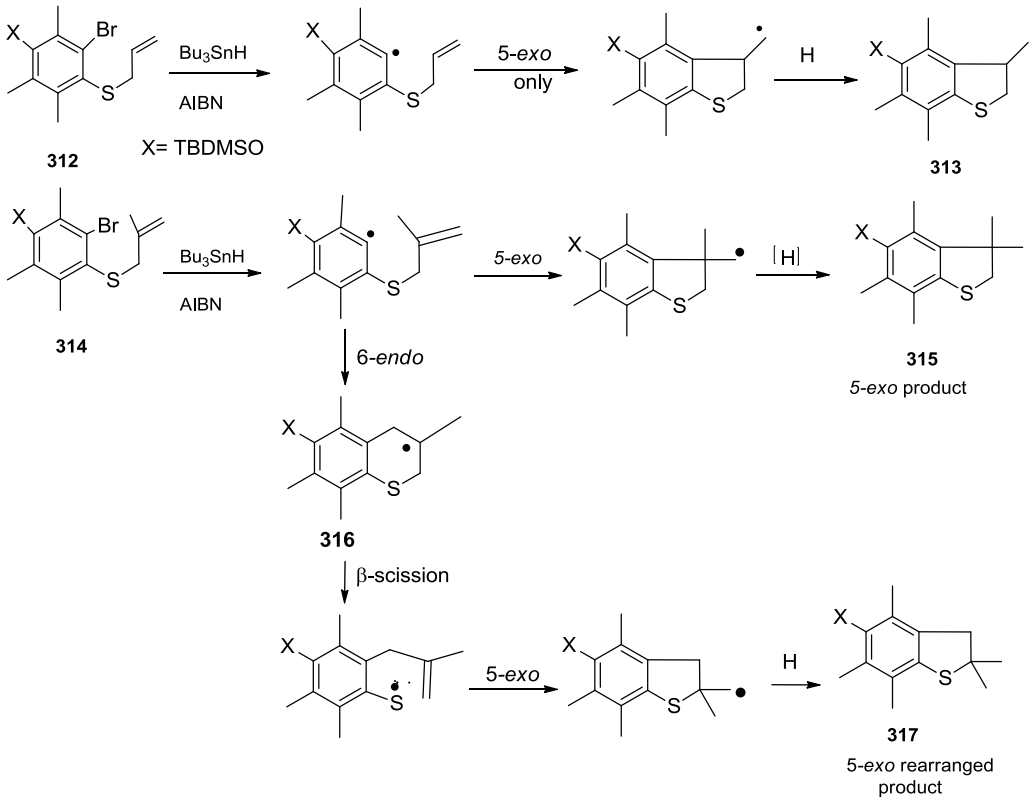
308 **311**

	X	309	310
a:	S	84	16
b:	SO	95.5	4.5
c:	SO_2	76	24

Scheme 102

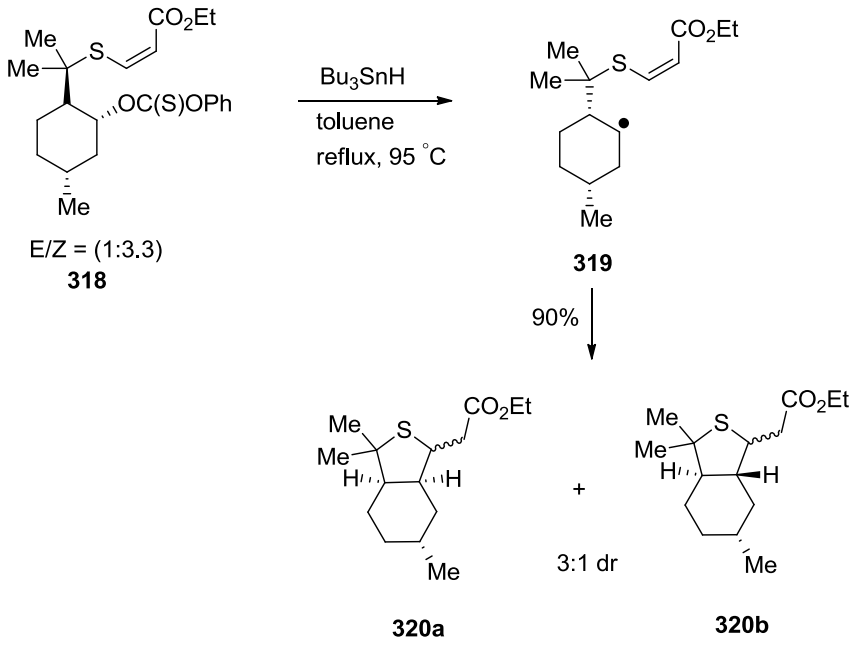
Engman and coworkers[134] demonstrated that substituents present in allylic moiety determined the prefered mode of the two competitive *5-exo* and *6-endo* modes of radical cyclizations. They found that Bu_3SnH/ AIBN mediated reductive radical cyclization of the 2-bromoaryl allyl sulfide **312** (**Scheme 103**), which lacked substituents in the allylic moiety, afforded only 2,3-dihydrobenzo[*b*]thiophene **313** in 55% yield via *5-exo* cyclization uncontaminated by any isomer thereof. However, 2-bromoaryl allyl sulfide **314** containing substituted allyl group, underwent reductive radical cyclization to afford the *5-exo* product dihydrobenzothiophene derivative **315** via 5-*exo* cyclization along with the rearranged isomer **317** via 6-*endo* cyclization in a 3:1 ratio. The formation of the rearranged product **317** could be accounted for by a series of transformations following *6-*

endo cyclization to **316**. The methyl substituent bonded to the radical centre in **316** made the *6-endo* mode of cyclization competitive by stabilizing the radical intermediate.



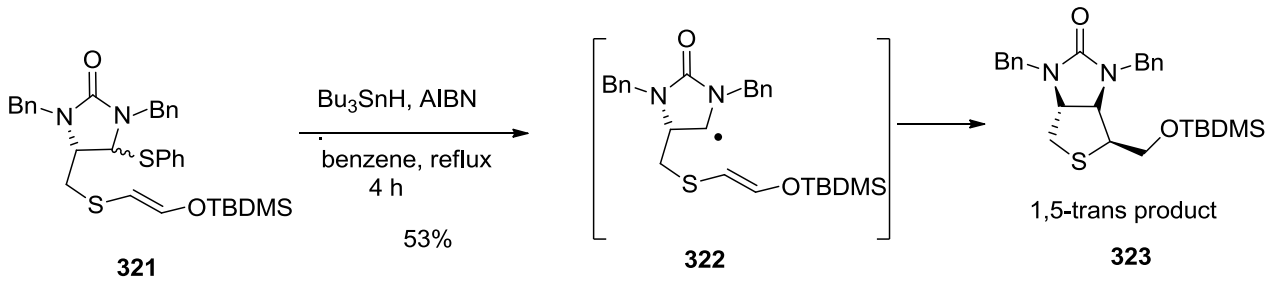
Scheme 103

Bachi and co-workers[135] constructed side chain functionalized thiobicyclic systems **320** (**Scheme 104**) through free radical cyclization of β-thioacrylates **318** prepared from (+)-pulegone in a 1:3.3 E/Z isomeric mixture. Heating the monothiocarbonate **318** in toluene at 95 °C in the presence of Bu_3SnH/AIBN generated the transient γ-radical **219**, which took part in a 5-*exo* ring-closure affording C-9 epimeric 8-thiabicyclo [4.3.0] nonane derivatives **320a** and **320b** in a 3:1 ratio and 90% yield.



Scheme 104

Chavan et al.[136] used naturally available cysteine derived chiral starting material, the silyl enol ether **321** (**Scheme 105**) a key intermediate for setting up the tetrahydrothiophene core of (+)-biotin derivative **323** via 5-*exo* radical cyclization. The enol ether **321** on treatment with Bu_3SnH in the presence of AIBN in refluxing benzene promoted an intramolecular *1,5-exo*-trig cyclization of the transient α-amido radical **322** onto the silyl enol ether moiety and produced exclusively the *trans* product **323** in good yield (53%).



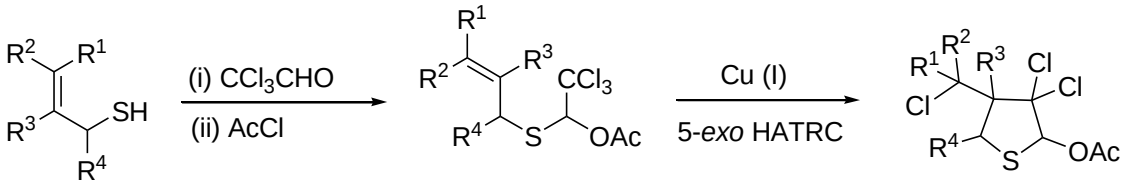
Scheme 105

3.2. Statement of the Problem

From the foregoing, it is clear that inspite of considerable synthetic potential of halogenated, 2-acetoxy and side chain functionalized THTs in the synthesis of natural and synthetic bioactive compounds, very few good methods are available for their synthesis. Halogenated THTs are generally prepared by halogenation of existing THTs, which are non-selective and produce inseparable mixture of products formed as a result of overchlorinations. 2-Acetoxy THTs have been prepared by using Pummerer reaction of THTs or multistep cyclizations of acyclic precursors having a latent acetoxy group to survive through the intervening steps to be generated at the end. Cyclization of acylic precursors having already installed halogen and/or acetoxy substituents with Na_2S is complicated because the halogen and acetoxy substituents may interfere in the reactions. Radical reactions are less sensititve to the nature of substituents including functional groups and other polar effect. However, radical reactions have not been well exploited in the synthesis of halogenated or functionalized THTs. Most of the reported radical reactions for the synthesis of THTs used the reductive Bu_3SnH-mediated cyclizations of unsaturated sulphides. Though these methods have been successful in synthesizing some side chain functionalized THTs, the same has not been reported for the synthesis of halogenated THTs. Moreover, being a reductive method, it does not retain the halogen substituent of the halo-sulphides precursors for further synthetic use. The alternative transition metal-catalyzed HATRC, which retains the useful halogen functionality in the cyclized product, appears to be promising in this regard for the synthesis of halogenated THTs.

However as seen in chapter 1, transition metal-catalyzed HATRC of halo-sulphides has not been reported so far. Therefore, it was considered worthwhile to attempt Cu (I)-

catalyzed HATRC of easily accessible 2,2,2-haloethyl allyl sulphides to synthesize chlorinated and functionalized THTs. The proposed strategy is sketched in **Scheme 106** which also allows installation of a 2-acetoxy group on the THT ring.

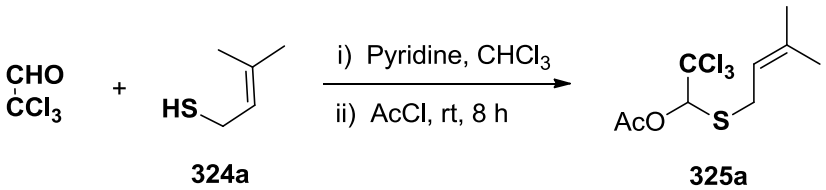


Scheme 106

3.3. Results and discussion

3.3.1. Preparation of 1-acetoxy-2,2,2-trichloroethyl prenyl sulphide 325a

With this idea, an HATRC precursor 1-acetoxy-2,2,2-trichloroethyl prenyl thioether **325a** (**Scheme 107**) was thought to be prepared by extending an efficient method reported in literature[137] for the synthesis of a few structurally similar 1-alkylthio-2,2,2-trichloroethyl carbonates that involved treatment of alkyl mercaptan with anhydrous chloral in the presence of pyridine followed by reaction of the hemithioacetal generated *in situ* with methyl chloroformate. Thus, stirring an equilmolar mixture of prenyl mercaptan **324a,** anhydrous chloral and pyridine in chloroform at 10 ˚C furnished a hemimonothioacetal *in situ* as indicated by ^{1}H NMR. Treatment of the hemimonothioacetal generated *in situ* with acetyl chloride furnished almost pure 1-acetoxy-2,2,2-trichloroethyl prenyl thioether **325a**.



324a **325a**

Scheme 107

It was further purified by silica gel column chromatography to afford the pure product in high isolated yield (82%). The structure of the thioether **325a** was supported by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry.

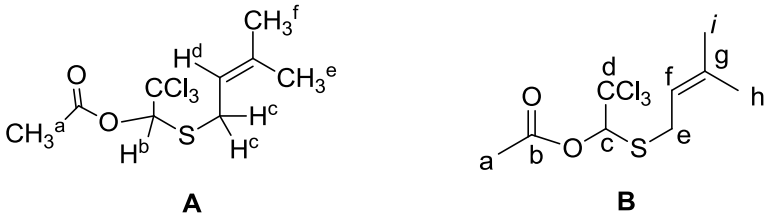


Fig. 14 ^{1}H NMR and ^{13}C NMR assignments for the structure 325a

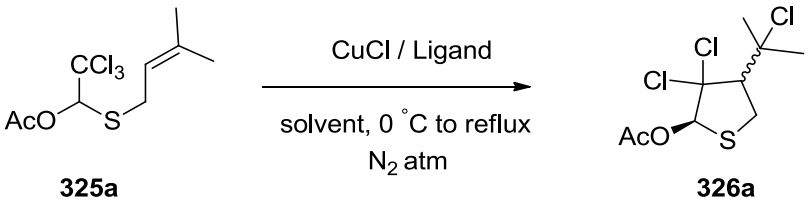
Thus, ^{1}H NMR spectrum of **325a** (**Fig. 116**) showed two singlets at δ 1.72 and δ 1.76 ppm integrating for three protons each, which were attributed to the protons H^{e} and H^{f} (**Fig. 14, Structure A**) of the two germinal methyl groups. It showed one singlet at δ 2.22 ppm integrating for three protons, which was attributed to the methyl protons H^{a} of the acetyl group. The multiplet at δ 3.50-3.55 ppm integrating for two protons was attributed to the two diastereotopic allylic protons H^{c} of the prenyl unit. The multiplet at δ 5.26-5.31 ppm integrating for one proton was attributed to the vinylic proton H^{d}. The singlet at δ 6.25 ppm integrating for one proton was attributed to the methine proton H^{b} of the carbon bonded to the acetoxy group.

The proton-decoupled ^{13}C NMR spectrum (**Fig. 117**) of **325a** showed three signals at δ 17.8, 20.8 and 25.7 ppm. The first two were assigned to the methyl carbons C^{i} and C^{h} of the prenyl group and the third to the methyl carbon C^{a} of the acetyl group (**Fig. 14, Structure B**). The signal at δ 31.5 ppm was attributed to the allylic methylene carbon C^{e} bonded to the sulphur atom. The two signals at δ 87.6 and 99.3 ppm were assigned to the

methine carbon C^c and the quaternary CCl_3 carbon C^d, respectively. The three signals at δ 118.6, 138.0 and 168.8 ppm were assigned to the vinylic methine carbon C^f, quaternary vinylic carbon C^g and carbonyl carbon C^b, respectively. These assignments were also supported by DEPT-135 spectrum. The IR spectrum of **325a** showed strong absorption at 1762 and 1205 cm^{-1} due to C=O and C-O bond stretching, respectively. The HRMS spectrum of this compound showed the $[M+Na]^+$ peak at m/z 312.9608, which is within the acceptable limit of deviation from the calculated value of 312.9595 for the formula $C_9H_{13}Cl_3O_2SNa$.

3.3.2. Chlorine atom transfer radical cyclization of 1-acetoxy-2,2,2-trichloroethyl prenyl sulphide 325a: Optimization of the reaction conditions

The reaction of the sulphide **325a** with varying amounts of CuCl was performed in different solvents under a nitrogen atmosphere in the presence of the commercially available ligands bpy, TMEDA and PMDETA. Two equivalents of TMEDA and one equivalent of bpy and the tridentate ligand PMDETA with respect to CuCl were used as per the normal practice in HATRC reactions. The progress of the reaction was monitored by TLC as well as by ^1H NMR spectra of the aliquots taken from time to time. Work up of the reaction mixture after completion of the reaction or after a reasonable amount of time in the cases of incomplete conversion, followed by purification by column chromatography gave a mixture of diastereomeric cyclized products **326a** (**Scheme 108**) in most of the cases. The combined yield of the products and cleanliness of the reaction were taken as significant parameters for optimization. The results are compiled in **Table 4**.



325a **326a**

Scheme 108

Table 4. Optimization of the reaction conditions in CuCl/Ligand-promoted HATRC of 325a[a]

S. No	CuCl mol (%)	CuCl/Ligand (mol ratio)	Solvent	Temperature	Time (h)	Product **326a** yield (%)[b]	Recovered **325a** (%)
1	100	CuCl/bpy (1:1)	DCE	reflux	6	-	80
2	100	CuCl/TMEDA (1:2)	DCE	reflux	6	25	60
3	60	CuCl/ PMDETA (1:1)	DCE	reflux	4	72	-
4	50	CuCl/PMDETA (1:1)	MeCN	reflux	3	75	-
5	20	CuCl/PMDETA/AIBN (1:1:2.5)	MeCN	reflux	3	67[c]	-
6	100	CuCl/PMDETA (1:1)	MeCN	rt	12	81	-
7	100	CuCl/PMDETA (1:1)	MeCN	0 °C	20	68	20

[a]All the reactions were performed with 1 mmol of **325a** under a nitrogen atmosphere.

[b]Mixture of diastereomers.

[c]Complex mixture, difficult to separate.

First, the reaction was performed under the generally employed conditions using a catalyst loading of 40 mol % in DCE at reflux condition under a N_2 atmosphere. Of the

three ligands employed, bpy the most common ligand in Cu (I)-catalyzed HATRC was found to be not effective at all, leading to the recovery of the unreacted starting material upto the extent of 80% after 6 h of reaction time even with stoichiometric amount (100 mol %) of the CuCl/bpy (1:1 mol ratio) catalyst. (**Table 4**, **S. No. 1**). There was no indication of formation of any product. TMEDA was only slightly better. (**S. No. 2**). PMDETA was observed to be the most effective ligand in terms of the product yield (72%, **Table 4**, **S. No. 3**). It is probably due to its being a tridentate ligand whereas other two are bidentate ligands.[4] However, even with this ligand, as much as (60 mol %) of the catalyst was required to complete the reaction. Acetonitrile as the solvent was observed to be nearly as effective as DCE in terms of the product yield (75%, **S. No. 4**). However, relatively lesser amount of the catalyst (50 mol %) and somewhat lesser reaction time were required in this case. It might be due to more solubility of CuCl/PMDETA complex in acetonitrile.[138] ^{1}H NMR of the crude products **326a** obtained from the reactions in both of the solvents showed the formation of some decomposed complex material, probably due to cleavage of the relatively weak C-S bond present in the substrate.[139] The decomposed sulphides could also have deactivate the active Cu (I)-catalyst, therefore necessitating higher catalyst loading.

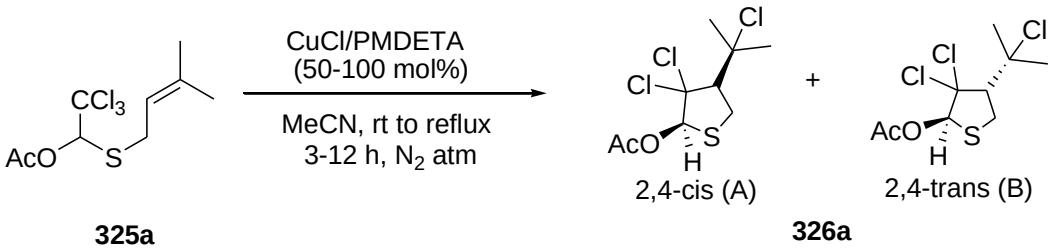
It has recently been found that continuous reduction of the Cu(II) species accumulated during Cu(I)-catalyzed HATRC reactions due to radical terminating side reactions, to the active Cu(I) species by a reducing agent such as AIBN lowered the catalyst loading considerably.[3,74] Therefore, with a view to reduce the catalyst loading in the above room temperature reaction, the reaction was performed by drop-wise addition of a solution of AIBN (0.5 equiv) in acetonitrile to the refluxing reaction mixture containing

325a, CuCl and PMDETA in acetonitrile. A positive effect was observed in this reaction with regard to a low catalyst loading (20 mol %), however an inferior result was obtained with respect to lower yield (67%) of the product (**S. No. 5**) probably due to decomposition of the starting sulphide. Moreover, the by-products of AIBN and other side products formed in the reaction were found to complicate the separation and purification of the cyclized products by column chromatography.

In order to prevent the loss of the starting material and formation of what are presumably the catalyst poisons due to decomposition of the sulphide substrates, the reaction was performed in acetonitrile at lower temperatures. The reaction at room temperature (25-30 ˚C) showed clean conversion of the starting material. No formation of the decomposed material was observed. The yield of the product also increased to 81% (**S. No. 6**). However, stoichiometric amount of the catalyst loading (100 mol %) and longer reaction time (12 h) was required to complete the reaction. Looking at the positive effect of a lower temperature on the cyclization of **325a**, another reaction was performed at 0˚C also. However, the starting material could not undergo complete conversion even with the stoichiometric amount of the catalyst loading (100 mol %) and prolonged reaction time (20 h). A lower amount of the product **326a** (68%) was isolated along with nearly 20 % of the starting material (**S. No. 7**).

The diastereoselectivity of the cyclization reaction was observed to depend on the reaction temperature. *Cis* (A) : *Trans* (B) (**Scheme 109**) diastereomeric ratio of the products obtained under three different conditions are given in **Table 5**. The ratios were calculated from intensities of the signals due to methine protons at the carbons bonded to

the acetoxy groups in the two diastereomers A and B in the ^{1}HNMR spectra of the crude reaction mixture.



325a **326a**

Scheme 109

Table 5. Effect of temperature on diastereomeric ratio of 326a

S. No.	CuCl/PMDETA (1:1) mol%	Temperature	Time (h)	Yield (%)	Isomeric ratio *cis* : *trans*[a]
1	100	rt	12	81	69 : 31
2	100	50 ˚C	8	78	55 : 45
3	50	reflux	3	75	41 : 59

[a] Calculated from the ^{1}H NMR spectra of the crude products.

The ^{1}H NMR of the crude product **326a** obtained from the reaction at room temperature showed highest diastereoselectivity (*cis* : *trans* = 69:31) (**Table 5**, **S. No. 1**) (**Fig 138, i**). At 50 ˚C, nearly equal amount of the two diastereomers (55:45) were formed (**Table 5**, **S. No. 2**) (**Fig. 138**, **ii**). At reflux a reversal in diastereoselectivity was observed, though the diastereoselectivity was low (*cis* : *trans* = 41:59) (**Table 5**, **S. No. 3**)(**Fig. 138**, **iii**).

In view of the above observations and low cost of the catalyst, the optimum reaction conditions in terms of the product yield, cleanliness of the reaction and

diastereoselectivity were considered as room temperature (25-30 ˚C) as the reaction temperature and acetonitrile as the solvent (**S. No. 6**) for further investigation even though a stoichiometric amount of the catalyst was required. A high diastereoselectivity ratio was also helpful in separation and purification of the mixture. The consumption of stoichiometric amount of CuCl/PMDETA at room temperature may be due to deactivation of the catalyst by the divalent sulphur substrates as well as the product. The tetrahydrothiophene rings are known to be ligands for copper salts.[140]

The crude product **326a** (**Fig 138, i**) obtained under the above chosen optimized conditions, was further purified by column chromatography to obtain the pure diastereomeric mixture.

The major *cis*-isomer could be separated in pure form by recrystallization of the purified mixture from DCM/*n*-hexane as colorless crystals leaving the minor *trans* isomer in the mother liquor along with the un-recrystallized *cis* isomer (*cis : trans* = 25:75). The structure of the major isomer was established by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and mass spectrometry. The stereochemistry was established by single crystal structure. The structure of the minor diastereoisomer was established by ^{1}H NMR (**Fig**. **140**) and ^{13}C NMR spectra (**Fig**. **143**) of the mother liquor. The structural features and stereochemistry of the major isomer will be discussed here.

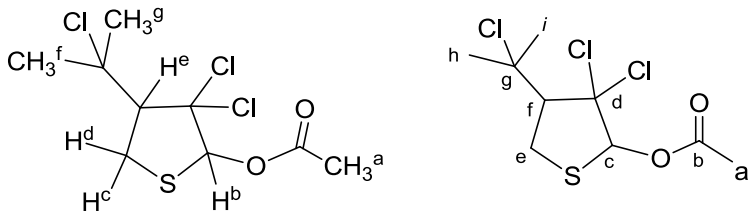


Fig.15 ^{1}H NMR and ^{13}C NMR assignments for the structure of 326a (**major isomer**)

The ^{1}H NMR spectrum (**Fig. 139**) of the major isomer of **326a** showed two singlets at δ 1.92 and 1.99 ppm integrating for three protons each due to the protons H^f and H^g of the germinal methyl groups (**Fig. 15**, **Structure A**). The singlet at δ 2.22 ppm integrating for three protons was attributed to the methyl protons H^a of the acetoxy group. The doublet of a doublet at δ 3.12 ppm with coupling constants of 11.1 and 6.0 Hz, which integrated for one proton, was attributed to the methine proton H^e. The dd at δ 3.30 ppm with coupling constants of 11.1 and 6.0 Hz, which integrated for one proton, was attributed to one of the methylene diasterotopic protons H^c or H^d. The triplet at δ 3.45 ppm with a coupling constant of 11.1 Hz, which integrated for one proton, was attributed to the other diastereotopic methylene proton H^d or H^c. The singlet at δ 6.34 ppm integrating for one proton was attributed to the methine proton H^b at the carbon bonded to the acetoxy group.

The proton-decoupled ^{13}C NMR spectrum of the major isomer of **326a** (**Fig. 142**) showed signals at δ 20.6 and 30.2 ppm which were assigned to the methyl carbon of acetoxy group C^a and methylene carbon C^e (**Fig. 15, Structure B**), respectively. The signals at δ 30.4 and 34.2 ppm were attributed to the methyl carbons C^h and C^i. The signal at 61.5 ppm was due to the methine carbon C^f. The signals at δ 71.1 and 86.1 ppm were attributed to the quaternary carbon C^g and the methine carbon C^c bonded to the acetoxy group, respectively. The signals at δ 90.3 and 169.3 ppm were assigned to the quaternary carbon C^d of the CCl_2 and the carbonyl carbon C^b of the ester group, respectively. These assignments were supported by DEPT-135 spectrum. The IR spectrum of **326a** showed a strong absorption at 1734 cm^{-1} due to the ester C=O bonds stretching. The HRMS spectrum of **326a** showed $[M+Na]^+$ peak at m/z 312.9594, which is within the acceptable limit of deviation from the calculated value of 312.9595 for the formula $C_9H_{13}Cl_3O_2SNa$.

The interpretation of ^{1}H NMR and ^{13}C NMR were further supported by HSQC (**Fig. 144**) of the product **326a** containing a mixture of both the isomers before recrystallization. The cross peaks in HSQC spectrum revealed that carbons C^{a}, C^{c}, C^{e} and C^{f} were correlated to H^{a}, H^{b}, (H^{c}, H^{d}) and H^{e}, respectively. The methine proton H^{e} appeared upfield as compared to the methylene protons H^{c} and H^{d} in the major isomer as well as in the minor isomer. These signals for the methylene diastereotopic protons H^{c} and H^{d} of the major isomer were well separated from each other. But the signals for one of the methylene protons H^{c} or H^{d} and the methine proton H^{e} were partially overlapping each other in the minor isomer. The structure and stereochemistry of the major diastereoisomer was also supported by X-ray crystallography. The ORTEP diagram (**Fig. 16**) of the major isomer of **326a** showed that acetoxy and chloroalkyl side chain substituents at C-2 and C-4, respectively were *cis* to each other.

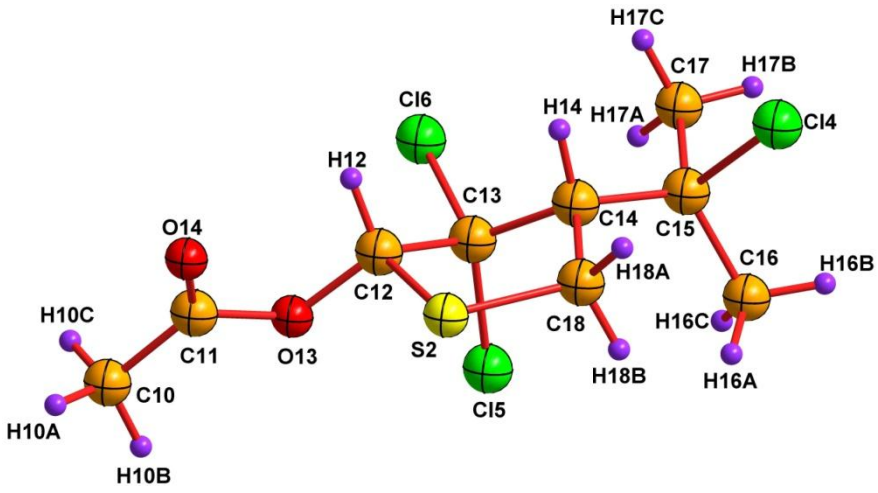
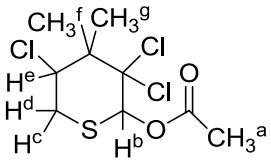


Fig. 16 ORTEP diagram of 3,3-dichloro-4-(2-chloropropan-2-yl)-5-methyl-tetrahydrothiophen-2-yl acetate 326a (major isomer)

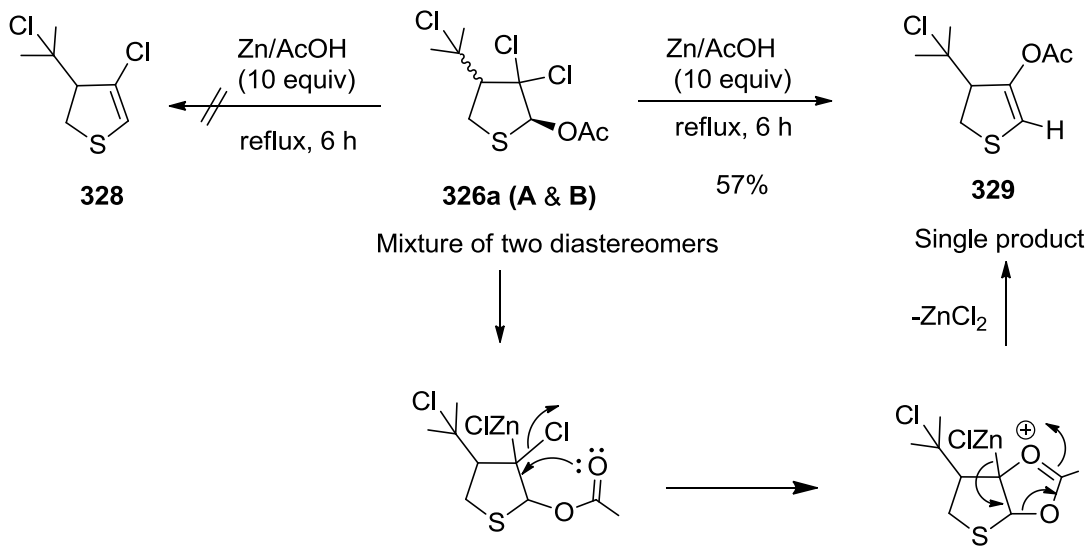
No 6-*endo* cyclization product **327** (**Fig. 17**) was isolated by column chromatography. ^{1}H NMR of the crude product **326a** showed no signals which could suggest the formation of **327**. The chemical shift (δ) of the methine proton H^{e} and the carbon it is bonded to, would be expected to be higher than those observed and are compatible with the structure of the 5-*exo* product **326a**.



327

Fig. 17 Structure of 3,3,5-trichloro-4,4-dimethyltetrahydro-2H-thiopyran-2-yl acetate

The regioseletivity of the reaction was further supported by converting the THT **326a** into dihydrothiophene **329** by treating the crude product **326a** with a suspension of Zn in acetic acid under reflux following a method reported in the literature[137] for dechlorodeacetoxylation. However, instead of formation of the expected dechlorodeacetoxylation product **328** (**Scheme 110**), an interesting dechlorinative rearrangement occurred to give the 3-acetoxydihydrothiophene **329** in 56% yield. The structure of the product was established by ^{1}H NMR (**Fig 181**), ^{13}C NMR (**Fig 182**) and IR spectroscopy and mass spectrometry. A mechanism involving a Zn-carbenoid species[141] has been proposed for the formation of **329**.



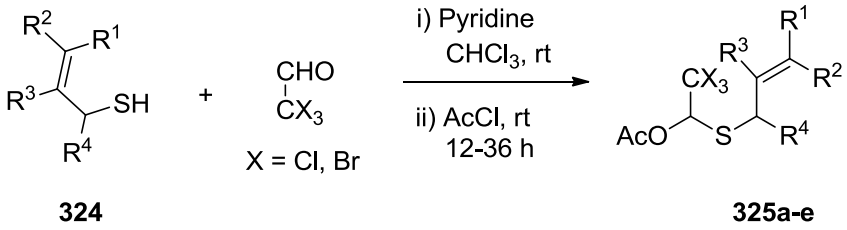
Scheme 110

3.3.3. Generalization of the scheme: Synthesis of other 3,3-dichloro-tetrahydrothiophen-2-yl acetates

In order to evaluate the scope of this methodology for the synthesis of chlorinated 2-acetoxytetrahydrothiophenes, it was considered to prepare some more 1-acetoxy-2,2,2-trihaloethyl allyl sulphide precursors and investigate their Cu (I)-mediated HATRC reactions. These polyhaloethyl allyl sulphides could also be accessed using other polyhalogen sources such as bromal. The variants of allyl mercaptan were easily accessible by reaction of allylic halides with thiourea following a method reported in the literature.[142] Thus, substituents such as alkyl and aryl can be easily introduced and fused and spiro rings can be accessed. Due to these reasons, the methodology was found to be fairly general for the synthesis of 2-chlorotetrahydrothiophenes with regard to change at almost all the positions of tetrahydrothiophene ring.

Thus, some 1-acetoxy-2,2,2-trihaloethyl allyl thioethers **325b-e** (**Scheme 111**, **Table 6**) were obtained by treating equimolar mixture of chloral/ bromal and allylic mercaptans in the presence of pyridine, followed by acetylation of the hemi-thioacetal with acetyl chloride. Purification of the crude products by column chromatography gave the thioethers **325b-e** in high yields.

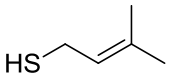
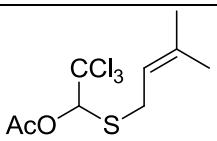
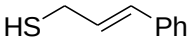
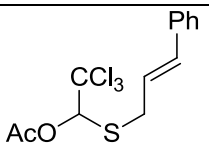
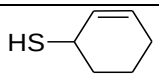
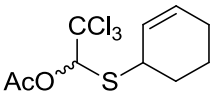
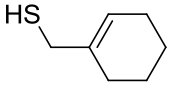
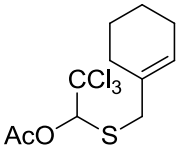
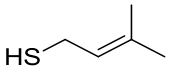
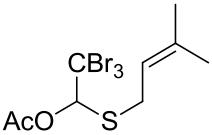
The acyclic precursor **325c** was obtained as mixture of two diastereomers. These diastereomers could not be separated by column chromatography. The ratio of diastereomers was determined by ^{1}H NMR spectra of the crude reaction mixture. The brownish bromo precursor **326e** turned black in color on slight heating. This black color disappeared on purification of the crude product by column chromatography on silica gel column, however, the yield of the purified product was found to reduce drastically to 40% possibly due to its decomposition on the column as well.



324 **325a-e**

Scheme 111

Table 6. Preparation of 1-acetoxy-2,2,2-trihaloethyl allyl thioethers 325a-*e*[a]

S. No.	Allyl mercaptan **324**	Trihaloacet-aldehyde	1-Acetoxy-2,2,2-trihaloethyl allyl thioether **325**		
			Structures and isomeric ratio	Time (h)	Yield (%)
1	a: 	CCl_3CHO		12	82
2	b: 	CCl_3CHO		12	78
3	c: 	CCl_3CHO	 50:50[b]	24	75
4	d: 	CCl_3CHO		12	73
5	e: 	CBr_3CHO		36	40

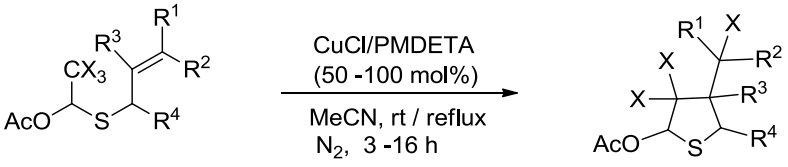
[a]The reactions were performed at 10 mmol scale and the products **325** were purified with column chromatography.

[b]Mixture of diastereomers.

After successful HATRC of **325a**, the radical cyclization protocol was successfully extended to the thioethers **325b-e** (**Scheme 112**). The corresponding THTs **326b-e** were obtained as mixtures of diastereomers in good combined yields. The precursors **325b** and

325d were cyclized under the optimized conditions with 1 equiv of CuCl/PMDETA complex in comparable amount of reaction time. However, the precursor **325c** did not undergo cyclization at room temperature under the optimized conditions. Therefore, the reaction was performed under reflux conditions with 50 mol% of the catalyst. The brominated precursor **330e** cyclized with a lower catalyst loading (70 mol%). The results are compiled in **Table 7**.

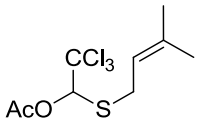
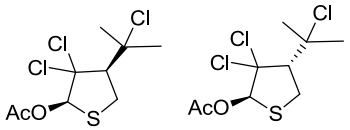
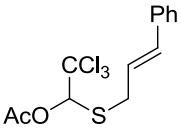
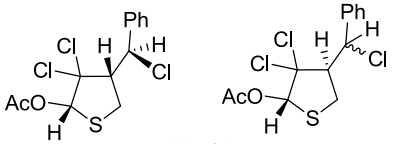
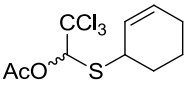
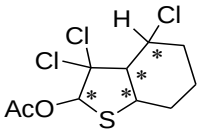
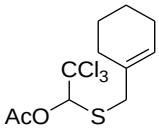
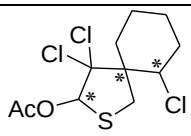
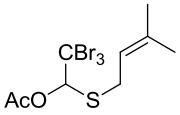
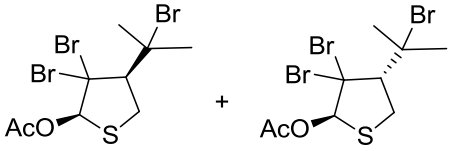
The diastereomeric ratios were determined by ^{1}H NMR of the crude products obtained after the work up of reaction mixtures. Purification of the crude products was done by the column chromatography using silica column to give a mixture of diastereomers free from the other impurities. The diastereomeric **326c** could be separated by column chromatography using silica gel column. In the cases of **326a-b**, the major diastereomers were separated by recrystallization but the minor products remained in the mother liquor along with some amounts of the major isomers. In the case of the bromo-derivative **326e**, both the isomers got recrystallized together in *n*-hexane at low temperature. Therefore, the diastereomers could not be separated. In proton decoupled ^{13}C NMR of the mixture of diastereomers in all the cases, most of the carbons appeared separate at appropriate positions indicating the presence of two (four in the case of **326d**) diastereomers.



325a-*e* **326a-*e***

Scheme 112

Table 7. CuCl/PMDETA-promoted synthesis of tetrahydrothiophenes 326 [a]

S. No	**325** Trihaloethyl allyl thioether	Tetrahydrothiophenes **326**		
		Structures (diastereomeric ratio)[b]	Time (h)	Yield (%)
1	a: 	 **A** 69 : 31 **B**	12	81
2	b: 	 **A** 55 : 45 **B** Mixture of two diastereomers (major isomer (**A**) *cis, anti*)	12	52
3	c:  50:50	 Mixture of two diastereomers (**A** : **B** = 60 : 40) CuCl/PMDETA (50 mol%, reflux)[c]	3	66
4	d: 	 Mixture of four diastereomers (**A**:**B**:**C**:**D** = 20:40:20:20)	12	67
5	e: 	 **A** 60 : 40 **B** CuCl/PMDETA (70 mol%, rt)[d]	10	69

[a]Unless otherwise mentioned, all the reactions were performed at 1 mmol scale with 1 equiv each of CuCl and PMDETA in acetonitrile at room temperature (25-30 ˚C) under a nitrogen atmosphere.

[b]The diastereomeric ratio in the crude product obtained after work up of the reaction mixture.

[c] Reaction was done at reflux with 50 mol% of each of CuCl and PMDETA.

[d] Reaction was done with 70 mol% each of CuCl and PMDETA.

The stereoselectivity and the isolated yields of the products were found to be the lowest in the case of the phenyl substituted derivative **326b** (55:45) (**Fig. 145 & 146**). However, the major diastereomer could be separated by recrystallization of the mixture obtained from column chromatography from DCM/*n*-hexane. (**Fig. 147 & 148**) The minor isomer remained in the mother liquor along with some amount of the major isomer in (80:20) ratio. The ^{1}H NMR of the crude product obtained after work up of the reaction mixture showed the presence of other unidentifiable side products also. ^{1}H NMR of the of the major *cis* isomer of **326b** (**Fig.147**) showed that the methine proton C<u>H</u>CH$_2$ and the diastereotopic methylene protons C<u>H</u>$_2$CH of the tetrahydrothiophene ring were not well separated from each other. The HSQC spectra (**Fig**. **149**) revealed that the methine proton was upfield in comparison to the diastereotopic methylene protons as in **326a**. The stereochemistry of the major pure diastereomer was established by single crystal X-ray diffraction which showed it to be *cis*, *anti*. The ORTEP diagram is shown in **Fig. 18**.

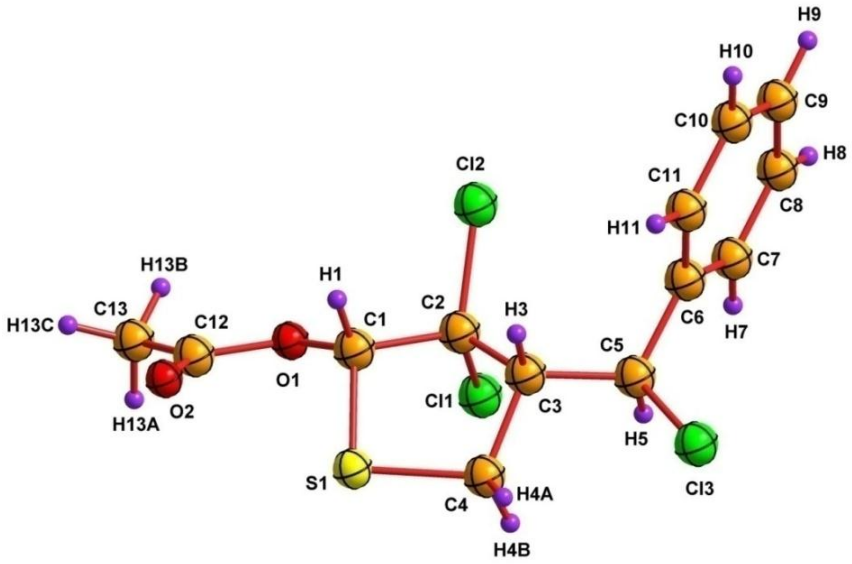


Fig. 18 ORTEP diagram of 3,3-dichloro-4-chloro(phenyl)methyl)-tetrahydrothiophen-2-yl acetate 326b (major isomer)

The stereochemistry of the minor isomer could not be determined. Presumably it could be the *trans* isomer with unknown stereochemistry at the chiral centre in the side chain.

The precursor **326c** could not cyclize completely under the optimized reaction conditions. The cyclization occurred only to the extent of nearly 20% as indicated by 1H NMR even after a longer (24 h) reaction time. However, it was found to undergo complete cyclization when treated with 50 mol % of CuCl/PMDETA in acetonitrile at reflux for 3 h. ^{1}H NMR of the reaction mixture showed the formation of two diastereomers (**Fig 150** & **152**) in a 60:40 ratio along with some decomposition. The two diastereomers could be purified and separated from each other by column chromatography in a combined yield of 66%. However, the stereochemistry of these isomers could not be established unambiguously.

The cyclization of **326d** with 1 equivalent of CuCl/PMDETA under the optimized condition led to the formation of a mixture of four compounds **326d** (**Table 7**)(**Fig. 154** & **155**) in a combined yield of 68 % as a viscous liquid. Separation and purification of the crude product by column chromatography by silica column led to separation of two isomers (**Fig. 156**) one of which was the major product as indicated by the relative intensities of the CH-OAc methine proton singlet in the ^{1}H NMR of the crude mixture (**Fig. 154**). Attempt to separate these isomers from each other by column chromatography did not succeed due to their similar RF values. On recrystallization, both of these isomers got crystallized together at low temperature. The gross structures of these isomers which are apparently diastereomers was established by ^{1}H NMR (**Fig. 156**), ^{13}C NMR (**Fig. 157**), HSQC (**Fig. 158**), IR spectroscopy and HRMS. Their stereochemistry, however, could not

be established. The other two minor products could not be isolated either by column chromatography or recrysatallization from the mixture of products.

The bromo precursor **325d** required a lower catalyst loading (70 mol%) for cyclization under the optimized conditions possibly due to weak C-Br bond. The ^{1}H NMR of the crude products (**Fig. 159**) showed it to be a diastereomeric mixture (60:40) of **326d**. However, these isomers could not be separated by column chromatography using silica gel column due to quite high solubility of the products in *n*-hexane. Both the major and minor isomers got crystallized together in *n*-hexane. As the products were analogous to the chloro THTs **326a**, it was also expected that under the same optimized reaction conditions, similar kind of the isomers would form. The X-ray diffraction of a single crystal picked out from the mixture of the crystals showed 1,3-*cis* relationships of the substituent at C-2 and C-4 positions. The ORTEP diagram is shown in **Fig 19**.

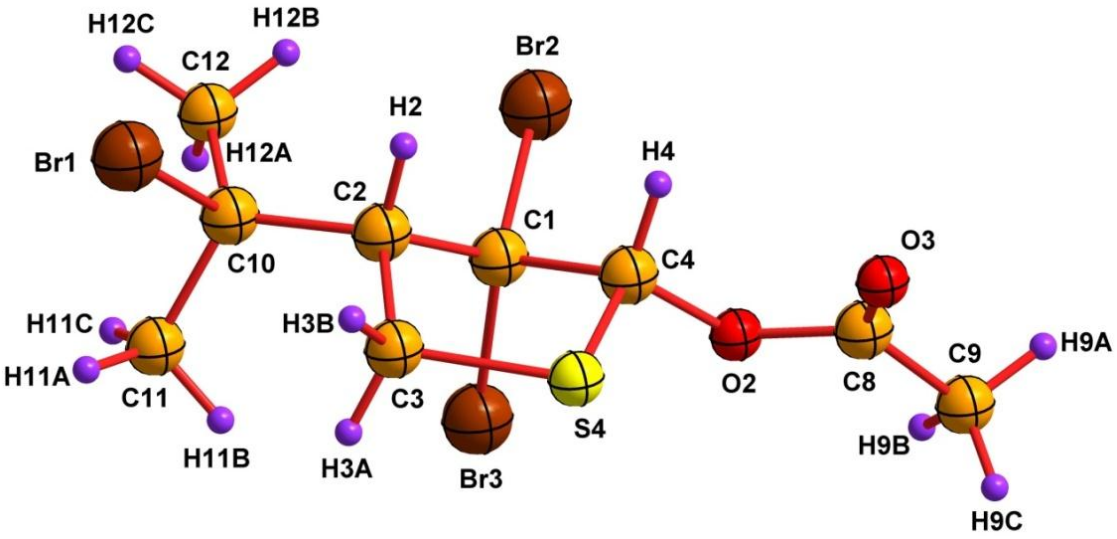
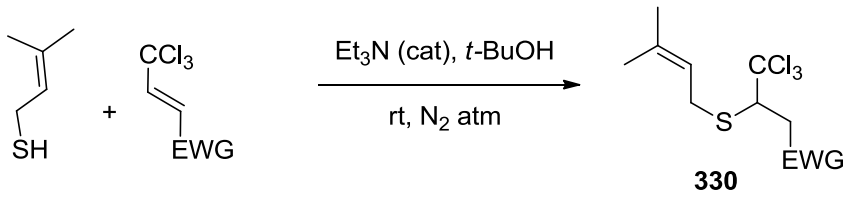


Fig. 19 ORTEP diagram of 3,3-dibromo-4-(2-bromopropan-2-yl)-tetrahydrothiophen-2-yl acetate 326e

Going by the trend in stereochemistry of the present cyclization reaction, it appears that single crystal of the major isomer was fortuitously picked out for X-ray diffraction spectroscopy.

Next, the scope of this methodology was extended to the chlorinated tetrahydrothiophenes having a functional group in a side chain at C-2. Literature survey revealed that alkyl sulphides underwent thia-Michael addition with many Michael acceptors.[143] Using this protocol, thia-Michael addition of prenyl mercaptan to trichloromethylated Michael acceptors **220** (**Scheme 113**) was performed to get some side chain functionalized 2,2,2-trichloroethyhl allyl sulphide acyclic precursors **330**. These acyclic precursors were prepared in good yields (68-84%) by simply stirring a mixture of prenyl mercaptan (1.1 equiv) and Michael acceptors **220** (1 equiv) (**Scheme 79**) in the presence of a catalytic amount of triethylamine (30-50 mol%) in *tert*-butanol at room temperature followed by purification by column chromatography. Functional groups such as ester, keto, cyano and nitro could easily be introduced in this manner.

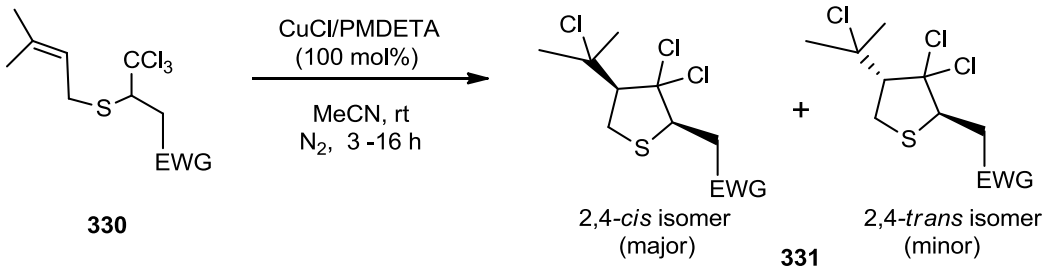


220 **330**

Entry	EWG	Time (h)	yield (%)
a:	COPh	8	80
b:	COMe	8	82
c:	CO_2Me	8	68
d:	NO_2	6	84
e:	CN	12	81

Scheme 113

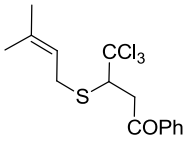
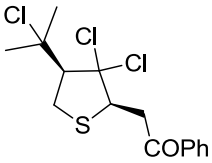
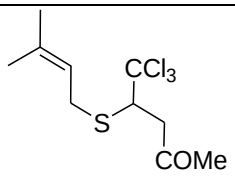
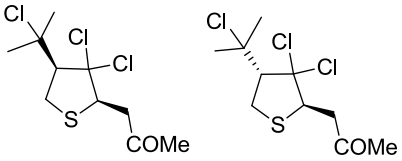
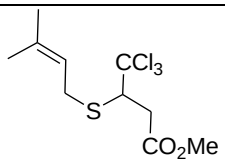
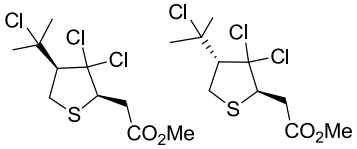
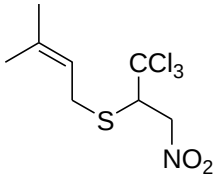
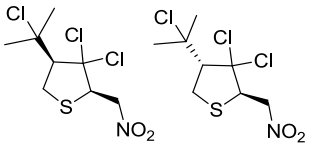
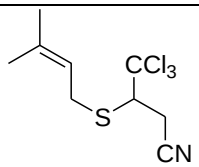
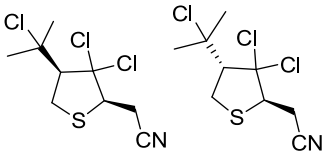
All the precursors underwent smooth CuCl/PMDETA-mediated 5-*exo* cyclization under the optimized reaction conditions to give the products **331** (**Scheme 113**, **Table 8**) in good to high combined yields. The ratios of the diastereomers were calculated by ^{1}H NMR of the crude products **331** which showed that the *cis* isomers were the major products. The purification of the crude products was done by column chromatography using silica gel column to obtain mixtures of diastereomers free from other impurities. All the mixtures were solid and the major *cis* diastereomers (except **331e**) were separated successfully by recrysatallization of the diastereomeric mixture. The minor diastereomers however, could not be separated from the diastereomeric mixture as pure single diastereomers. The results are compiled in **Table 8**.



Scheme 114

The structures of all the products were determined by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and HRMS.

Table 8. Preparation of side chain functionalized tetrahydrothiophenes 331a-e [a]

S. No.	Trichloroethyl prenyl thioether **330**	Side chain functionalized tetrahydrothiophenes **331**		
		Structures and *cis : trans*[b] ratio	Time (h)	Combined isolated yield (%)
1	a: 	 single isomer	10	83
2	b: 	 (A) 80 : 20 (B)	16	82
3	c: 	 (A) 76 : 24 (B)	16	69
4	d: 	 (A) 80 : 20 (B)	16	74
5	e: 	 (A) 60 : 40 (B)	16	80

[a]All the reactions were performed with 1 mmol of **330** under a N_2 atmosphere.

[b]Calculated from ^{1}H NMR spectra of the crude products.

The [1]HNMR of the crude product **331a** showed the presence of a single isomer. The purification by column chromatography gave a crystalline solid. The structure of **331a** was also supported by HSQC (**Fig. 163**) and COSY (**Fig. 164**) NMR of the products. The *cis* stereochemistry of **331a** was established by single crystal X-ray diffraction spectroscopy. The ORTEP diagram is shown in **Fig 20**.

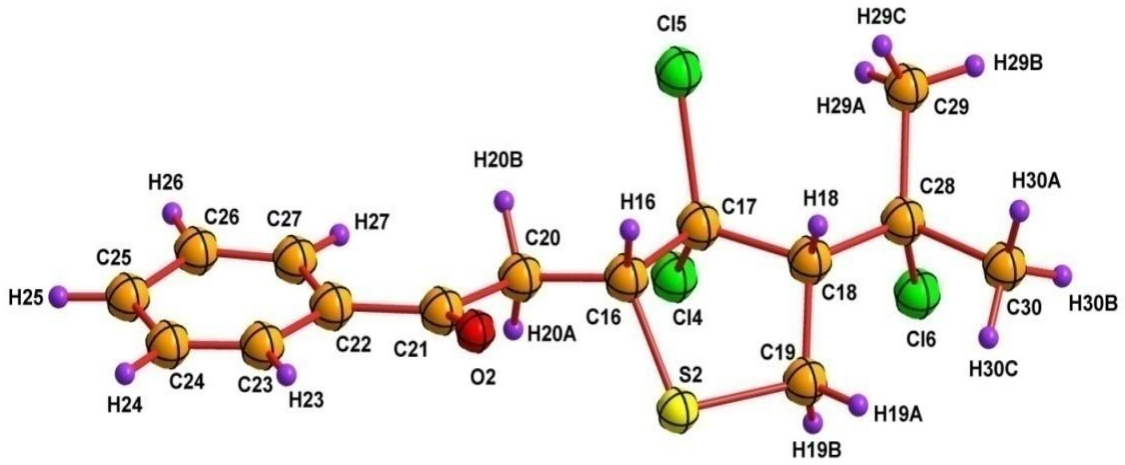
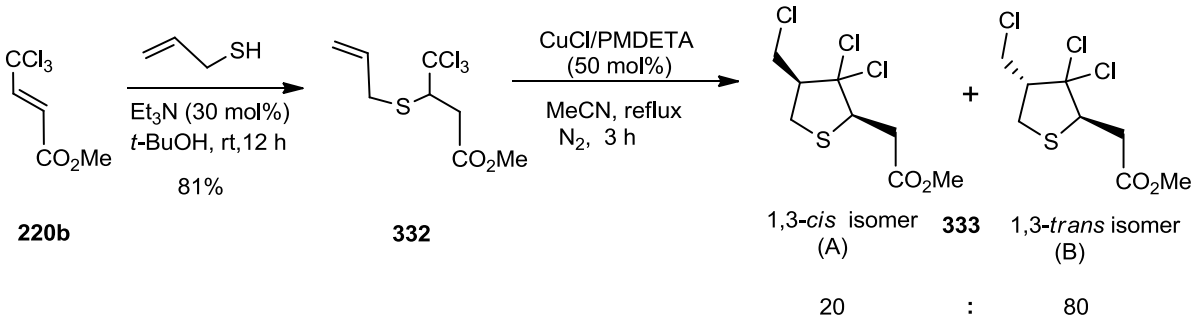


Fig. 20 ORTEP diagram of 2-3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)-1-phenylethanone 331a

The spectral features of the major diastereomers of the tetrahydrothiophenes **331b-e** were found to be similar to **331a** with expected substituent dependent minor differences and therefore, the stereochemistry of the major diastereomers in these cases was presumed to be 1,3-*cis*. The structure of the minor diastereomer **331c** (**B**) was established using the [1]H NMR and [13]C NMR of the crude product **(Fig 169** & **170)** and the major diastereomer spectra (**Fig. 171** &**172**)**.** As the spectra of the crude products **331b** and **331d** were not clear enough to identify the structure of the minor diastereomers, their structures were

established using the ^{1}H NMR and ^{13}C NMR of the diastereomeric mixture (**Fig 167**&**168** in the case of **331b**) and (**Fig. 175** &**176** in the case of **331d**) obtained after the partial separation of the major diastereomer by column chromatography of their corresponding crude product.

In order to examine the effect of temperature on the stereoselectivity of the cyclization, it was thought to perform the cyclization reaction of **332** (**Scheme 115**) in acetonitrile under reflux condition. This might increase the proportion of the thermodynamically more stable 1,3-*trans* diastereomer or even reverse the stereoselectivity. If so, the *trans* isomer could be separated and purified by recrystallization as pure single isomer and its stereochemistry could be established.



220b 332

Scheme 115

Thus, the precursor **332** was heated under reflux in acetonitrile with 50 mol% of CuCl/PMDETA complex for 3 h. The ^{1}HNMR of crude product (**Fig. 179,** inset) obtained after the usual work up of the reaction mixture showed it to be 80:20 diastereomeric mixture. However, it showed some decomposed side products as well, like it was observed in the case of **326a** under these conditions (**Table 5, S. No.3**). Only the major diastereomer could be separated in pure form by column chromatography. The other diastereomer was

obtained along with the decomposed side products and could not be further separated and identified well. The pure product was then recrystallized from *n*-hexane to obtain the compound in pure form. The structure was established by usual spectroscopic methods. The X-ray crystal structure (**Fig 21**) showed this product to be indeed *1,3-trans* diastereomer. The stereochemistry of **333** also suggested that possibly the stereochemistry of the minor products obtained from **326** and **331** under the optimized conditions at room temperature was also 1,3-*trans*. The reversal of stereoselectivity in the reaction of **332** even when it had unsubstituted S-allyl group instead of a bulkier S-prenyl group as in **330** also indicated the importance of the effect of the temperature on the stereoselectivity of the reaction.

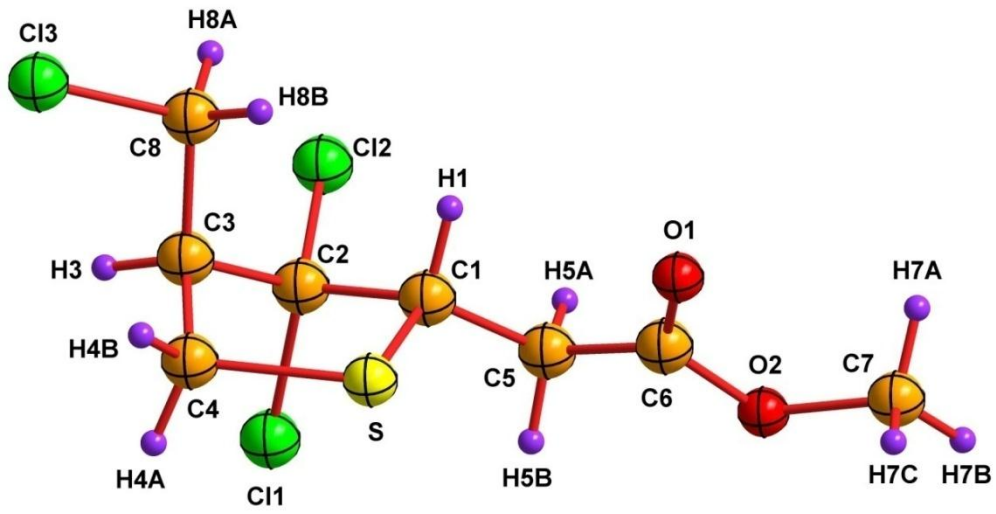


Fig. 21 ORTEP diagram of methyl 2-{3,3-dichloro-4-(chloromethyl)-tetrahydrothiophen-2-yl} acetate 333 (*1,3-trans*-isomer)

All the side chain functionalized tetrahydrothiophenes **331a-e** and **333** were found to be relatively more stable than 2-acetoxy-THTs **326a-e**. The 2-acetoxy-THTs underwent

decomposition after nearly one month even when stored at low temperatures. The signs of decomposition were change in the color from colorless to yellow/red and more foul smell.

3.4. Conclusion

The present chapter describes a mild and regioselective CuCl/PMDTA-promoted halogen atom transfer radical cyclization of substituted 2,2,2-trichloroethyl allyl sulphides for the synthesis of diversely substituted tetrahydrothiophenes. It suggests that the Cu (I)-mediated HATRC of of 2,2,2-trichloroethyl allyl sulphides needs strong multidentate ligands to withstand the possible deactivating effect of the effects of S-copper complex interactions to make the cyclization succeed, albeit with high catalyst loading. The steric hinderence by the substituents α to the sulphur atom might have also contributed in discouraging the CuCl-Sulphur interactions. The chlorine, bromine and acetoxy groups and the side chain functional groups in the tetrahydrothiophenes are potential centres for further manipulation in advanced synthesis including that of natural products and synthetically important compounds. However, the stereochemistry in the cyclization reactions is not high and needs to be addressed in future.

3.5. Experimental Section

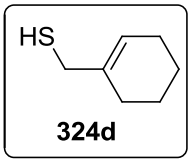
3.5.1. Preparation of starting material

3.5.1.1. Preparation of allyl mercaptans 324

All the allylic mercaptans **324** (except **324d**) are known and were prepared by a method reported in the literatures.[142] The same method was extended to the synthesis of the unknown mercaptan **324d** also with slight modifications. It was prepared by heating an

equimolar mixture of 1-(chloromethyl)cyclohex-1-ene (1.30 g, 10 mmol) and thiourea (0.76g, 10 mmol) in methanol (40 mL) under reflux. After the disappearance of the allylic chloride (6 h) as indicated by monitoring the progress of the reaction by TLC, the reaction mixture was stirred with one equivalent ethylene diamine (0.66 mL, 0.601 g, 10 mmol) at 10 ˚C for 30 min. To the solution, water (100 mL) was added and the aqueous solution was extracted with DCM (2x50 mL). The combined organic layer was washed with brine (2x25 mL), dried (Na_2SO_4) and concentrated to obtain **324d** in good yield (0.822 g, 63%).

*Cyclohexenyl methane thiol **324d**:*



324d

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.52–1.80 {m, 5H, (4H, $2CH_2$ and 1H, $SH_,$), 1.95-2.20 (m, 4H, CH_2), 3.20 (d, 2H, *J* = 9.0 Hz, CH_2S), 5.76-5.78 (m, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1 (CH_2), 22.5 (CH_2), 25.3 (CH_2), 26.5 (CH_2), 40.9 (CH_2), 127.5 (CH), 132.5 (C) ppm; IR (KBr): ν_{max} 3024(m), 2933(s), 2560(w), 1641(m), 1340(m), 1255(m), 1195(m), 746(m) cm^{-1}.

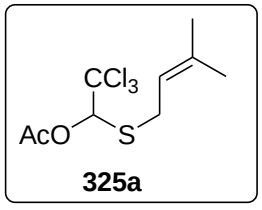
3.5.1.2. Preparation of 1-allylthio-2,2,2-trichloroethyl acetates 325a-e

These previously unknown compounds were prepared using a method reported in the literature[137] in which a few 1-(akylthio)-2,2,2-trichloroethyl carbonates were prepared by reacting an equimolar mixture of an alkyl mercaptan, anhydrous chloral and pyridine to obtain hemithioacetal *in situ* which was further treated with methyl chloroformate.

Typical Procedure: To a solution of anhydrous chloral (0.98 mL, 1.474 g, 10 mmol) or bromal (1.05 mL, 2.807 g, 10 mmol) in dry chloroform (40 mL) at 10 ˚C, the allylic mercaptan **324** (10 mmol) was added with stirring. The stirring was continued and the

solution was allowed to warm to room temperature over about 0.5 h. Anhydrous pyridine (0.80 mL, 0.791 g, 10 mmol) was added and the solution was then stirred for 0.5 h. With continuous stirring, acetyl chloride (0.714 mL, 0.745 g, 10 mmol) was added drop-wise over a period of 10 min at room temperature. The stirring was continued for 12-36 h at the same temperature. After completion of the reaction as indicated by TLC, the solvent from the reaction mixture was evaporated under reduced pressure. To the residual mass was added diethyl ether (150 mL) and resulting solution was stirred on a magnetic stirrer for 15 min and filtered. The filtrate was washed with brine (2x25 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to obtain almost pure 1-acetoxy-2,2,2-trichloroethyl allyl thioethers **325a-e**. These were further purified by column chromatography on a silica gel column using *n*-hexane/EtOAc (100:0 to 98:2, v:v) as the solvent for elution to obtain the thioethers **325a-e** in high isolated yields (73-82 %). The bromo derivative **326e** was obtained in comparatively lower (40%) yield.

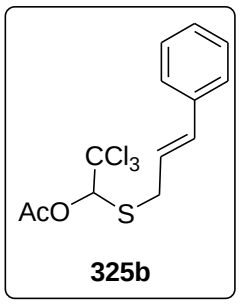
*2,2,2-Trichloro-1-(3-methylbut-2-enylthio)ethyl acetate **325a***:



325a

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300M Hz): δ 1.72 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.50-3.55 (m, 2H, CH_2S), 5.26-5.31(m, 1H, CHOAc), 6.25 (s, 1H, CH) ppm: ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.8 (CH_3), 20.8 (CH_3), 25.7 (CH_3), 31.5 (CH_2), 87.6 (CH), 99.3 (C), 118.6 (CH), 138.0 (C), 168.8 (C) ppm; IR (KBr): ν_{max} 2937(s), 1762(s), 1666 (w), 1442(m), 1372(s), 1205(s), 1125(w), 1021(s), 922(m), 798(s), 750(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{13}Cl_3O_2SNa$ 312.9595, found 312.9608.

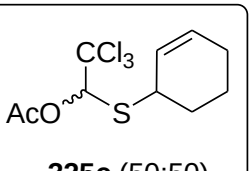
2,2,2-Trichloro-1-(3-phenylallylthio)ethyl acetate ***325b*****:**



325b

White crystals, mp 39 °C (DCM : *n*-hexane); δ ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.22 (s, 3H, CH_3), 3.66 (dd, 1H, *J* = 13.5, 6.3 Hz, CH_2S), 3.79 (dd, 1H, *J* = 13.5, 8.1 Hz, CH_2S), 6.27-6.37(m, 1H, olefinic CH), 6.44 (s, 1H, CHOAc), 6.69 (d, 1H, *J* = 15.6 Hz, olefinic CHPh), 7.30-7.42 (m, 3H, aryl CH), 7.48 (d, 2H, *J* = 7.2 Hz, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.5 (CH_3), 35.5 (CH_2), 87.2 (CH), 98.9 (C), 124.8 (CH), 126.2 (CH), 127.7 (CH), 128.4 (CH), 133.7 (CH), 136.0 (C), 168.6 (C) ppm; IR (KBr): ν_{max} 3029(m), 2932(s), 1760(s), 1590(w), 1493(m), 1421(m), 1374(s), 1294(w), 1198(s), 1024(s), 972(s), 795(s), 745(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{13}Cl_3O_2SNa$ 360.9587, found 360.9594.

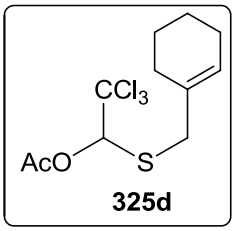
2,2,2-Trichloro-1-(cyclohex-2-enylthio)ethyl acetate ***325c*****:**



325c (50:50)

Colorless liquid, diastereomeric mixture (50:50); δ ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.59–2.08 (m, 6H, $3CH_2$), [2.20 & 2.22 (2s, 3H, CH_3CO)], 3.81–3.85 (m, 1H, CHS), 5.75 (dd, 1H, *J* = 18.3, 10.2 Hz, olefinic CH), 5.84–5.87 (m, 1H, olefinic CH), [(6.37 (s) + 6.40 (s)), 1H, CHOAc)] ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.6 (CH_2), 19.2 (CH_2), 20.78 (CH_3), 20.82 (CH_3), 24.7 (CH_2), 29.2 (CH_2), 29.7 (CH_2), 42.4 (CH), 43.7 (CH), 87.5 (CH), 87.6 (CH), 98.8 (C), 99.5 (C), 125.7 (CH), 125.9 (CH), 131.3 (CH), 131.9 (CH), 168.7 (C), 169.2 (C) ppm; IR (KBr): ν_{max} 3029(m), 2863(s), 1759(s), 1644(w), 1436(m), 1370(s), 1295(m), 1207(s), 1128(m), 1020(s), 974(s), 921(m), 797(s), 751(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{13}Cl_3O_2SNa$ 324.9589, found 324.9594.

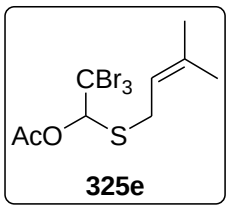
2,2,2-Trichloro-1-(cyclohexenylmethylthio)ethyl acetate ***325d*****:**



325d

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.52–1.68 (m, 4H, CH_2S), 1.95-2.20 (m, 4H, cyclohexenyl CH_2), [2.21 (s) + 2.22 (s), 3H, CH_3CO)], 3.25 (d, 1H, *J* = 13.5 Hz, CH_2S), 3.45 (d, 1H, *J* = 13.5 Hz, CH_2S), 5.77 (s, br, 1H, olefinic CH), [6.26(s) + 6.27(s), 1H, C<u>H</u>AOc)] ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8 (CH_3), 22.0 (CH_2), 22.5 (CH_2), 25.2 (CH_2), 26.6 (CH_2), 40.9 (CH_2), 87.5 (CH), 99.3 (C), 127.6 (CH), 132.5 (C), 169.0 (C) ppm; IR (KBr): ν_{max} 2930(s), 2860(s), 1762(s), 1625(w), 1436(m), 1370(m), 1207(s), 1127(m), 1018(s), 922(m), 798(s), 750(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{11}H_{15}Cl_3O_2SNa$ 338.9752, found 338.9751.

2,2,2-Tribromo-1-(3-methylbut-2-enylthio)ethyl ***325e****:*



325e

Brownish liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.72 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.56-3.60 (m, 2H, CH_2S), 5.25-5.33 (m, 1H, olefinic CH), 6.30 (s, 1H, C<u>H</u>OAc) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.9 (CH_3), 20.8 (CH_3), 25.7 (CH_3), 32.0 (CH_2), 43.9 (C), 89.4 (CH), 118.5 (CH), 138.2 (C), 168.7 (C) ppm; IR (KBr): ν_{max} 2971(m), 1759(s), 1664(w), 1442(m), 1373(m), 1022(s), 908(m), 729(m), 678(m) cm^{-1}. HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{13}Br_3O_2SNa$ 448.8043, found 448.8042.

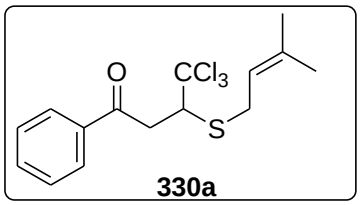
3.5.1.3. Preparation of side chain functionalized 2,2,2-trichloroethyl allyl thioethers 330 and 332

These previously unknown thioethers were prepared by a method reported in the literature[143] where thia-Micheal addition of an alkyl mercaptan to β-trichloromethyvinyl

phenyl ketone occurred smoothly. This method was extended to prepare the allylic mercaptans and other β-trichloromethyl-substituted Michael acceptors having functional groups such as cyano, nitro and ester (synthesis is mentioned in **chapter 2**).

General procedure: A solution of freshly prepared prenyl mercaptan (1.124 g, 11 mmol) or allyl mercaptan (0.816 g, 11 mmol) and β-trichloromethy-substituted Michael acceptors **220** (10 mmol) and a catalytic amount of triethylamine (0.304 g, 0.46 mL, 3 mmol in the case of **330a-d** and 0.51 g, 0.70 mL, 5 mmol in the case of **330e**) in *tert*-butanol (30 mL) was stirred at room temperature (25-30 ˚C). After disappearance of the starting material (6-8 h) as monitored by TLC and further confirmed by ^{1}H NMR of aliquots taken from time to time, the solvent was removed under reduced pressure on a rotavapor. The residual mass was purified by column chromatography on a silica gel column using *n*-hexane/ethylacetate (100:0 to 98:2, v:v) as the solvent for elution to obtain the functionalized prenyl thioethers **330a-e** and the allyl thioether **332** in good to high yields (68-85%) and 81%, respectively.

4,4,4-Trichloro-3-(3-methylbut-2-enylthio)-1-phenylbutan-1-one ***330a*****:**

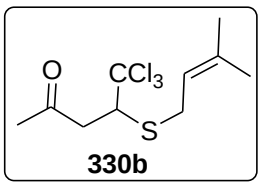


330a

White solid, mp 54 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz); δ 1.69 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 3.52-3.67(m, 2H, CH_2S overlapped with multiplet at 3.67-3.75), [3.67-3.75 (m, 2H, CH_2CO), 4.24 (dd, 1H, *J* = 8.4, 3.6 Hz, CHS), 5.19-5.25 (m, 1H, olefinc CH), 7.50 (t, 2H, *J* = 7.4 Hz, aryl CH), 7.61 (t, 1H, *J* = 7.2 Hz, aryl CH), 7.99 (d, 1H, *J* = 8.4 Hz, aryl CH) ppm: ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.8 (CH_3), 25.6 (CH_3), 33.9 (CH_2), 43.2 (CH_2), 60.9 (CH), 104.7 (C), 118.5 (CH), 128.1 (CH), 128.6 (CH), 133.4 (CH), 136.4 (C),

137.7 (C), 195.1 (C) ppm; IR (KBr): ν_{max} 2974(m), 2921(s), 1678(s), 1591(m), 1445(s), 1347(s), 1254(s), 1220(m), 1021(s), 983(m), 755(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{17}Cl_3OSNa$ 372.9965, found 372.9958.

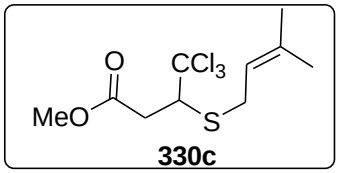
5,5,5-Trichloro-4-(3-methylbut-2-enylthio)pentan-2-one ***330b****:*



330b

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz); δ 1.71 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 3.03 (dd, 1H, *J* = 17.4, 9.9 Hz, CH_2CO), 3.27 (1H, *J* = 17.4, 3.6 Hz, CH_2CO), 3.48-3.64 (m, 2H, CH_2S), 3.98 (dd, 1H, *J* = 9.9, 2.4 Hz, CH-S), 5.22-27 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.7 (CH_3), 25.6 (CH_3), 30.8 (CH_3), 33.8 (CH_2), 47.5 (CH_2), 60.1 (CH), 104.3 (C), 118.5 (CH), 137.6 (C), 203.3 (C) ppm; IR (KBr): ν_{max} 2971(m), 2924(s), 1722(s), 1668(w), 1418(m), 1362(s), 1243(m), 1149(m), 845(m), 768(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{15}Cl_3OSNa$ 310.9804, found 310.9801.

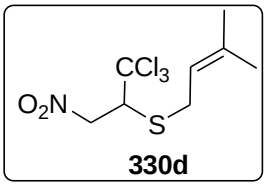
Methyl 4,4,4-trichloro-3-(3-methylbut-2-enylthio)butanoate ***330c****:*



330c

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.71 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.77 (dd, 1H, *J* = 16.2, 10.8 Hz, CH_2CO), 3.30 (dd, 1H, *J* = 16.2, 2.7 Hz, CH_2CO), 3.49 (dd, 1H, *J* = 12.0, 7.5 Hz, CH_2S), 3.60 (dd, 1H, *J* = 12.0, 8.4 Hz, CH_2S), 3.77 (s, 3H, CH_3), 3.87 (dd, 1H, *J* = 10.8, 2.7 Hz, CHS), 5.22-5.27 (m, 1H, olefinic CH) ppm: ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.8 (CH_3), 25.6 (CH_3), 33.7 (CH_2), 39.1 (CH_2), 52.1 (CH_3), 61.4 (CH), 103.9 (C), 118.5 (CH), 137.7 (C), 170.2 (C) ppm; IR (KBr): ν_{max} 2957(s), 1748(s), 1665 (w), 1440(s), 1359(m), 1253(s), 1208(s), 1159(m), 1073(m), 1024(m), 793(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{15}Cl_3O_2SNa$ 326.9743, found 326.9751.

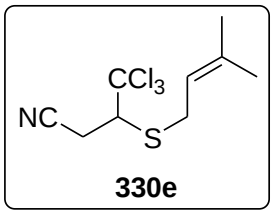
(3-Methylbut-2-enyl)(1,1,1-trichloro-3-nitropropan-2-yl)sulfane ***330d****:*



330d

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.38 (dd, 1H, *J* = 12.6, 7.2 Hz, CH_2S), 3.58 (dd, 1H, *J* = 12.6, 9.0 Hz, CH_2S), 4.18 (dd, 1H, J = 9.6, 3.3 Hz, CHS), 4.60 (dd, 1H, *J* = 13.5, 9.6 Hz, CH_2NO_2), [5.13-5.19 {m, 2H, (1H, olefinic CH and 1H, CH_2NO_2) overlapped signals}] ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.8 (CH_3), 25.7 (CH_3), 33.4 (CH_2), 61.5 (CH), 77.5 (CH_2), 101.1 (C), 118.0 (CH), 139.0 (C) ppm; IR (KBr): ν_{max} 2973(m), 2926(s), 1662(w), 1563(s), 1435(m), 1374(s), 1026(w), 797(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_{12}C_{l3}NO_2SNa$ 313.9542, found 313.9547.

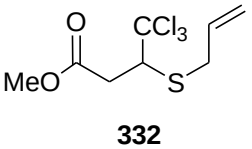
4,4,4-Trichloro-3-(3-methylbut-2-enylthio)butanenitrile ***330e*****:**



330e

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.74 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.85 (dd, 1H, *J* = 16.8, 10.8 Hz, CH_2CN), 3.34 (dd, 1H, *J* = 16.8, 2.7 Hz, CH_2CN, partially overlapped with dd at δ 3.42 ppm), 3.42 (dd, 1H, *J* = 12.6, 6.3 Hz, CH_2S), 3.57 (dd, 1H, *J* = 10.8, 2.7 Hz, CHS), 3.68 (dd, 1H, *J* = 12.6, 9.0 Hz, CH_2S), 5.32-5.38 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.9 (CH_3), 24.0 (CH_2), 25.7 (CH_3), 33.2 (CH_2), 60.2 (CH), 102.2 (C), 116.5 (C), 118.5 (CH), 138.6 (C) ppm; IR (KBr): ν_{max} 2973(s), 2925(s), 2251(m), 1664(m), 1429(s), 1379(m), 1229(s), 1009(m), 781(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{12}Cl_3NSNa$ 293.9648, found 293.9648.

Methyl 3-(allylthio)-4, 4, 4-trichlorobutanoate ***332:***



332

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.79 (dd, 1H, *J* = 16.5, 10.5 Hz, CH_2CO), 3.34 (dd, 1H, *J* = 16.5, 2.7 Hz,

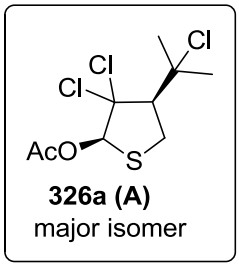
CH_2CO), 3.37 (dd, 1H, *J* = 13.2, 6.9 Hz, CH_2S), 3.58 (dd, 1H, *J* = 13.2, 8.1 Hz, CH_2S), 3.79 (s, 3H, CH_3), 3.88 (dd, 1H, *J* = 10.5, 2.7 Hz, CHS), 5.06-5.19 (m, 2H, olefinic CH_2), 5.70-5.86 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.4 (CH_2), 39.1 (CH_2), 52.1 (CH_3), 60.3 (CH), 103.9 (C), 118.9 (CH_2), 132.9 (CH), 170.1 (C) ppm; IR (KBr): ν_{max} 2947(m), 1742(s), 1636(w), 1435(m), 1360(m), 1252(s), 1215(s), 1161(s), 1024(m), 992(s), 924(m), 792(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_{11}Cl_3O_2SNa$ 298.9437, found 298.9438.

3.5.2. CuCl/PMDETA-mediated regioselective cyclization of 2,2,2-trichloroethyl allyl sulphides 325, 330 and 332: Preparation of the halogenated and side chain functionalized tertahydrothiophenes 326, 331 and 333

General procedure: A flame-dried two-neck round-bottom flask was charged with CuCl (0.100 g, 1mmol) (0.050 g, 0.5 mmol, in the case of **325c** and **332**) and degassed acetonitrile (20 mL) under a N_2 atmosphere using Schlenk technique. PMDETA (0.2 mL, 0.173 g, 1 mmol) (0.1 mL, 0.086 g, 0.5 mmol in the case of **325c** and **332**) was injected to the suspension. Next, the 2,2,2-trichloroethyl allyl thioether **325**, **330** or **332** (1 mmol) was added. The reaction mixture was again degassed and filled with N_2 atmosphere. It was stirred at room temperature (25-30 ˚C). Monitoring the progress of the reaction by TLC indicated the completion of the reaction after 10-16 h (3 h at reflux in the case of **325c** and **332**). The acetonitrile solvent was evaporated under reduced pressure and the residual mass was taken up in ethyl acetate (100 mL). The resulting solution was washed with brine (2x25 mL), dried (Na_2SO_4) and filtered. The crude product obtained after evaporation of

ethyl acetate was further purified by column chromatography using silica gel column and *n*-hexane/ethylacetate (99:1 to 95:5, v:v) as the solvent for elution. The tetrahydrothiophenes **326**, **331** and **333** were thus obtained as mixtures of diastereomers in good to high yields (52-81%, 69-83% and 64%, respectively). In the case of **331a**, a single diastereoisomer was obtained. These were further purified and separated by recrysatallization from *n*-hexane or *n*-hexane-DCM.

*Cis-3,3-Dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl acetate **326a (A)***:



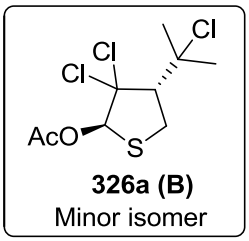
326a (A)
major isomer

Major isomer, colorless crystals, mp 67 ˚C (*n*-hexane-DCM); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.12 (dd, 1H, *J* = 11.1, 6.0 Hz, C<u>H</u>-CH_2), 3.30 (dd, 1H, *J* = 11.1, 6.0 Hz, CH_2S), 3.45 (t, 1H, *J* = 11.1 Hz, CH_2S), 6.34 (s, 1H, C<u>H</u>-OAc) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): 20.6 (CH_3), 30.2 (CH_2), 30.4 (CH_3), 34.2 (CH_3), 61.5 (CH), 71.1 (C), 86.1 (CH), 90.3 (C), 169.3 (C) ppm; IR (KBr): ν_{max} 2931(s), 1734(s), 1457(m), 1374(s), 1252(s), 1132(s), 1018(m), 812(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{13}Cl_3O_2SNa$ 312.9595, found 312.9594.

X-ray crystal structure data of 326a (A) major isomer

Formula sum: $C_9H_{13}Cl_3O_2S_1$, Formula weight: 176.65 g/mol; Crystal system: monoclinic; Space group: P 1 21 1 (4); Unit cell dimensions: a = 7.746(3) Å b = 9.952(4) Å c = 16.723(7) Å α = 90.00(0)°, β = 89.997(7)°, γ = 90.00(0)°; Cell volume = 1289.15(90) $Å^3$, Z = 6; Density calculated = 1.36517 g/cm^3; R_{All} = 0.0962. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989268).

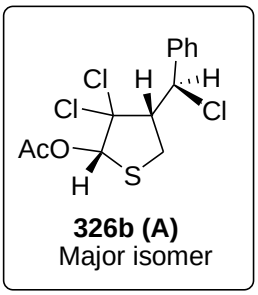
*(Trans)-3,3-Dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl acetate **326a (B)**:*



326a (B)
Minor isomer

Minor isomer, viscous liquid (contains 25% major isomer); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.88 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.13-3.27 [m, 2H, (1H, C<u>H</u>CH_2 and 1H, CH_2S)], 3.32 (dd, 1H, *J* = 8.7, 6.0 Hz, CH_2S), 6.18 (s, 1H, CHOAc) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): 20.9 (CH_3), 29.9 (CH_2), 30.6 (CH_3), 34.6 (CH_3), 60.4 (CH), 70.7 (C), 88.0 (CH), 91.0 (C), 168.7 (C) ppm; IR (KBr): ν_{max} 2984(s), 1757(s), 1452(m), 1372(m), 1214(s), 1115(m), 1018(m), 773(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{13}Cl_3O_2SNa$ 312.9595, found 312.9603.

(*Cis*)*-3,3-Dichloro-4-((S)-chloro(phenyl)methyl)-tetrahydrothiophen-2-ylacetate **326b (A)**:*



326b (A)
Major isomer

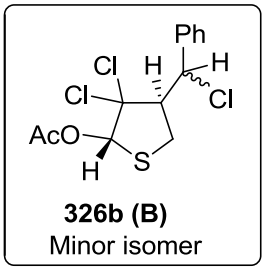
Major isomer, white crystals, mp 77 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 3H, CH_3CO), 3.28-3.34 [m, 2H, (1H, CH_2S and 1H, methine C<u>H</u>CH_2) partially overlapped the dd at δ 3.43 ppm}], 3.43 (dd, 1H, *J* = 12.0, 6.0 Hz, CH_2S), 5.31 (d, 1H, *J* = 7.8 Hz, CHCl), 6.27 (s, 1H, C<u>H</u>OAc), 7.37 (d, 3H, *J* = 5.7 Hz, aryl CH), 7.45 (d, 2H, *J* = 5.1 Hz, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6 (CH_3), 32.5 (CH_2), 58.8 (CH), 62.6 (CH), 86.2 (CH), 91.0 (C), 127.9 (CH), 128.6 (CH), 129.1 (CH), 139.3 (C), 169.5 (C) ppm; IR (KBr): ν_{max} 3027(w), 2933(m), 1743(s), 1494(w), 1432(m), 1373(m), 1232(s), 1068(s), 1022(m), 920(m), 731(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{13}Cl_3O_2SNa$ 360.9595, found 362.9594.

X-ray crystal structure data of 326b (A) major isomer

Formula sum: $C_{13}H_{13}Cl_3O_2S$, Formula weight: 96.53 g/mol; Crystal system: monoclinic; Space group: P 1 21/c 1 (14); Unit cell dimensions: a =12.274 (2) Å b = 13.914 (2) Å c =

9.3389 (16) Å α = 90.000(0)°, β =109.951(3)°, γ = 90.000(0)°; Cell volume = 1499.18(40) $Å^3$, Z = 17; Density calculated = 1.81752 g/cm^3; R_{All} = 0.0419. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989263).

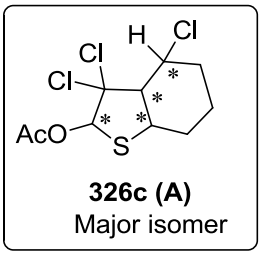
*(Trans) 3,3-Dichloro-4--chloro(phenyl)methyl)-tetrahydrothiophen-2-yl acetate **326b (B):***



326b (B)
Minor isomer

Minor isomer, viscous colorless liquid (containing 20% of major isomer); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.20 (s, 3H, CH_3CO), [3.20-3.44 {m, 3H, (2H, CH_2S and 1H, C<u>H</u>CH_2)}], 5.31 (d, 1H, *J* = 7.8 Hz, CHCl), 6.28 (s, 1H, C<u>H</u>OAc), 7.36-7.39 (m, 3H, aryl CH), 7.44-7.46 (m, 2H, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4 (CH_3), 32.2 (CH_2), 58.4 (CH), 62.5 (CH), 86.4 (CH), 91.5 (C), 127.7 (CH), 128.8 (CH), 129.3 (CH), 139.4 (C), 168.8 (C) ppm; IR (KBr): ν_{max} 2925(m), 1757(s), 1660(m), 1496(s), 1454(m), 1371(s), 1213(s), 1078(m), 1020(m), 743(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{13}Cl_3O_2SNa$ 360.9595, found 362.9594**.**

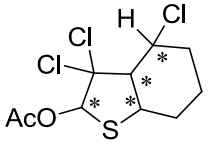
*3,3,4-Trichloro-octahydrobenzo[b]thiophen-2-yl acetate **326c (A)***:



326c (A)
Major isomer

Major isomer, colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.68-2.06 (m, 5H, cyclohexyl CH_2), 2.13 (s, 3H, CH_3CO), 2.30-2.35 (m, 1H, cyclohexyl CH_2), 3.23 (d, 1H, *J* = 8.4 Hz, C<u>H</u>CHCl), 3.78-3.87 (m, 1H, CHS), 4.94 (s, br, 1H, CHCl), 6.33 (s, 1H, CHOAc) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.9 (CH_2), 21.0 (CH_3), 30.8 (CH_2), 31.2 (CH_2), 39.9 (CH), 56.4 (CH), 57.1 (CH), 85.7 (CH), 92.2 (C), 168.8 (C) ppm; IR (KBr): ν_{max} 2933(s), 1759(s), 1446(m), 1371(m), 1215(s), 1064(m), 1018(s), 762(m) cm^{-1}. HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{13}Cl_3O_2SNa$ 324.9599, found 324.9592.

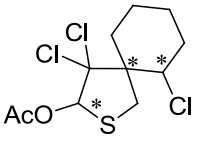
3,3,4-Trichloro-octahydrobenzo[b]thiophen-2-yl acetate ***326c (B)***:



326c (B)
Minor isomer

Minor isomer, **c**olorless solid, mp 40 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.65-2.00 (m, 5H, cyclohexyl CH_2), 2.23 (s, 3H, CH_3CO), 2.36-2.39 (m, 1H, cyclohexyl CH_2), 3.06 (dd, 1H, *J* = 6.0, 5.7 Hz, C<u>H</u>CHCl), 4.05 (dd, 1H, *J* = 12.6, 5.7 Hz, CHS), 4.62 (dd, 1H, *J* = 11.1, 6.0 Hz, CHCl), 6.25 (s, 1H, CHOAc) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.0 (CH_2), 20.9 (CH_3), 29.1 (CH_2), 34.3 (CH_2), 43.0 (CH), 55.8 (CH), 59.4 (CH), 85.9 (CH), 92.1 (C), 169.1 (C) ppm; IR (KBr): ν_{max} 2937(s), 2861(m), 1760(s), 1446(w), 1369(m), 1212(s), 1095(m), 1053(m), 1017(m), 764(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{13}Cl_3O_2SNa$ 324.9599, found 324.9594.

Spiro(cyclohexyl)dihydrothiophene ***326d (A &B)***:



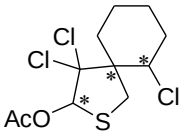
326d

First two major isomers (**A:B** =1:2)
of four diastereomers (**A:B:C:D** =1:2:1:1)

Isolated from the mixture of four diastereomers (**A:B:C:D = 1:2:1:1**). First two diastereomer (**A:B= 1:2**), colorless solid, mp 46 ˚C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): 1.30–2.40 [{(m)(major + minor isomer), 8H, cyclohexyl CH_2} + {2.16 (s)(major isomer) + 2.20 (s)(minor isomer), 3H, CH_3CO}, 11H], [2.74 (d, *J* = 7.2 Hz)(major isomer) + 2.80 (t, 1H, *J* = 6.2 Hz)(minor isomer), 1H, CHCl], 3.73 (d, 1H, *J* = 11.4 Hz, CH_2S)(major + minor isomers), [3.88 (d, *J* = 11.4 Hz)(major isomer) + 4.08 (d, *J* = 11.4 Hz)(minor isomer), 1H, CH_2S], [6.34 (s)(major isomer) + 6.40 (s)(minor isomer), 1H, C<u>H</u>OAc] ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.84 (CH_2), 20.86 (CH_3), 20.9 (CH_2), 21.0 (CH_3), 21.5 (CH_2), 21.8 (CH_2), 21.9 (CH_2), 23.5 (CH_2), 32.9 (CH_2), 33.5 (CH_2), 51.5 (CH), 52.8 (CH), 53.0 (CH_2), 53.4 (CH_2), 57.2 (C), 57.6 (C), 85.2 (CH), 85.7 (CH), 95.4 (C), 96.0 (C), 168.8

(C), 169.1 (C) ppm; IR (KBr): νmax 2940(s), 2865(w), 1757(s), 1451(m), 1370(m), 1214(s), 1019(s), 960(m), 761(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{11}H_{15}Cl_3O_2SNa$ 338.9750, found 338.9751.

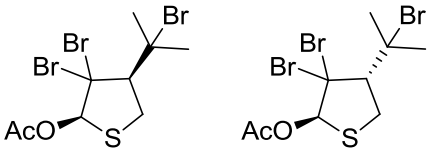
*Spiro(cyclohexyl)dihydrothiophene **326d (C & D):***



326d
Other two isomers (**C:D** =1:1)
of four diastereomers (**A:B:C:D** =1:2:1:1)

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ [1.30–2.40 {(m, 8H, cyclohexyl CH_2) + 2.16, 2.19 (2s, 3H, CH_3CO)}, 11H], 2.71-2.79 (m, 1H, CHCl), [3.75 (d, 1H, *J* = 11.4 Hz) + 3.84 (d, 2H, *J* = 11.4 Hz) + 3.90 (d, 1H, *J* = 11.4 Hz), 2H, CH_2S], [6.0 (s) + 6.1 (s), 1H, C<u>H</u>OAc] ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7 (CH_2), 20.94 (CH_3), 20.97 (CH_2), 21.0 (CH_3), 21.5 (CH_2), 21.8 (CH_2), 21.9 (CH_2), 23.5 (CH_2), 32.4 (CH_2), 37.6 (CH_2), 52.9 (CH), 53.0 (CH_2), 53.4 (CH_2), 55.8 (CH), 74.0 (C), 74.9 (C), 78.5 (CH), 80.1 (CH), 93.6 (C), 95.3 (C), 167.8 (C), 168.2 (C) ppm; IR (KBr): ν_{max} 2934(s), 2869(m), 1761(s), 1447(m), 1370(m), 1207(s), 1020(s), 955(m), 761(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{11}H_{15}Cl_3O_2S$ 338.9750, found 338.9755.

*3,3-Dibromo-4-(2-bromopropan-2-yl)-tetrahydrothiophen-2-yl acetate **326e (A&B)***:



326e (A) **326e (B)**
mixture 60 : 40

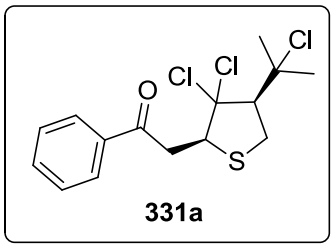
Light brown crystals (mixture 60:40), mp 67-70 °C (*n*-hexane) (diastereomeric mixture 60:40), ^1H NMR ($CDCl_3$, 300 MHz): δ 1.88, 1.91, 1.96, 2.07 (4s, 6H, germinal methyls $2CH_3$), [2.23 (s)(major isomer) + 2.58 (s)(minor isomer), 3H, $COCH_3$)], 2.96 [(dd, 0.6H, *J* = 11.1, 6.0 Hz, $CHCBrMe_2$)(major isomer)], 3.10 [(dd, 0.6 H, *J* = 11.4, 6.0 Hz, CH_2S)(major isomer)], 3.11-3.22 [(m, 0.6H, CH_2S, major isomer) + (m, 0.4 H, $CHCBrMe_2$, minor isomer)], 3.33-

3.42 (m, 0.8H, CH_2S, minor Isomer), [6.16 (s, 0.6H, CHOAc, major isomer) + 6.35 (s, 0.4 H, CHOAc, minor isomer)] ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7 (CH_3), 30.5 (CH_3), 30.8 (CH_2), 31.8 (CH_2), 32.0 (CH_3), 34.4 (CH_3), 36.0 (CH_3), 61.7 (CH), 62.4 (CH), 67.4 (C), 71.6 (C), 80.2 (C), 80.5 (C), 86.4 (CH), 87.2 (CH), 169.4 (C), 169.5 (C) ppm; IR (KBr): ν_{max} 2985(s), 1753(s), 1449(m), 1376(m), 1212(s), 1110(m), 1077(m), 1041(m), 757(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{13}Br_3O_2SNa$ 448.8043, found 448.8024.

X-ray crystal structure data of 326e (A) major isomer

Formula sum: $C_9H_{13}Br_3O_2S_1$, Formula weight: 140.99 g/mol; Crystal system: orthorhombic; Space group: P c a 21 (29); Unit cell dimensions: a=7.772(3) Å b = 16.938(7) Å c = 10.080(4) Å α = 90.00(0)°, β = 90.00(0)°, γ = 90.00(0)°; Cell volume = 1326.95(100) $Å^3$, Z = 14; Density calculated = 2.46993 g/cm^3; R_{All} = 0.0885. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989269).

(*Cis*)-*2-(3,3-Dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)-1-phenylethanone* ***331a***:



331a

White crystals, mp 107 °C (*n*-hexane-DCM); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.94 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 3.13 (dd, 1H, *J* = 10.2, 7.8 Hz, $CHCMe_2$), 3.24-3.38 (m, 2H, CH_2S), 3.48 (dd, 1H, *J* = 18.0, 10.2 Hz, CH_2CO), 3.88 (dd, 1H, *J* = 18.0, 1.8 Hz, CH_2CO), 4.38 (dd, 1H, *J* = 10.2, 1.8 Hz, CHS), 7.49 (t, 2H, *J* = 7.5 Hz, aryl CH), 7.60 (t, 1H, *J* = 7.35 Hz, aryl CH), 8.01 (d, 2H, *J* = 7.2 Hz, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.2 (CH_2), 30.7 (CH_3), 34.6 (CH_3), 40.6 (CH_2), 56.2 (CH), 64.4 (CH), 71.3 (C),

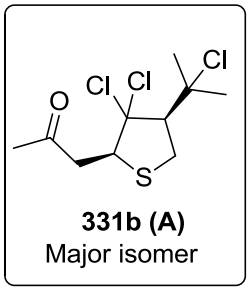
93.7 (C), 128.1 (CH), 128.7 (CH), 133.6 (CH), 136.0 (C), 196.4 (C) ppm; IR (KBr): ν_{max} 2980(m), 2908(m), 1678(s), 1591(m), 1452(m), 1372(m), 1303(m), 1242(m), 1209(m), 754(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{17}Cl_3OSNa$ 372.9968, found 372.9958.

X-ray crystal structure data of *331a*

Formula sum: $C_{15}H_{17}Cl_3O_1S_1$, Formula weight: 173.63 g/mol; Crystal system: triclinic; Space group: P 1 (1); Unit cell dimensions: a = 6.6035(18) Å, b = 9.504(3) Å c = 13.442(4) Å α = 88.650(5)° β = 86.748(4)° γ =74.724(4)°; Cell volume = 812.47(40) $Å^3$, Z = 4; Density calculated = 1.41939 g/cm^3; R_{All} = 0.1126. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989285).

(*Cis*)-*1-(3,3-Dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)propan-2-one*

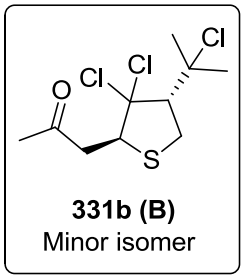
331b *(A):*



331b (A)
Major isomer

Colorless crystals, mp 41°C (*n*-hexane), diastereomeric mixture (80:20); Major isomer, ^1H NMR ($CDCl_3$, 300 MHz): δ 1.92 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.24 (s, 3H, CH_3CO), 2.92 (dd, 1H, *J* = 18.3, 10.2 Hz, CH_2CO), 3.06 (dd, 1H, *J* = 10.2, 7.5 Hz, $CHCClMe_2$), 3.21-3.37 [m, 3H, (1H, CH_2CO and 2H, CH_2S)], 4.17 (d, 1H, *J* = 9.9 Hz, CHS) ppm; C^{13}NMR ($CDCl_3$, 300 MHz): 29.1 (CH_2), 30.2 (CH_3), 30.7 (CH_3), 34.6 (CH_3), 45.0 (CH_2), 55.6 (CH), 64.3 (CH), 71.3 (C), 93.3 (C), 205.0 (C) ppm; IR (KBr): ν_{max} 2921(m), 1720(s), 1413(m), 1360(s), 1175(m), 816(s), 772(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{15}Cl_3OSNa$ 310.9801, found 310.9801.

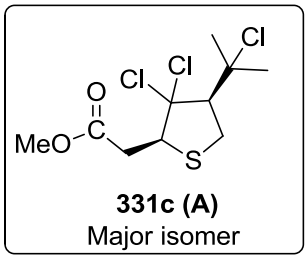
(Trans)-1-(3,3-Dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)propan-2-one ***331b(B)****:*



331b (B)
Minor isomer

Colorless solid mp 41°C (*n*-hexane), Minor isomer, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.83 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.85 (dd, 1H, *J* = 18.0, 7.5 Hz, CH_2CO), 2.99 (dd, 1H, J = 10.5, 7.8 Hz, CH_2CO)], 3.12-3.20 [m, 3H (1H, C<u>H</u>CMe_2Cl and 2H, CH_2S)], 4.05 (dd, 1H, *J* = 10.5, 3.6 Hz, CHS) ppm; C^{13} NMR ($CDCl_3$, 300 MHz): 29.9 (CH_2), 30.3 (CH_3), 30.4 (CH_3), 34.4 (CH_3), 49.8 (CH_2), 57.6 (CH), 64.0 (CH), 71.7 (C), 93.7 (C), 204.4 (C) ppm; IR (KBr): ν_{max} 2987(m), 1715(s), 1451(m), 1362(s), 1165(m), 1115(m), 772(m) cm^{-1}.

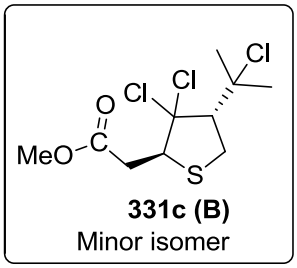
(Cis)-Methyl 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetate ***331c (A)****:*



331c (A)
Major isomer

Major isomer, colorless crystals, mp 53 ˚C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.72 (dd, 1H, *J* = 16.8, 10.5 Hz, CH_2CO), 3.08 (dd, 1H, *J* = 10.2, 8.1 Hz, C<u>H</u>CMe_2Cl), [3.26-3.33 {m, 3H, (2H, CH_2S + 1H, CH_2CO)}, 3.71 (s, 3H, C<u>H</u>$_3$OAc), 4.17 (dd, 1H, *J* = 10.5, 1.5 Hz, CHS) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.1 (CH_2), 30.5 (CH_3), 34.6 (CH_3), 35.6 (CH_2), 52.2 (CH), 56.8 (CH_3), 64.5 (CH), 71.3 (C), 92.9 (C), 171.0 (C) ppm; IR (KBr): ν_{max} 2948(m), 1737(s), 1443(s), 1376(m), 1202(s), 1117(m), 1021(m), 786(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{15}Cl_3O_2Na$ 326.9744, found 326.9751.

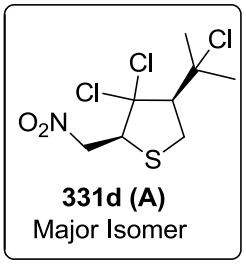
(Trans)-Methyl 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetate ***331c (B):***



331c (B)
Minor isomer

Minor isomer; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.62 (dd, 1H, *J* = 16.2, 10.8 Hz, CH_2CO), 2.96-3.38 [m, 4H, (1H, $CHCMe_2Cl$, 2H, CH_2S and 1H, CH_2CO], 3.72 (s, 3H, CH_3O), 4.04 (dd, 1H, *J* = 10.8, 4.2 Hz, CHS) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.7 (CH_2), 30.3 (CH_3), 34.4 (CH_3), 41.2 (CH_2), 49.7 (CH), 58.8 (CH_3), 63.4 (CH), 71.5 (C), 93.1 (C), 170.6 (C) ppm; IR (KBr): ν_{max} 2984(s), 1740(s), 1436(s), 1373(s), 1202(s), 1171(m), 1015(s), 894(m), 784(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{15}Cl_3O_2Na$ 326.9744, found 326.9757

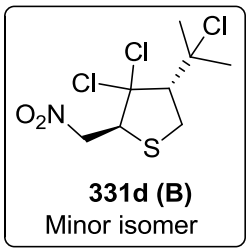
(Cis)-3,3-Dichloro-4-(2-chloropropan-2-yl)-2-(nitromethyl)-tetrahydrothiophene ***331d (A):***



331d (A)
Major Isomer

Major isomer, reddish low melting solid 40-42 ˚C (*n*-hexane), diastereomeric mixture (80:20); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92 (s, 3H, CH_3): 1.96 (s, 3H, CH_3), 3.04 (dd, 1H, *J* = 9.6, 7.8 Hz, $CHCMe_2Cl$), 3.26-3.40 (m, 2H, CH_2S), 4.46-4.57 [m, 2H, (1H, CH_2NO_2 + 1H, CHS)}, 4.99-5.12 (m, 1H, CH_2NO_2) ppm: ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.8 (CH_2), 30.5 (CH_3), 34.4 (CH_3), 58.8 (CH), 63.7 (CH), 70.9 (C), 78.9 (CH_2), 90.8 (C) ppm; IR (KBr): ν_{max} 2985(m), 2933(m), 1558(s), 1423(m), 1376(s), 1115(m), 790(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_{12}Cl_3NO_2SNa$ 313.9546, found 313.9547.

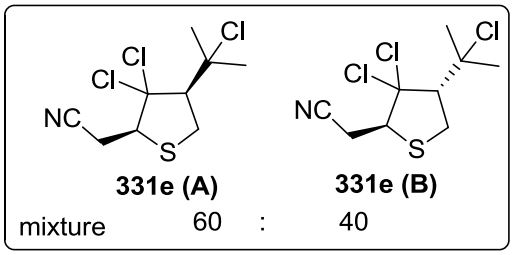
(Trans)-3,3-Dichloro-4-(2-chloropropan-2-yl)-2-(nitromethyl)-tetrahydrothiophene ***331d (B)****:*



331d (B)
Minor isomer

Minor isomer; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92 (s, 3H, CH_3): 1.96 (s, 3H, CH_3), 3.13 (dd, 1H, *J* = 10.2, 8.4 Hz, $CHCMe_2Cl$), 3.27-3.39 (m, 2H, CH_2S), 4.50-4.57 (m, 1H, CHS), 4.66 (dd, 1H, *J* = 14.1, 9.6 Hz, CH_2NO_2), 5.16 (dd, 1H, *J* = 14.1, 2.7 Hz, CH_2NO_2) ppm: ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.5 (CH_2), 30.6 (CH_3), 34.5 (CH_3), 57.3 (CH), 64.5 (CH), 70.6 (C), 76.3 (CH_2), 90.6 (C) ppm; IR (KBr): ν_{max} 2984(s), 2947(s), 1553(s), 1446(m), 1376(s), 1124(s), 794(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_{12}Cl_3NO_2S$ 313.9546, found 313.9557.

2-(3,3-Dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetonitrile ***331e (A& B)****:*

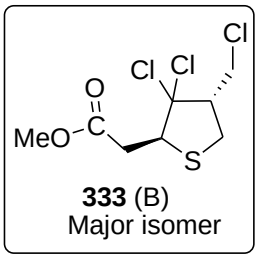


331e (A) **331e (B)**
mixture 60 : 40

Colorless solid, mp 51 °C (*n*-hexane), diastereotopic mixture (60:40); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.93 & 1.94 (s, 6H, $2CH_3$), [2.80 (dd, *J* = 16.8, 9.3 Hz)(major isomer) + 2.92 (dd, *J* = 16.8, 7.8 Hz)(minor isomer), 1H, CH_2CN)], [3.03-3.07 (m)(minor isomer) + 3.10-3.13(m)(major isomer), 1H, CH_2CN], [3.16-3.44 (m)(major isomer) + 3.21-3.24 (m)(minor isomer), 3H{1H, C<u>H</u>CMe_2Cl and 2H, CH_2S}], [3.97 (dd, 1H, *J* = 7.8, 4.8 Hz)(minor isomer) + 4.08 (dd, *J* = 9.3, 4.2 Hz)(major isomer), 1H, CHS)] ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.0 (CH_2), 25.6 (CH_2), 29.2 (CH_2), 30.2 (CH_2), 30.5 (CH_3), 30.6 (CH_3), 34.4 (CH_3), 34.5 (CH_3), 56.9 (CH), 58.8 (CH), 63.2 (CH), 64.6 (CH), 70.8 (C), 91.8 (C), 92.3 (C), 116.5 (C), 116.7 (C ppm; IR (KBr): ν_{max} 2982(s), 2934(s), 2247(m), 1454(s). 1413(s),

1374(s), 1225(m), 1120(s), 785(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{12}Cl_3NSNa$ 293.9648, found 293.9648.

(*Trans*)-*Methyl 2-(3,3-dichloro-4-(chloromethyl)-tetrahydrothiophen-2-yl)acetate* ***333(B):***



333 (B)
Major isomer

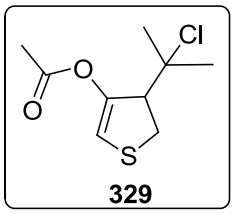
Major isomer from diastereomeric mixure (80:20); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.68 (dd, 1H, *J* = 16.8, 10.5 Hz, CH_2CO), 2.94-2.99 [m, 2H, (1H, CH_2S and 1H, C<u>H</u>CHCl)], 3.21 (dd, 1H, *J* = 16.8, 3.6 Hz, CH_2CO partially overlapped with multiplet at 3.28-3.34), 3.28-3.34 (m, 1H, CH_2S), 3.62 (t, 1H, *J* = 10.5 Hz, CH_2Cl), 3.70 (s, 3H, C<u>H</u>$_3$OAc), 4.03 (d, 1H, *J* = 12.6 Hz, CHS), 4.12 (dd, 1H, *J* = 10.5, 3.9 Hz, CH_2Cl) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.4 (CH_2), 39.8 (CH_2), 42.9 (CH_2), 52.2 (CH_3), 55.3 (CH), 57.8 (CH), 94.3 (C), 170.5 (C) ppm; IR (KBr): ν_{max} 2994(m), 1733(s), 1443(s), 1376(m), 1304(s), 1204(s), 1023(m), 897(m), 819(s) cm^{-1}; HRMS (ESI+): calc $C_8H_{11}Cl_3O_2SNa$ 298.9449, found 298.9438.

X-ray crystal structure data of 333(B)

Formula sum: $C_8H_{11}Cl_3O_2S$, Formula weight: 96.53 g/mol; Crystal system: orthorhombic; Space group: P 21 21 21 (19); Unit cell dimensions: a = 7.434(8) Å b = 8.170(8) Å c = 19.35(2) Å α = 90.000(0)°, β = 90.000(0)°, γ = 90.000(0)°, Cell volume = 1175.24(200) $Å^3$, Z = 13; Density calculated = 1.77298 g/cm^3; R_{All} = 0.1842. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989284).

3.5.3. *4-(2-Chloropropan-2-yl)-4,5-dihydrothiophen-3-yl acetate **329**.*

This reaction was done following a method reported in the literature[137] in which an acyclic 2,2,2-trichloroethyl alkyl carbonate was treated with a suspension of Zn/AcOH under reflux to eliminate the chlorine and carbonate group at the vicinal positions to produce a double bond.



329

The tetrahydrothiophene **326a** (0.110 g, 0.5 mmol) was heated with Zn powder (0.458 g, 5 mmol) in acetic acid (10 mL) at reflux. The progress of the reaction was monitored by TLC which indicated the completion of the reaction after 6 h. The completion of the reaction was also confirmed by ^{1}HNMR of the aliquot drawn from the reaction mixture. After the completion of the reaction, the reaction mixture was poured into ice cold water (50 mL) and extracted with ethyl acetate (4x25 mL). The combined organic solvent was washed with brine (2x25 mL), dried (Na_2SO_4) and filtered. The filtrate was evaporated under reduced pressure. The crude product thus obtained was further purified by column chromatography using silica gel column and *n*-hexane:EtOAc (90:10 to 80:20, v:v) as the solvent for elution to obtain the dihydrothiophene **329** (0.067 g, 56%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.55 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 3.22 (dd, 1H, *J* = 12.0, 4.5 Hz, 1H, CH_2S), 3.55 (t, 1H, *J* = 11.4 Hz, C<u>H</u>CMe_2Cl), 3.93 (dd, 1H, *J* = 10.5, 4.5 Hz, CH_2S), 6.22 (s, 1H, vinylic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): 22.43 (CH_3), 23.31 (CH_3), 24.45 (CH_3), 32.5 (CH_2), 55.2 (CH), 83.9 (C), 119.8 (C), 125.0 (CH), 170.3 (C) ppm; IR (KBr): ν_{max} 3078(s), 2984(m), 2932(s), 1732(s), 1576(m), 1460(s), 1368(s), 1252(s), 1128(s), 1018(s), 946(m), 811(s), 612(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{13}Cl_1O_2SNa$ 243.0210, found 243.0217.

CHAPTER 4

One step synthesis of 2,3-difunctionalized tri- and tetrasubstituted 4-chloro *N*-H pyrroles by CuCl/PMDETA-catalyzed *5-endo* radical cyclization-aromatization

4.1. Introduction

Pyrrole is one of the most important heterocyclic compounds. It is structural constituent of a broad range of natural products and bioactive compounds[144] displaying a variety of physiological activities.[145] Many natural and synthetic pyrroles are versatile synthetic intermediates.[146] Pyrroles have also found application in material science.[147]

A number of naturally occurring pyrroles have no substituent at the nitrogen atom (hereafter referred to as *N*-H pyrroles). *N*-H Pyrroles including those occurring in nature show coordination[144a-c] with various metals using the *N*H centre, for example porphyrins, hemoglobin, etc. The *N*-H pyrroles are also involved in molecular recognition phenomenon,[144c] for example, in bacterial red pigment prodigiosin, a transporter of chloride anions and protons across phospholipid membranes.[148] The *N*H functionality of synthetic pyrroles has been exploited for synthesis of many natural products[149] such as Lukinol A,[149b] peramines,[149c]etc. It has also been used in material science, for example in the synthesis of derivatives of 4,4-difluoro-4-boradipyrrin (BODIPY) system used in laser manufacture, image diagnosis and chemosensor.[147b] In many other applications also, *N*-substituted pyrroles are no substitutes.[145]

Many natural *N*-H pyrroles possess chlorine atoms including that occupying the β-position and other functional groups. They exhibit interesting medicinal properties.[144] For example, Pioluteorine[144d] **334** (**Fig. 22**), a secondary metabolite isolated from bacterial sources is antibacterial. The marine natural products marinopyrroles **335** showed good activities against methacillin-resistant *staphylococcus aureus*strains.[144e] The Roseophillin **336**, isolated from *Streptomyces griseoviridis*is a 2-substituted-3-chloropyrrole possessing antileukemic property.[144f] 3-Chloro-2-(3-nitro-4-chlorophenyl)pyrrole **337** called

pyrrolnitrin, isolated from bacteria *pseuomonas pyrociniae*, has fungicidal and bactericidal properties.[144g] The simpler 2-acetyl-5-chloropyrrole **338** is found in the volatile flavor of cocoa butter.[144h] Pyralomicinones **339**, unique heterocyclic natural products isolated from the microorganism *microtetraspora spiralis* is antibacterial.[144i] Rumbrin **340**, a pyrrolylpolyene isolated from an *auxarthron umbrinum* strain showed anticancer and cytoprotective activities.[144j]

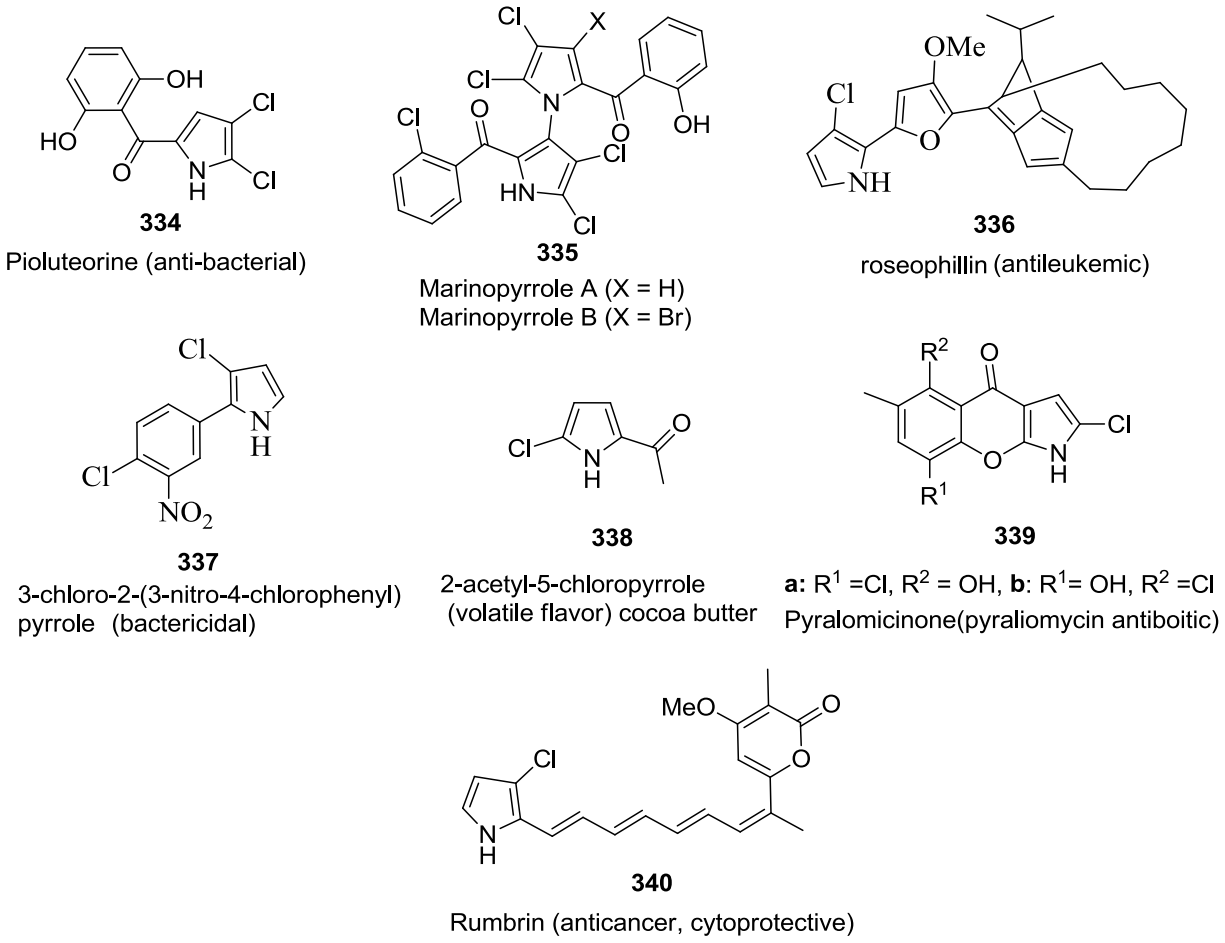


Fig. 22 Some chlorinated and functionalized natural *N*-H pyrroles and their biological activities

Various synthetic β-chloro *N*H-pyrroles substituted with alkyl, aryls and functional groups such as keto, ester, acid groups and their derivatives (**Fig. 23**) have found an important place in pharmaceutical applications.[150]

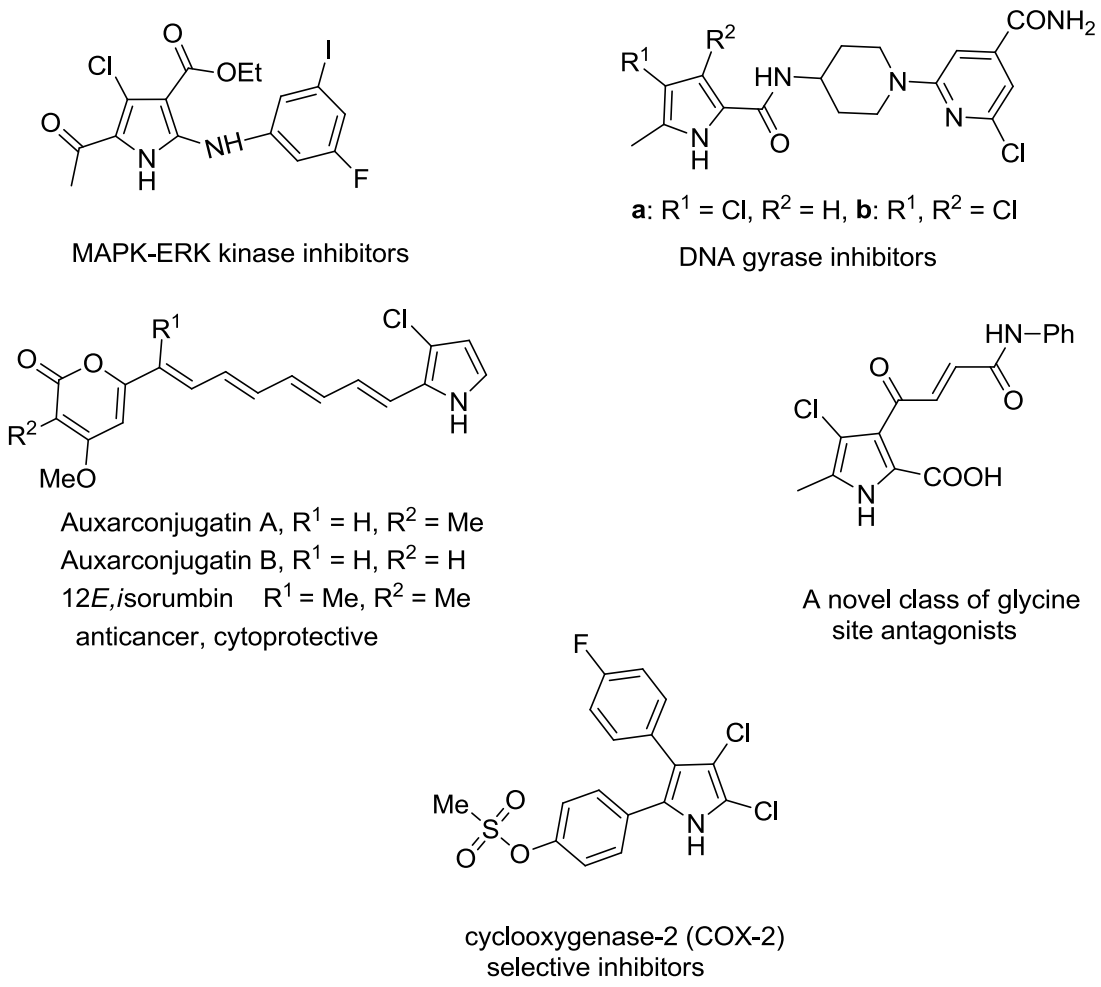


Fig. 23Some chlorinated and functionalized synthetic *N*-Hpyrroles for pharmaceutical applications

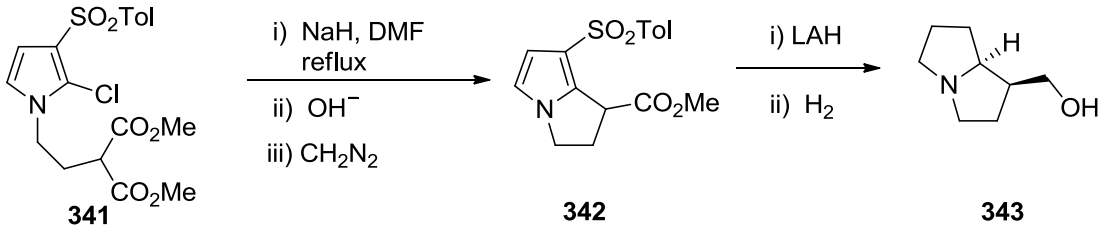
Thepyrrole nucleus and its substituents such as halo, keto and ester are exploited for the construction of a variety of natural products[149] and potentially useful aliphatic,[151] alicyclic[152] and aromatic compounds.[153] Thus,synthesis of such substituted pyrroles continues to receive unabetted attention. Here, only synthetic importance and synthetic

methods of pyrrolesbearingchloro, keto and ester substituents (here in after referred to as functionalized chloropyrroles), which are relevant to the present work will be described briefly.

4.1.1Synthetic importance of chloropyrroles

A chlorine atom present on the pyrrole ring is replaced by suitable substituents. It also acts as a useful blocking group for regioselective substitution reactions which can be easily removed by reduction. By virtue of these properties, chlorinated pyrroles have been used in synthesis of complex heterocycles,pharmaceutically important compounds and natural products.

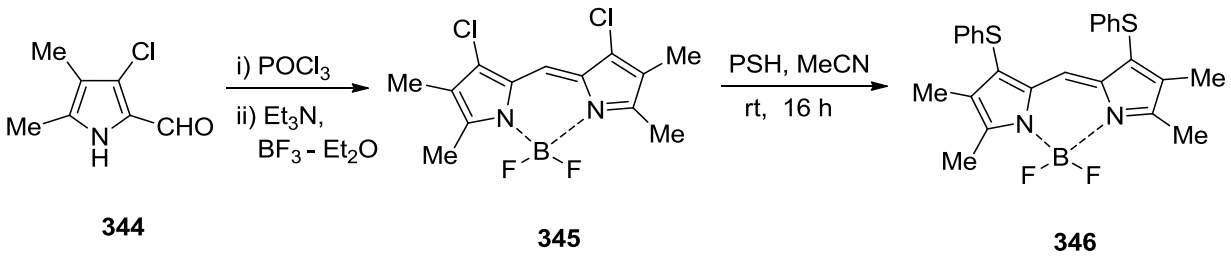
Nucleophilic displacement of chlorine atom of chloropyrroles is difficult but found to occur in activated pyrroles.Isoretronecanol **343** (**Scheme 116**)was constructed from the chloro pyrrole **341**through a sequence of reactions starting with intramolecular nucleophilic substitution of the chlorine atom to give **342**.Reduction of the tosyl moiety of **342**and its subsequent hydrogenation over rhodium on alumina at 1 atmafforded**343**.The presence of the tosyl group is essential for carrying out what is otherwise a very difficult and rare example of a nucleophilic displacement on a pyrrole ring.[154]



Scheme 116

Treatment of the chloropyrrole aldehyde**344**(**Scheme 117**)withphosphorus oxychloride in dichloromethane efficiently gave the dipyrromethene. After activation by a

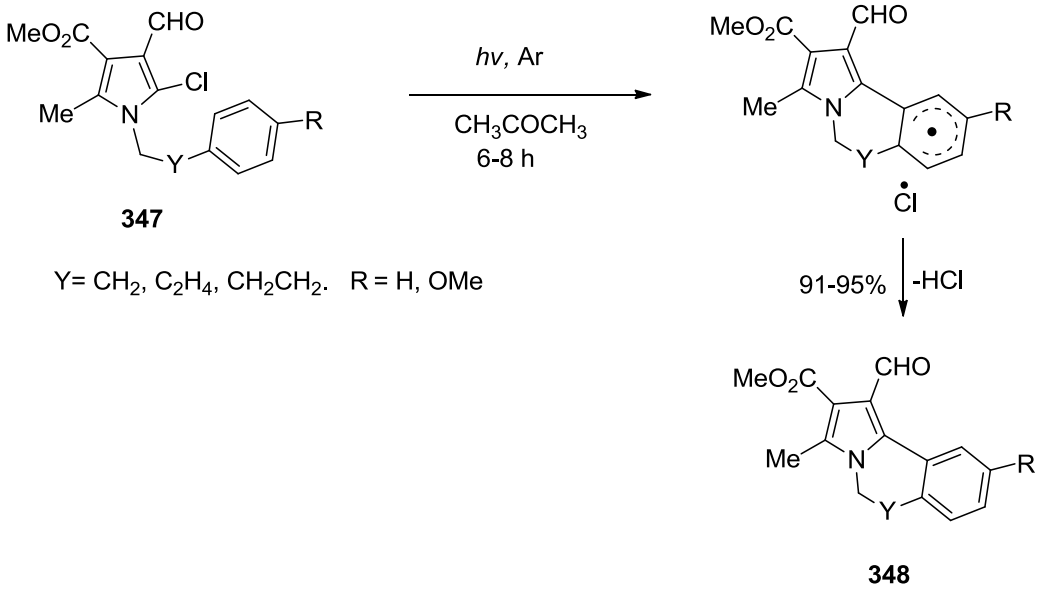
standard complexation reaction with boron trifluoride etherate, the chlorine atoms of the resultant dye **345** were easily substituted with a strong nucleophile thiophenol to yield the product **346.**[155]



344 **345** **346**

Scheme 117

Many chloropyrroles are reported to undergo cyclization reaction with benzene ring. For example, Zhang and coworkers[156] reported an intramolecular photochemical cross-coupling reaction of 2-chloropyrrole-3-carbaldehydes **347** (**Scheme 118**) with benzene ring to form **348** in excellent yields.



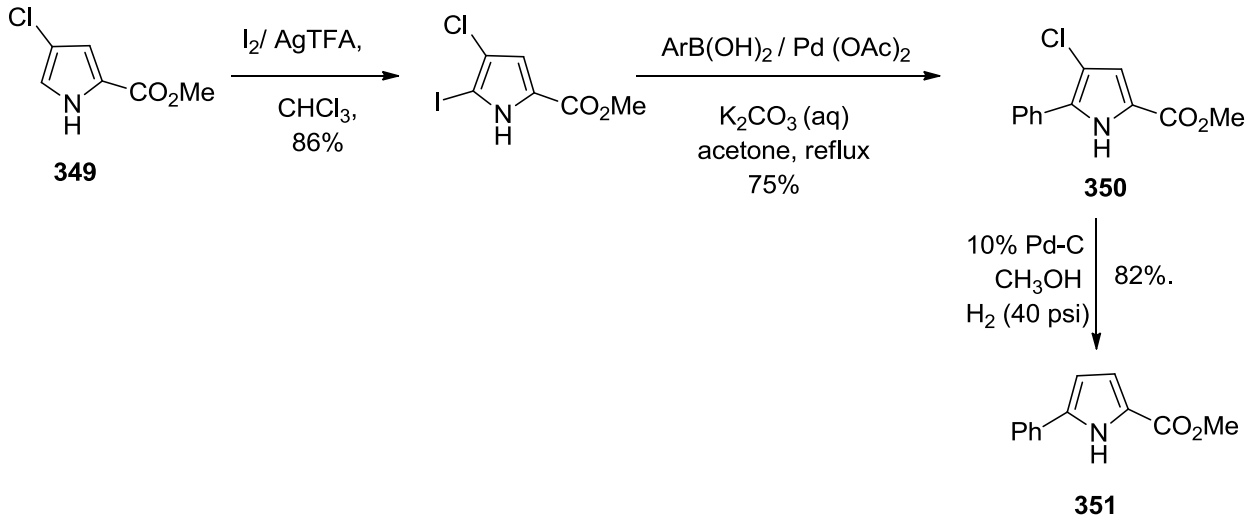
347

Y= CH_2, C_2H_4, CH_2CH_2. R = H, OMe

348

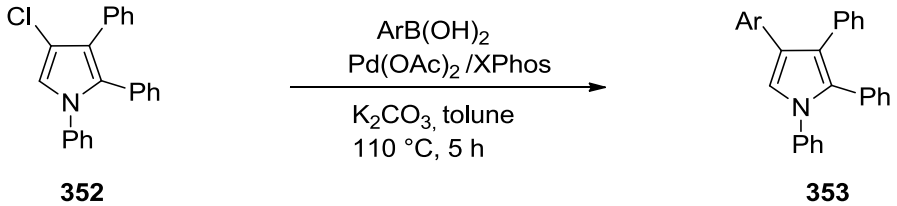
Scheme 118

The chlorine substituent is a removable blocking group. It allowed regioselective iodination of **349** (**Scheme 119**) at the C-5 position. Subsequent arylation by Suzuki cross-coupling yielded the aryl pyrrole derivative **350**, which could be deblocked to **351** by removing the chlorine substituent by catalytic hydrogenation. This methodology was exploited to complete a formal short synthesis of the natural product lukinol A in a few steps.[149b]



Scheme 119

The synthetic utility of chlorine atom of **352** (**Scheme 120**) was demonstrated by replacing it with aryl group by Suzuki coupling to form 3-arylpyrrole derivatives **353** in excellent yield.[157]

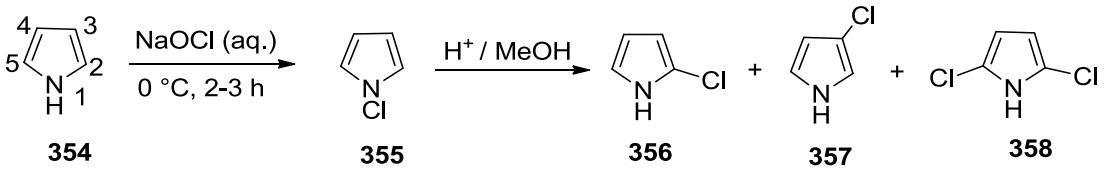


Scheme 120

4.1.2. Synthesis of β-chloropyrroles

4.1.2.1. Synthesis of β-chloro pyrroles by chlorination methods

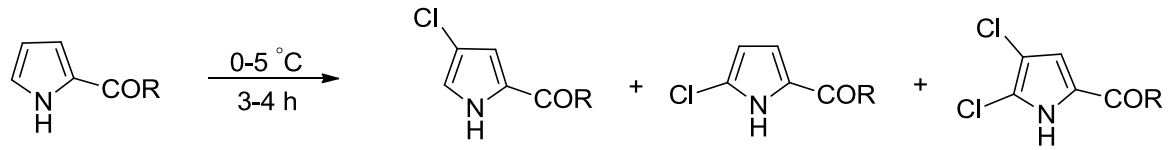
In solution, the parent unsubstituted pyrrole is well known to undergo predominant or exclusivekinetic electrophilic substitution at the 2(or α) or 5(or α′) position with most of the electrophilic reagents.[158]Simple electrophilic substitution reactions such as nitration, sulfonation, formylation, halogenations, etc., therefore gave rise to 2-substituted pyrroles to the almost complete exclusion of the3-substituted derivatives. In few cases, when the parent pyrrole **354** (**Scheme 121**)was treated with aqueous NaOC1in CCl_4,*N*-chloropyrrole **355**was formed which underwent acid catalyzed rearrangement in methanol to give 2-chloropyrrole **356,** 3-chloropyrrole **357,** and 2,5-dichloropyrrole **358**.[159]



354 **355** **356** **357** **358**

Scheme 121

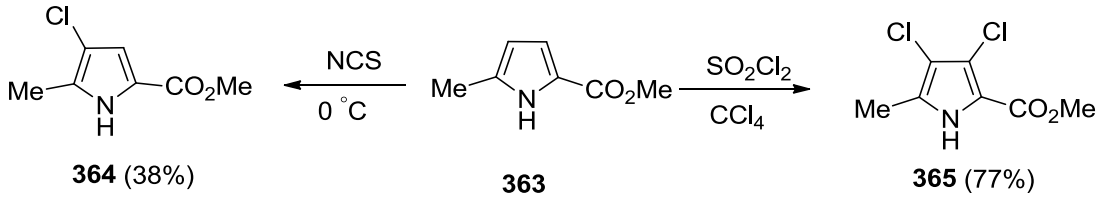
However, the chlorination behavior of substituted pyrroles varied with chlorinating agents, reaction conditions[160]and nature and position of the substituents.[161]For example, while the chlorination of the pyrrolyl ketone **359a** (**Scheme 122**)with SO_2Cl_2 in DCM yielded a mixture of **360a, 361a** and **362a**,[162]its chlorination with Cl_2 in AcOH on the other hand, gave the 4,5-dichloro-1-acetylpyrrole **362b** exclusively in 80% yield.[163] Theester analogue **359c**on treatmentwith SO_2Cl_2 in ether gave 4-chloro-*N*-H pyrrole-2-carboxylate **360c** in high yield. The 4,5-dichloropyrrole **362c** was not detected.



359		360	361	362
R	**Reagents**	**yield(%)**	**Yield(%)**	**Yield(%)**
a: Me	SO_2Cl_2/DCM	40-50%	20-30%	10-20%
b: Me	Cl_2/AcOH	-	-	80%
c: OEt	SO_2Cl_2/ Ether	70%	10%	-

Scheme 122

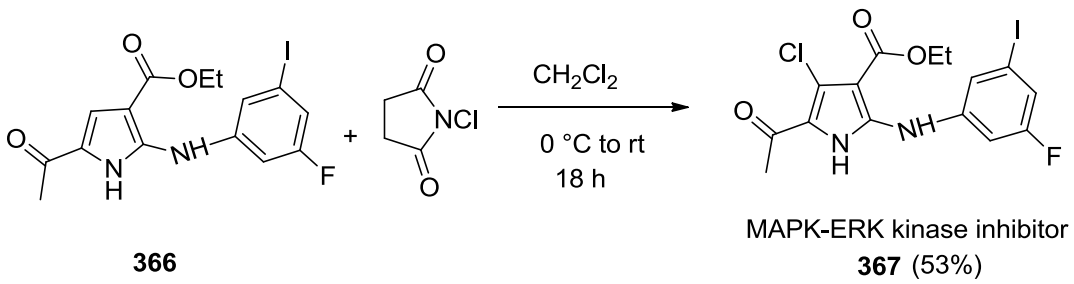
Sherer and coworker[150b] found monochlorinationof 5-methyl-pyrrole-2-carboxylate **363**(**Scheme 123**) to the pyrrole **364**to behighly difficultand low yielding as compared to dichlorination to the 3,4-dichlorinated pyrroles**365**.



364 (38%) **363** **365** (77%)

Scheme 123

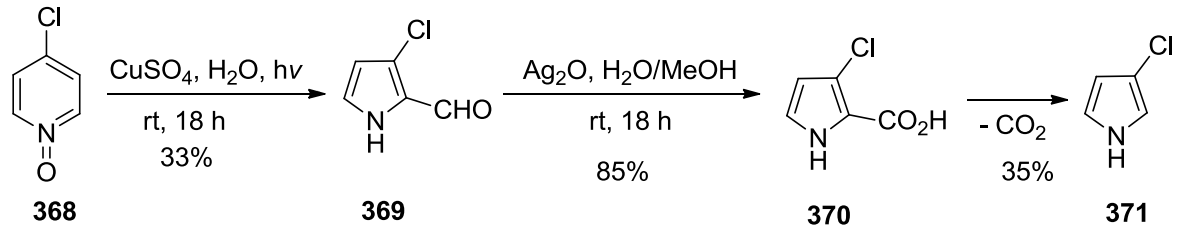
However, chlorination of the difunctionalized trisubstituted pyrrole **366**(**Scheme 124**) having a lone unoccupied ring position was realized successfully with NCS to obtain the tetrasubstituted functionalized β-chloro pyrrole **367**neededfor pharmaceutical application in moderate yield.[150a,164]



Scheme 124

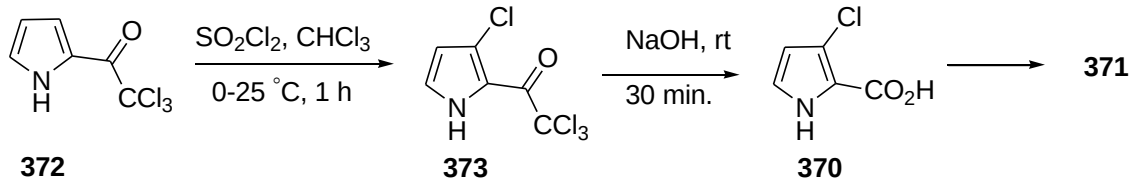
As 3(or β)-chloropyrroles are important synthetic intermediates, finding reliable, efficient and regioselective procedures to prepare the lessreadily accessible β-chloropyrroles has thus been the objective of numerous investigationsin the past.Synthetic routes have historically reliedon low-yielding direct halogenationof the pyrrole ring(**Scheme 121-124**).

A few alternative approaches also emerged. 3-Chloropyrrole **371** (**Scheme 125**) was prepared by photochemical ring contraction of 4-chloropyridine *N*-oxide**368**in the presence of $CuSO_4$. The pyrrolecarbaldehyde**369** (**Scheme 125**)thus obtained on subsequent oxidationgave the acid **370**which ondecarboxylationproducedβ-chloropyrrole **371**.[165]



Scheme 125

Strategies involving the use of directing or blocking group were also adopted.[166]To beof wide synthetic use, the directing group on pyrrole should be amenable to easy removal after the desired substitution.[160c,]The deactivating trichloroacetyl group at C-2position was considered to be a suitable directing group. Thus, 2-trichlorolacetyl pyrrole **372**(**Scheme 126**)underwent regioselective chlorination with SO_2Cl_2 in chloroform to give 3-chloro-2-trichloroacetyl derivative **373**whichwas easily converted to 3-chloropyrrole-2-carboxylic acid**370**by haloform reaction. The acid**370**was then decarboxylated to yield the 3-chloropyrrole**371**.[144j,]



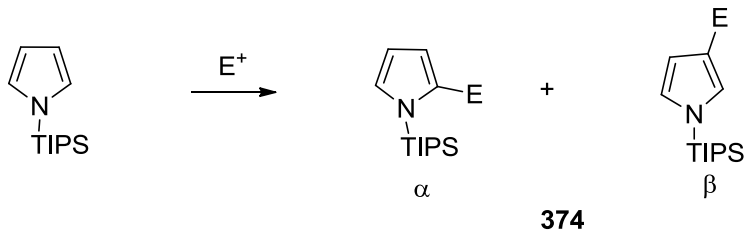
372 **373** **370**

Scheme 126

The main drawback to this route to 3-chloropyrrole was the reliance on thefinal decarboxylation step for removal of the 2-substituent which is low yielding.

In an alternative approach, Muchowski and co-workers[158a]employed a bulky triisopropylsilyl (TIPS) substituent at 1-positionto block the α- and α′- positions of the pyrrole nucleus. The TIPS group could be introduced easily and removed at the final stage by treatment with fluorides. This strategy led some types of substitutionsto occur almost exclusively at the β position. Although bromination, iodination and nitration of 1-(TIPS)pyrrole**374Scheme 127**) with molecular bromine occurred with excellent

regioseletivity,its chlorination with NCSor sulfurylchloride was not achievable with great selectivity.

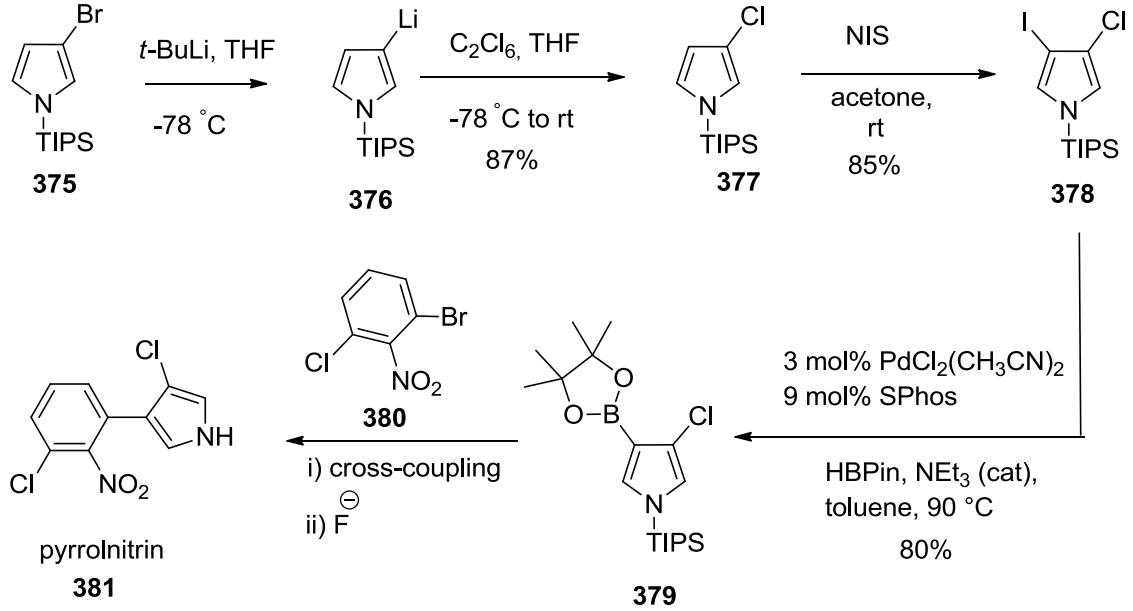


Reagents	NBS,	NCS	$I_2/Hg(OAc)_2$	Acetyl-NO_3
β :α	25:1	0.7: 1.1	1:0	11:1

Scheme 127

4.1.2.2. Synthesis of β-chloropyrroles by metalation methods

An alternative metal-halogen exchange protocol was employed successfully to obtain 3-chloropyrrole in high yield.[168] For example, The organolithium compound **376** (**Scheme 128**) generated from 1-(TIPS)-bromopyrrole **375** was reacted with hexachloroethane to get

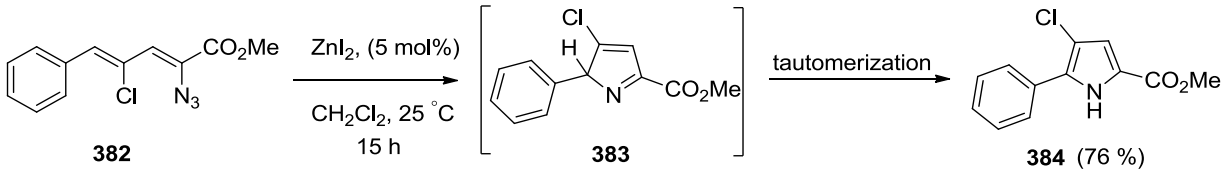


Scheme 128

1-(TIPS)-3-chloropyrrole **377** in nearly quantitative yield.[144g] Treatment of **337** with NIS followed by Pd-catalyzed borylationof the iodinated product **378** gave the boronated ester **339** easily**.** The boronate ester **379** on subsequent Pd-catalyzed cross-coupling reaction with the arylbromide **380** and removal of the TIPS blocking group gave the anti-bacterial pyrrolnitrin **381**.

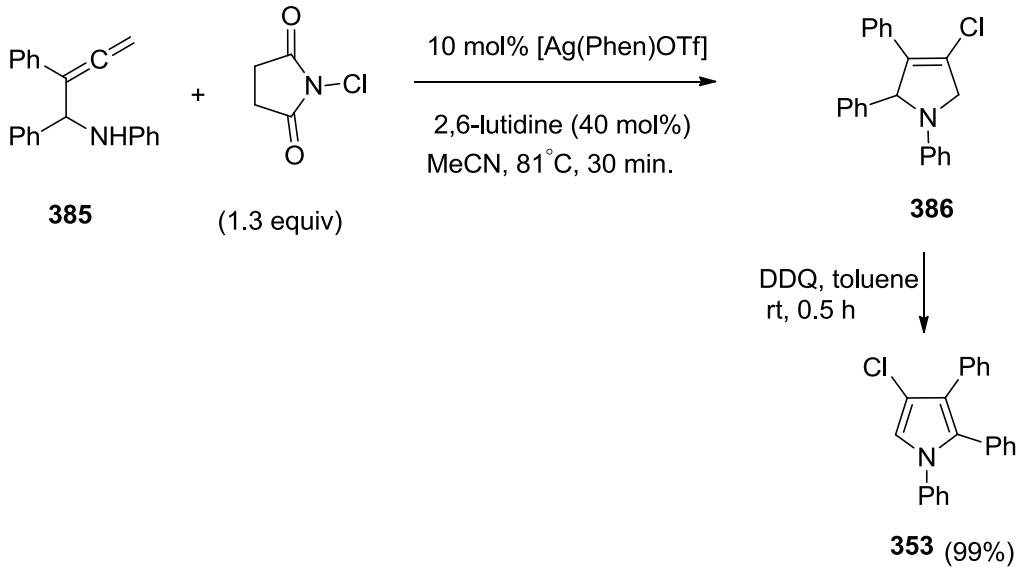
4.1.2.3. Synthesis of β-chloropyrroles by acyclic route

Most of the reports on regioselective synthesis of β-chloropyrroles are based on cyclization of chlorinated acyclic precursors. For example, the chlorodienyl azide **382** (**Scheme 129**) underwent ZnI_2-mediated decomposition, followed by nitrene insertion into the vinylic C-H bond to give **383** which on tautomerization at room temperature afforded the β-chloropyrrole **384** in good yield.[169]



Scheme 129

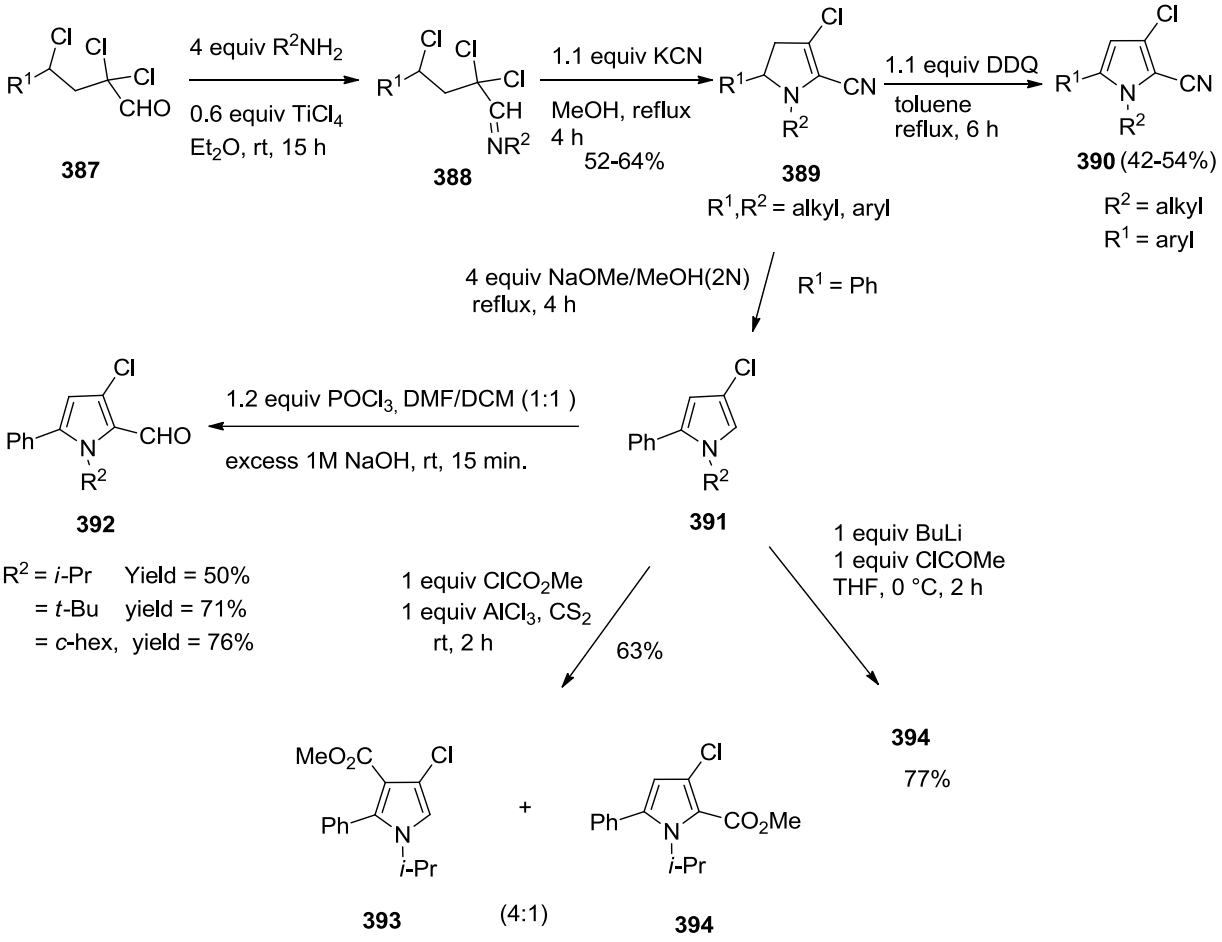
Sai and Matsubara[157]reported that the allene **385** (**Scheme 130**) underwent intramolecular chloroamination on reaction with *N*-chlorosuccinimide in the presence of 2,6-lutidine as a base and 1,10-phenanthroline-ligated cationic silver complex as a catalyst to give chlorinated pyrroline **386**.The pyrroline **386** on treatment with DDQ underwent dehydrogenation to give the β-chloropyrrole **353** in excellent yield.



Scheme 130

Kimpe and coworkers[65a,170] reported the synthesis of 3-chloropyrroles by acyclic route and their functionalization. The α,α,γ-trichloroimines **388** (**Scheme 131**) were obtained by imination of the aldehydes **387**with amines in the presence of titanium (IV) chloride. The imines **388** on treatment with potassium cyanide in methanol yielded 5-aryl-3-chloro-2-cyano-2-pyrrolines **389** in good yields. The 2-pyrrolines **389** were oxidized by DDQ to the chlorocyanopyrroles **390**. Treatment of the pyrrolines **389** with sodium methoxide in methanol at reflux resulted in the formation of the 3-chloropyrroles **391** after cyanide expulsion. The pyrrole **391** underwent Vilsmeier formylation with DMF-$POCl_3$ to furnish the 3-chloropyrrole-2-carbaldehydes **392** along with minor amounts of the isomeric β-formylated chloropyrroles (10%–35%).The pyrrole **391**(R^2 = *i*-Pr) underwent Friedel-Crafts acylation when treated with methyl chloroformate and $AlCl_3$ in carbon disulfide to yield a mixture of the β-chloropyrrole carboxylates **393** and **394** in 4:1ratio. The minor

regioisomer **394** was obtained exclusively by α-lithiation followed by treatment with methyl chloroformate.



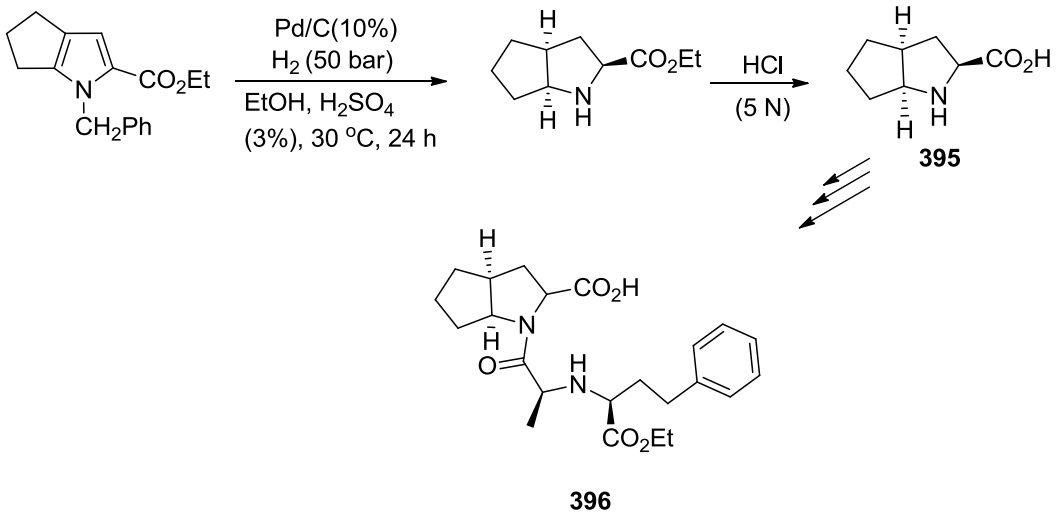
Scheme 131

4.1.2.4. Synthetic importance of*N*-Hpyrroles bearing keto and/or ester groups

The pyrrole nucleus,[171-172] the ester and keto groups and the *N*-H centre of pyrrole undergo a variety of reactions. Thesereactionshave been employed in the synthesis of

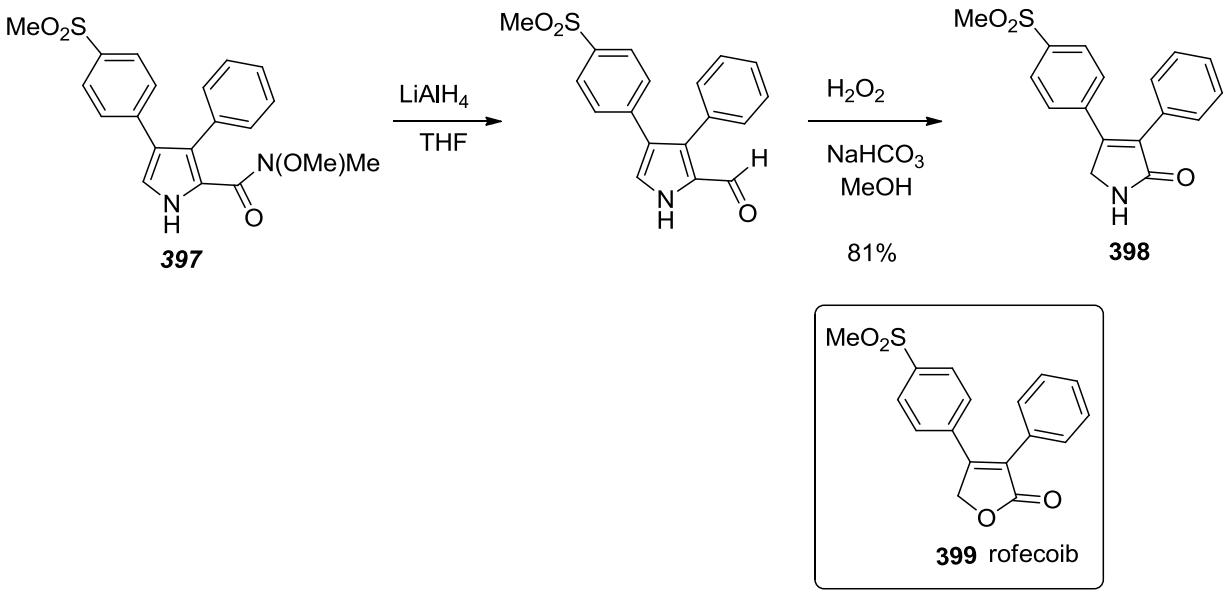
otherheterocycles, ring expansion, functional group transformations and natural product synthesis.[173-174]

The pyrrole nucleus can be fully reduced to pyrrolidine. This property of pyrrole nucleus[171]has been used to synthesize, 2-azabicyclo-[3.3.0]octane-3-carboxylicacid**395** (**Scheme 132**) a key precursor to a highly active angiotenin converting enzyme inhibitor Hoe 498 (**396**).



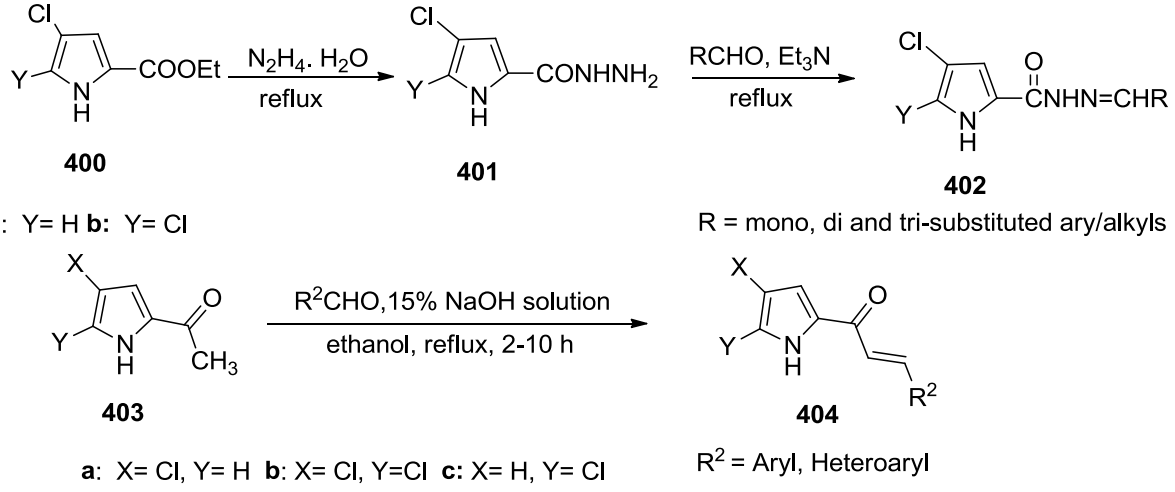
Scheme 132

The functionalized pyrrole nucleus has been transformed into pyrrolin-2-ones.[32-33]For example, Pelkey and coworkers [173] reported construction of both symmetrical and unsymmetrical 3,4-diaryl-3-pyrrolin-2-ones. Thus, reduction of thepyrrole-2-carboxamide **397**(**Scheme 133**) followed by treatment of the aldehyde thus obtainedwith H_2O_2 gave the unsymmetrical 3,4-diaryl pyrrolin-2-one **398**. This methodology was used to prepare *N*-H lactam analogue of the selective cyclooxygenase-II (COX-II) inhibitor,rofecoxib**399**.



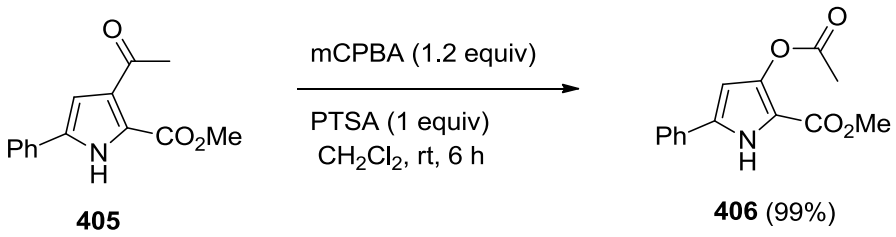
Scheme 133

Rane and Telvekar[162]synthesized novel chloropyrrole based aroylhydrazones and chalcones by using the ester and keto groupsof the chloropyrroles **400** and **403**(**Scheme 134**), respectively for antimicrobial activity. Theester group of the chloropyrrole **400** was converted to hydrazide to give **401**,which on condensation with aldehydes yielded arylidene-*N*-H pyrrole-2-carbohydrazides**402**.The 2-acetyl-*N*-H pyrroles**403** were condensed with aldehydes to give chloropyrrole chalcone derivatives**404**.



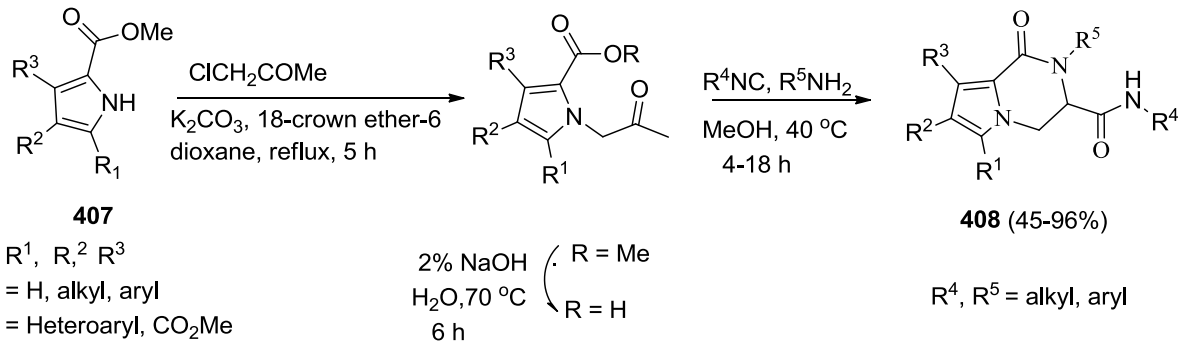
Scheme 134

The acetyl group present at 3-position of the pyrrole**405** (**Scheme 135**)was transformed to an ester **406**by Baeyer–Villiger oxidation with *meta*-chloroperbenzoic acid (MCPBA) in the presence of an acid in nearly quantitative yield.[174]



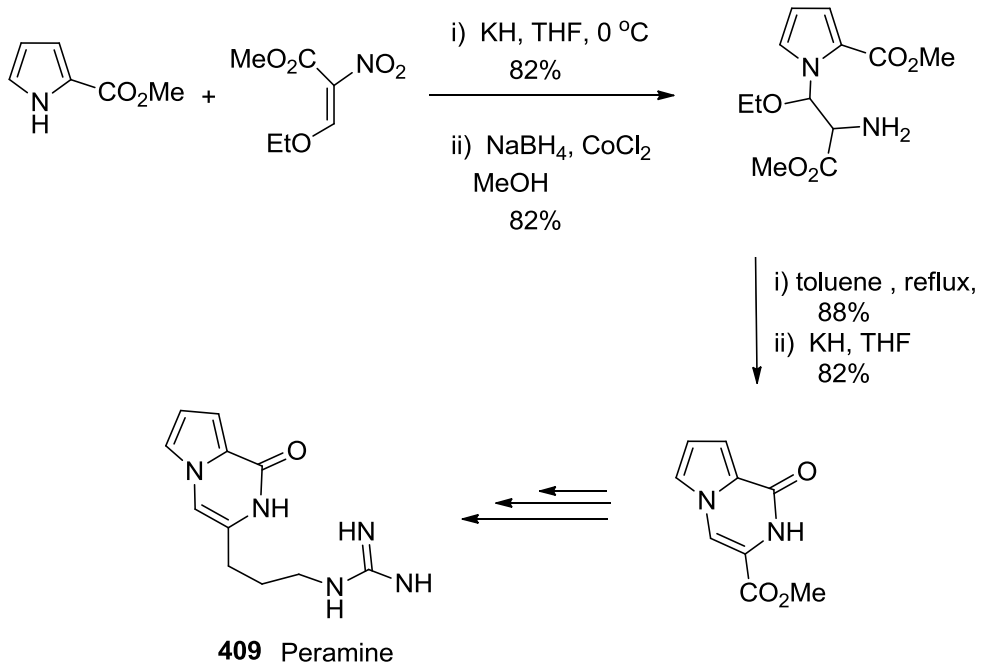
Scheme 135

The *N*H centre and ester group in pyrroles have been used in the synthesis of heterocycles.[175] For example, the *N*H and ester group of the pyrrole **407** (**Scheme 136**) have been used in the synthesis of pyrrole-fused 1-oxo-1,2,3,4-tetrahydropyrazine heterocyclic structures**408**through amodification of four-component Ugi-condensation. Thissynthetic method required the use of *N*H centre in order to introduce the necessary keto group through substitution reaction with 1-chloroacetone for cyclocondensation reaction in the next step.[175a]



Scheme 136

By making use of NH and ester group of methyl pyrrole-2-carboxylate, Brimbleet al.[149c]synthesized Peramine**409**(**Scheme 137**),an insect antifeedant, isolated from *Acremoium loliae*.



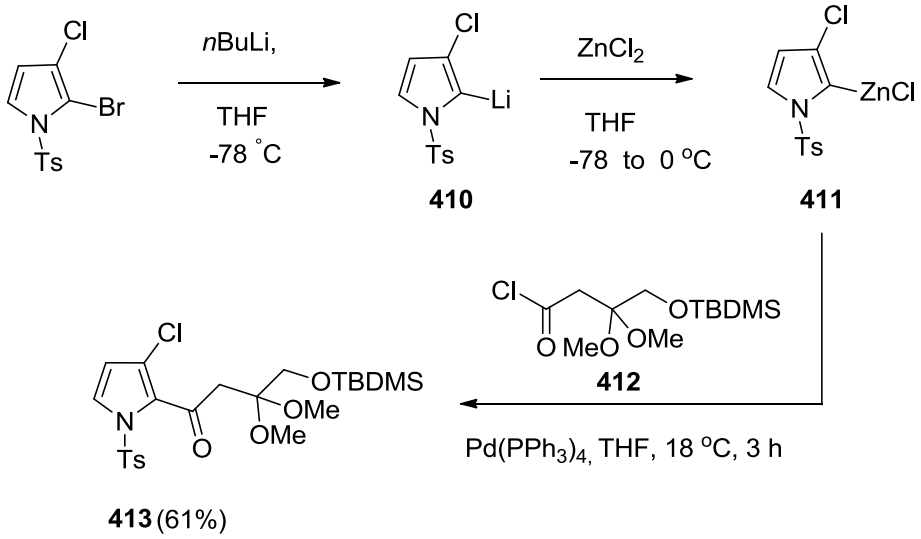
Scheme 137

4.1.2.5. Synthesis of ester and keto functionalized β-chloropyrroles

As a result of wide spread natural occurrence and applications of pyrroles, many synthetic methods for the construction of the pyrrole structurein generalhave emerged.[176] However, these methods are generally not suitable for the synthesis functionalized and/or chlorinated pyrroles. The classical Knorr, Paal–Knorr and Hantzsch synthesesand their several modifications[177]still have some limitationsin terms of efficiency, functional group compatibility, regiospecificity,and substituent diversity.[178]Thering-contraction and expansion routes have been used for the synthesis of alkyl and aryl substituted pyrroles[179] except in very few cases where functionalized pyrroles were prepared.[180]Very few of

cycloaddition reactions [4+1],[3+1], [3+2]etc., have been successful in the synthesis of polysubstituted functionalized *N*-H pyrroles directly.[181]

Some electrophilic substitution reactions (**Scheme 131**)andmetal-catalyzed coupling reactions of thepre-existing β-chloropyrroles followed by reaction with electrophiles have succeeded in the synthesis of functionalized β-chloropyrroles.For example, Fürstner and Weintritt[182]introduced functional groupsonC2-Zincated β-chloropyrrole**411**(**Scheme 138**) which was generated through transmetallation of the corresponding C2-lithiated species **410**using $ZnCl_2$. Pd(0)-catalyzed arylation of **411**with a range of aryl and acyl halides. For example, **412**gave the corresponding substituted products such as **413**. The coupling product**413** was used in the total synthesis of antitumor agent, roseophilin.



Scheme 138

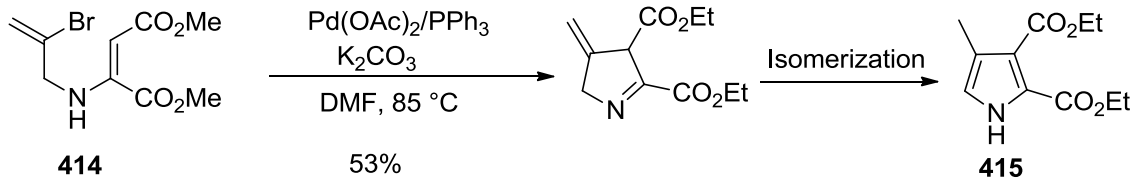
However, these functionalization routes to obtain β-chloropyrroles either via electrophilic substitution reaction or metal-catalyzed coupling reactions require pre-

existing β-chloropyrroles as the starting material, the synthesis of which is not a trivial matter as described earlier under section**Section 4.1.2.2**.By using these reactions, only disubstituted β-chloropyrroles and a few trisubstituted β-chloropyrroles have been prepared.

4.1.2.6.Synthesis of functionalized pyrroles by metal-catalyzed reactions using activated acetylenes and functionalized enamines

A survey of literatures on functionalized tri-and tetrasubstituted pyrroles including the chlorinated ones, revealed that metal-catalyzed acyclic routes werebetter routes to access such pyrroles.[144c,183]These methods includedisomerization of unsaturated imines,[184]isonitrile/ketonecouplings,[185]alkyne additions to chromium carbenes,[186]multi-component reactions[187]and cyclization of enamines,[188]etc.These methods used activated acetylenesor enamines either as substrates or as intermediates in thereactions.

ThePd-catalysed intramolecular Heck reaction of the bromoenamine**414**(**Scheme 139**)followed by isomerizationgave the tri-substituted functionalized pyrrole**415**in moderate yield.[188]

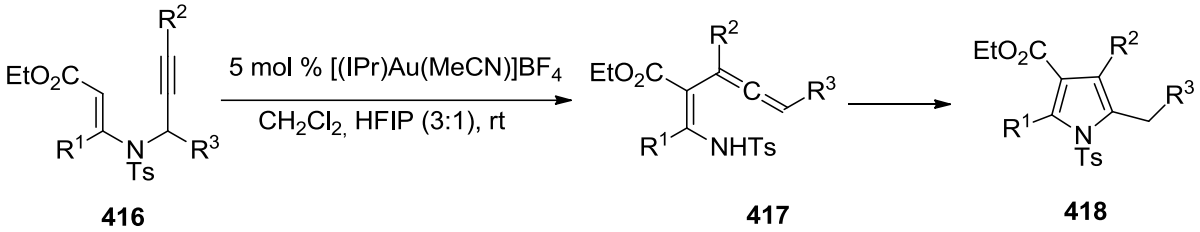


414 53% **415**

Scheme 139

Hanzawa and coworkers[189]reported cationic *N*-heterocyclic carbene-gold(I) complex-catalyzed formation of tri- and tetrasubstituted pyrroles **418** (**Scheme 140**) in

DCM by amino-Claisen rearrangement of *N*-propargyl-enamine derivatives **416** followed by cyclization of the allenyl enamine intermediates **417**.



416 **417** **418**

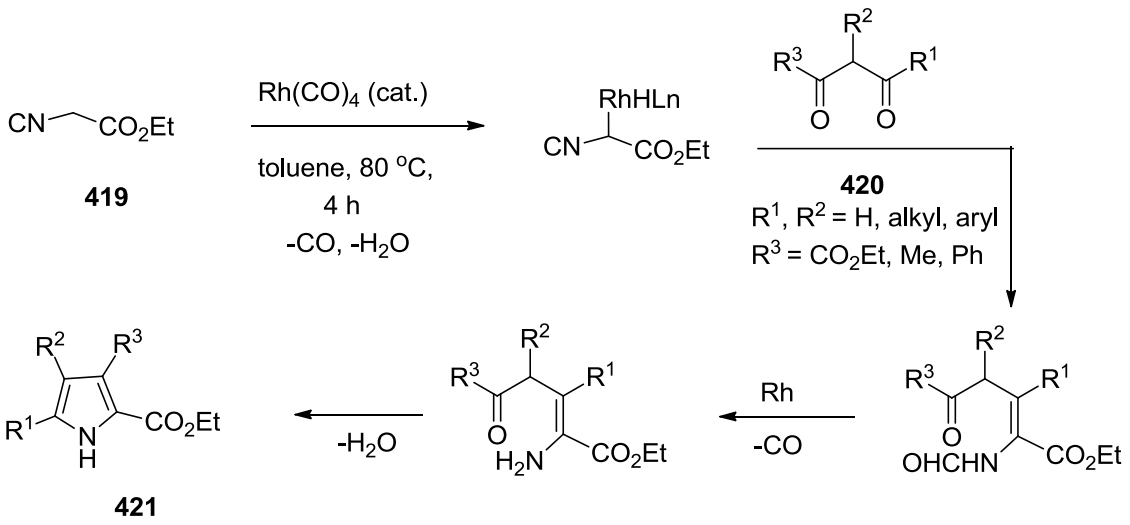
IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
HFIP = hexafluoroisopropanol

418	**R^1**	**R^2**	**R^3**	**time (h)**	**yield (%)**
a	CO_2Et	H	H	22	38
b				22	68 (in HFIP)
c	Ph	H	H	2	81
d	Me	H	H	1	93
e	Me	Me	H	2	89
f	Me	Ph	H	1	85
g	Me	H	*n*-C_5H_{11}	1	87

Scheme 140

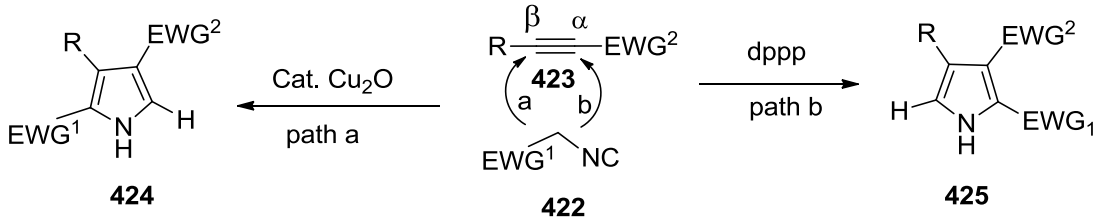
Under these reaction conditions, although phenyl and alkyl substituted pyrroles **418** were obtained in high yields, the precursor **416a** ($R^1 = CO_2Et$) produced the pyrrole diester **416a** in only 38% yield. However, the yield of **416a** increased to 68% when the reaction was done in hexafluoroisopropanol (HFIP).

Murahashi and coworkers[190] reported a synthesis of the pyrroles **421** (**Scheme 141**) by rhodium-catalyzed reaction of the isonitrile **419** with the 1,3-dicarbonyl compounds **420** in high yields.



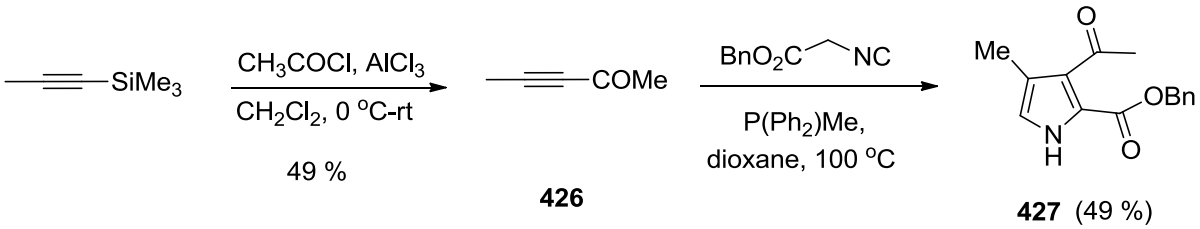
Scheme 141

Yamamoto and coworkers[191] reported that the copper-catalyzed reaction of the isocyanides **422** (**Scheme 142**) with electron-deficient alkynes **423** produced the trisubstituted pyrroles **424** in good yields, whereas the phosphine-catalyzed reaction of **422** with **423** afforded the regioisomeric trisubstituted pyrroles **425**, regioselectively. The reversal of the regioseletivity of the heteroaromatization was attributed to normal Michael addition of the metalated isocyanide to the *β*-carbon of **422** (path a) while addition of the nucleophilic isocyanide to the α-carbon of the phosphonium adduct of the alkyne and dppp (path b).



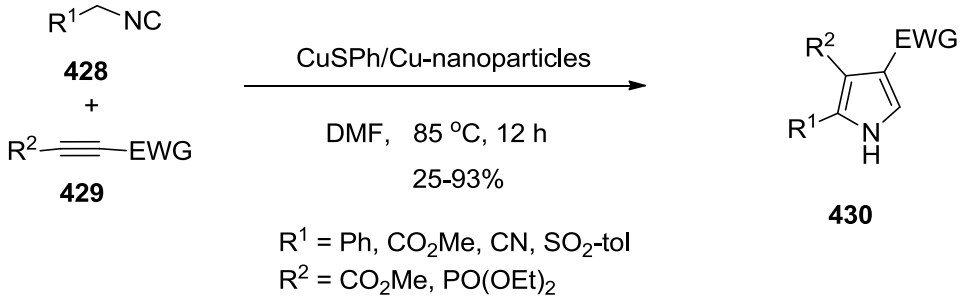
Scheme 142

However,Martin et al.[192]employedpath bto prepare the tri-substituted 2,3-difunctionalized pyrrole**427**(**Scheme 143**) and found that the phosphine-catalyzed reaction of **426**with benzyl isocyanoacetate gave the pyrrole **427**in only moderate yield.



Scheme 143

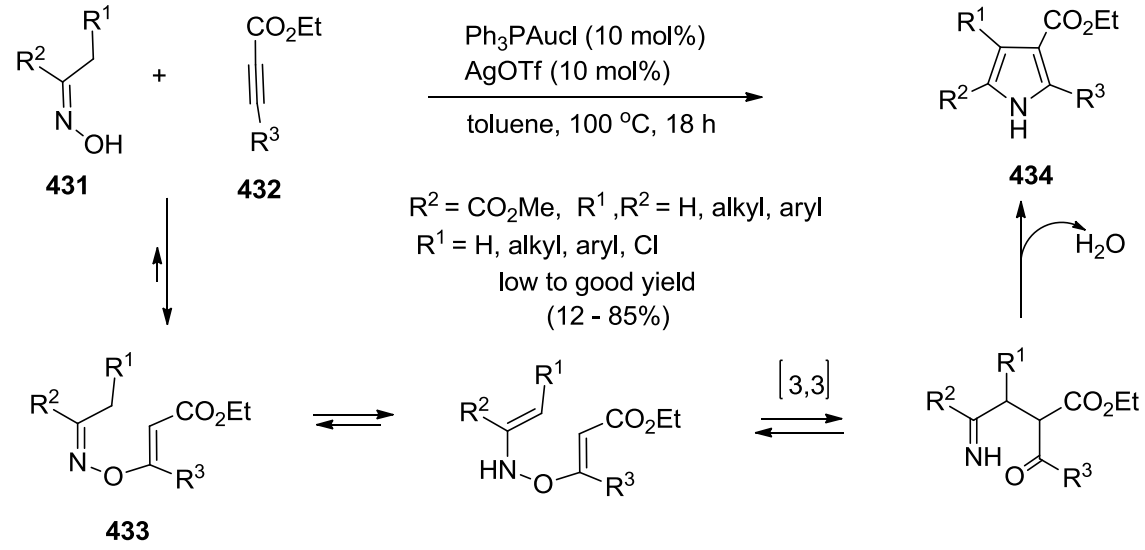
de Meijere and coworkers[193]screened a variety of copper catalysts and found that a combination of copper sulphides and copper nanoparticles were suitable catalysts formetal mediated cycloaddition reaction(**path a, Scheme 144**) of substituted methyl isocyanides **428**with electron-deficient acetylenes **429** to afford the functionalized 2,3,4-trisubstituted pyrroles**430**.



Scheme 144

Only one report was found to mention direct synthesis of a functionalized β-chlorinated *N*-H pyrrole in moderate yield.Camp and coworkers[194]reported gold-catalyzed regioselective synthesis of highly substituted pyrroles**434**(**Scheme 145**)using oximes and alkynes.Initial gold-catalyzed addition of the oxime **431**through its oxygen atomto the

activated alkyne **432**afforded the O-vinyloxime**433**.The oxime **433**subsequently transformed to the pyrrole **434**via gold-catalyzed tautomerization, [3,3]-sigmatropic rearrangementand cyclodehydration processes. However, the scope of this methodology was limited.The oximes containing 2-furyl, 2-thienyl and other heteroaryl substituents

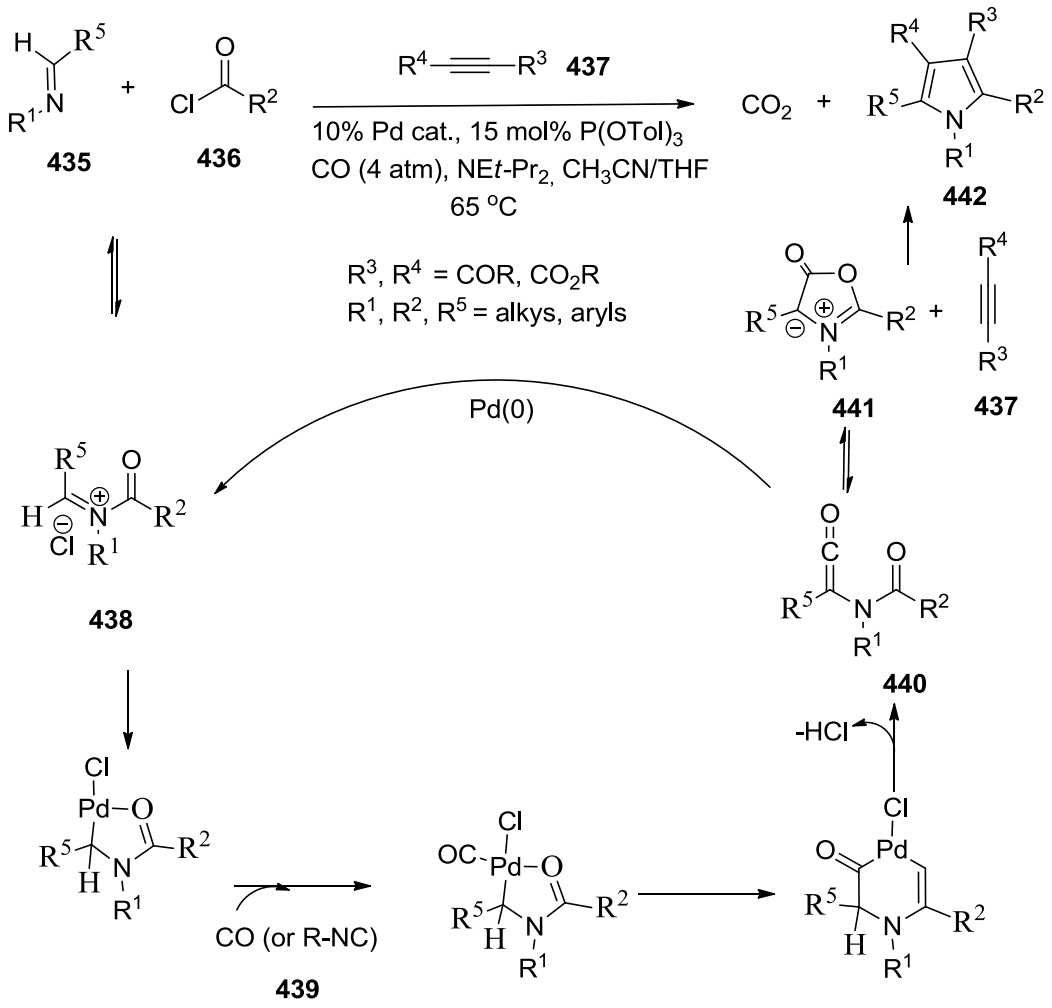


Scheme 145

and chlorine atoms were not suitable substrates in this methodology and were found to produce the products in low to moderate yields.

Arndtsen and coworkers[195]reported a palladium-catalyzed multi-component strategy for the synthesis of highly substituted and functionalized pyrroles **442**(**Scheme 146)** by using the imines**435**,the acid chlorides**436**and the alkyne **437**.The role ofthe palladium catalyst was to mediate the coupling of an *in situ* generated*N*-acyliminium salt **438**with CO to form a ketene intermediate **440**which existed in equilibrium with the 1,3-dipole **441**. Subsequent 1,3-dipolar cycloaddition with alkynes **437** followed by extrusion of CO_2 furnished the pyrroles**442**.In this reaction, CO was not incorporated into the

finalproduct**442.** The efficiency of this synthesis was increased by replacing CO with more nucleophilic isocyanides **439**(R-NC),such ascyclohexyl isocyanide.



Scheme 146

In a majority of pyrroles synthesized bythismulticomponent methodology, the functional groups were positioned at the C-3 and C-4 of the ringand were obtained in moderate to good yields. While stable imines of aromatic aldehydes are viable reagents, enolizable substrate such as simple alkyl-substituted imines and aliphatic acid chlorides instead underwent more rapid decomposition.

4.2. Statement of Problem

There is considerable current interest in paving the way for using chloro compounds in synthesis in the place of bromo or iodo analogous due to their higher stability and lower cost.[196]From the foregoing, it is obvious that β-chloropyrroles are valuable synthons as the chlorine atom can be substituted through transition metal catalyzed cross-coupling andother reactions.Itisalso reductively removable blocking group which allowed regioselective substitution on the pyrrole ring.This would give access to substituted pyrroles includingnaturally occurring and synthetically important compounds, which are generally difficult to prepare.

However, as is clear from **sections4.1.2.1** to**4.1.3.3**,there are very few reported methods for the preparation of functionalized β-chloropyrroles, particularly those which are tri-ortetra-substitutedand bear a chlorine atom at the β-position. Furthermore, these methods have their own limitations with regard to the yields, the nature of the other substituents and the substitution pattern.The methods based on functionalization of pre-existing β-chloropyrrole ring via electrophilic substitution are not typically general and are restricted to particularly stable pyrroles due to low stability of pyrrole ring under acidic conditions. There may be the problem of the regioseletivity also. These methods require simple β-chloropyrroles to start with which are not easily accessible. Protocols forthe synthesis of simple β-chloropyrroles required for this purpose by chlorination of existing pyrrole ring suffer from the problems of regioseletivity and over-chlorination leading to the formation of mixtures of chlorinated products, difficulties in separation and low yields of the products.The methods based on the chlorination of the functionalized pyrroles suffer from some of the problems inherent to chlorination protocols as mentioned above, such as

regioseletivity. Therefore, they may require the use of a directing or blocking groups and thus wastage of time and resources. Methods involving metallation of pyrrole derivatives followed by quenching with various electrophiles are mostly limited to simple*N*-protected pyrroles.

Though a number of synthetic approachesto functionalized pyrroleshave been reported (**Section 4.1.3.6**) due to their potential in the synthesis of heterocyclic compounds and natural products, these methods have their own limitations with regard to availability of the substrates, low yields of the products, the nature of the other substituents and the substitution pattern. Many others need to be further complemented with mild and general approaches.

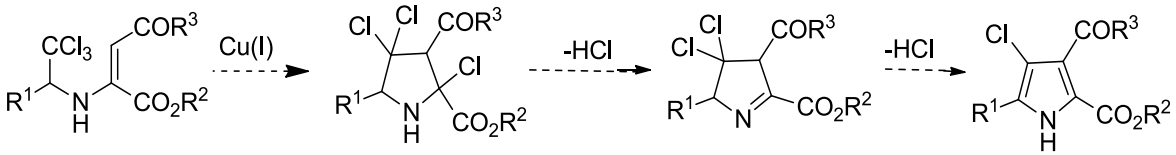
The classical methods such Knorr, Paal–Knorr, and Hantzsch syntheses have some limitations with regard to limited flexibility in substitution pattern, require stoichiometric amounts of the reagents which produce significant amounts of waste salts, especially with regard to the preparation of functionalized substituted pyrroles.

Many reported multicomponent reactions for the synthesis of functionalized pyrroles suffer from slow rate of catalysis which precludes the use of less stable substrates. (**Scheme 146**) The functionalized pyrroles obtained by these methods have functional groups (keto, ester) at the 3 and/or 4-position of the pyrrole ring. The metal-catalyzed synthesis of functionalized pyrroles havetypically beenused to prepare di- and tri-substituted pyrroles (**Section 4.1.3.6**). Tetrasubstituted pyrroles, especially 2,3-difunctionalized ones are not readily accessed.Many of these methods are limited to the synthesis of alkyl and aryl substituted pyrroles. None of these methods have been extended to the synthesis of

functionalized chloropyrroles except one, where in a solitary β-chloro functionalized pyrrole was obtained in moderate yield.

The diversely functionalized *N*-H pyrroles are valuable synthetic intermediates in which the *N*H group can be harnessed for further synthetic exploitation.However, most of the reported methods for the synthesis of *N*-H pyrroles take recourse to the wasteful protection-deprotection methodology. Direct synthesis of *N*-H pyrroles adorned with diverse functionalities has been one of the most cherished goals in pyrrole synthesis. However, there is paucity of reports on the synthesis of tri- and tetrasubstituted *N*-H pyrroles having contiguous functional groups including a chlorine atom at one of the β-positions.

Therefore, we proposea flexible synthetic approach to tri- and tetra substituted2,3-difunctionalized 4-chloro-*N*-H pyrroles via a regioselective Cu (I)-catalyzed *5-endo*radical cyclization of easily accessible *N*-2,2,2-trichloroethylenamines, as shown in **Scheme 147**.



Scheme 147

There was also an element of curiosity in putting this approach to test because Cu(I)-catalyzed 5-*endo* radical cyclization of enamines has not been reported so far.In the crucial step, these *N*-trichloroethylenamineswere expected to undergo intramolecular regioselective HATRC in the presence of a catalytic amount of a copper complex. Though 5-*endo* radical cyclization is not a favorable process, it was thought that stabilization of the radical intermediate obtained after cyclization by captodative effect of the adjacent

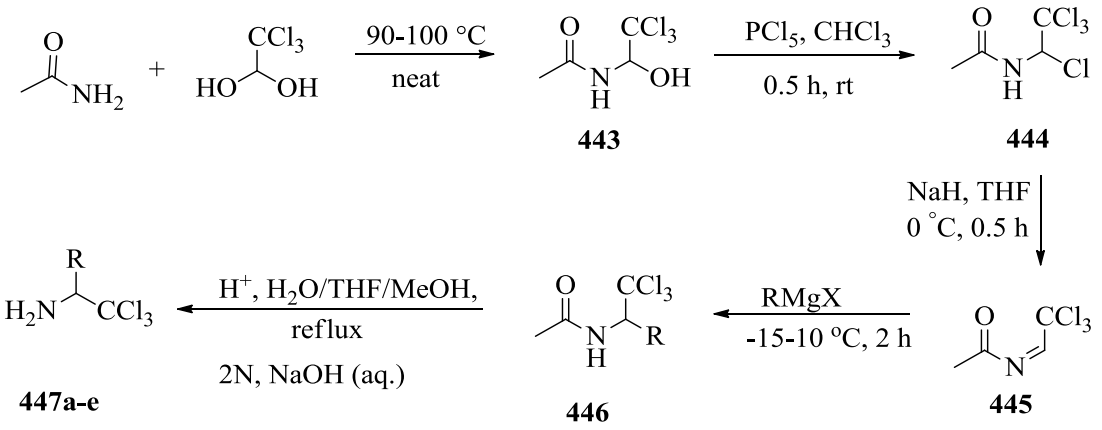
electron withdrawing and donating groups might favor this cyclization. The α-chloroamine functionality in the cyclization product may undergo spontaneous dehydrochlorination to pyrroline derivative which could be aromatized to the functionalized 4-chloropyrrole by dehydrochlorination.

4.3.1 Results and Discussion

To realize the above said objective, the HATRC precursors *N*-2,2,2-trichloroethylenamines were thought to be prepared from 2,2,2-trichloroethyl amineby exploiting the known chemistry.[197]Therefore, first it was decided to prepare 2,2,2-trichloroethyl amines.However, most of the reported methods[198] for the synthesis of 1-substituted 2,2,2-trichloroethyl amines are multistep,[198a]low yielding[198b-c] and substituent specific.[198d]Therefore, a new and simpler method for the synthesis of 1-substituted 2,2,2-trichloroethyl amines was developed which involved addition of Grignard reagents to *N*-acetylchloroalimine.

Thus, melting a solid mixture of chloral hydrate and acetamide by heating at 90-100 ˚C and recrystallizing the crude product gave the *N*-protectedhemiaminal, chloralacetamide **443**(**Scheme 148**) in quantative yield.[197a]Treatment of a suspension of chloralacetamide **443**with phosphorus pentachloride in dry chloroform at room temperature (20-25˚C) afforded the tetrachloroderivative **444** which was used as such in the next step.[197a]The tetrachloride **444**underwent ready dehydrochlorination to produce the *N*-acetylimine **445** on treatment with one mole equivalent of sodium hydride in THF at 0 ˚C.[197b] This solution containing the imine **445** on treatment with one equivalent of a pre-prepared Grignard reagent at -15 ˚C for 2 h yielded the *N*-(1-substituted-2,2,2-

trichloroethyl)acetamide**446**.[197c]The amides**446** on acid hydrolysis[197d-3] followed by neutralization with 2N NaOH solution furnished the trichloroethyl amines **447**in good overall yields (**Table 9**) which were used without any further purification in the synthesis of enamines.



Scheme 148

Table 9. Synthesis of 1-substituted 2,2,2-trichloroethyl amines447a-e

S. No.	R	**446**[a] Yield from **443**(%)	**447**[b]	
			Time (h)	One step yield (%)
1	a: Ph	81	8	73
2	b: 4-$MeOC_6H_4$	80	8	66
3	c: 4-ClC_6H_4	78	8	71
4	d: *n*-Butyl	88	16	81
5	e: 2-thienyl	83	12	76

[a]Reaction was performed by taking 20 mmolof **443** and the products were purified with columnchromatography on a small pad of neutral alumina.

[b]Reaction was performed by taking 10 mmol of **446**.

The present synthesis used inexpensive and commercially available chloral hydrate as the starting material and was found to work well for the synthesis of a variety of 1-substituted 2,2,2-trichloroethyl amines having alkyl, aryl and heteroaryls groups as substituents.

All these 2,2,2-trichloroethyl amines**447**were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry.The spectral features of these amines are exemplified by taking a representative example oftheamine**447a**(**Fig. 24**).

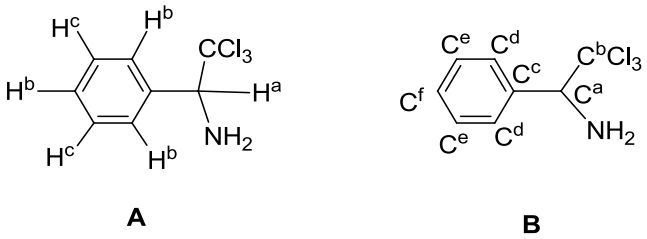


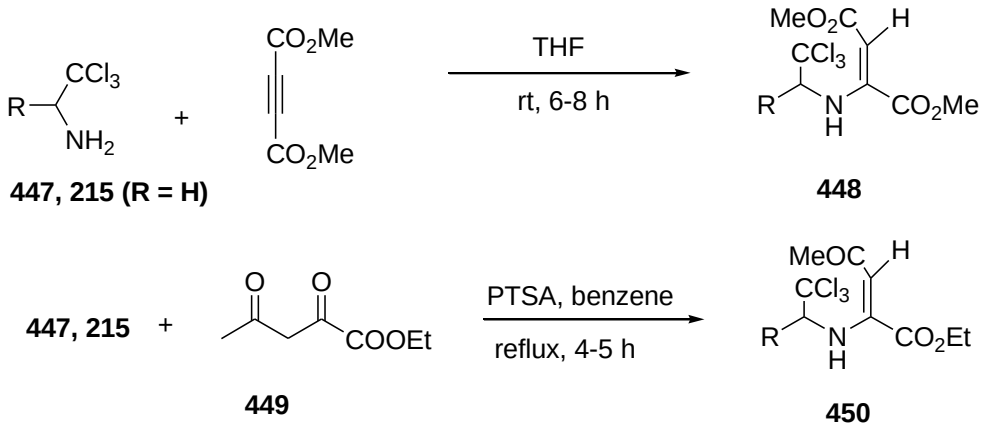
Fig. 24^{1}H NMR and ^{13}C NMR assignmentsfor the structure of 447a

The ^{1}H NMR spectrum of **447a** (**Fig. 193**)showeda singlet at δ2.30 ppm integrating for two protons which disappeared on shaking with D_2O. It was attributed to the two*N*H protons. The singlet at δ 4.63 ppm integrating for one proton was attributed to the proton H^a(**Fig. 24**, **Structure A**) bonded to the methine carbon. The multiplet at δ 7.36-7.39 ppmintegrating for three protons was attributed to the protons H^bat the *ortho* and *para* positions of the benzene ring.Themultiplet at δ 7.49-7.54 ppm integrating for twoprotonswere attributed tothe *meta*protons H^c.

In the proton-decoupled ^{13}C NMR spectrum of **447a**(**Fig 194**), the two signals at δ71.8 and 105.5 ppm were attributed to the methine carbon$C^a$and the CCl_3 carbonsC^b (**Fig. 24. Structure B**), respectively. The three signals at δ 127.9, 128.9 and 129.2 ppm were attributedto the CH carbonsC^d, C^e and C^f, respectively of the benzene ring. The signal at δ

136.5 ppm wasassigned to the quaternary carbon C^c. These assignmentswere also supported by DEPT-135 spectrum. The HRMS spectrum of this compound showed the $[M+H]^+$peak at m/z 223.9795, which was within the acceptable limit of deviation from the calculated value of 223.9799 for the formula $C_8H_9Cl_3N$.

The HATRC precursors *N*-2,2,2-trichloroethylenamine **448**(**Scheme 149**)were thought to be preparedby aza-Michael addition of 2,2,2-trichloroethyl amines**447** to DMAD relying on the well known addition of amines to DMAD.[199]It worked well. Thus, stirring an equimolar solution of the trichloromethyl amines**447**orthe parent 2,2,2-trichloroethyl amine **215** and DMAD in THF at room temperature (25-30 ˚C) for 6-8 h followed by purification by column chromatography on basic alumina column afforded the enamines**448**in high yields as shown in **Table 10**.



Scheme 149

Besides,variation in the substituentin the amine fragment as realized above, variation in functional groups in the ene fragment was also realized as follows. Ethyl acetylpyruvate **449** was prepared by condensation of acetone with diethyl oxalate in the presence of NaOEt (Na in ethanol) as reported in the literature.[200]Relying on well known

condensation reaction between amines and β-diketones to form enamines,[201] an equimolar solution of the pyruvate **449** and the 2,2,2-trichloroethyl amine **447**or **215** in benzene was heated at reflux for 4-5 h in the presence of a catalytic amount of PTSA in a Dean-Stark apparatus. Simple work up of the reaction mixture and purification by column chromatography on basic alumina column furnished the enaminoketoesters**450** in good yields. (**Table 10**)

Table 10.Synthesis of *N*-2,2,2-trichloroethylenamines 448 and 450[a]

S. No.	R	**448**		**450**	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1	a: Ph	8	73	5	64
2	b: 4-$MeOC_6H_4$	8	74	5	64
3	c: 4-ClC_6H_4	8	73	5	63
4	d: *n*-Bu	7	75	5	65
5	e: 2-thienyl	8	78	5	70
6	f: H	6	80	4	78

[a]All the reactions were performed at 10 mmol scale.

The enaminodiesters**448**andthe enaminoketoesters**450**were characterized byIR, ^{1}H NMR and^{13}C NMR spectroscopy and mass spectrometry.The NH groups of the enaminodiesters and enaminoketoesters showed contrasting spectral features.Contrary to the NH groups of the enaminoketoesters **450a-f**,the NH groups of the enaminodiesters **448a-f**did not show the conventional characteristics of an amino NH in their IR or^{1}H NMR spectra. In the IR spectra of **448a-f**, the N-H bond stretching was not clearly visible and

appeared as a broad but weak signal. In their ^{1}H NMRspectra, the *N*H proton signalsdid not disappear after shaking the solution with D_2O,although they appeared considerably downfield (> δ 9 ppm) in the enaminodiesters **448a-f**as well as enaminoketoesters **450a-f**.The single crystal structure of **448e**(**Fig. 25**)revealed the formation of a 6-membered chelate ring through a short distance (2.008A˚) hydrogen bonding.This, very strong-N-H···O=C hydrogen bonding may be the reason for the non-disappearance of the *N*H protons in the enaminoesters**448a-f** on D_2O shaking.It is clearly visible in ORTEP diagram of **448e** as shown in **Fig. 25**.

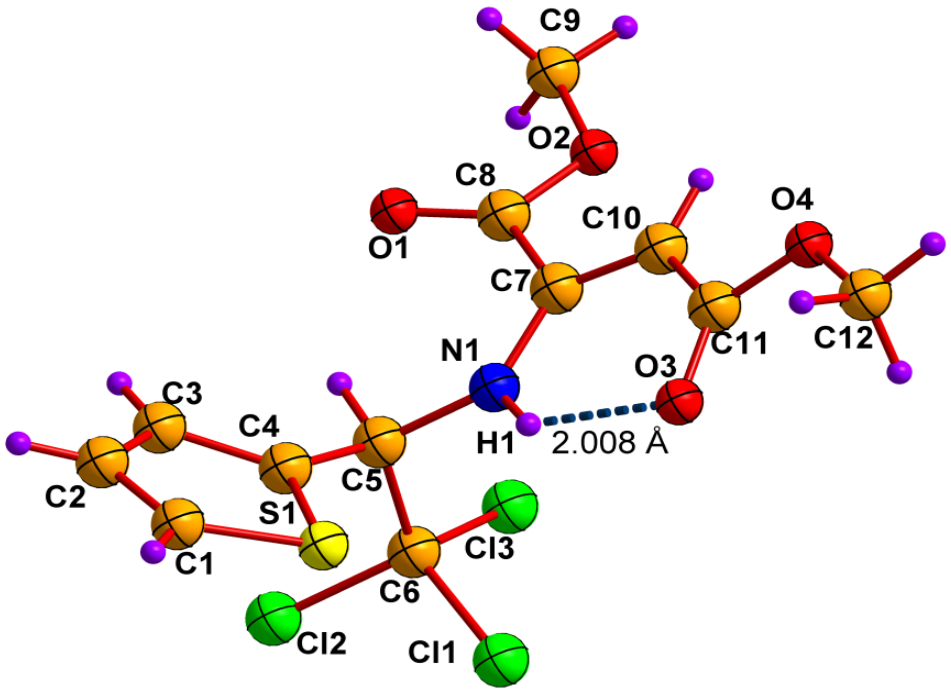


Fig.25ORPET diagram of dimethyl 2-(2,2,2-trichloro-1-(thiophen-2-yl)ethylamino)fumarate 448e

In the case of enamino ketoesters **450a-f**, the *N*H group displayed the usual expected characteristics in their IR and ^{1}H NMR spectra. In IR spectra clearly visible, broad and medium to strong N-H stretching was observed and in the ^{1}H NMR spectra, the

NH proton signals disappeared on shaking the solution with D_2O. They exhibited IR and NMR spectra compatible with their structures.

Other spectral features of enaminodiesters **448** are exemplified by taking **448a** as a representative case.The ^1H NMR spectrum of **448a**(**Fig 203**)displayed all the expected proton signals at the expected positions. Itshowed two singlets at δ 3.76and 3.80 ppmintegrating for three protons eachwhich were attributable to the CH_3 protons H^a and H^b(**Fig. 26, Structure A**), respectively of the two methyl ester groups. The singlet at δ 5.46 ppm and the doublet at δ 6.01ppm with a coupling constant (*J*) of 10.5 Hz, each integrating for one proton were assigned to the olefinic CH proton $H^c$and methine proton H^d, respectively.The multipletat δ 7.38-7.40 ppmintegrating for three protons were assigned to the two *ortho* and one *para*protons H^e of the benzene ring.The multiplet at δ 7.55-7.58 ppmintegrating for two protons was attributed to the two *meta*protonsH^f. The doublet integrating for one proton at δ 9.40 ppm with a coupling constant (*J*) of 10.5 Hz, was attributable to the *N*H proton. The *N*H proton did not disappear onshaking with D_2O probably due to very strong intramolecular (-N··H··O=C) hydrogen (**Fig.26**).

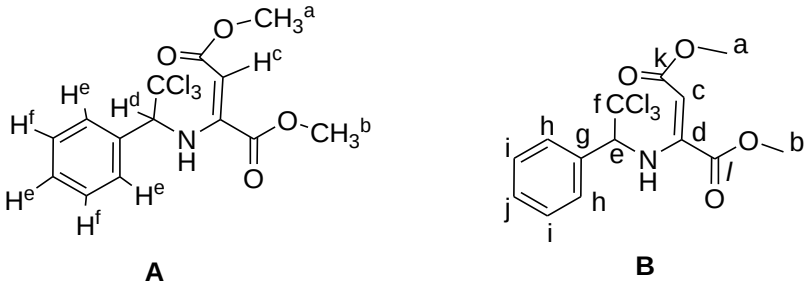


Fig. 26^{1}H NMR and ^{13}C NMR assignmentsfor the structure of 448a

The proton-decoupled ^{13}C NMR spectrumof **448a** (**Fig. 204**) displayed all the expected carbon signals. The two signals at δ 51.2 and δ 52.9 ppm were attributed to the

two methyl carbonsC^a and C^b, (**Fig. 26, Structure B**), respectively of the two ester groups. The three signals at δ 71.3, 92.6 and 102.2 ppm were attributedto the methine, olefinic and CCl_3 carbons C^c, C^e and C^f,respectively.The three signals at δ 128.1, 129.0 and 129.4 ppm were assigned to the CH carbon C^h, $C^i$and C^j, respectivelyof the benzene ring.The two signals at δ 135.1 and 148.6 ppm were attributed to the quaternary carbons of phenyl and olefinic groupC^g and C^d, respectively. The remaining two signals at δ 163.5 and 170.3 ppm were attributed to the quaternary carbons C^k and C^l, respectively of the ester carbonyl groups. These assignments were also supported by the DEPT-135 spectrum. The IR spectrum of **448a**did not show clear signal forthe N-H bond stretching.The two strong signals at 1726 and 1666 cm^{-1} were due to the C=O stretching vibrationsof the ester groups present at α- and β-positions with respect to the NH group, respectively.The HRMS spectrum of this compound showed the $[M+Na]^+$ peak at m/z 387.9881, which was within the acceptable limit of deviation from the calculated value of 387.9896for the formula $C_{14}H_{14}Cl_3NO_4Na$.

Other enaminodiesters **448b-f** showed spectral features very similar to those described above for **448a**. Slight variations due to change in the substituents were as expected.

Stereochemistry of enaminodiesters448

The stereochemistry of the C=C bond of the enamines **448**was established by comparing the observed chemical shifts (δ) of the olefinic and NH protons and stretching frequencies (*v*) of the C=C and C=O bond with those in the literature[202]for the *Z*and *E* isomers of structurally very similar dimethylbut-2-en-1,4-dioate*i.e*. dimethyl 1-alkylaminofumarate (*Z*) anddimethyl 1-alkylaminomaleate (*E*). The reported values for the two isomers are

shown in (**Fig**.**27**). For comparison the observed values for the enaminodiesters**448** are also given.

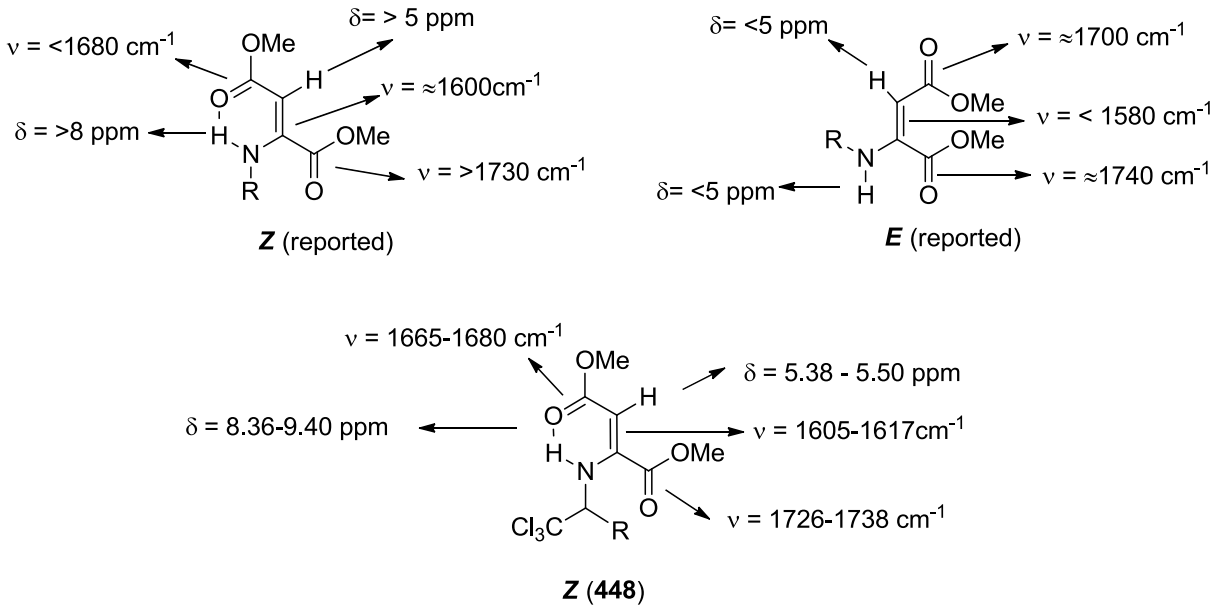


Fig. 27Comparison of the reported spectral characterstics for *Z* and *E* isomers of *N*-alkylenaminodiesters with the observed values for the *N*-2,2,2-trichloroethylenaminodiesters 448

From the**Fig. 27**, it is clear that the observed characteristic spectroscopic data are closer to the ones reported for the *Z* isomer of *N*-alkylenaminodiesters.[202]The large difference in the chemical shifts of NH protons of the *Z* and *E* isomers of the reported compounds proved to be quite helpful diagnostic features. The closeness of the observed chemical shift values of the NH protons of the *N*-2,2,2-trichloroethylenaminodiesters **448**established the *Z* stereochemistry of these compounds reasonably well.

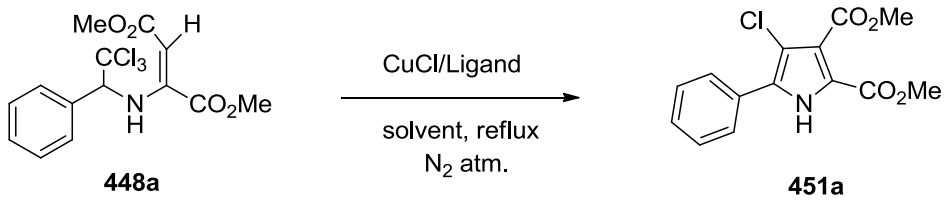
The Z-stereochemistry of **448**was further supported by single crystal X-ray diffraction spectroscopy by the ORTEP diagram of **448e** as shown in **Fig. 25**.

The spectral features of the enaminoketoesters **450a-f** were also compatible with their structures. The spectral features of these compoundswere similar to those reported for enaminodiesters **448a-f**with minor differences expected due to the presence of a keto group instead of an ester group, except those mentioned above. For example, the carbonyl bond stretching frequency for the keto group was observed to be below 1680 cm^{-1} and the chemical shift of the NH protons were greater than δ 10 ppm. Both these features again indicate strong intramolecular hydrogen bondinginvolving the keto carbonyl and thus indicating the Z stereochemistry. The stereochemistry of the enaminoketoesters **450a-f**was also establishedby comparing the ^{1}H NMR chemical shifts of the vinylic and NH protons and IR absorption frequency of C=O bond of the keto and ester groups with those reported in the literature[203]for *Z* and *E* isomers of similar *N*-alkylenaminoketoesters. The observed values for **450a-f** were close to those reported for the Z isomers, showing that **450a-f** also had the Z configuration at the carbon-carbon double bond.

4.3.2. Copper(I)-catalyzed chlorine atom transfer radical cyclization of dimethyl 2-(2,2,2-trichloro-1-phenylethylamino)fumarate 448a:Optimization of the reaction conditions

Next, the enaminodiester**448a** was chosen as a representative member of the enamines **448**and**450** to investigate the crucial Cu(I)-catalyzed chlorine atom transfer radical cyclization. Many experiments were performed on **448a** in refluxing DCEwith varying amounts of CuCl under a nitrogen atmosphere in the presence of some commercially available ligands, such as bpy, TMEDA and PMDETA, usully employed in copper (I)-catalyzed HATRC reactions, in order to optimize the reaction conditions.The

effect of acetonitrile, another solvent usually employed in Cu(I)-catalyzed HATRC was also looked into. The results are compiled in **Table 11**.



Scheme 150

Table 11.Optimization of reaction conditions for chlorine atom transfer radical cyclization of448a[a]

S.No.	CuCl(mol eq)/Ligand (mol eq)/AIBN(mol eq)	solvent	Time (h)	**448a** Recovered starting material(%)	**451a** Isolated Yield (%)
1	CuCl(1.3)/bpy (1.3)	DCE	24	90	-
2	CuCl(1.3)/TMEDA (2.6)	DCE	24	75	15
3	CuCl(1.3)/PMDETA (1.3)	DCE	24	-	74
4	CuCl(0.7)/PMDETA(0.7)/AIBN(1.0)	DCE	6	-	84
5	CuCl(0.4)/PMDETA(0.4)/AIBN(2.0)	DCE	12	35	42
6	AIBN (1.0)	DCE	6	92	-
7	CuCl(0.4)/PMDETA(0.4)/Pyridine(1.0)	DCE	24	-	65
8	CuCl(0.4)/PMDETA(0.9)/AIBN (0.5)	DCE	20	-	68
9	CuCl(0.7)/PMDETA(0.7)/AIBN(1.0)	MeCN	5	-	75

[a]Allthe reactions were performed with 1 mmol of **448a**at reflux temperature under a N_2 atmosphere.

It was pleasantly noted that all the cases wherein the reaction occurred, it proceeded beyond the cyclization step to afford the aromatic 4-chloropyrrole **451a**(**Scheme 150**)probably by double dehydrochlorination-aromatization of the initial 5-*endo* cyclization product assisted by the basic ligand.[44]This would make the proposed synthetic scheme even more attractive. The product **451a** was purified by column chromatography on a short path neutral alumina column.

Of the three ligands employed bpy, the most common ligand in Cu(I)-catalyzed HATRC was found to be effective not at all, leading to the recovery of the unreacted starting material upto the extent of 90% even with more than stoichiometric amount (130 mol %) of the CuCl/bpy catalyst and prolonged reaction time (24 h). There was no indication of formation of any product (**Table 11**, **S. No. 1**). TMEDA was slightly better but still gave unacceptable result (**S. No. 2**). The PMDETA was observed to be the most effective ligand in terms of the product yield (74%) (**S. No. 3**). However, even with this ligand, the high catalyst loading (130 mol%) required to complete the reaction and the long reaction time (24 h) were still not encouraging.The high catalyst loading and sluggish reaction rate for the 5-*endo* cyclization of the *N*-H enamine **448a** was not unusual. The 5-*endo* HATRC of some even *N*-substituted trihaloenamides have been found to proceed extremely slowly with 1 equivalent of CuCl in the presence of more activating ligands such as Me_6-tren.[43]

In order to reduce the catalyst loading, easily accessible and mild reducing agent,AIBN was chosen to regenerate the active Cu(I) catalystfrom the inactive Cu(II)-catalysts presumably accumulated over the long reaction time. This method of catalyst regeneration using a catalytic amount of AIBN has been found to be quite successful in

Cu (I)-catalyzed HATRC reactions.[204]Initial experiments with varying amounts of AIBN, showed positive effects of AIBN with respect to lowering the catalyst loading and reaction time. However, catalytic amounts ofAIBN did not give satisfactory results. Finally, by using 1 equiv of AIBN from the beginning of the reaction, the amount of the catalyst CuCl/PMDETA was almost halved from 130 mol% to 70 mol% and the time of the reaction was dramatically reduced from 24 h to 6 h. The isolated yield of the product **451a** was also improved from 74% to 84%.(**S. No. 4**).Dropwise addition of a solution of 1 equiv. of AIBN in DCE took a longer time (8 h) for the completion of the reaction. Further attempt to lower the catalyst loading gave inferior results even with higher amount of AIBN (**S. No. 5**). Although AIBN is a well known radical initiator, it has been reported to be ineffective in the absence of Cu (I) catalyst in the HATRC of bromoacetamides.[204]The same was supported in the present case also. When the reaction of **448** with 1 equiv. of AIBN was performed in refluxing DCE in the absence of CuCl/PMDETA catalyst, no reaction occurred in comparable amount of time and the starting material **448a** was recovered to the extent of 92%(**S. No. 6**)

The high CuCl/PMDETA catalyst loading required to complete the reaction in the absence of AIBN might also be partly due to decomposition of the active CuCl/PMDETA complex by HCl liberated during the reaction, besides other radical terminating side reactions.[42b,205]This possibility was supported by the fact that the reaction proceeded to completion in 24 h with a lower (40 mol%) catalyst loading in the presence of 1.0 equiv of an additional base pyridine to give the product**451a** in 65% isolated yield(**S. No. 7**).However, it was not a clean reaction giving side products. Moreover, the lower product yield (65%) and the long reaction time (24 h) still remained disconcerting.The

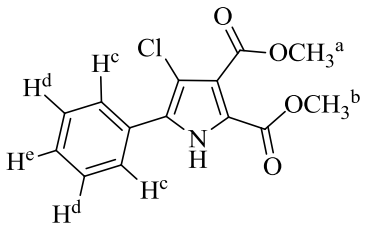
synergistic effect of an additional amount (0.5 equiv) of the triamine ligand PMDETA as an additional base and AIBN (0.5 equiv) was not observed (**S. No. 8**). In this case also, the reaction was not clean, the reaction time (20 h) was not sufficiently shortened and the product yield (68%) was not improved. It appeared that an additional amount of the base was rather detrimental to the enamine substrate **448a**. The sensitivity of the enamines having a free *N*H group towards a base has been noticed earlier also.[188]

Acetonitrile is another solvent frequently used in Cu(I)-catalyzed HATRC reactions. When the reaction of **448a** was performed in the presence of 70 mol% of CuCl/PMDETA and 1 equiv of AIBN in refluxing acetonitrile, the reaction mixture blackened as against the gradual colour change in DCE from green to orange to red. Though the reaction was observed to be complete in a slightly shorter time (5 h) probably due to better solubility of the copper complex catalyst, the very same solubility characteristic made the removal of the copper complex difficult during work up. This led to greater loss of the product, which could beisolated in a lower yield (75%). (**S. No. 9**)In the case of DCE as the reaction medium, the finished copper complex catalyst could be removed simply by filtrationof the reaction mixture or by washing with brine.

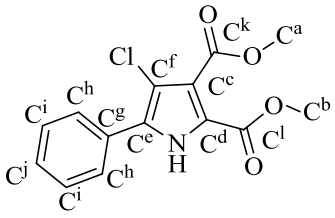
Thus, it was concluded that the optimum conditions for the cyclization in terms of reaction time, product yield,cleanliness of the reaction and ease of work up entailed the use of 70 mol% of CuCl/PMDETA (1:1 mol ratio) as the catalyst, 1 equivalent of AIBN as the promoter and DCE as the solvent in the cyclization of **448a**.

The structure of the product **451a** was established by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and mass spectrometry. Thus, the ^{1}H NMR spectrum of **451a** (**Fig. 231**) displayed all the expected proton signals. It showed two singlets at δ 3.75 and 3.93 ppm

integrating for three protons each, which were attributable to the CH_3 protons H^a and H^b, (**Fig. 28**, **Structure A**), respectively of the two ester groups.The multiplet atδ 7.37-7.46



A



B

Fig.28^{1}H NMR and ^{13}C NMR assignmentsfor the structure of 451a

ppm integrating for threeprotons, was assigned tothe*meta*protons H^d and the *para* proton H^e of the phenyl ring. The doublet at δ 7.68 ppm with a coupling constant (*J*) of 8.1 Hz integrating for two protons was assigned to the *ortho* protons H^c. The broad singlet at δ 10.28 ppm integrating for one proton, which disappeared after shaking with D_2O,was attributable to the *N*Hproton.The doublet due to the *N*H protons of the starting enamine **448a** had shifted downfield from 9.40 to 10.28 ppm in the chloropyrrole **451a**and had collapsed to a broad singlet. The alkene proton H^c and the benzylic protonH^d(**Fig. 26**)that were present in the ^{1}H NMR spectrum of the starting enamine **448a** had disappeared in the product **451a**. These features strongly indicated that the 5-*endo* cyclization product initially formed had aromatized to the chloropyrrole **451a** by dehydrochlorination. The downfield shift in the signals of methyl protons of the ester groups and the *ortho* protons of the benzene ring in going from the enamine **448a** to the pyrrole **451a** could be easily explained in terms of involvement of the lone pair of electrons of the nitrogen atom into the aromatic sextet.

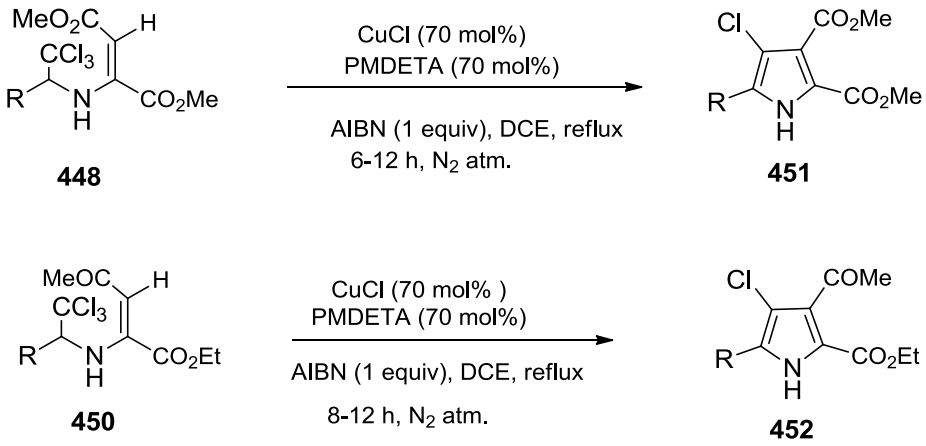
The proton-decoupled ^{13}C NMR spectrum of **451a** (**Fig. 232**) displayed all the expected carbon signals. The two signals at δ 52.38 and 52.42 ppm were assigned to the

two methyl carbons C^a and C^b (**Fig. 28**, **Structure B**), respectively of the two ester groups. The three new signalsat δ 110.6, 119.6, 121.3 ppm were assigned to the quaternary carbons C^f, C^c and C^d, respectively of the pyrrole ring. The three signals at δ 127.5, 128.7 and 128.8 ppm were assigned to the CH carbons C^i, $C^j$and C^h, respectively of the phenyl ring.The two signals at δ 128.9 and 132.2ppm were attributed to the quaternary carbonsC^e and$C^g$of the pyrrole and the phenyl ring, respectively. The remaining two signals at δ 160.4 and 164.0 ppm were attributed to the quaternary carbons C^k and C^l, respectively of the carbonyl carbon of the ester groups. These assignments were also supported by the DEPT-135 spectrum. The IR spectrum of **451a** showedstrong absorptionatν_{max} 3276 cm^{-1}due tothe N-H stretching vibration. The two strong signals at 1729 and 1694 cm^{-1} were due to the C=O stretching vibration of the α- and β-ester groups, respectively. The HRMS spectrum of this compound showed the $[M+Na]^+$ peak at m/z 316.0347, which was within the acceptable limit of deviation from the calculated value of 316.0340 for the formula $C_{14}H_{12}ClNO_4Na$.

The spectra data assignments for **451a** were in concurrence with those reported in the literature[194] for the same 4-chloropyrrole synthesized by another method.

4.3.3. Generalization of the Cu(I)-catalyzed cyclization reaction

After successful cyclization of the enamine **448a**under the optimized conditions as identified above and the characterization of the 4-chloropyrrole **451a**,the scope of this one pot CuCl/PMDETA-catalyzed HATRC-aromatization methodology was successfully extended to the other enamines **448**and **450**(**Scheme 151**).In all the cases, the 4-chloro-2,3-difunctionalized *N*-H pyrroles **451** and **452** were obtained in respectable yields(**Table 12**).



Scheme 151

Table 12.Synthesis of 4-chloro-*N*-Hpyrrolediesters 451 and 4-chloro-*N*-H pyrrole ketoesters 452[a]

S. No.	R	**451**		**452**	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1	a: Ph	6	84	8	73
2	b: 4-$MeOC_6H_4$	6	77	8	75
3	c: 4-ClC_6H_4	6	78	8	73
4	d: *n*-Bu	8	73	8	67
5	e: 2-thienyl	8	83	9	75
6	f: H	12	67	12	63

[a]All the reactions were performed with1 mmol of the enamines,70 mol% of CuCl, 70% /PMDETA and 1 mmolof AIBN in refluxing DCE undera N_2atmosphere.

The scope of the reaction was demonstrated to include a variety of 2,3-difunctionalized-4-chloro-*N*-H pyrroles having variable substituents such as ester or a keto group at C-3 and an aryl, alkyl or heteroaryl substituent at the C-5 positions. Such pyrroles without a substituent at the C-5 positions (R = H) were also accessible by this approach, though they required a longer time (12 h) for their formation from the corresponding enamines. The synthetic chemistry involved here is robust and high yielding. It appears that perhaps the synthetic scheme is as much general as the accessibility of the enamine substrates. As pointed out earlier, such polyfunctionalized pyrroles which are difficult to access otherwise, could be of considerable synthetic value.

The structures of the pyrroles **451** and **452** were supported by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS. Their IR and NMR spectral features are similar to those described earlier for the representative pyrrole **451a** with expected substituent dependent slight variations. Unlike the enaminodiesters **448a-f**, the*N*H protons of the 4-chloropyrroles **451** and **452** were found to be D_2O-exchangeable. Further support to the proposed structures was forthcoming from single crystal X-ray diffraction spectroscopy of the 2-thienyl derivative **451e** and 2-(4-methoxyphenyl)derivative**452b**as representatives of the diester and ketoester families.The ORTEP diagrams are shown in **Fig. 29** and **30**, respectively.

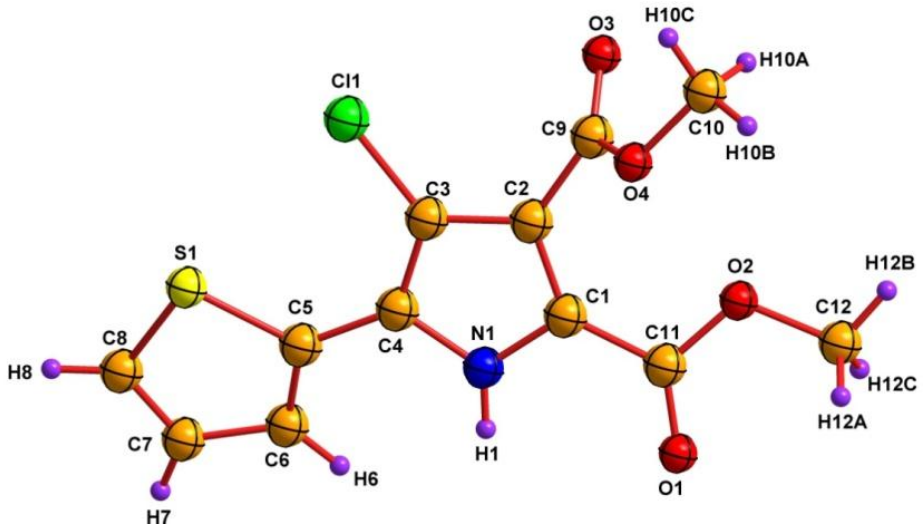


Fig.29ORTEP diagram of dimethyl 4-chloro-5-(thiophen-2-yl)-1H-pyrrole-2,3-dicarboxylate 451e

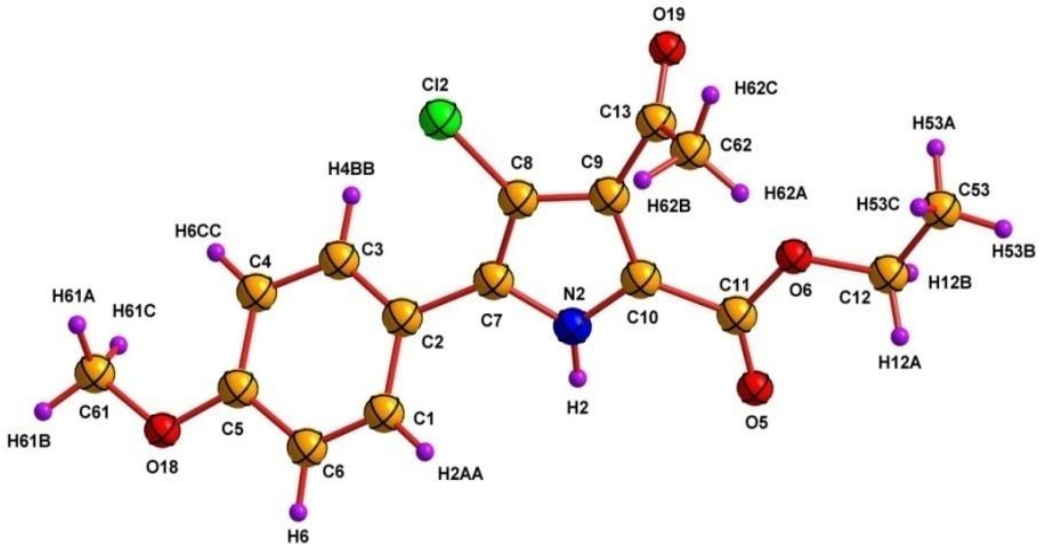
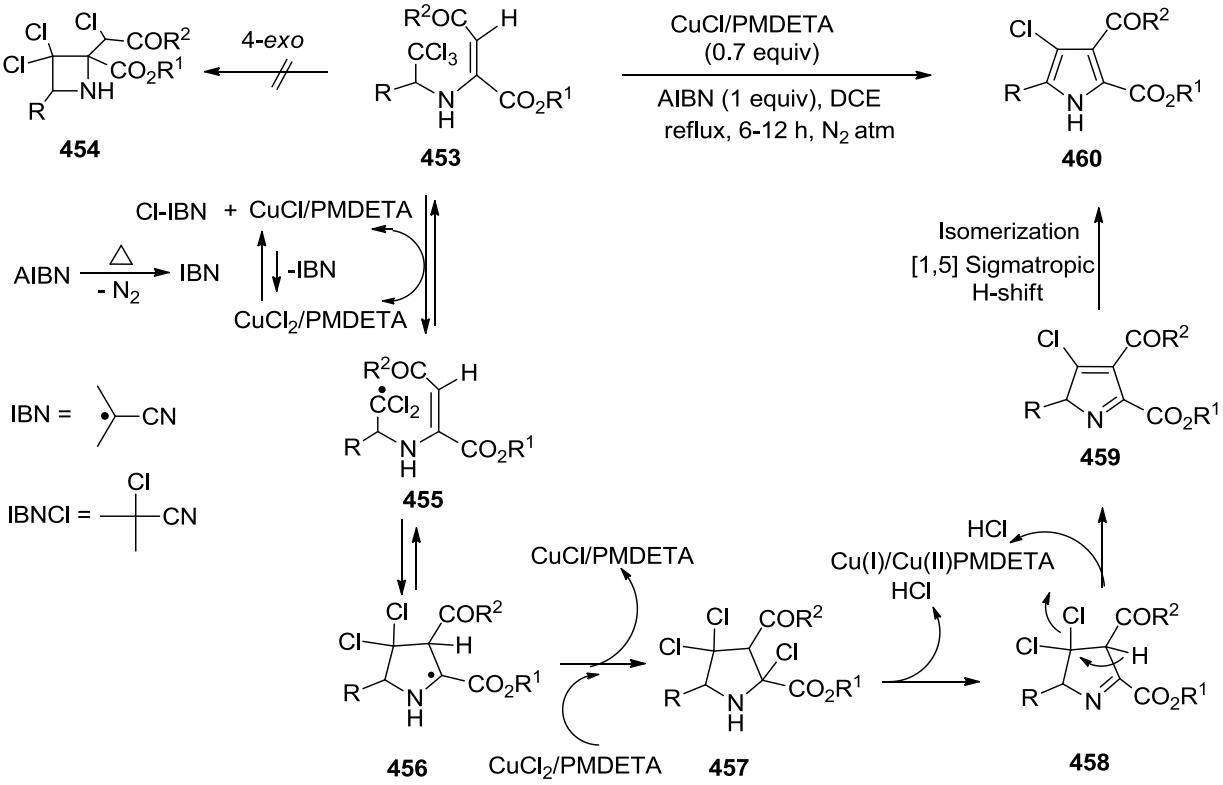


Fig. 30ORTEP diagram of ethyl 3-acetyl-4-chloro-5-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate452b

4.3.4. Probable mechanism

The following mechanism was proposed for the formation of the 4-chloropyrroles **451** and **452**. No 4-*exo* cyclization product **454** (**Scheme 152**) was detected in the



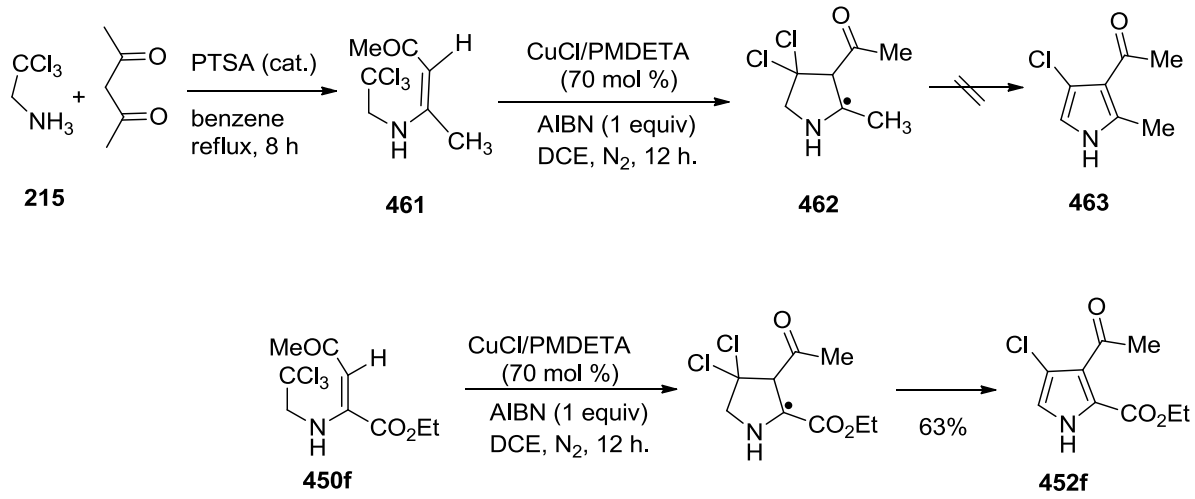
Scheme 152

cyclization of the enamines **448** and **450**.Though 4-*exo* radical cyclizations are kinetically favorable reactions according to the Baldwin's rules,[37]they are highly reversible due to high ring strain and more steric congestion in the transition state leading to the formation of the radical intermediate by 4-*exo* cyclization.5-*Endo-trig*radical cyclizationsare kinetically disfavored processes due to stereoelectronic disadvantage in the attack by a radical centre at the alkenic bondbut the products are thermodynamically more stable due to less ring strain. Moreover, the attachment of a carbonyl group to the alkenic carbon has been reported to facilitate 5-*endo* radical cyclization by changing the trajectory for radical attack to a less strained one. [206]The consequence of this new trajectory is a less strained transition state for the 5-*endo* cyclization. The presence of the ester carbonyl on the radical acceptor C=C bond and possibly the equilibrating reaction conditions arguably enforced by

the relatively high reaction temperature in the present cyclization reactions (refluxing DCE) might have led to the formation of the thermodynamically controlled 5-*endo* cyclization product. The preference for the formation of 5-*endo* products at higher temperatures has been observed earlier.[207]

It was also thought that 5-*endo* cyclizationwas observed because of stabilization of the radical intermediate **456**by captodative effect[208]of the electron donating *N*H and electron withdrawing ester substituents. Captodative stabilization-promoted 5-*endo* radical cyclizationto the exclusion of even more favorable 5-*exo* radical has been observed earlier[209]during Bu_3SnH/AIBN mediated reaction of *N*-(β-haloethyl)-*N*-allylenamides having an additional olefinic bond in the *N*-allylic substituent capable of undergoing 5-*exo* cyclization. However, the exclusive formation of 5-*endo* products instead of 5-*exo* products could also be due to the preferred conformation of the haloenamides suitable for the 5-*endo* cyclization.[210]The same group observed only 5-*endo* cyclization to the exclusion of 5-*exo* cyclization in Cu (I)-catalyzed HATRC of similar *N*-allylic haloenamides where the radical intermediate formed on 5-*endo* cyclization, was not stabilized by captodative effect.[208]However, in the present case, the enamines may not be predisposed in a conformation suitable for 5-*endo* cyclization and captodative effect may be a valid reason for the observed 5-*endo* cyclization. Theoretical calculations went a step further and predicted that 5-*endo* cyclizations were not only thermodynamically but also kinetically favored.[39]In order to provide credence to this possibility, the trichloroethyl enamine **461**(**Scheme 153**)having a methyl group in the place of the α-ester group was synthesized in 65% yield by the reaction of the 1-unsubstituted 2,2,2-trichloroethyl amine**215**(**Chapter 2**)with acetyl acetone under the conditions mentioned earlier for the synthesis of other

enamines**450**(**Scheme 149**).The reaction of this enamine with CuCl/PMDETA/AIBN in refluxing DCE under usual optimized reaction conditions for 12 h did not give the pyrrole**463.**Only the starting material was recovered to the extent of 70% along with some decomposed products.In contrast, the enaminoketoester **450f** underwent the cyclization smoothly. Clearly, in the case of the enaminoketone **461**, the incipient radical intermediate **462** (R= Me) could not be stabilized by the captodative effect.[208]



Scheme 153

It was therefore concluded that the presence of the carbonyl group on the radical acceptor alkenic bond, high reaction temperature and capto-dative stabilization of the radical intermediate formed on cyclization, all might have contributed to promote the generally unfavorable 5-*endo* cyclization leading to the formation of the 5-*endo* cyclization product exclusively.

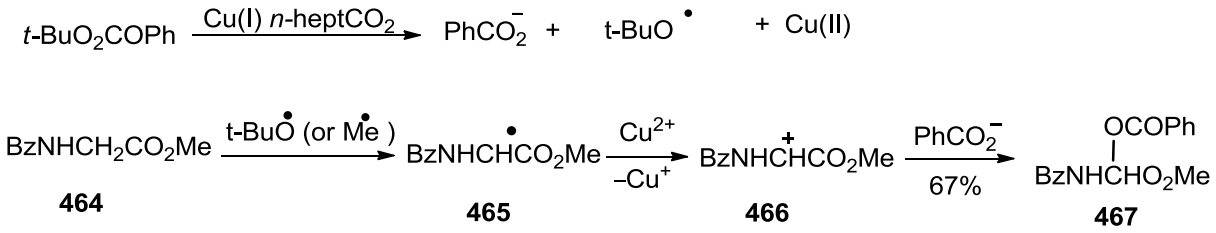
The captodative stabilization of the radical intermediate **456**might also promote the reaction by reducing the reversibility of the 5-*endo*cyclization. At the same time, it may reduce thereactivity of the radical in abstracting a chlorine atom from $CuCl_2$/PMDETAcomplex in the next step leading to the formation of α-chloropyrrolidine

intermediate **457**. This would result in accumulation of the $CuCl_2$/PMDETA complex and disruption of the catalytic cycle. The role of AIBN appeared to restore the catalytic cycle by continuously reducing $CuCl_2$/PMDETA to the active catalyst CuCl/PMDETA.

The α-chloropyrrolidine intermediate **457**(**Scheme 152**)was expected to spontaneously eliminate a molecule of HCl under the reaction conditions to form a pyrroline intermediate **458.** Dehydrochlorination of the products during HATRC is not unusual (**Scheme 20, Chapter-1**).The pyrroline intermediate **458**couldthen undergo another dehydrochlorination probably promoted by the basic ligand to give the isopyrazole (or 2H-pyrrole) intermediate **459**. The latter was expected to finally afford the aromatic 4-chloro-*N*H-pyrroles **460**by concerted[1,5]-sigmatropic H-shift. The pyrroline intermediate**458**, however, could not be isolated. When the reaction of **448a** with 70 mol% each of CuCl and PMDETA in the presence of 1equivalent of AIBN was intercepted after 4 h, 2 h before the completion of the reaction, no pyrroline derivative of the type **458**could be isolated or detected by ^{1}H NMR. Only the pyrrole **451a** and the unreacted starting material**448a**were obtained on purification by column chromatography. Probably the pyrroline **458** had high propensity to aromatize under the reaction conditions.

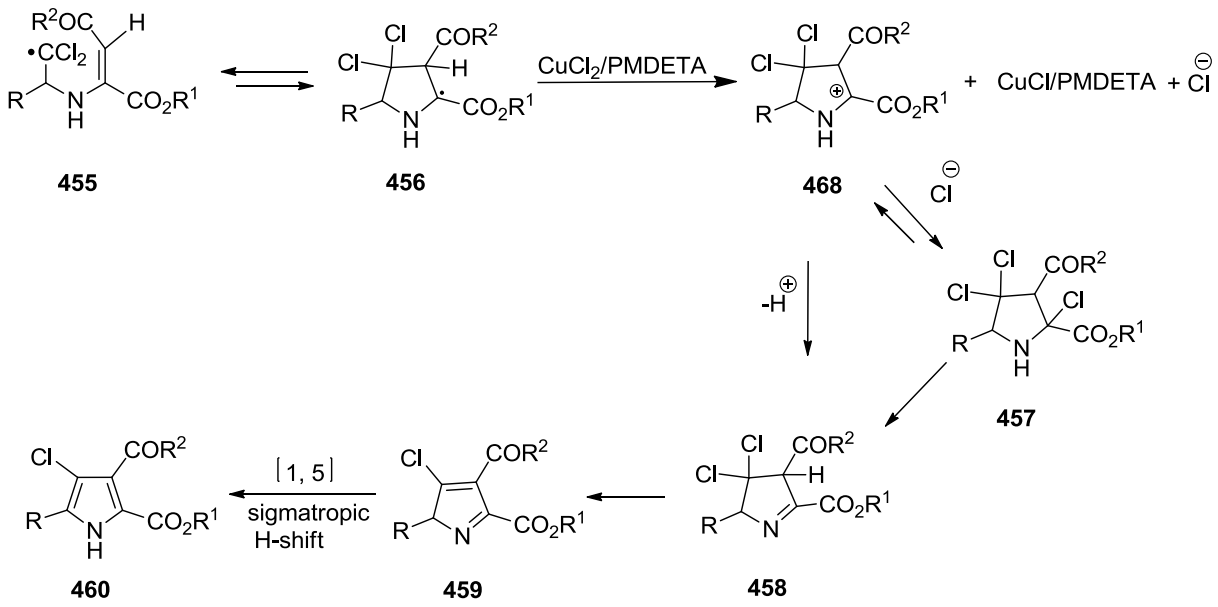
The precise mechanism of formation or otherwise of the α-chloropyrrolidine intermediate **457**might be debatable. Free radicals in general are well known to be oxidized by many redox active metal ions.[41,211]In some Cu (I)-catalyzed HATRC of haloenamides,the closest kin of the present enamines, the *N*-acyliminium ions have been proposed to be formed by oxidation with Cu (II) of the radical intermediates produced after 5-*endo* cyclization.[39,42b,44,212]In Ni/AcOH[40]and Bu_3SnH[207,213]-mediated reaction of such substrate also, *N*-acyliminium ions were formed. In these cases, the formation of the *N*-

acyliminium ion was proposed to occur by oxidation of the radical with the starting haloenamide.[40,207,213]In most of these cases, the radicals undergoing oxidation were tertiary and not captodative and thus were prone to oxidation. The*N*-acyliminium ion underwent deprotonation easily to give the alkene. Captodatively stabilized radicals, similar to **456** (**Scheme 152**) are known to get oxidized by Cu (II) to carbocations. For example, treatment of the *N*-benzoylglycine methyl ester**464**(**Scheme 154**) with *tert*-butyl perbenzoate in the presence of Cu(I)octanoate gave the α-benzoyloxyglycine derivative**467** via Cu(II) mediated oxidation of the captodactive radical **465**tothe cationic intermediate **466**.[214]



Scheme 154

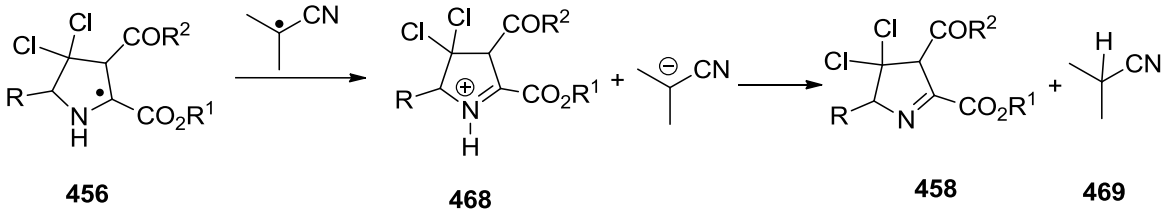
In the present case also, the $CuCl_2$/PMDETA produced in the first step might oxidize the radical intermediate **456**(**Scheme 155**) to the carbocationic intermediate **468**, which might reversibly combine with the chloride ion generated during the oxidation to form the α-chloropyrrolidine intermediate **457** or might eliminate a proton to give the pyrroline intermediate **458** directly without involving the α-chloropyrrolidine intermediate **457**. This would also regenerate the active catalyst CuCl/PMDETA. However, both these processes, the chlorine atom transfer from $CuCl_2$/PMDETA to the radical **456** and oxidation of **456** to carbocation **468** by single electron transfer to $CuCl_2$/PMDETA, appeared to be slow probably due to low solubility of the $CuCl_2$/PMDETA complex in the medium.



Scheme 155

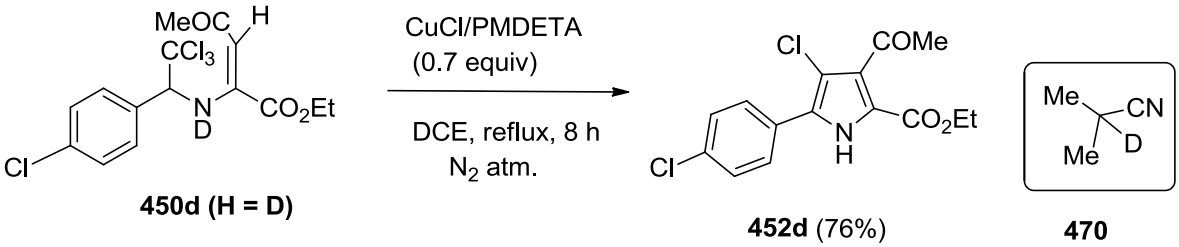
This is indicated by the reaction of **448a** with CuCl/PMDETA in the absence of AIBN (**Table 11**, **S. No. 3**), where the reaction required long time (24 h) and large amount of the catalyst (1.3 equivalent of each of CuCl and PMDETA to complete the reaction. In the presence of a reasonably good amount of AIBN used in the present reactions, the chlorine atom transfer mechanism appeared to be preferentially promoted. The high concentration of soluble and more reactive IBN radical would more efficiently reduce the $CuCl_2$/PMDETA to regenerate the active catalyst CuCl/PMDETA. Presumably, it might also serve as a soluble halogen carrier in the chlorine atom transfer step leading to the formation of the α-chloropyrrolidine intermediates **457**. Further due to continuous consumption of the $CuCl_2$/PMDETA by the IBN radical, the concentration of the former would considerably decrease in the solution, thus disfavoring the oxidation of the captodatively stabilized radical**456**to the carbocationic intermediate**468**.

It might be argued that the IBN radical might also oxidize the captodatively stabilized radical **456** to the carbocationic intermediate **468**(**Scheme 156**) as the radicals produced by Bu_3SnH/peroxide-mediated 5-*endo* cyclization of the haloenamides have been reported to be oxidized to the corresponding carbocation by peroxide.[215]



Scheme 156

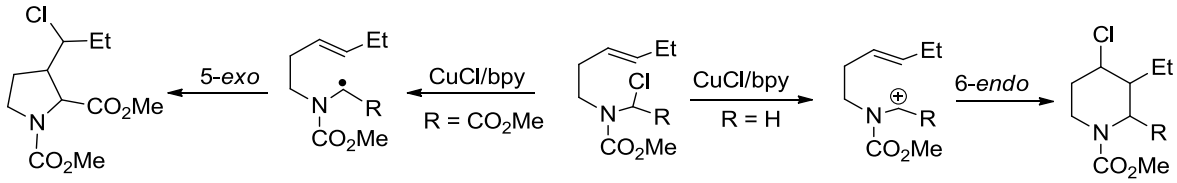
However, treatment of deutrated *N*-D-enamine **450c**(**Scheme 157**)under the usual reaction conditions and HRMS of the reaction mixture showed no m/z value corresponding to Me_2CDCN **469**or Me_2CHCN**470.**This observation may probably go against this mechanism.



Scheme 157

That the oxidation of captodative radicals similar to **456**is not always competitive with its other reactionshas been shown by Udding etal[216.]They found that CuCl/bpy catalyzed cyclization of the carbamate **471** (R = H) (**Scheme 158**) changed from a cationic process, leading to the piperidine**472**by characteristic carbocationic 6-*endo* cyclization into a radical

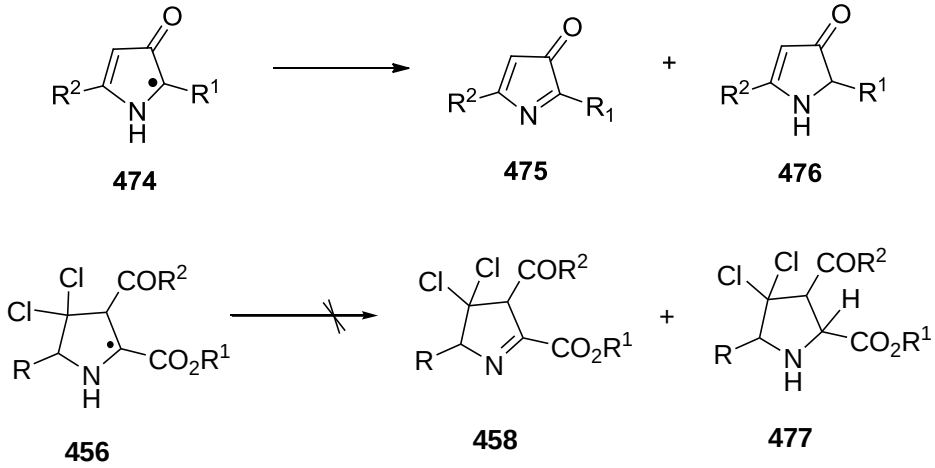
process leading to the pyrrolidine**473**by 5-*exo* cyclization upon introducing an ester substituent at the reactive carbon atom due to capto-dative stabilization of the radical intermediate, which preferred to undergo 5-*exo* cyclization instead of oxidation by Cu (II). Even in the case of the reported haloenamides cyclizations, only the electron rich tertiary radicals, which are prone to oxidation, have been reported to be oxidized. In some cases, the cations have been trapped by alcohols.[4]



473 **471** **472**

Scheme 158

Captodative radicals of the type**456**are known to disproportionate.[217]For example, the 3-oxopyrrol-2-yl radicals**474**(**Scheme 159**) disproportionate to the pyrrolones**475** and

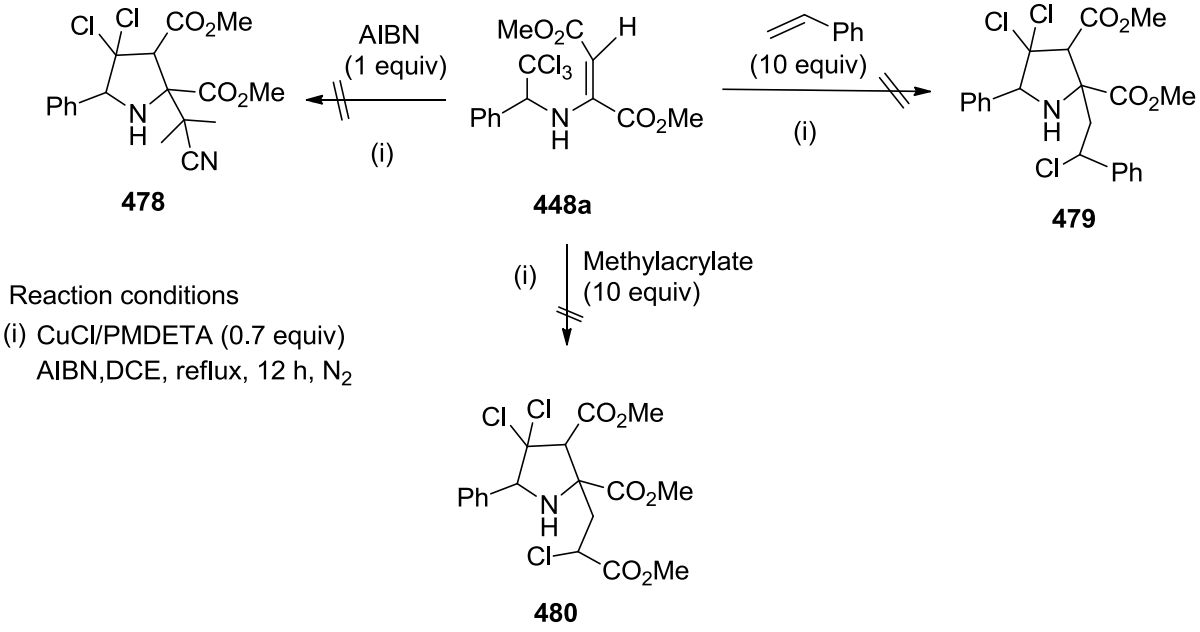


Scheme 159

pyrrolinones**476**. Similarly, the captodative radicals**456** might be expected to disproportionate to the pyrroline intermediate **458** and pyrrolidines**477**. However, in none of the cyclization reactions of the present investigation, the pyrrolidine **477** or a

conceivable product derived from it was isolated or detected, thus ruling out this possibility.

In the haloenamide 5-*endo* cyclizations mediated by Bu_3SnH/AIBN, the captodative radical has been trapped by coupling with IBN radical[213,218] and by intermolecular as well as intramolecular additionsto alkenes.[219]The trapping of an *N*-acyliminium ion intermediate by alcohol in some cases has already been mentioned earlier[42,44](**Scheme 41**, **Chapter 1**).However, in the present study, attempts to trap the captodative radical **456** or the cationic intermediate **468**in similar ways failed. IBN radical coupled products such as **478** (**Scheme 160**) were not isolated or detected in any of the cyclization reactions \

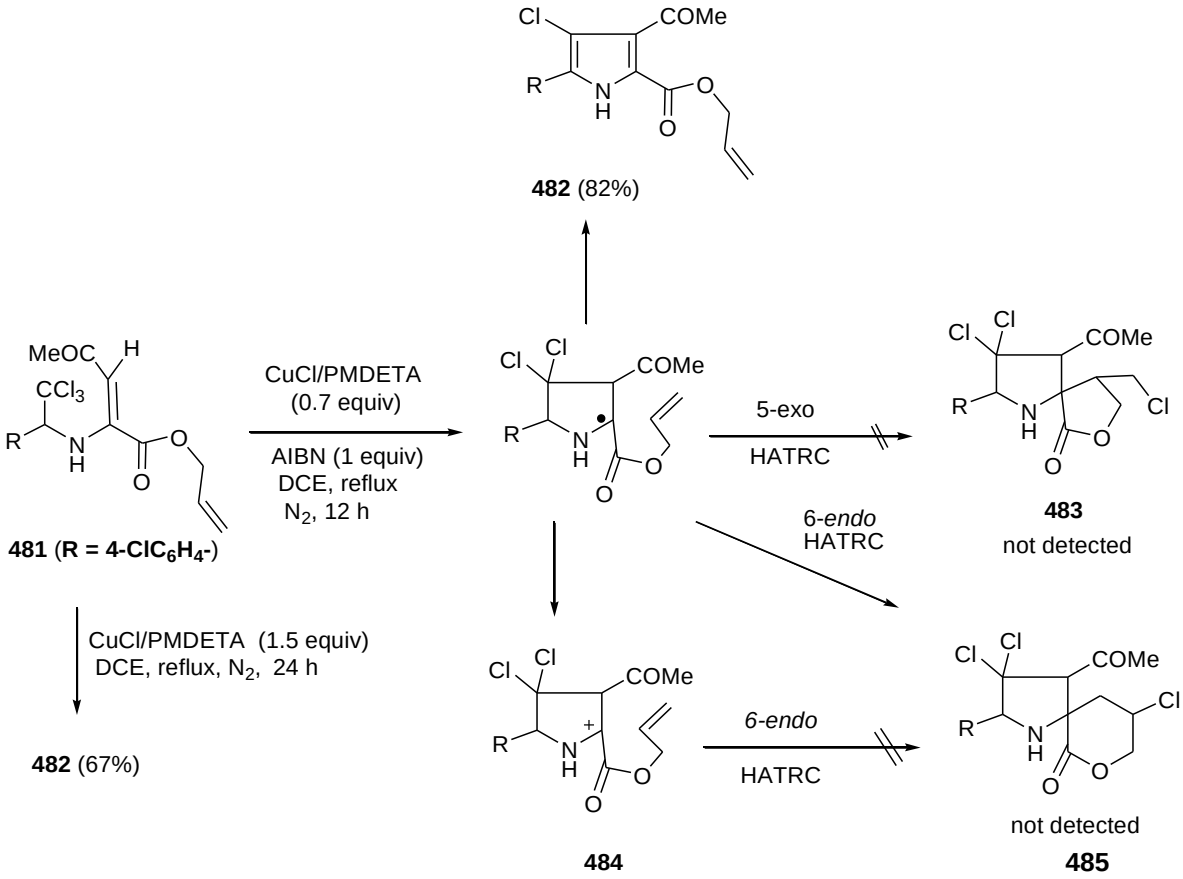


Scheme 160

carried out under the optimized conditions even though all these experiments were performed in the presence of large excess (1 equivalent) of AIBN. When**448a** was subjected to the usual optimized radical conditions in the presence of 10 equiv of styrene

or methyl acrylate, no alkene adducts **479** or **480** were isolated or detected. Only the pyrrole **451a** (69%, in the case of methyl acrylate, 65% in the case of styrene)was isolated along with some unidentifiable, probably polymeric sticky material.[73]

Further, no tandem cyclization product **483** or **485**(**Scheme 161**) was observed when the reaction of enamine allyl ester **481** was subjected to the radical cyclization

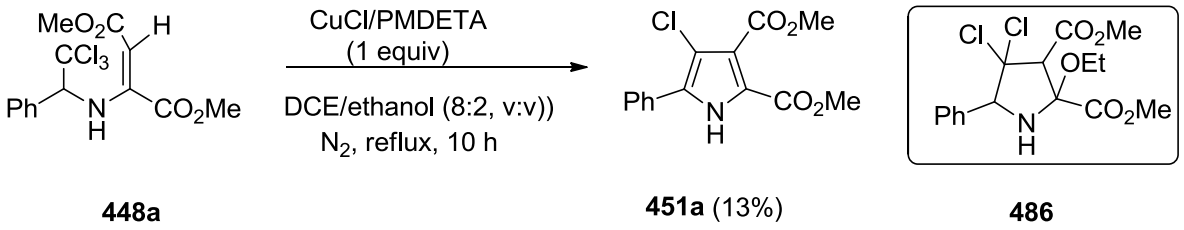


Scheme 161

reaction under the optimized conditions for 12 h. Only the corresponding pyrrole **482** was isolated in 82% yield. The result was the same when **481** was treated with 1.5 equiv of CuCl/PMDETA in the absence of AIBN in DCE under reflux for 24 h, except that the corresponding product **482** was isolated in a lower isolated yield of 67%.5-*Endo*-5-*exo*

tandem cyclization product **483**was expected to arise by a radical-radical processes whereas the 5-*endo*-6-*endo* tandem cyclization product **485** could arise from the radical-radical[27,213,219] and/or radical-cation processes.[216,220]However, the radical-cation processes appeared to be less likely any ways because the cation **484** may undergo fast deprotonation under the reaction conditions. Though failure to trap the radical intermediate may be understood in terms of faster rate of its oxidation as compared to cyclization, it could be also due to faster rate of the chlorine atom abstraction.

For the sake of curiosity,when the enamine **448a** was treated with CuCl/PMDETA (1 equiv) in ethanol/DCE mixture (2:8, v/v) for 16 h,(**Scheme 41**, **Chapter 1**) most of the enamine **448a**was found to decompose.[42,44]The addition product **486**(**Scheme 162**) could not be isolated or detected as suspected. The chloropyrrole**451a** could be isolated by column chromatography in 13% yield.



448a **451a** (13%) **486**

Scheme 162

Even if the adduct **486** had been formed it might have been unstable under the reaction conditions and might have led to the formation of chloropyrroles **451a** by successive elimination of ethanol and HCl. The poor yield of **451a** was arguably due to the decomposition of the enamine **450a** under the reaction conditions.

It may be tempting to consider the results of this experiment to support the involvement of the cationic intermediate. However, these results could also be explained in terms of ready solvolysis of α-chloropyrrolidine intermediate of the type **457**(**Scheme 152**) with ethanol, as structurally similar α-chloroglycine ester derivatives are known to be moisture sensitive.[220b]In fact, the structure of the *N*-H enamine substrates used in the present cyclization did not allow to prove or disprove the involvement of the cationic intermediate **468** (**Scheme 155**) confidently. From the foregoing account, however, the cationic intermediate **468**appears less likely to be involved in these reactions.

4.4. Conclusion

The present chapter describes a single step regioselective method involving CuCl/PMDTA complex catalyzed *5-endo-trig*chlorine atom transfer radical cyclization of 2,2,2-trichloroethylenaminesfollowed by aromatization by double dehydrochlorination for the synthesis of tetra- and trisubstituted 2,3-difunctionalized 4-chloro-*N*-H pyrroles from readily accessible trichloroethylamines under milder conditions.It provides examples of successful 5-*endo* radical cyclization of enamines for the first time. The generally unfavorable, 5-*endo* cyclization appears to be facilitated by stabilization of the intermediate radical by capto-dative effect among other factors. The formation of a cationic intermediate by oxidation of the capto-dative radical intermediate by Cu (II) or other reactions could not be established. The present method of 4-chloropyrrole synthesis allows the introduction of a variety of substituents, alkyl, aryl and heteroaryl substituent at the C-5 position and keto and ester groups at the C-2 and C-3 positions.

Many naturally occurring and pharmaceutically important *N*-H pyrroles contain chloro, keto and ester functionality. The present method may be useful for the synthesis of chloro-analogs of such pyrrolesto study structure–activity relationships. These highly functionalized chloropyrroles are expected to be versatile synthetic intermediates for the synthesis of valuable aliphatic, alicyclic and aromatic compounds. It is free of the wasteful NH-protection and deprotection steps.

4.5. EXPERIMENTAL SECTION

4.5.1 Preparation of starting materials

Ethyl acetopyruvate **449** was prepared by condensation of acetone and diethyl oxalate.[200]

4.5.1.1. *N*-(1-substituted-2,2,2-trichloroethyl)acetamides, 446a-e

The previously known *N*-(2,2,2-trichloro-1-hydroxy)ethyl acetamide **443** and*N*-(1,2, 2,2-tetrachloroethyl)acetamide **444** were prepared by the method reported in the literature.[197a]The condensation product **443**of chloral hydrate and acetamide furnished **444**on chlorination with PCl_5. The previously known *N*-acetylchloralimine[221]**445**was prepared by modifying a reported procedure[197b] so as to suit the next reactions to be performed in the same pot without isolation.[197b] The N-(-substituted 2,2,2-trichloro)ethyl acetamides **446** were prepared by treatment of Grignard reagents with **445**, generated *in situ*following a method reported in the literature[197c] for the preparation of similar trifluorinated compounds.

General procedure: A solid mixture of acetamide (3.62 g, 40 mmol) and chloral hydrate (6.946 g, 42 mmol) was heated at 90-100 ˚C until complete melting.The reaction mixture

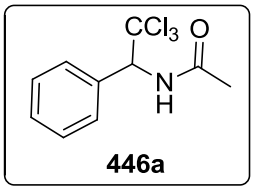
was allowed to cool and solidify. The solid thus obtained was powdered and washed with cold chloroform and recrystallized from ethanol-water to give chloralacetamide **443** (7.40 g, 90%) as white needles, mp154 ˚C (Lit.[197a]mp 156 ˚C)

To a stirred suspension of chloralacetamide **443** (4.13 g, 20 mmol) in dry chloroform (100 mL), a suspension of phosphorus pentachloride (4.165 g, 20 mmol) in dry chloroform (60 mL) was slowly added with stirring over a period of 10 min. The temperature of the reaction was carefully controlled and was not allowed to rise above 20 ˚C. The stirring was continued for another 30 min. During this time the evolution of HCl and a progressive loss of turbidness of reaction mixture were perceptible and the mixture became totally transparent. Then chloroform was removed under reduced pressure to get *N*-(1,2,2,2-tetrachloroethyl) acetamide **444** as a white solid mass in quantitative yield.[56a] It was used as such in the next step.

To a solution of the *N*-(1,2,2,2-tetrachloroethyl)acetamide **444** in THF (60 mL), NaH (0.800 g, 60% as dispersion in mineral oil, 20 mmol) was added with stirring at 0 ˚C. The stirring was continued for 0.5 h at the same temperature.[197b] This solution of *N*-acetylchloral imine **445**,thus obtained was cooled to -15 ˚C under a N_2 atm and to this solution a solution of Grignard reagent (20 mmol, 1 equiv) prepared earlier by a reaction of alky or aryl or heteroaryl bromides (20 mmol) with magnesium (0. 486 g, 20 mmol) in THF by usual procedure, was added. The reaction mixture was stirred for 2 h at the same temperature and then the temperature was allowed to slowly rise to 0 ˚C. The stirring was continued for a further 30 min duration. The reaction mixture was then quenched at 10 ˚C by addition of a saturated aq. solution of NH_4Cl (20 mL) slowly and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried (Na_2SO_4) and filtered. The

solvent from the filtrate was removed under reduced pressure and the residue was purified by column chromatography on a basic alumina column using a mixture *n*-hexane/ethyl acetate (9:1, v/v) asthe solvent for elution to obtain *N*(-1-substituted-2,2,2-trichloroethyl)acetamide **446** high yields (78-88%).

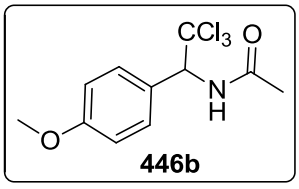
*N-{(2,2,2-trichloro-1-phenylethyl)}acetamide**446a**:*



446a

Light yellow crystals, mp 140˚C (chloroform-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.12 (s, 3H, CH_3), 5.98 (d, 1H, *J* = 10.0 Hz, CH), 6.49 (d, br, 1H, *J* = 9.5 Hz, NH, D_2O-exchangeable), 7.39-7.40 (m, 3H, CH), 7.52 (d, 2H, *J* = 6.9 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.3 (CH_3), 66.6 (CH), 101.5 (C), 128.2 (CH), 129.2 (CH), 129.4(CH), 134.9 (C), 169.2 (C) ppm; IR (KBr); ν_{max} 3273(s), 3062(w), 2925(w), 1659(s), 1545(s), 1375(m), 1272(m), 806(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{10}Cl_3NONa$ 287.9719, found 287.9720.

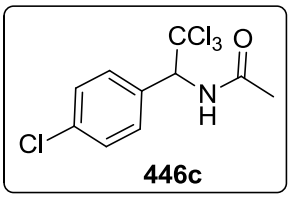
*N-{2,2,2-trichloro-1-(4-methoxyphenyl)ethyl}acetamide **446b**:*



446b

Light yellow crystals, mp 124 ˚C (chloroform-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 5.93 (d, 1H, *J* = 9.9 Hz, CH), 6.54 (d, br, *J* = 9.0 Hz, NH, D_2O-exchangeable), 6.90 (d, 2H, *J* = 8.4 Hz, CH), 7.44 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.3 (CH_3), 55.3 (CH_3), 66.2 (CH), 102.0 (C), 113.6 (CH), 126.9 (C), 130.6 (CH), 160.1 (C), 169.1 (C) ppm; IR (KBr); ν_{max} 3247(s, br), 3039(w), 1654(s), 1614(m), 1539(s), 1515(s), 1277(m), 1250(s), 1030(s), 834(w), 799(m), 752(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{11}H_{12}Cl_3NO_2Na$ 317.9836, found 317.9826.

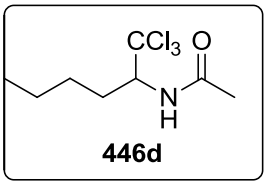
*N-{2,2,2-trichloro-1-(4-chlorophenyl)ethyl}acetamide**446c**:*



446c

Light yellow solid, mp 148 ˚C (chloroform-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 3H, CH_3), 5.94 (d, 1H, *J* = 9.6 Hz, CH), 6.60 (d, br, *J* = 9.6 Hz, NH, D_2O-exchangeable), 7.35 (d, 2H, *J* = 7.5 Hz, CH), 7.46 (d, 2H, *J* = 7.5 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.3 (CH_3), 66.1 (CH), 101.0 (C), 128.5 (CH), 130.7 (CH), 133.4 (C), 135.4 (C), 169.1 (C) ppm; IR (KBr): ν_{max} 3253(s, br), 3071(m), 1660(s), 1557(s), 1462(w), 1374(m), 1296(m), 1098(w), 804(m)cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_9Cl_4NONa$ 321.9330, found 321.9330.

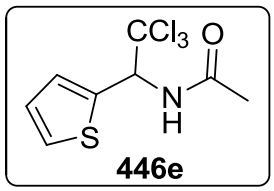
*N-(1,1,1-trichlorohexan-2-yl)acetamide**446d***:



446d

Light yellow solid, mp 80-82 ˚C (chloroform-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (t, 3H, *J* = 6.75 Hz, CH_3), 1.25-1.46 (m, 4H, CH_2), 1.50-1.58 (m, 1H, CH_2), 2.10 (s, 3H, CH_3), 2.16-2.24 (m, 1H, CH_2), 4.70 (ddd, 1H, *J* = 12.9, 10.2, 2.4 Hz, CH), 5.71 (d, br, 1H, *J* = 9.6 Hz, NH, D_2O-exchangeable) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (CH_3), 22.1 (CH_2), 23.1 (CH_3), 28.0 (CH_2), 30.6 (CH_2), 63.6 (CH), 103.0 (C), 170.4 (C) ppm; IR (KBr): ν_{max} 3296(s, br), 1661(s), 1534(s), 1495(m), 1372(m), 1270(m), 1128(w), 1018(w), 802(m), 721(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_{14}Cl_3NONa$ 268.0027, found 268.0033

*N-{2,2,2-trichloro-1-(thiophen-2-yl)ethyl}acetamide**446e**:*



446e

Light yellow crystals, mp 156 ˚C (chloroform-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ2.11 (s, 3H, CH_3), 6.29 (d, 1H, *J* = 9.3 Hz,

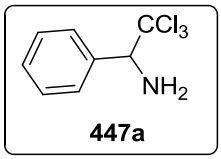
CH), 6.40 (d, br, *J* = 9.3 Hz, NH, D_2O-exchangeable), 7.03 (t, 1H, *J* = 4.4 Hz, CH), 7.28 (d, 1H, *J* = 3.0 Hz, CH), 7.35 (d, 1H, *J* = 4.5 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.2 (CH_3), 63.2 (CH), 101.1 (C), 126.5 (CH), 129.4 (CH), 137.1 (C), 168.9 (C) ppm; IR (KBr): ν_{max}3251 (s, br), 3045(m), 1660(s), 1542(s), 1435(w), 1271(m), 1211(s), 1139(w), 810(m), 715(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_8Cl_3NOSNa$ 293.9288, found 293.9284.

4.5.1.2.1-Substituted 2,2,2-trichloroethyl amines 447a-e: Hydrolysis of 446

2,2,2-Trichloroethyl amines were prepared by acid hydrolysis of *N*-(1-substituted-2,2,2-trichloroethyl)acetamides**446**by using methods reported in the literature[197d-e] for acid-catalyzed hydrolysis of N-substituted acetamide derivatives.

General procedure: A mixture of *N*-(1-substituted-2,2,2-trichloroethyl)acetamide **446**(10 mmol), 5N H_2SO_4(or 4N HCl in the case of **446b**) (50 mL) and methanol (50 mL) was heated at reflux. After completion of the reaction as indicated by disappearance of the starting acetamide on TLC monitoring (8-16 h), the reaction mixture was allowed to cool to room temperature (25-30 ˚C). It was washed with benzene (2x20 mL) to remove any organic residue. The aq. phase was cooled at 0 ˚C and NaOH (aq. 2N) was added to it with stirring. The solution became gradually turbid in this process. The addition of NaOH solution was stopped when the pH of the turbid suspension rose to 9-10. The suspension was further stirred for 15 min and extracted with ethyl acetate (3x30 mL). The combined extract was dried (Na_2SO_4), filtered and evaporated under reduced pressure to obtain 1-substituted 2,2,2-trichloroethylamines **447** in good yield (**Table 9**). The amines were directly used without further purification.

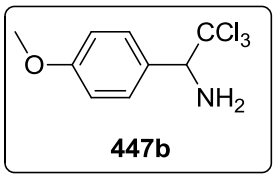
*2,2,2-Trichloro-1-phenylethanamine***447*a*:**



447a

Light yellow liquid; ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.30 (s, br, 2H, NH_2, D_2O-exchangeable), 4.63 (s, 1H, CH), 7.36-7.39 (m, 3H, CH), 7.49-7.54 (m, 2H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 71.8(CH), 105.5 (C),127.9(CH), 128.9 (CH), 129.2 (CH), 136.5 (C) ppm; IR(KBr): ν_{max} 3405, 3337(s, br), 3036(w), 1684(w), 1612(s), 1496(m), 1271(w), 1077(w), 807(s), 746(s) cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_8H_8Cl_3NH$ 223.9799, found 223.9795.

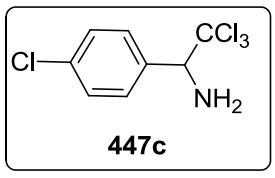
*2,2,2-Trichloro-1-(4-methoxyphenyl)ethanamine***447*b*:**



447b

Light red liquid; ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.10 (s, br, 2H, NH_2, D_2O-exchangeable), 3.78 (s, 3H, CH_3), 4.59 (s, 1H, CH), 6.89 (d, 2H, *J* = 8.4 Hz, CH), 7.44 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ55.2 (CH_3), 71.3 (CH), 105.9 (C), 113.4 (CH), 128.6 (C), 130.3 (CH), 160.0 (C) ppm;IR(KBr):ν_{max}3370, 3299(m, br), 2911(m), 1611(s), 1461(w), 1515(s), 1253(s), 1190(m), 1031(m), 799(s) cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_9H_{10}Cl_3NOH$ 253.9899, found 253.9901.

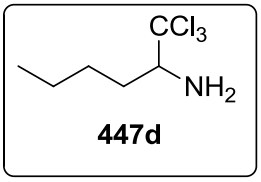
2,2,2-Trichloro-1-(4-chlorophenyl)ethanamine **447*c*:**



447c

Yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.21 (s, br, 2H, NH_2, D_2O-exchangeable), 4.62 (s, 1H, CH), 7.35 (d, 2H, *J* = 8.4 Hz, CH), 7.47 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 71.1 (CH), 101.8 (C),128.2(CH), 130.5 (CH), 132.0 (C),135.0 (C)ppm;IR(KBr):ν_{max} 3378, 3329(NH_2, br), 2924(w), 1662(m), 1597(w), 1488(s), 1093(s), 818(s), 775(s) cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_8H_7Cl_4NH$ 257.9407, found 257.9405.

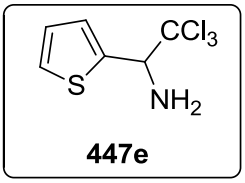
1,1,1-Trichlorohexan-2-amine **447*d*:**



447d

Light red liquid; ^{1}H NMR ($CDCl_3$, 300MHz); δ 0.94 (t, 3H, *J* = 7.5 Hz, CH_3), 1.26-1.52 (m, 4H, CH_2), 1.58-1.71[m, 3H (1H,CH_2, 2H, NH_2, D_2O-exchangeable)], 2.02-2.12 (m, 1H, CH_2), 3.24 (d, 1H, *J* = 9.3 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (CH_3), 22.3 (CH_2), 29.6 (CH_2), 31.6 (CH_2), 68.8 (CH), 108.0 (C) ppm; IR(KBr): ν_{max}3406, 3332(m, br), 2959(s), 2866(m), 1618(m), 1459(m), 1375(w), 801(s)cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_6H_{12s}Cl_3NH$ 204.0105, found 204.0108.

2,2,2-Trichloro-1-(thiophen-2-yl)ethanamine **447*e*:**



447e

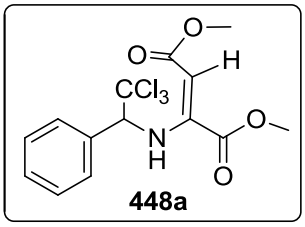
Yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.29 (s, br, 2H, NH_2, D_2O-exchangeable), 4.92 (s, 1H, CH), 6.95(dd, 1H, *J* = 5.1, 3.6 Hz,CH), 7.19 (br, s, 1H, CH), 7.27(dd, 1H, *J*= 5.1, 0.9 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ68.3 (CH), 104.8 (C), 126.0 (CH), 126.2 (CH), 128.3 (CH), 138.9 (C) ppm; IR(KBr):ν_{max} 3391, 3322(m, br), 3080(w), 1686(m), 1611(m), 1505(w), 1247(w), 806(s), 709(s) cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_6H_6Cl_3NSH$ 229.9365, found 229.9359.

4.5.2.1. Preparation of *N*-2,2,2-trichloroethylenamines 448a-f

The previously unknown enamines**448a-f**were prepared by Michael addition of trichloroethyl amines to DMAD following a procedure reported in the literature[199] for the preparation of similar enamines by addition of other amines to DMAD.

General procedure: A solution of the 2,2,2-trichloroethylamine **447** (10 mmol) and dimethylacetylenedicarboxylate (DMAD) (1.23 mL, 1.421 g, 10 mmol) in THF was stirred at room temperature (25-30 ˚C) for 5-6 h. After the completion of the reactions as indicated by TLC, the THF was evaporated under reduced pressure and the residual mass was purified by column chromatography using basic alumina column. The column was run through initially by *n*-hexane then by a solution of ethyl acetate in *n*-hexane (1%, v:v).The enamines **448a-f**were thus obtained in 66-81% yields as mentioned in **Table 10**.

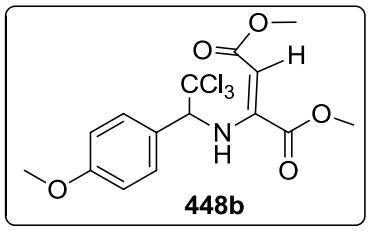
*Dimethyl 2-(2,2,2-trichloro-1-phenylethylamino)fumarate***448*a***:*



448a

Light yellow crystals, mp 78 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 3.76 (s, 3H, CH_3), 3.80(s, 3H, CH_3), 5.46 (s, 1H, CH), 6.01 (d, 1H,*J*=10.5Hz, CH), 7.38-7.40 (m,3H, CH), 7.55-7.58 (m, 2H,CH), 9.40 (d, br, 1H,*J*=10.5 Hz, NH, not D_2O-exchangeable)ppm; ^{13}CNMR ($CDCl_3$, 75 MHz): δ 51.2 (CH_3), 52.9 (CH_3), 71.3 (CH), 92.6 (CH), 102.2 (C), 128.1 (CH), 129.0 (CH), 129.4 (CH), 135.1 (C), 148.6 (C), 163.5 (C), 170.3 (C) ppm; IR (KBr):ν_{max}3236(w, br), 2958(w), 1726(s), 1666(s), 1605(s), 1443(m), 1278(s), 1230(s), 1121(m), 1023(m), 786(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{14}Cl_3NO_4$ Na 387.9896, found 387.9881.

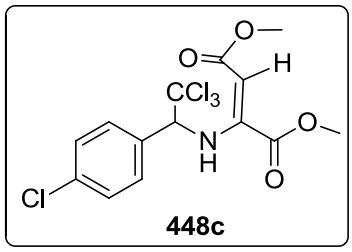
*Dimethyl 2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethylamino)fumarate***448*b***:*



448b

Yellow crystal, mp 38 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 3.76 (s, 3H, CH_3),3.79 (s, 3H, CH_3), 3.80(s, 3H, CH_3), 5.44(s, 1H,CH), 5.95 (d, 1H,*J*=10.2Hz, CH), 6.91 (d, 2H,*J*=7.5Hz, CH), 7.48 (d, 2H, *J*=7.5Hz,CH), 9.34(d, br, 1H,*J*=9.0Hz, NH, not D_2O-exchangeable)ppm;^{13}CNMR($CDCl_3$, 75MHz): δ 51.2 (CH_3), 52.8 (CH_3), 55.2 (CH_3), 70.9 (CH), 92.3 (CH), 102.5 (C), 113.5 (CH), 127.2 (C), 130.5 (CH), 148.7 (C), 160.0(C), 163.6 (C), 170.4 (C)ppm; IR (KBr):ν_{max}3250(m), 3005(w), 1733(s), 1684(m), 1614(s), 1515(m), 1444(m), 1268(s), 1216(s), 1110(m), 1028(m), 795(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{16}Cl_3NO_5Na$ 417.9972, found 417.9986.

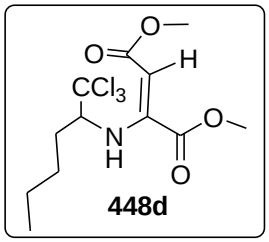
*Dimethyl 2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)fumarate***448c***:*



448c

Light yellow liquid; ^{1}H NMR ($CDCl_3$, 300MHz):δ 3.77 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 5.50 (s, 1H, CH), 6.01(d, 1H,*J*=10.5Hz, CH), 7.37 (d, 2H, *J* = 8.4 Hz, CH), 7.50 (d, 2H, *J* = 8.4 Hz, CH), 9.36 (d, br, 1H, *J* = 11.7 Hz, NH, not D_2O-exchangeable)ppm; ^{13}CNMR($CDCl_3$,75MHz): δ 51.3 (CH_3), 52.9 (CH_3), 70.8 (CH), 93.1 (CH), 101.7(C), 128.4 (CH), 130.7 (CH), 133.7(C), 135.1(C), 148.2 (C), 163.5 (C), 170.4 (C)ppm; IR (KBr):ν_{max}3257(w), 2996(m), 1735(s), 1672(s), 1614(s),1490(m), 1442(m), 1273(s), 1223(s), 1098(m), 1023(m), 814(m), 776(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{13}Cl_4NO_4Na$ 421.9486, found 421.9491.

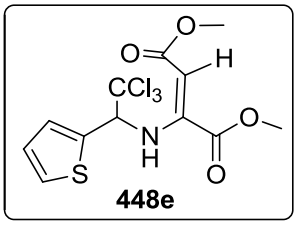
*Dimethyl 2-(1,1,1-trichlorohexan-2-ylamino)fumarate***448d***:*



448d

Light yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.94 (t, 3H, *J*=7.2Hz,CH_3), 1.34-1.70 (m, 5H, CH_2), 2.17-2.26 (m, 1H, CH_2), 3.72 (s, 3H, CH_3), 3.84(s, 3H, CH_3), 4.73 (t,1H, *J*=9.8 Hz,CH), 5.38 (s, 1H, CH), 8.39 (d, br, 1H,*J*=10.5Hz, NH, not D_2O-exchangeable)ppm; ^{13}CNMR($CDCl_3$,75MHz): δ13.8(CH_3), 22.2 (CH_2), 28.2 (CH_2), 31.6 (CH_2), 51.0 (CH_3) 52.8 (CH_3), 68.2 (CH), 91.5 (CH), 104.1 (C), 150.7 (C), 163.7 (C), 170.1 (C)ppm; IR(KBr):ν_{max}3263(m), 2957(s), 1738(s), 1677(s), 1615(s), 1442(m), 1272(s), 1222(s), 1155(m), 1091(w), 1033(m), 786(s), 708(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{12}H_{18}Cl_3NO_4Na$ 368.0194, found 368.0194

*Dimethyl 2-(2,2,2-trichloro-1-(thiophen-2-yl)ethylamino)fumarate***448e***:*



448e

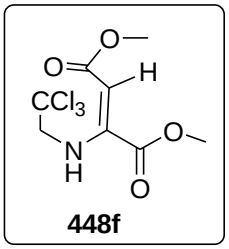
Yellowish crystals, mp 89 ˚C(DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 5.50 (s, 1H,CH), 6.34 (d, 1H, *J* = 10.2 Hz, CH), 7.03 (t ,1H, *J* = 4.5 Hz, CH), 7.30 (d, 1H, *J* = 3.3 Hz, CH), 7.36 (d, 1H, *J* = 5.1 Hz, CH), 9.18 (d, br, 1H, *J* = 10.2 Hz, NH, not D_2O-exchangeable) ppm; ^{13}CNMR ($CDCl_3$, 75 MHz): δ 51.3 (CH_3), 53.0 (CH_3), 67.8 (CH), 93.3 (CH), 101.9 (C), 126.5 (CH), 126.7 (CH), 128.8 (CH), 137.6 (C), 148.0 (C), 163.6 (C), 170.1 (C)ppm; IR (KBr): ν_{max} 3190(w), 3093(w), 1732(s), 1665(s), 1615(s), 1439(m), 1275(s), 1237(s), 1111(m), 1033(w), 855(m), 716(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{12}H_{12}Cl_3NO_4SNa$ 393.9461, found 393.9445.

X-ray crystal structure data of 448e

Formula sum:$C_{12}H_{12}Cl_3NO_4S$, Formula weight:110.54 g/mol; Crystal system: monoclinic; Space group: P 1 21/c 1 (14); Unit cell dimensions: a=14.181(4) Å b=10.740(3) Å c=10.757(3) Å,α =90.00(0)°,β=94.286(5)°,γ= 90.00(0)°; Cell volume = 1633.75(70) $Å^3$, Z = 16; Density calculated = 1.79753 g/cm^3; R_{All} = 0.0976.Detailed X-ray crystallographic

data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989267).

*Dimethyl 2-(2,2,2-trichloroethylamino)fumarate***448*f*:**



448f

Light yellow crystals, mp 44 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 3.73 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 4.42 (d, 2H,*J*= 7.2 Hz, CH_2), 5.45 (s, 1H, CH), 8.78 (s, br, 1H, NH, not D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.0 (CH_3), 52.7 (CH_3), 61.4 (CH_2), 92.8 (CH), 98.8 (C), 149.1 (C), 163.4 (C), 169.7 (C) ppm; IR (KBr): ν_{max} 3299 (m), 3125(w), 1730(s), 1684(s), 1617(s), 1438(s), 1215(s), 1120(m), 1016(s), 780(s), 704(m)cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_{10}Cl_3NO_4Na$ 289.9746, found 289.9748.

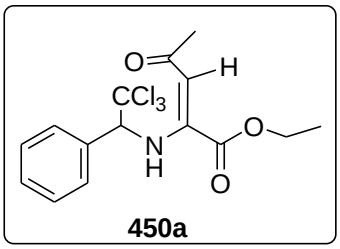
4.5.2.2. Preparation of *N*-(2,2,2-trichloroethyl)enamines 450a-f derived from ethyl acetopyruvate

The previously unknown enamines **450a-f** were prepared by using a method reported in the literature,[201]in which similar enamineswere prepared by acid-catalyzed azeotopic condensation reaction of various 2,4-dioxoester derivativeswith nonchlorinatedprimary amines.

General procedure: A solution of the 2,2,2-trichloroethylamine**447 or 215** (10 mmol), ethylacetopyruvate **449**(1.582 g, 10 mmol) and a catalytic amount of PTSA (0.344 g, 2 mmol) in benzene was heated at reflux in a Dean Stark apparatus. The progress of the reaction was monitored by TLC as well as by ^{1}H NMR of aliquots taken from the reaction mixture from time to time. After completion of the reaction (4-5 h), the reaction mixture

was cooled to room temperature (25-30 ˚C). The benzene was evaporated under reduced pressure. The purification of the residual mass on basic alumina column by running through with *n*-hexane followed by a solution of ethyl acetate in *n*-hexane (1%, v/v) as the solvent for elution furnished the enamine **450a-f** in 63-78% yield.

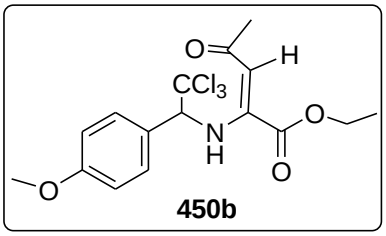
(*Z*)-*Ethyl-4-oxo-2-(2,2,2-trichloro-1-phenylethylamino)pent-2-enoate***450*a***:*



450a

Light yellow crystals, mp 73 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 1.31 (t, 3H,*J*=7.1 Hz, CH_3), 2.22 (s,3H, CH_3), 4.27 (q, 2H, *J* = 7.1 Hz, CH_2), 5.80 (s, 1H, CH), 6.06 (d, 1H, *J* =10.2 Hz, CH), 7.37-7.40 (m,3H, CH), 7.56-7.59 (m, 2H, CH), 11.41(d, br,1H,*J*=9.6Hz, NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 30.1 (CH_3), 62.3 (CH_2), 71.5 (CH), 99.7 (CH), 101.8 (C), 128.1 (CH), 129.1 (CH), 129.5 (CH), 134.8 (C), 148.6 (C), 163.2 (C), 199.7 (C) ppm; IR (KBr): ν_{max} 3112(w), 2992(m), 1724(s), 1625(s), 1591(s), 1363(m), 1269(s), 1212(m), 1016(m), 803(m), 748(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{16}Cl_3NO_3Na$ 386.0084, found 386.0088.

*(Z)-Ethyl 4-oxo-2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethylamino)pent-2-enoate***450*b***:

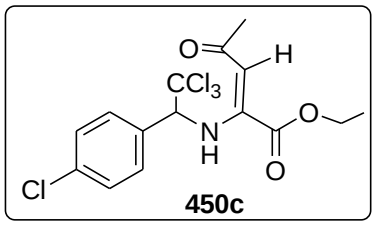


450b

Light yellow liquid; ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.31 (t, 3H,*J*=7.1 Hz, CH_3),2.22 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 4.26(q, 2H, *J*= 7.1 Hz, CH_2), 5.78 (s, 1H, CH), 6.00 (d,1H, *J*= 9.9 Hz, CH), 6.91 (d, 2H, *J* = 8.7 Hz, CH), 7.485(d, 2H, *J*=8.7Hz, CH), 11.36(d, br,1H,*J*=9.3Hz, NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 13.9 (CH_3), 30.1 (CH_3), 55.3 (CH_3), 62.3 (CH_2), 71.1(CH), 99.5(CH), 102.2(C), 113.6 (CH), 126.9 (C), 130.7 (CH), 148.7 (C), 160.1 (C), 163.2 (C), 199.5 (C) ppm; IR

(KBr):ν_{max}3207(w), 2986(m), 1729(s), 1630(s), 1585(s), 1513(m), 1461(m), 1261(s), 1180(s), 1026(s),799(m), 755(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{16}H_{17}Cl_3NO_4Na$ 416.0187, found 416.0194.

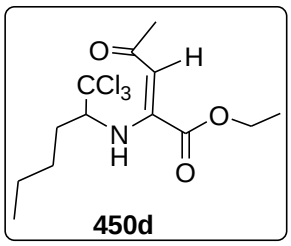
(*Z*)-*Ethyl 4-oxo-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)pent-2-enoate***450c***:*



450c

Light yellow crystal, mp 87 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.22 (t, 3H,*J*=7.1 Hz, CH_3), 2.15 (s,3H, CH_3), 4.19 (q, 2H, *J*= 7.1 Hz, CH_2), 5.75 (s, 1H, CH), 5.98 (d,1H, *J*=10.2Hz, CH), 7.28 (d, 2H,*J*=8.1 Hz, CH), 7.43 (d, 2H, *J*=8.4Hz, CH), 11.40 (d, br,1H,*J*=9.3Hz, NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 13.9 (CH_3), 30.2 (CH_3), 62.3(CH_2), 70.9 (CH), 100.0 (CH), 101.4 (C), 128.4 (CH), 130.8 (CH,), 133.4 (C), 135.2 (C), 148.1(C), 163.1 (C), 199.8 (C)ppm; IR (KBr):ν_{max}3055(w), 1727(s), 1632(s), 1590(s), 1493(m),1365(s), 1268(s), 1206(s), 1095(m), 1021(m), 769(m) cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_{15}H_{15}Cl_4NO_3H$ 397.9878, found 397.9879.

*(Z)-Ethyl 4-oxo-2-(1,1,1-trichlorohexan-2-ylamino)pent-2-enoate***450d***:*

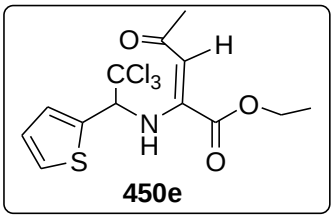


450d

Light yellow solid, mp 37-40 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 0.80 (t, 3H, *J*=7.1 Hz,CH_3), 1.19-1.55 (m, 9H,CH_2, CH_3), 2.05 (s,3H, CH_3), 4.18 (q, 2H, *J*= 7.1 Hz, CH_2), 4.68 (t, 1H, *J*= 10.0 Hz, CH), 5.59 (s, 1H, CH), 6.38 (d,1H, *J*=10.5 Hz, CH), 10.16 (d, br,1H,*J* =10.5Hz, NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): 13.6 (CH_3), 13.7 (CH_3), 22.0 (CH_2), 28.0 (CH_2), 29.8 (CH_3), 31.3 (CH_2), 61.9 (CH_2), 68.1 (CH), 99.9 (CH), 103.4 (C), 150.3 (C), 163.1 (C), 198.9 (C)ppm; IR (KBr):ν_{max}3206(w), 2960(s), 2928(s0, 1729(s), 1634(s), 1590(s), 1456(w), 1366(s),

1271(s), 1198(s),1154(m), 1092(s),1017(m), 797(s), 758(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{20}Cl_3NO_3$ Na366.0394, found 366.0401

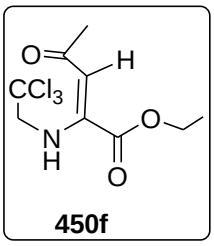
*(Z)-Ethyl 4-oxo-2-(2,2,2-trichloro-1-(thiophen-2-yl)ethylamino)pent-2-enoate***450*e*:**



450e

Light yellow crystal, mp 66 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300MHz):δ 1.34 (t, 3H,*J* =7.1 Hz, CH_3), 2.21 (s,3H, CH_3), 4.31(q, 2H, *J*= 7.1 Hz, CH_2), 5.82 (s, 1H, CH), 6.38 (d, 1H, *J* = 10.2 Hz, CH), 7.02 (t, 1H, *J* = 4.2 Hz, CH), 7.31 (d, 1H, *J* = 3.3 Hz, CH), 7.36 (d, 1H, *J* = 5.4 Hz, CH), 11.15 (d, br, 1H, *J* = 11.4 Hz, NH, D_2O-exchangeable) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 14.0 (CH_3), 30.2 (CH_3), 62.4 (CH_2), 67.8 (CH), 100.1 (CH), 101.5 (C), 126.5 (CH), 126.8(CH), 129.0 (CH,), 137.2 (C), 147.9 (C), 163.2 (C), 199.7 (C)ppm; IR (KBr):ν_{max}3113(w), 2999(m), 1724(s), 1631(s), 1588(s), 1362(m), 1262(s), 1202(m), 1016(m), 745(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{14}Cl_3NO_3SNa$ 391.9642, found 391.9652.

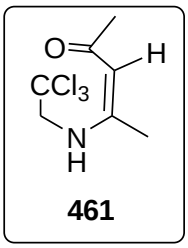
*(Z)-Ethyl 4-oxo-2-(2,2,2-trichloroethylamino)pent-2-enoate***450*f*:**



450f

Light yellow solid, mp 41 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300MHz):δ 1.35 (t, 3H,*J*=7.1 Hz, CH_3), 2.20 (s,3H, CH_3), 4.32 (q, 2H, *J*= 7.1 Hz, CH_2), 4.45 (d, 2H, *J*= 7.2 Hz, CH_2), 5.79 (s, 1H, CH), 10.55 (s, br, NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 13.9 (CH_3), 30.2 (CH_3), 61.5 (CH_2), 62.3 (CH_2), 98.5 (C), 100.2(CH), 149.2 (C), 163.2 (C), 199.5 (C)ppm; IR (KBr):ν_{max}3199(m), 2992(m), 1727(s), 1628(s), 1593(s), 1476(w), 1423(m), 1265(m), 1022(s), 977(m), 771(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{12}Cl_3NO_3$ Na 309.9770, found 309.9775.

*(Z)-4-(2,2,2-Trichloroethylamino)pent-3-en-2-one****461****:*

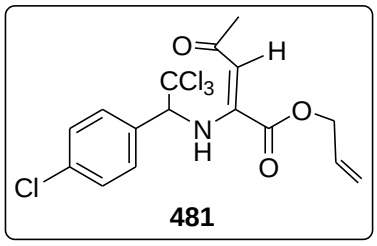


461

It was prepared by acid-catalyzed condensation reaction between trichloroethyl amine **215**(1.485 g, 10 mmol)of acetyl acetone (1.002 g, 1.02 mL, 10 mmol) for 8 h in same manner as other enamines **450a-f**. It was obtained (1.475g. 64.7 %) as yellowish solid, mp 63 ˚C (DCM-*n*-Hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 2.05 (s, 3H, CH_3), 2.07 (s,3H, CH_3), 4.14 (d, 2H, *J*= 4.8 Hz, CH_2), 5.14 (s, 1H, CH), 11.37 (s, br, NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 18.9 (CH_3),29.2 (CH_3), 61.4 (CH_2), 97.9 (CH), 98.1 (C), 160.8 (C), 196.9 (C)ppm; IR (KBr):ν_{max}3012(m), 2933(w), 1615(s), 1580(s), 1505(m), 1456(w), 1296(m), 1246(m), 974(w), 793(m), 708(s) cm^{-1};

Like other enamines **448**and **450**, the^{1}H NMR showed that olefinic and *N*H protons were present at δ 5.14 and 11.37ppm, respectively. Therefore, it was also assigned the Z-geometry.

*(Z)-Allyl 4-oxo-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)pent-2-enoate**481**:*



481

It was also prepared by acid-catalyzed condensation reaction between trichloroethyl amine **447c** (2.590 g, 10 mmol) and allyl acetopyruvate (1.72 g, 10 mmol) for 8 h in same manner as other enaminoketoesters**450a-f**under reflux condition in benzene using Dean-Stork apparatus. It was obtained in good yield(2.84 g. 69 %) as light yellow low melting solid, mp 40-42 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.16 (s, 3H, CH_3), 4.64 (d, 2H, *J* = 5.6 Hz, CH_2), 5.22-5.31 (m, 2H, CH_2), 5.78-5.91 (m, 1H, CH), 5.85 (s, 1H, CH), 6.03 (d, 1H, *J* = 7.2 Hz, CH), 7.30 (d, 2H, *J* = 8.4 Hz, CH), 7.46 (d, 2H, *J* = 8.4 Hz, CH), 11.34 (d, br, 1H, *J* = 9.9 Hz, NH, D_2O-

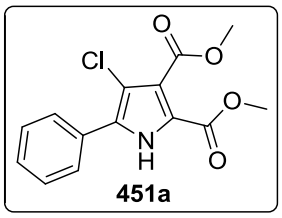
exchangeable) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.9 (CH_3), 66.4 (CH_2), 70.7 (CH), 100.1 (CH), 101.2 (C), 119.5 (CH_2), 128.1 (CH), 130.5 (CH), 130.7 (CH), 133.2 (C), 134.9 (C), 147.5 (C), 162.5 (C), 199.4 (C) ppm; IR (KBr): ν_{max} 3378 (w), 2934(m), 1729(s), 1589(s), 1490(m), 1364(w), 1265(s), 1213(m), 1096(s), 1021(m), 972(w), 772(s)cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_{16}H_{15}Cl_4NO_3H$ 431.9704, found 431.9698Like other enamines **448**and **450**, the^1H NMR showed that the olefinic and *N*H protons resonated at δ 5.85 and 11.35 ppm, respectively. Therefore, it was also assigned the Z-geometry.

4.5.3.Preparation of aromatic tri- and tetrasubstituted 3,4-difunctionalized 4-chloro pyrroles 451,452 and 482: CuCl/PMDETA-catalyzed regioselective one step *5-endo* cyclization-aromatization of *N*(-2,2,2-trichloroethyl)enamines 448, 450 and 481 in the presence of AIBN.

General procedure: A flame-dried two-neck round-bottom flask was charged with CuCl (70mg, 0.7 mmol) and degassed DCE (30 mL) under a N_2 atmosphere using Schlenk technique. PMDETA (0.146 mL, 0.121g, 0.7 mmol) was injected to the suspension and the suspension was stirred magnetically for 10 min. Next, the 2,2,2-trichloroethyl enamine**448**, **450 or 481** (1 mmol) and solid AIBN (0.137g, 1 equivalent) were added. The reaction mixture was degassed again by applying vacuum and refilled with the N_2 gas. The solution was then heated at reflux with stirring. After completion of reaction (6-12 h) as indicated by TLC monitoring, the reaction mixture was cooled and the solvent was evaporated. Ethyl acetate (150 mL) was added to the residual mass and the resulting solution was washed with brine (25 mL x 3) till the color of the solution became (reddish or yellowish). The

combined aqueous layer was treated with ammonium chloride solution and extracted with ethyl acetate to ascertain that there is no loss of the product into the aqueous layer along with copper complexes. All the organic extract was combined and dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residual mass was purified by column chromatography using neutral alumina column using a mixtures *n*-hexane/ethyl acetate (9:1-8:2, v/v) as the solvents for elution. The product thus obtained was further purified by recrysatallization from *n*-hexane-chloroform or *n*-hexane-DCM to obtain the 2,3-difunctionalized 5-substituted 4-chloropyrroles **451** and **452** in (63-84%) good to high yields and **482** (0.280 g, 82%).

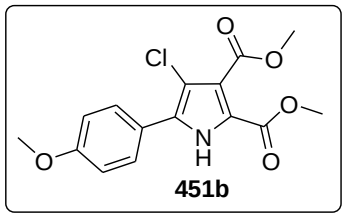
*Dimethyl 4-chloro-5-phenyl-1H-pyrrole-2,3-dicarboxylate**451a**:*



451a

White crystals, mp 96 ˚C (chloroform-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 3.75 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 7.37-7.46 (m, 3H, CH), 7.68 (d,2H,*J* = 8.1 Hz, CH), 10.28 (s, br, 1H,NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.38 (CH_3), 52.42 (CH_3), 110.6 (C), 119.6 (C), 121.3 (C), 127.5 (CH), 128.7 (CH), 128.8 (CH), 128.9 (C), 132.2 (C), 160.4 (C), 164.0 (C) ppm; IR (KBr):ν_{max}3276(s), 2954(w), 1729(s), 1694(s), 1570(w), 1518(m), 1452(s), 1267(s), 1213(s), 1074(s), 1030(w), 774(s) cm^{-1};HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}ClNO_4Na$ 316.0340, found 316.0347.

*Dimethyl 4-chloro-5-(4-methoxyphenyl)-1H-pyrrole-2,3-dicarboxylate**451b**:*

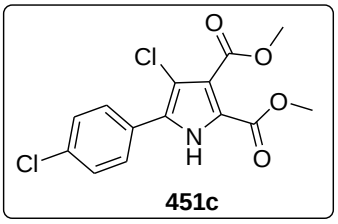


451b

Light yellow crystals, mp 82 ˚C (chloroform-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 3.80 (s, 3H, CH_3), 3.82 (s, 3H,

CH_3), 3.93 (s, 3H, CH_3), 6.95 (d,2H,*J*=8.4 Hz, CH), 7.61(d,2H,*J* =8.4Hz,CH), 10.04 (s, br, 1H,NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 52.3 (CH_3), 52.4 (CH_3), 55.3 (CH_3), 109.9 (C), 114.1 (CH), 119.1 (C), 121.2(C),121.4 (C), 128.8(CH), 132.1 (C), 159.9 (C), 160.3 (C), 164.1 (C)ppm; IR (KBr):ν_{max}3285 (s), 2958(w), 1744(s), 1686(s), 1566(m), 1448(s), 1299(s), 1264(s), 1084(m), 995(w), 828(m), 762(w), 721(m)cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{14}ClNO_5Na$ 346.0461, found 346.0453.

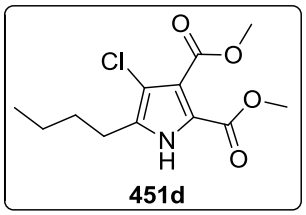
*Dimethyl 4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2,3-dicarboxylate**451c***:



451c

White crystals, mp 130 ˚C (chloroform-*n*-hexane); ^1H NMR (DMSO300MHz):δ 3.81 (s, 6H, both CH_3), 7.43 (d,2H,*J*= 8.4 Hz,CH), 7.62(d,2H,*J*= 8.4 Hz,CH), 12.99 (s, br, 1H,NH, D_2O exchangeable)ppm; ^{13}C NMR (DMSO, 75 MHz):δ 52.6 (CH_3), 52.8 (CH_3), 109.1 (C), 121.0 (C), 121.1 (C), 128.0 (C), 129.0 (CH), 130.3(CH), 131.1 (C), 133.8 (C), 159.8 (C), 164.0 (C)ppm; IR (KBr):ν_{max}3286(s), 2958(w),1743(s), 1686(s), 1567(w), 1449(w), 1344(w), 1298(m), 1264(m), 1084(w), 720(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{11}Cl_2NO_4Na$ 349.9950, found 349.9957.

*Dimethyl 5-butyl-4-chloro-1H-pyrrole-2,3-dicarboxylate**451d***:

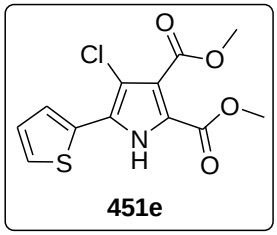


451d

Light yellow crystals, mp 63-65 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300MHz): δ 0.89 (t, 3H, *J*=7.2Hz, CH_3), 1.24–1.36 (m,2H,CH_2), 1.54-1.64 (m,2H,CH_2), 2.64 (t, 2H, *J*=7.5Hz, CH_2),3.84 (s, 3H, CH_3), 3.90 (s,3H, CH_3), 10.27 (s, br, 1H,NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 13.6 (CH_3), 22.1 (CH_2), 24.9 (CH_2), 30.6 (CH_2), 52.1 (CH_3), 52.2(CH_3), 110.9

(C), 118.1 (C), 119.8 (C), 134.7 (C), 160.7 (C), 164.3 (C)ppm; IR (KBr):ν_{max}3208(m), 2993(s), 1726(s), 1624(s), 1591(s), 1496(m), 1363(m), 1266(m), 1211(s), 1081(w), 1017(m), 783(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{12}H_{16}NClO_4Na$ 296.0647, found 296.0660.

*Dimethyl 4-chloro-5-(thiophen-2-yl)-1H-pyrrole-2,3-dicarboxylate**451e**:*



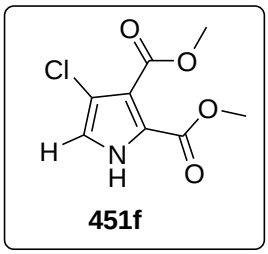
451e

Yellow crystals, mp 118 ˚C (chloroform-*n*-hexane); ^{1}H NMR (DMSO, 300MHz):δ 3.82 (s, 6H, CH_3), 7.17(t,1H,*J* =4.8Hz, CH), 7.66 (d, 1H, *J* = 5.4 Hz,CH), 7.78(d, 1H, *J*=3.0Hz, CH), 12.99 (s, br, 1H,NH, D_2O-exchangeable)ppm; ^{13}C NMR (DMSO, 75 MHz):δ 52.6 (CH_3), 52.8 (CH_3), 108.6 (C), 120.7 (C), 121.0 (C), 127.3 (C), 127.5 (CH), 127.7 (CH), 127.8 (CH), 130.1 (C), 159.7 (C), 163.9 (C)ppm; IR (KBr):ν_{max}3355(s), 3096(w), 1705(s), 1533(m), 1486(w), 1361(m), 1277(s), 1203(m), 1061(w), 843(m), 718(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{12}H_{10}ClNO_4SNa$ 321.9907, found 321.9911.

X-ray crystal structure data of 451e

Formula sum:$C_{12}H_{10}ClNO_4S$, Formula weight:110.54 g/mol; Crystal system: monoclinic; Space group: P 1 21/c 1 (14); Unit cell dimensions: a=7.671(5) Å b=17.173(11) Å c=9.709(6) Å,α = 90.00(0)°,β=92.479(11)°,γ= 90.00(0)°; Cell volume = 1277.81(140) $Å^3$, Z = 12; Density calculated = 1.72368 g/cm^3; R_{All} = 0.0828.Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989266).

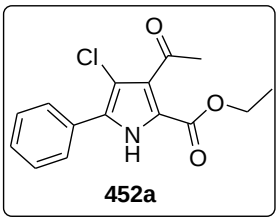
*Dimethyl 4-chloro-1H-pyrrole-2,3-dicarboxylate**451f**:*



451f

Light yellow crystals, mp 56 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz) δ 3.87 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 6.95 (d, 1H,*J*=3.0 Hz, CH), 9.47 (s, br, 1H, NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 52.3(CH_3), 52.4 (CH_3), 114.0(C), 119.4 (C), 119.9 (CH), 121.0 (C), 160.0 (C), 163.9 (C)ppm; IR (KBr):ν_{max}3307(s), 3135(m), 1745(s), 1706(s), 1555(w), 1492(s), 1440(s), 1386(s), 1351(s), 1279(s), 1233(s), 1117(m), 1060(m), 991(m), 766(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_8ClNO_4Na$ 240.0039, found 240.0034.

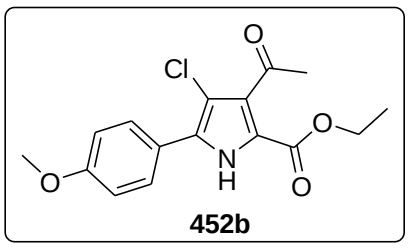
*Ethyl 3-acetyl-4-chloro-5-phenyl-1H-pyrrole-2-carboxylate**452a**:*



452a

Light yellow crystals, mp 98 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 1.11 (t, 3H, *J*=7.1 Hz, CH_3), 2.44 (s, 3H,CH_3), 4.02 (q, 2H,*J*= 7.1 Hz, CH_2), 7.25 (m, 3H, CH), 7.54 (d, 1H,*J*=6.9Hz, CH), 10.54 (s, br, 1H,NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.7 (CH_3), 31.8 (CH_3), 61.3 (CH_2), 108.6 (C), 118.2 (C), 127.3 (CH), 128.3 (CH), 128.4 (CH), 128.8 (C), 129.7(C), 132.2 (C), 159.9 (C), 198.2(C)ppm; IR (KBr):ν_{max}3284(s), 2985(w), 1697(w), 1564(w), 1477(s), 1445(s), 1362(w), 1292(w), 1189(s), 1026(m), 772(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{14}ClNO_3Na$ 314.0555, found 314.0554.

*Ethyl 3-acetyl-4-chloro-5-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate **452b**:*



452b

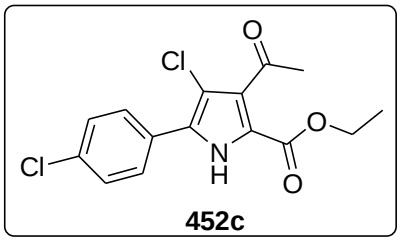
White crystal, mp 121 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 1.24 (t, 3H, *J*=7.1 Hz, CH_3), 2.53 (s, 3H,CH_3),3.77 (s,3H, CH_3), 4.20 (q, 2H,*J*= 7.1 Hz, CH_2), 6.90 (d, 2H, *J* = 8.7 Hz, CH), 7.52(d,2H, *J*=8.7Hz,

CH),9.59 (s, br, 1H, NH, D_2O- exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 32.0 (CH_3), 55.3 (CH_3), 61.5 (CH_2), 108.5 (C), 114.3 (CH), 117.9 (C),121.5 (C), 128.8 (CH), 130.0 (C), 132.1 (C), 159.9 (C), 160.0 (C), 198.2 (C)ppm; IR (KBr):ν_{max}3276(s), 2980(w), 1686(s), 1612(w), 1568(w), 1480(m), 1436(m), 1268(s), 1185(m), 1027(m), 841(w),744(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{16}H_{16}NClO_4Na$344.0653, found 344.0660.

X-ray crystal structure data of 452b

Formula sum:$C_{16}H_{16}ClNO_4$, Formula weight:155.58 g/mol; Crystal system: triclinic; Space group: P 1 (1); Unit cell dimensions: a=7.903(2) Å b=14.700(4) Å c=15.425(5) Å, α=112.657(5)°, β=99.530(6)°, γ=97.737(6)°; Cell volume = 1591.65(80) $Å^3$, Z = 9; Density calculated = 1.46074 g/cm^3; R_{All} = 0.1044.Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989270).

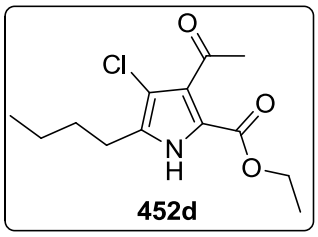
*Ethyl 3-acetyl-4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2-carboxylate**452c**:*



452c

Light yellow crystals, mp 146 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300MHz):δ 1.25 (t, 3H, *J* =7.1 Hz, CH_3), 2.52 (s, 3H,CH_3), 4.19 (q, 2H,*J*= 7.1 Hz, CH_2), 7.35 (d, 2H, *J*=8.4Hz, CH), 7.62 (d,2H, *J*=8.4 Hz, CH),9.77(s, br, 1H,NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 32.0 (CH_3), 61.7 (CH_2), 109.5 (C), 118.7 (C), 127.5 (C), 128.6(CH),129.1 (CH), 130.1 (C), 130.8 (C), 134.9 (C), 159.9 (C), 197.8 (C)ppm; IR (KBr):ν_{max}3281(s), 1689(s), 1632(s), 1559(w), 1477(w), 1442(m), 1284(m), 1186(m), 1093(w), 1053(s), 1015(w), 836(w), 738(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{13}Cl_2NO_3Na$ 348.0151, found 348.0165.

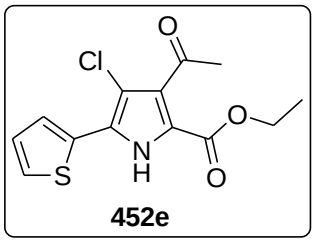
*Ethyl 3-acetyl-5-butyl-4-chloro-1H-pyrrole-2-carboxylate**452d**:*



452d

Colorless solid, mp 58-60 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz):δ 0.82 (t, 3H, *J*=7.2 Hz, CH_3), 1.23-1.31 (m, 5H, CH_2andCH_3), 1.45-1.57 (m, 2H,CH_2), 2.49 (s, 3H,CH_3), 2.56 (t, 2H,*J* =7.8 Hz, CH_2), 4.24 (q, 2H,*J* = 7.2 Hz, CH_2), 10.35 (s, br, 1H, NH, D_2O-exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 13.5 (CH_3), 13.9 (CH_3), 22.0 (CH_2), 24.8 (CH_2),30.6(CH_2), 31.8 (CH_3), 61.0 (CH_2), 109.2 (C), 116.8 (C), 128.6 (C), 134.8 (C), 160.2 (C),198.4 (C)ppm; IR (KBr):ν_{max}3270(s), 2957(m), 1683(s), 1502(m), 1447(m), 1420(m), 1268(m), 1190(s), 1106(w), 1047(w), 741(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{18}ClNO_3Na$ 294.0856, found 294.0867.

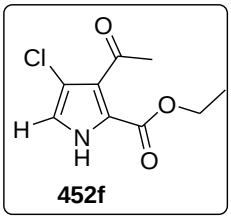
*Ethyl 3-acetyl-4-chloro-5-(thiophen-2-yl)-1H-pyrrole-2-carboxylate**452e**:*



452e

Light red crystals, mp 111 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.32 (t, 3H, *J*=7.1 Hz, CH_3), 2.60 (s, 3H,CH_3), 4.31 (q, 2H,*J*= 7.1 Hz,CH_2), 7.10(t, 1H, *J*=4.3Hz, CH), 7.39 (d, 1H, *J*=5.1Hz,CH), 7.49 (d, 1H, *J*=3.6Hz , CH), 9.87 (s, br, 1H, NH, D_2O- exchangeable)ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 31.9 (CH_3), 61.6 (CH_2), 109.2 (C), 118.3 (C), 126.0 (CH), 126.4(CH), 127.1 (C), 127.4 (CH), 129.9 (C) 130.2 (C), 159.8 (C),197.7 (C)ppm; IR (KBr): ν_{max} 3299(s), 3106(w), 1692(s), 1582(w), 1529(m), 1483(m), 1450(s), 1365(m), 1272(s), 1186(s), 1045(w, 1017(w), 850(w), cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{12}ClNO_3SNa$ 320.0116, found 320.0119.

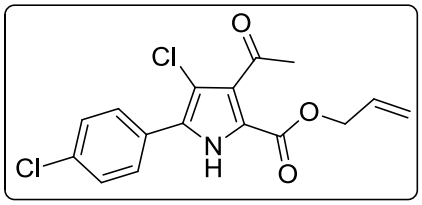
*Ethyl 3-acetyl-4-chloro-1H-pyrrole-2-carboxylate**452f***:



452f

Yellow crystals, mp 43 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, 3H, *J* = 7.1 Hz, CH_3), 2.52 (s, 3H, CH_3),4.24 (q, 2H, *J* = 7.1 CH_2), 6.81 (d, 1H, *J* = 1.8 Hz, CH), 10.03 (s, br, 1H, NH, D_2O-exchangeable) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 31.9 (CH_3), 61.4 (CH_2), 112.2 (C), 119.8 (C), 120.1 (CH), 128.0 (C), 159.6 (C), 198.0 (C) ppm; IR (KBr): ν_{max} 3288(s, br), 2984(m), 1715(s), 1551(w), 1481(m), 1444(m), 1386(s), 1267(s), 1182(s), 1047(s), 1016(w), 779(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{10}ClNO_3Na$ 238.0235, found 238.0241.

Allyl 3-acetyl-4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2-carboxylate ***482****:*



Yellow solid, mp 132 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.58 (s, 3H, CH_3), 4.67-4.68 (m, 2H, CH_2), 5.26-5.36 (m, 2H, CH_2), 5.83-5.96 (m, 1H, CH), 7.41 (d, 2H, *J*=8.1Hz, CH), 7.62 (d, 2H, *J*= 8.1 Hz, CH),10.02(s, br, 1H,NH, D_2O-exchangeable) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 32.0 (CH_3), 66.1 (CH_2), 109.5 (C), 118.6 (C), 119.3 (CH_2), 127.5 (C), 128.7(CH), 129.1(CH), 130.3(C), 131.0(CH), 131.2(C), 134.9(C), 159.6(C),197.8(C)ppm; IR (KBr): ν_{max} 3257(s), 2969(m), 1692(s), 1556(w), 1445(s), 1357(m), 1282(s), 1185(s), 1091(w), 954(m), 729(m)cm^{-1};HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{16}H_{13}Cl_2NO_3Na$ 360.0165, found 360.0165.

4.5.4. Experiments towards attempted trapping of the intermediates in the CuCl/PMDETA-catalyzed cyclization of enamine 448a

Attempted trapping of radical intermediate 456 with alkenes: A flame-dried two-neck round-bottom flask was charged CuCl with (0.070g, 0.7 mmol) and degassed dichloroethelene (40 mL) under a N_2 atmosphere using Schlenk technique. PMDETA (0.146 mL, 0.121g, 0.7 mmol) was injected to this suspension and the suspension stirred

for 10 minutes. Next, the enamine **448a** (0.367 g, 1 mmol) and AIBN (0.137 g, 1 mmol) and styrene (1.15 mL, 1.041g, 10 mmol) or methyl acrylate (0.9 mL, 0.861g, 10 mmol) wereinjected and the mixture was heated at reflux with stirring for12 h. Some sticky polymeric materials were observed on the inner surface of the round bottom flask..The purification of the crude product by column chromatography as described earlier under **section 4.5.2**. furnished pyrrole **451a** (0.190 g, 65% in the case of styrene) and (0.200 g, 69%, in the case of methyl acrylate).

Attempted trapping of the carbocationic intermediate 468 with ethanol:

A similar reaction as above was done by taking the CuCl (0.100 g, 1mmol), PMDETA (0.20 mL, 0.173 g, 1 mmol) and the enamine **448a** (0.367 g, 1 mmol) in a mixture of DCE: ethanol (40 mL, 4:1, v:v) at reflux under a nitrogen atmosphere for (10 h). Periodic monitoring of the reaction by TLC showed development of many spots.. The ^{1}H NMR of the crude product thus obtained showed the formation of a complex mixture of products. Attempts to separate the products by column chromatography gave only a small amount of **451a** (0.040 g, 13%). Other product could not be separated and purified.

CHAPTER 5

Synthesis of 2,3-difunctionalized tri- and tetrasubstituted 4-chlorofurans by one step Cu (I)-catalyzed *5-endo* radical cyclization-aromatization

5.1. Introduction

Furans are one of the most common of the five membered heterocyclic compounds. Furan nucleus is a key structural unit of many naturally occurring compounds such as furanosteroids,[222] furanosesquiterpenes,[223] furanocembranolides,[224] pentacyclic polyketides[225] and pseudopteranes[226] etc (**Fig. 31**).

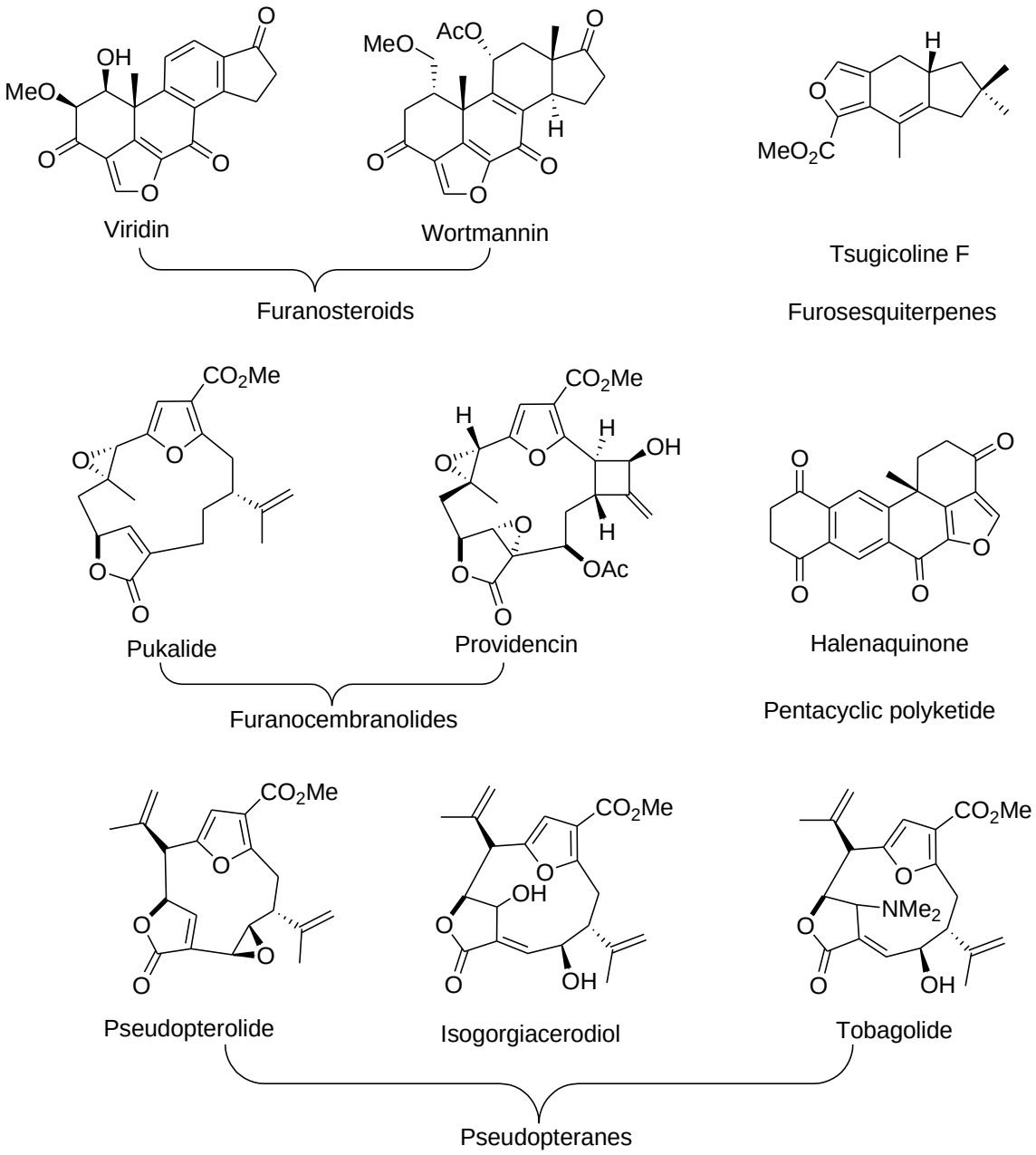
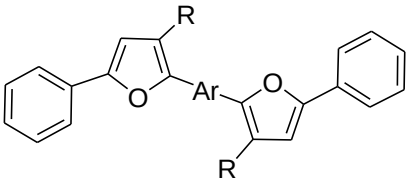


Fig. 31 Some naturally occurring polysubstituted functionalized furans

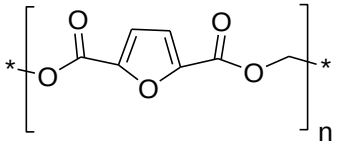
Most of the compounds show interesting biological activities such as anti-inflammatory,[223a] anti-feedant,[223a] cytotoxicity,[224a] anti-microbial,[227] antitumor,[228] and several other useful activities. This heterocycle also finds application in perfumery and in medicinal field as it is the core structural unit of many flavours, fragrance[229] and several commercially important pharmaceuticals.[230]

This heterocycle also finds applications in the chemistry of materials[231] for example a new class of highly stable furan-based hole transporting oligomeric materials (**Fig. 32**) has found their use in electroluminescent devices.[231a]



a: Ar = C_6H_4 R = Ph
b: Ar = C_6H_4-C_6H_4 R = Ph
c: Ar = C_6H_4-C_6H_4- R = Bu

oligomeric furan



biodegradable furan polyester

Fig. 32 Examples of furan based materials

A large number of the naturally occurring furans have keto and/or ester substituents on the furan ring (**Fig. 31**). Many polysubstituted synthetic furans contain halogen, ester and/ or keto functional groups. Such furans are reported to undergo a variety of chemical reactions at these substituents as well as at the furan ring.[232] Both the furan ring and the substituents are exploited for the construction of a variety of natural products and potentially useful acyclic, alicyclic and aromatic compounds.[232c-e] Therefore, synthesis of variously substituted furans having one or more functional groups (hereafter referred to as functionalized furans) receive unabated attention.[233]

Functionalized furans having the functional group at β-position(s) are of special interest. Many bioactive naturally occurring furans possess keto and/or ester group(s) at the β-positions (**Fig. 31**). β-Functionalized furans including the β-halofurans can serve as a gateway to access these and many other natural and potentially useful synthetic furans having substituents other than the functional groups at these positions.

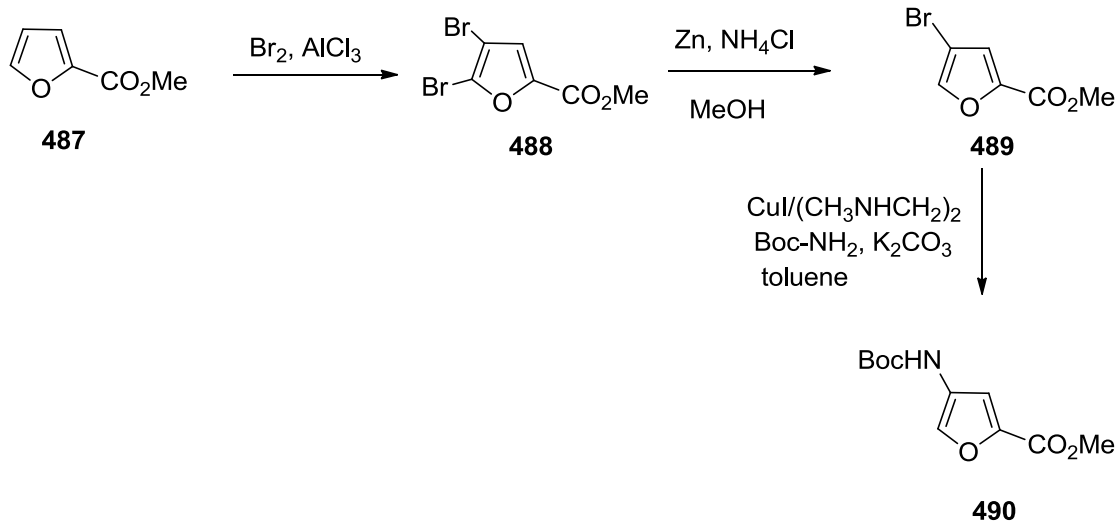
However, the synthesis of β-substituted furans are not straight forward. Direct electrophilic substitution of furan ring suffers from the complications arising out of the high reactivity and acid sensitivity of the furan ring. Moreover, the electrophilic substitution and the lithiation of furan ring occur at the α-position(s). Electrophilic β-substitution may occur when both the α and α′-position are occupied. This generally limits its scope to the synthesis of those β-substituted furans in which both the α-positions are occupied. Even then there is possibility of the problem of regioselectivity. Regiospecific synthesis of β-substitution furans having either or both the α-positions unsubstituted is difficult. Thus, such β-substitution furans having either or both the α-positions unoccupied are prepared by special techniques or cyclization of suitably substituted acyclic precursors. Here synthetic importance and methods for the synthesis of functionalized furans having halo, keto and/ or ester substituents particularly at the β-position(s), which are relevant to the present work, will be discussed briefly.

5.1.1. Synthetic importance of halofurans

Halofurans, particularly the β-halofurans are versatile synthons for regiospecific synthesis of β-substituted furans as they can be transformed into a variety of β-substituted furans by classical nucleophilic aromatic substitution,[234] or by modern and broader metallation[235] or metal-catalyzed coupling reactions[236] without the problem of regioselectivity and thereby to various heterocyclic, carbocyclic, acyclic and aromatic compounds.[237] In this respect, bromo and iodofurans have served particularly well to the

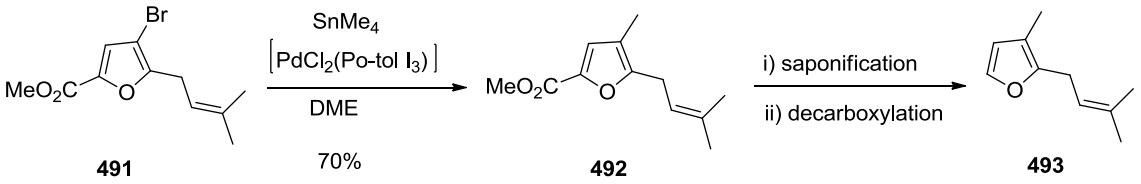
synthesis of furanoid and other naturally occurring as well as synthetic bioactive and other medicinaly useful molecules.[238]

For example, Brucoli et al.[239] synthesized antitumor-antibiotics proximicins A, B and C using methyl 4-Boc-aminofuran-2-carboxylate **490** (**Scheme 163**) which in turn was obtained by copper-catalyzed amidation of the bromofuran **489** with t-butyl carbamate in good yield. However, the preparation of β-bromofurans **489** was not straight forward. Methyl 2-furoate **487** was brominated in the presence of $AlCl_3$ to obtain the methyl dibromofuroate **488**, which was selectively debrominated with zinc to yield the methyl 4-bromo-2-furoate **489**.



Scheme 163

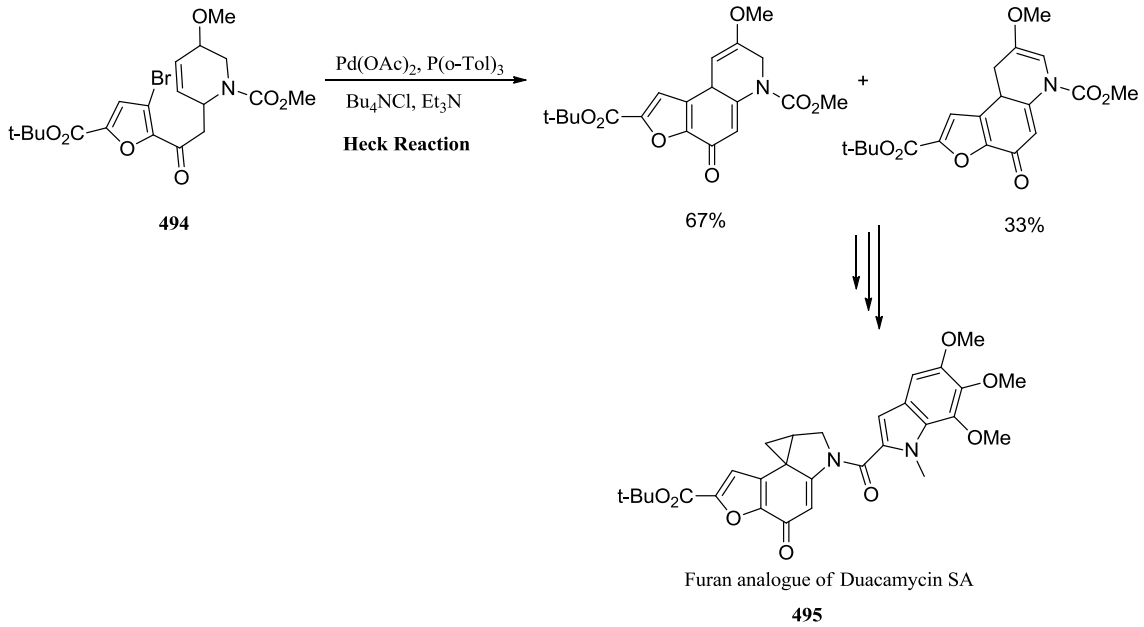
Bach and Kruger[240] reported a synthesis of rosefuran **493** (**Scheme 164**) using the functionalized β-bromofuran **491** via Stille cross-coupling reaction. The electron withdrawing group ester group rendered the oxidation-sensitive furan skeleton more stable during the reaction and this functional group in the coupled product **492** could be easily removed using simple chemistry.



491 492 493

Scheme 164

The furan analogue of Duacamycin SA **495** (**Scheme 165**) has been synthesized by Muratake et al.[241] using Heck reaction of the functionalized 3-bromo furan **494** as the key step.



494 67% 33%

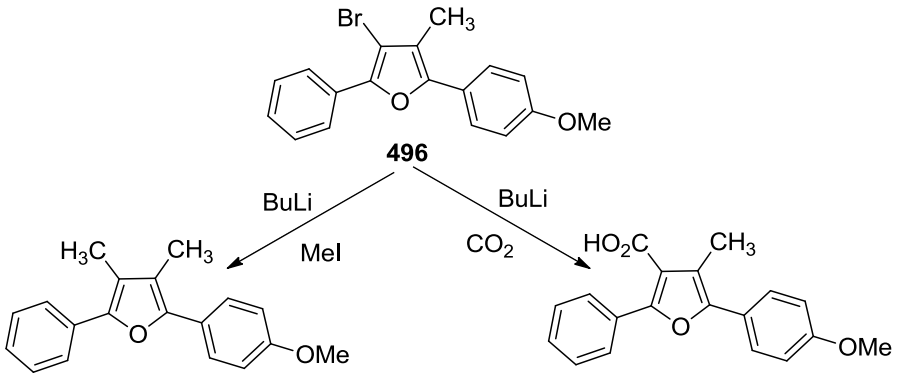
Furan analogue of Duacamycin SA

495

Scheme 165

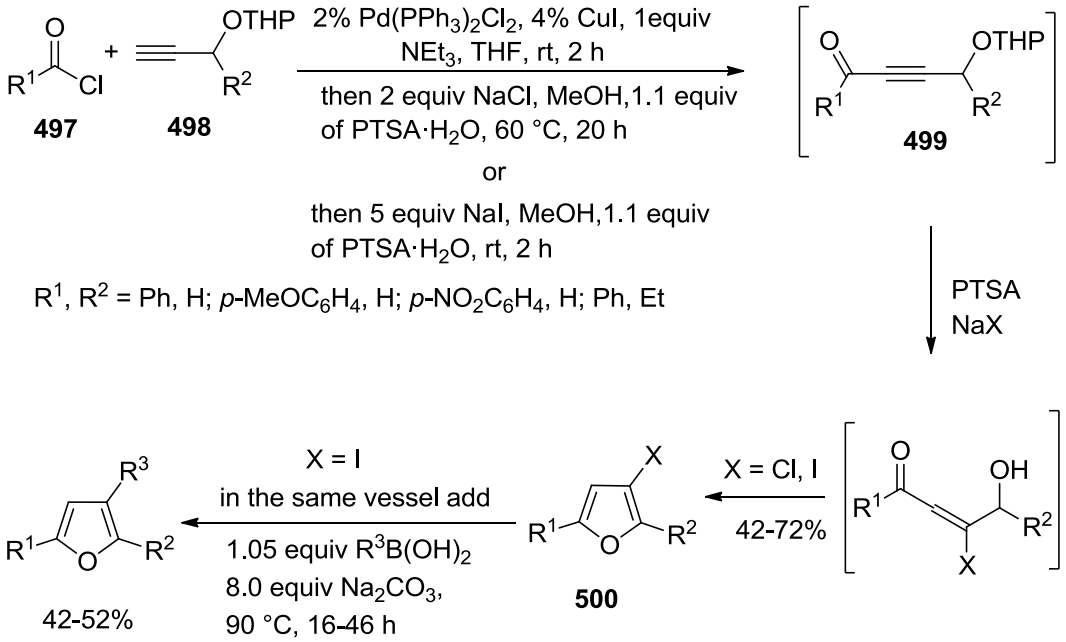
The bromine substituents of highly substituted β-bromofuran ring has been used for introducing not only alkyl, aryls, heteroaryls but also functional groups on the furan rings.

The bromo group of tetrasubstituetd furan **496** (**Scheme 166**) was replaced by methyl and carboxy groups through bromine-lithium exchange.[242]



Scheme 166

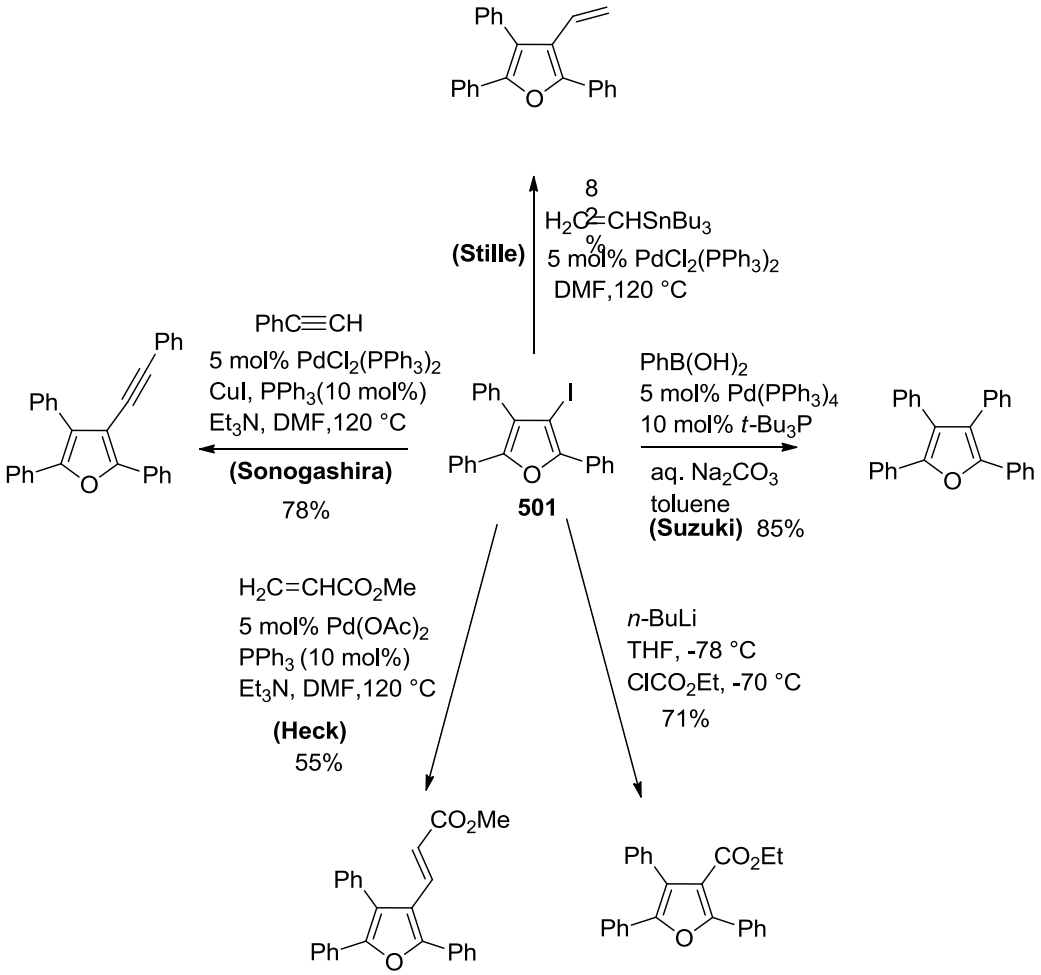
Müller and co-workers[243] reported an elegant three component one pot reaction to furnish 2,5-disubstituted 3-chloro or iodofurans **500 (Scheme 167)**. The reaction sequence combined an initial Sonogashira coupling of acid chlorides **497** with THP-protected propargyl alcohols **498,** PTSA-mediated Michael addition of NaI or NaCl to the protected 3-hydroxyalkynones **499,** thus formed, alcohol deprotection and cyclodehydration all in one pot to furnish the disubstituted 3-iodofurans or 3-chlorofurans **500** in moderate to good yields.



Scheme 167

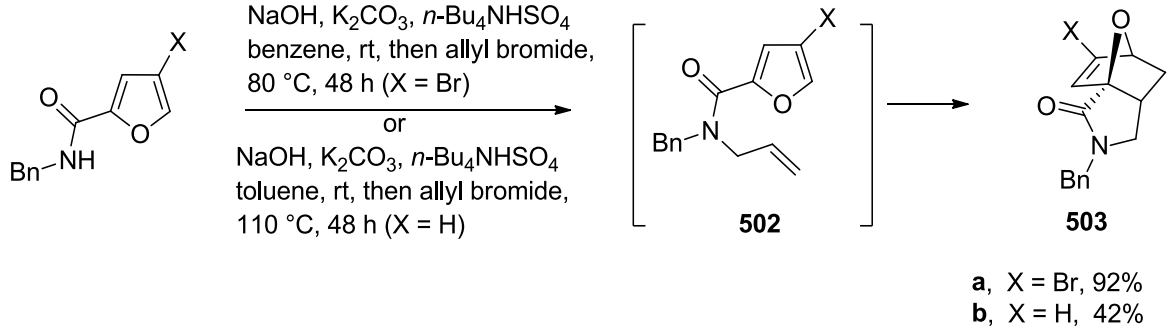
The authors also extended the reaction for the synthesis of substituted 3-arylfurans by applying Suzuki coupling with various aryl boronic acids in the same pot without isolating the 3-iodofurans (**Scheme 167**). The two sequential cross coupling reactions occurred with the same amount the catalyst. The yields of the 3-arylfurans in the one pot procedure were comparable to the overall yields obtained when the Suzuki coupling was performed separately.

Recently, Luh and co-workers[244] demonstrated synthetic utility of the 3-iodofurans **501** (**Scheme 168**) in transition metal-catalyzed carbon-carbon bond forming reactions such as Suzuki, Sonogashira, Stille, Heck couplings and the classical halogen-metal exchange followed by trapping with electrpohiles.



Scheme 168

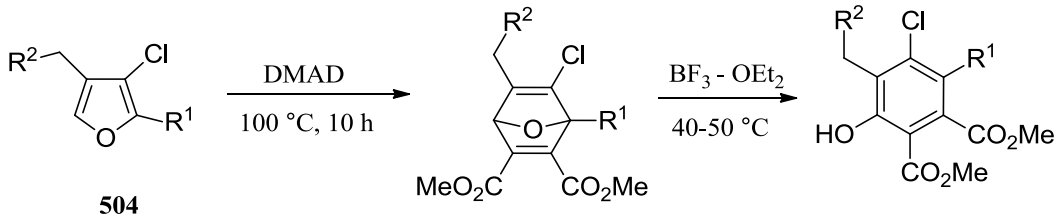
The halogen atom at the β-position of furan ring has been found to assist intramolecular Diels-Alder reaction in simple and functionalized β-halofurans. Thus, the 5-bromofurancarboxamide **502a** (**Scheme 169**) having an allyl group substituted at the nitrogen atom afforded the intramolecular Diels-Alder cycloadduct **503a** in 92% yield on heating at reflux in benzene for 48 h. However, the reaction of the corresponding non-brominated furancarboxamide **502b** resulted in the formation of the cycloadduct **503b** in only 42% yield in 48 h at reflux in toluene at 110 ˚C, showing the positive influence of the bromine on the furan Diels-Alder reaction.[245]



Scheme 169

The β-chlorine atom of chlorofurans also influences the reactivities of the furan ring[246] as well as provides a site for manipulation[247] in a simple manner.

Ram and Kumar[10b] demonstrated the importance of chlorine atom in furan Diels–Alder reaction (the so called halogen effect in Diels-Alder reactions). The Diels–Alder reactions of 4-substituted 2-(2-furanyl)-, 2-styryl-, and 2-crotyl-3-chlorofurans **504** (**Scheme 170**) with dimethyl acetylenedicarboxylate (DMAD) occurred exclusively on the chlorofurano diene moiety and not on the non-chlorinated furano diene or the chlorinated exocyclic diene alternatives.

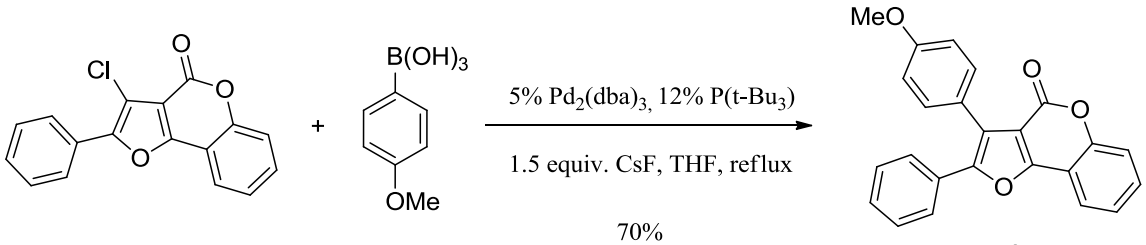


504

a: R^1 = furyl, R^2 = H
b: R^1 = styryl, R^2 = H
c: R^1 = crotyl, R^2 = Ph

Scheme 170

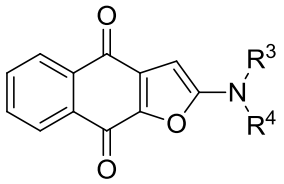
Simple chlorofurans are less reactive in transition metal catalyzed coupling reactions or nucleophilic substitution reactions, however, the β-chlorine atom present in the functionalized furan ring can be replaced. For example, Cheng and Hu[247] demonstrated Suzuki coupling of the chlorofurochromenone **505** (**Scheme 171**) with 4-methoxyphenylboronic acid **506** to give **507** in good yield.



505 **506** **507**

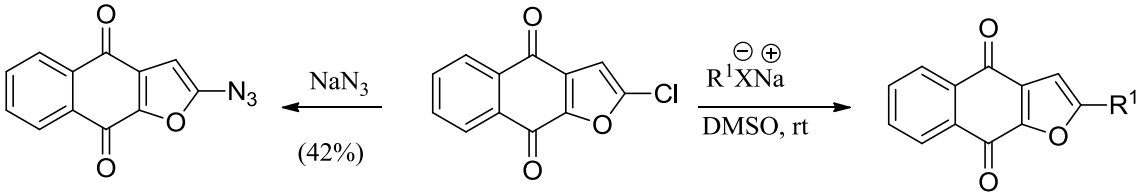
Scheme 171

The chlorine substituent of the chlorofuran **508** (**Scheme 172**) was easily replaced by a variety of nucleophiles without transition metal catalysis. In these reactions, **508** behaved as activated chloroarenes and sulphur and nitrogen nucleophiles were found to be better than oxygen and carbon nucleophiles in replacing the chlorine substitiuent.[248]



R,^{3} R^4 =1°, 2° alkyl, cycloalkyl (48-67%)

NHR^{3}R^4 ↑ DMSO,rt

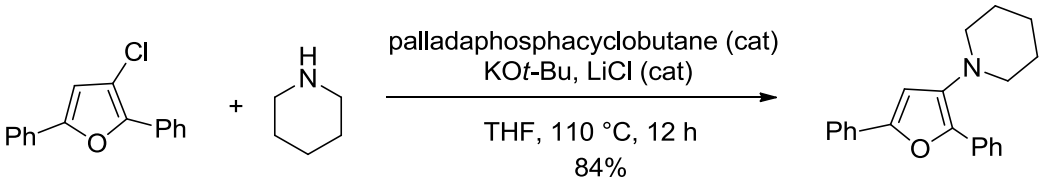


508

$R^1X^-Na^+$	**(equiv)**	**Time**	**Yield (%)**
R^1 = PhONa	(2.5)	0.5 h	55
R^1 = PhSNa	(2.5)	0.5 h	63
R^1 = MeSNa	(2.5)	5 min.	62
R^1 = $(C_2H_5O_2C)_2CHNa$	(5.0)	6 h	28

Scheme 172

The β-chlorine atom of even the unactivated furan **509** (**Scheme 173**) could be replaced by amination reaction in the presence of a suitable palladium catalyst to give the aminated furan **510** in high yields.[249]



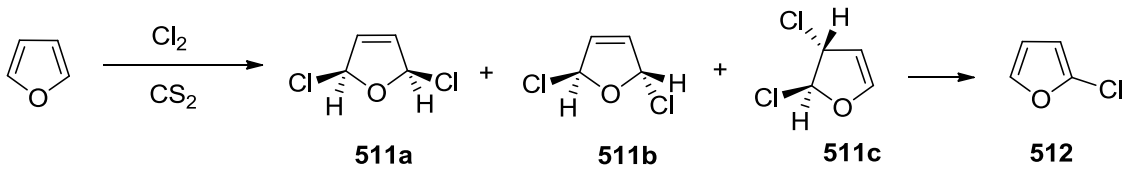
509 **510**

Scheme 173

5.1.2. Synthesis of functionalized β-chlorofurans

Although reasonably good number of reports are available on the preparation of β-bromo and iodofurans.[250] Only a few deal with the preparation of chlorofurans. However, synthesis of chloro compounds in general and chlorofurans in particular, is industrially important because of their lower cost and higher stability. Although less reactive, recent development have brought chloroarenes and chloroheteroarenes in the domain of transition metal catalyzed cross-coupling reaction.[251]

Preparation of chlorofurans by direct chlorination of furan ring with molecular chlorine is complicated. For example, chlorination of furan with chlorine in CS_2 has been reported to give a mixture of *cis*- and *trans*-2,5-dichloro-2,5-dihydrofuran **511a** (**Scheme 174**) and **511b** and *trans*-2,3-dichloro-2,3-dihydrofuran **511c**. These compounds slowly decomposed to 2-chlorofuran **512**.[252]

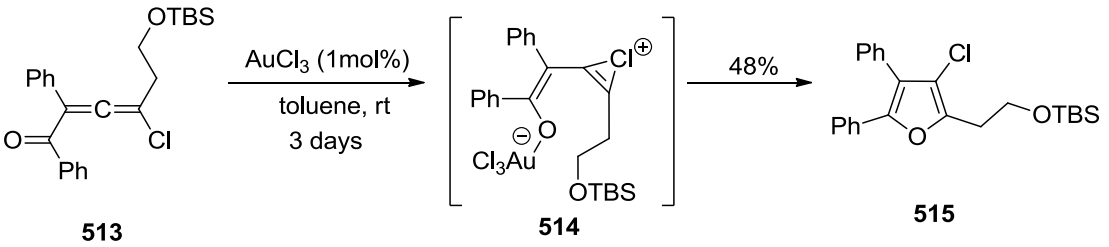


Scheme 174

Synthesis of β-chlorofurans has been scarcely reported. A few methods deal with the synthesis of β-chlorofurans by cyclization of acyclic precursors. This laboratory used HATRC approach to synthesize di- and trisubstituted β-chlorofurans having one of the α-positions unsubstituted (**Chapter 1, Scheme 8**).

Widely used metal-catalyzed cycloisomerization approach to the synthesis of furans is less effective in the synthesis of β-chlorofurans. For example, Gevorgyan and co-workers[253] reported a synthesis of the tetrasubstituted chlorofuran **515** (**Scheme 175**)

by Au (III)-catalyzed cycloisomerization of the corresponding chloro-substituted allenyl ketone **513** in relatively lower yield. Moreover, only one example was reported. The longer reaction time (3 days) and low yield were attributed to the less effective participation of Cl atom to form the halirenium ion intermediate **514**.



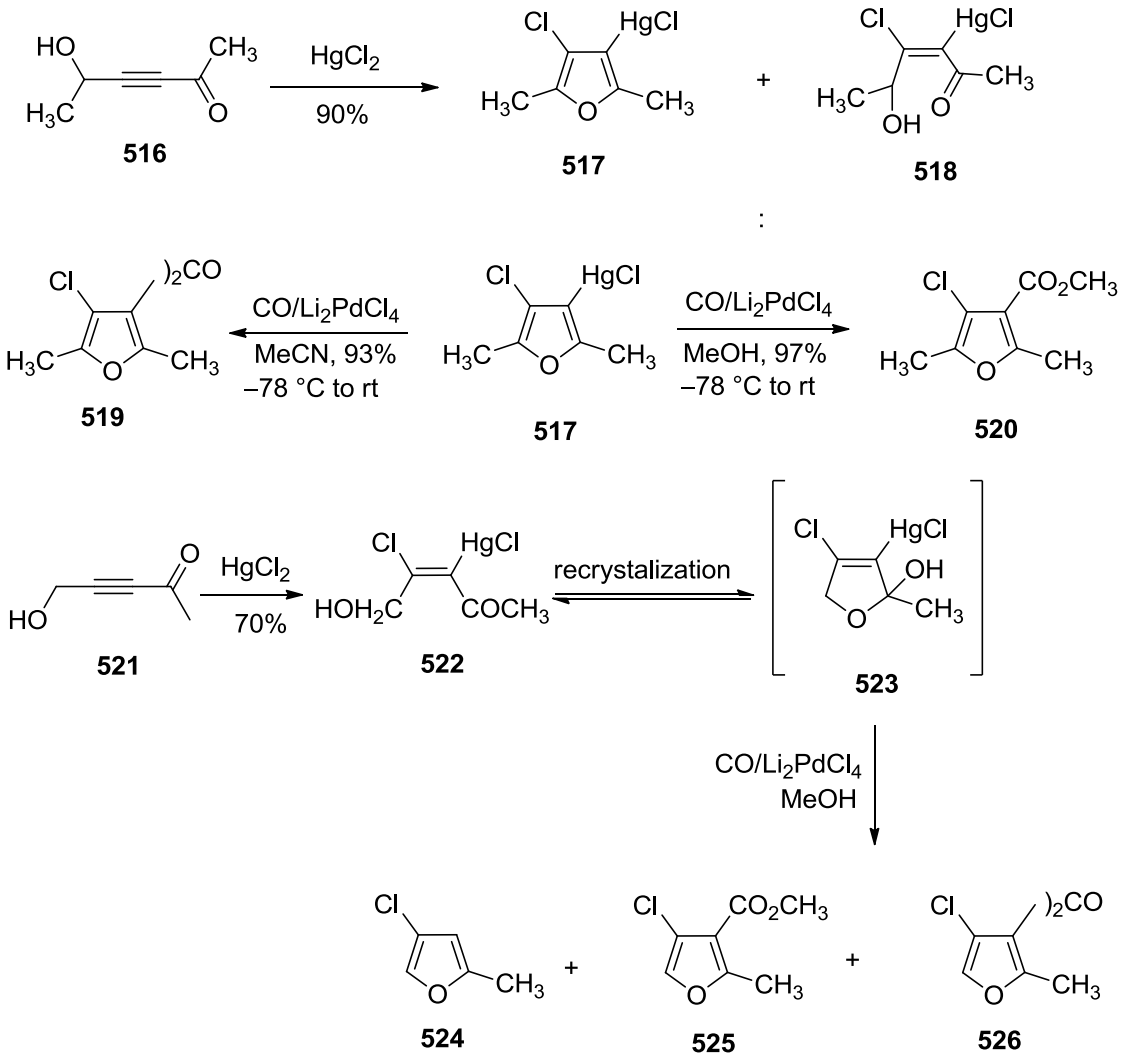
513 **514** **515**

Scheme 175

Further, there are only a few reported methods for the preparation of functionalized β-chlorofurans such as those having keto or ester groups.

Larock et al.[254] reported that mercuration of the acetylenic alcohol **516** (**Scheme 176**) gave a mixture of furanyl mercurial **517** and vinyl mercurial **518** in a ratio of 5:95. Pure 3-furanyl mercurial **517** was obtained in 63% yield by either carrying out the reaction at reflux in benzene or by re-crystallizing the crude mixture twice from benzene. Carbonylation of the furanyl mercurial **517** afforded either the corresponding methyl ester **520** or the symmetrical ketone **519** depending on the reaction medium. The mercuration of the hydroxyalkynone **521** under similar conditions gave the vinyl mercurial **522** as the major product in 70% isolated yield. Recrystallization of **522** and subsequent ^{1}H NMR spectroscopy revealed that a small amount of **522** had partially isomerized to the hemiketal **523**. These compounds could not be obtained in pure forms. Carbonylation of the mixture of these compounds with CO in the presence of Li_2PdCl_4 as a catalyst led to the formation of a mixture of the compounds **524**, **525** and **526**. The 2-

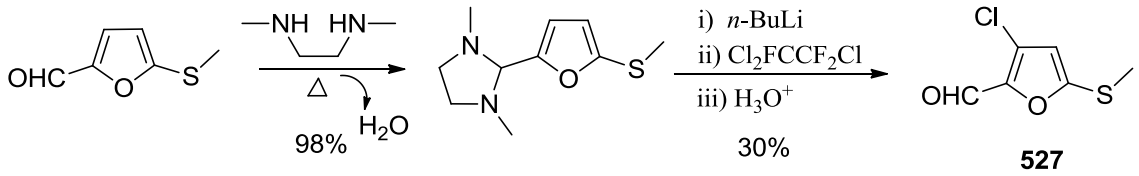
substituted and 2,3-disubstituted 4-chlorofurans **524** and **525** were identified by gas chromatography and mass spectral data and could not be isolated. The 4-chlorofuran derivative **526** was isolated in 30% yield.



Scheme 176

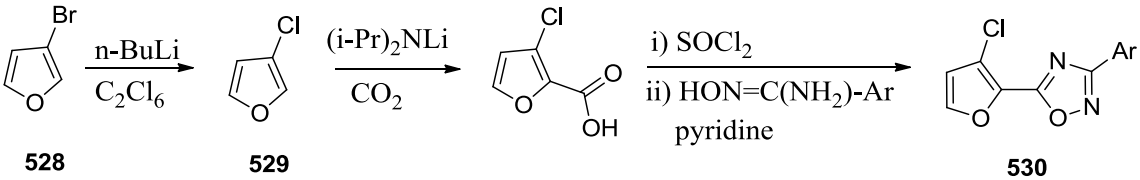
A few reactions of rather limited scope for β-chlorination of the pre-existing furan ring have been reported.

Basarab et al.[255] synthesized the β-chlrofuran carbaldehyde **527** (**Scheme 177**) in low yield by following a multistep protocol involving aldehyde protection, chelation-directed β-metallation, chlorination and hydrolysis.



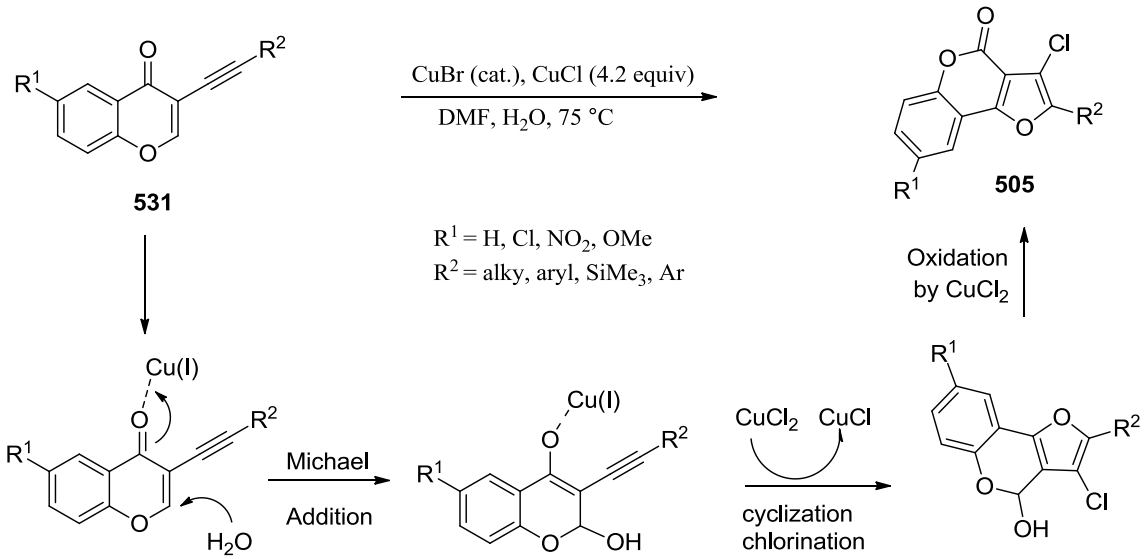
Scheme 177

Cai and coworkers[256] took resort to replacing the bromine atom of β-bromo furan **528** (**Scheme 178**) with a chlorine atom by bromine-lithium exchange with *n*-butyllithium followed by chlorination with hexachloroethane to obtain the 3-chlorofuran **529**. The 3-chlorofuran was used to prepare the 3-chlorofuran analogs **530** of 3-chlorothiophene derivatives, which are novel apoptosis inducers. The 3-chlorofuran analogs **530** have the benefit of possessing improved solubility profile as compared to their 3-chlorothiophenes analogs.



Scheme 178

Cheng and Hu[257] developed a $CuBr/CuCl_2$-catalyzed synthesis of chlorofuro[3,2-*c*]coumarins **505** (**Scheme 179**) through addition, cyclization, oxidation and chlorination of 2-(1-alkynyl)-2- alken-1-ones **531** wherein excess $CuCl_2$ worked as the oxidising and chlorinating agent.



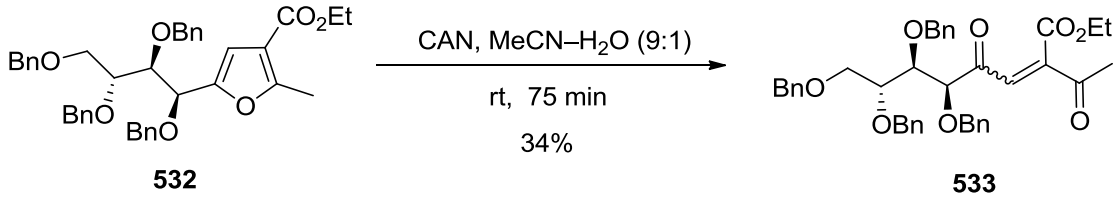
Scheme 179

5.1.3. Synthetic importance of furancarboxylic acid esters and furanyl ketones

5.1.3.1. Synthetic importance of furan ring

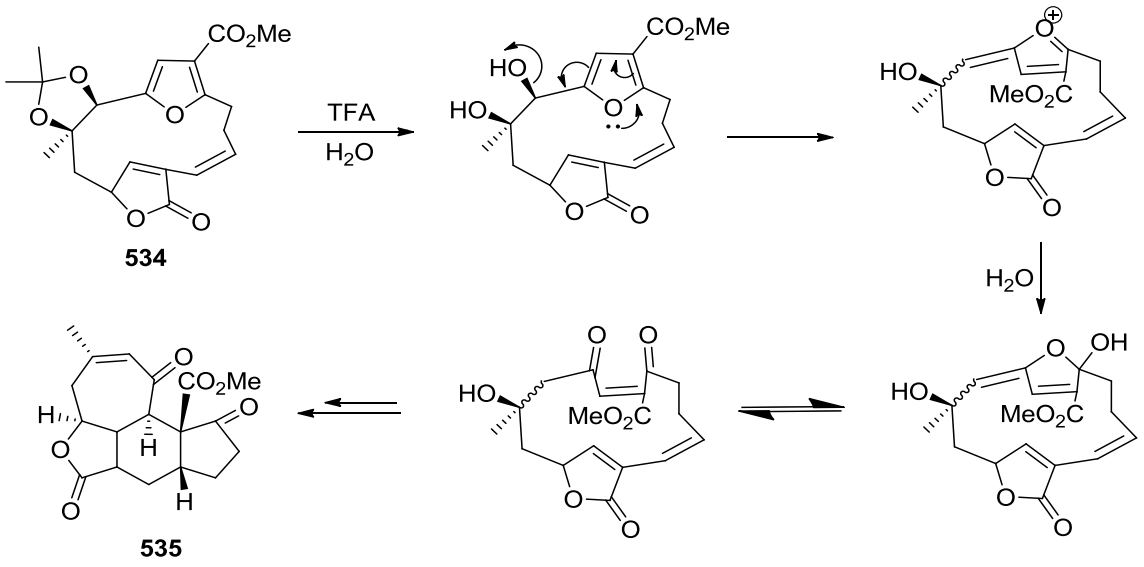
The furans ring of furancarboxylic acid esters and furanyl ketones have been widely used in the synthesis.

Robina and coworkers[258] reported that the polyhydroxyalkylfuran **532** (**Scheme 180**) having a β-ester group, on treatment with 5 equiv. of CAN in MeCN–H_2O underwent oxidative opening of the furan ring to give a mixture of two geometrical isomers **533** in a 1:1.3 ratio in 34% combined yield.



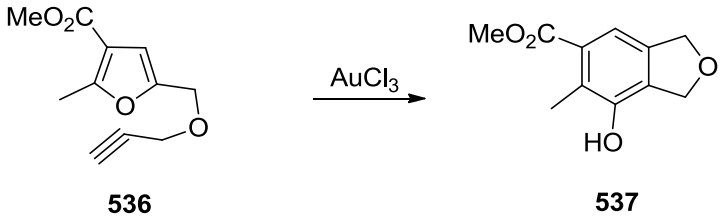
Scheme 180

Li and Pattenden[259] demonstrated that the furan ring of the furancarboxylate **534** (**Scheme 181**) opened to a diketo-esters on treatment with TFA (trifluoroacetic acid) containing water to finally furnish the 5,6,7-tricyclic compound **535**, an alternative ring system found in plumarellide, in a single step and >90% yield.



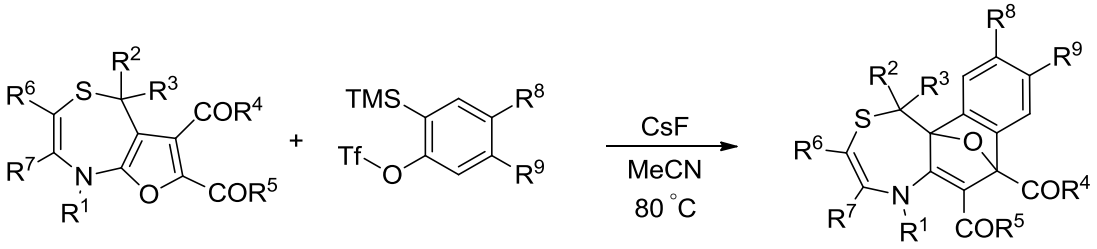
Scheme 181

Hashimi et al.[260] reported gold-catalyzed cycloisomerization of **536** (**Scheme 182**) through intramolecular furan-alkyne cycloaddition to yield the phenolic dihydroisobenzofuran **537** in good yield. They found that the deactivating ester group, on the 4-position of the furan ring did not hinder the catalysis by gold.



Scheme 182

Ding et al.[261] showed that no matter electron-rich, electron-deficient or hindered the furans rings of **588** (**Scheme 183**) were, they reacted with a set of benzynes derived from **539** to furnish the corresponding 7-oxanorbornadienes **540** in excellent yields. The latter were found to be useful intermediates in the total synthesis of natural products and analogs.

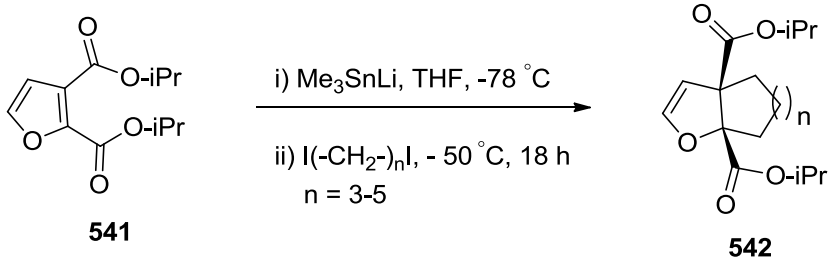


538 **539** **540**

R^1, R^2, R^3 = alkyl, aryl; R^4 = alkoxy, alkyl, aryl; R^5 = alkoxy
R^6 = H, alkyl, R^7= alkyl, R^6-R^7= C_6H_4 , R^7= alkyl, aryl, R^8-R^9 = $(CH_2)_3$, CH_2OCH_2

Scheme 183

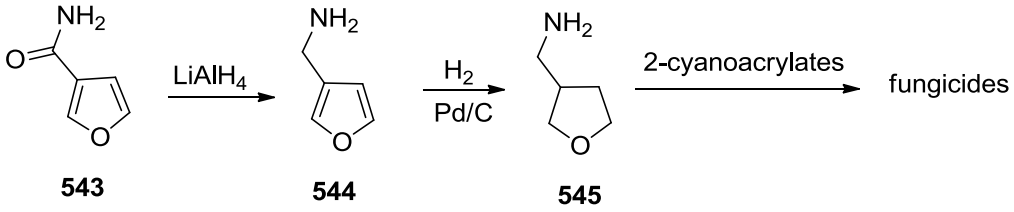
Sardina and coworkers[262] developed a stereoselective dearomatization–annulation of the aromatic furan-2,3-dicarboxylate **541** (**Scheme 184**) to give a range of highly functionalized bicyclic molecules **542**. Treatment of a THF solution of **541** with Me_3SnLi (2.15 equiv) at -78 °C and trapping of the bisenolate intermediate formed therein with ω-diiodoalkanes (1.20 equiv) afforded the dearomatized bicyclic products **542** in 63% (n = 3), 59% (n = 4) and 48% (n = 5) yields, respectively with complete stereoselectivity (*cis* stereoisomer only).



541 **542**

Scheme 184

On catalytic hydrogenation over Pd/C, the furan ring is completely reduced to tetrahydrofuran.[263] The reduction of furan-3-carboxamide **543** (**Scheme 185**) with $LiAlH_4$ provided furan-3-ylmethanamine **544** in 69% yield. Further reduction by catalytic hydrogenation over Pd/C gave (tetrahydrofuran-3-yl)methanamine **545** in 77% yield, which on reaction with 2-cyanoacrylates, yielded a superior fungicide.



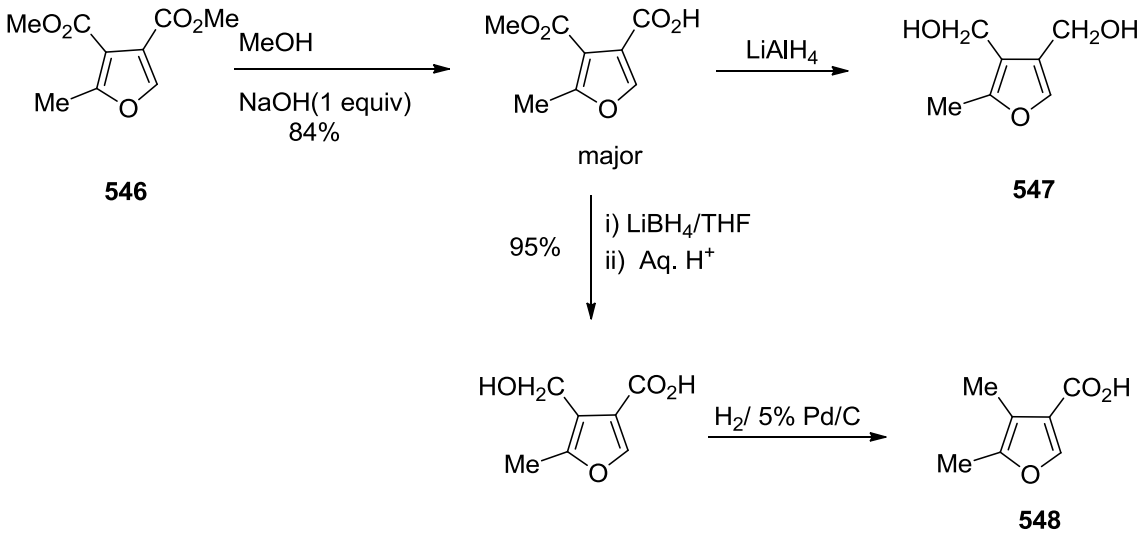
543 **544** **545**

Scheme 185

5.1.3.2. Synthetic importance of ester and keto groups of furan ring

The ester and keto groups of furans have been easily transformed into other groups and the products have been used in syntheses of natural products and pharmaceutically important compounds.

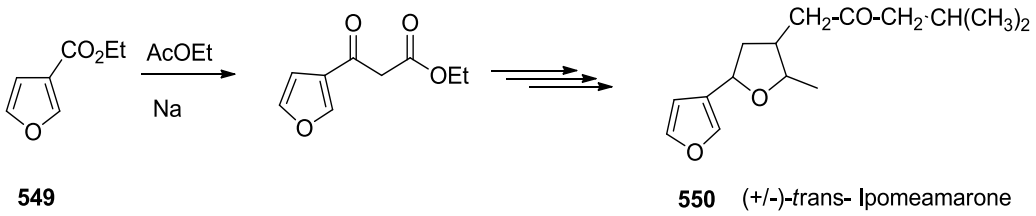
Manna and Holland[264] reported the importance of ester groups in introducing variety on furan ring with the help of simple reactions. They conveterd the furans-2,3-dicarboxylate **546** (**Scheme 186**) into diol **547**and the monocarboxylic acid **548**.



546 **547** **548**

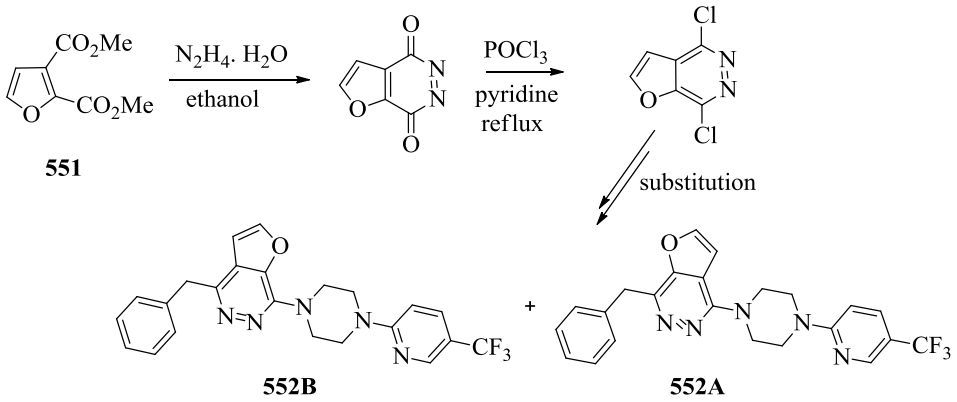
Scheme 186

The β-ester groups of furan ring have played a pivotal role in natural product synthesis. Kubota[265] used furan-β-carboxylate **549** (**Scheme 187**) as the starting material in the synthesis of natural product ipomeamarone **550** which had been extracted from sweet potato.



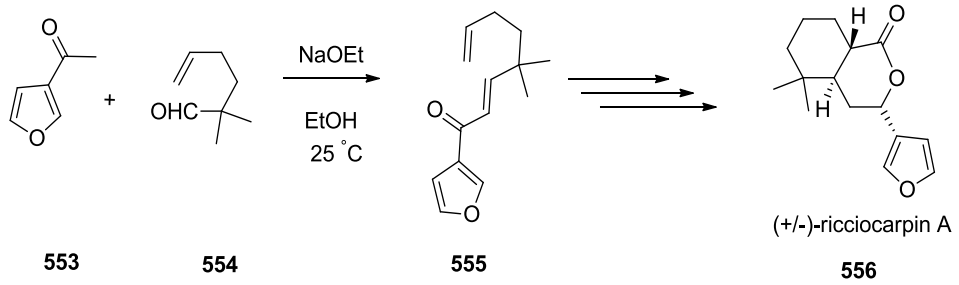
Scheme 187

Miller-Moslin et al.[266] synthesized the pyridazine ring-fused furan antagonists **552** (**Scheme 188**) from furan-2,3-dicarboxylic acid dimethyl ester **551** through a three step simple transformation for their evaluation as anti-tumor agents.



Scheme 188

The acetyl group of 3-acetylfuran was used in a concise total synthesis of the potent molluscicide (±)-ricciocarpin A.[267] 3-Acetylfuran **553** (**Scheme 189**) underwent aldol condensation with 2,2-dimethylhex-5-enal **554** to the afford the olefinic furanyl enone **555**. The furanyl enone **555** was used as the starting material in the preparation of a natural product, the potent molluscide ricciocarpin A **556** in good overall yield.

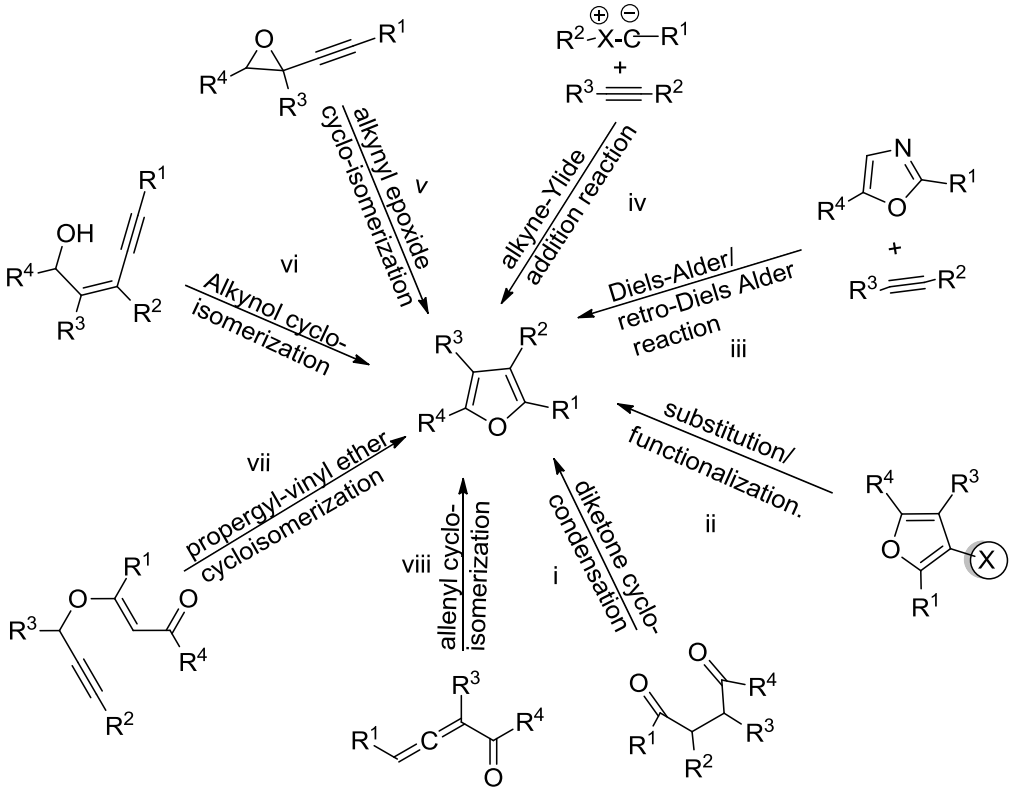


553 554 555 556

Scheme 189

5.1.4. Synthesis of furancarboxylic acidesters and furanyl ketones

There are two approaches which have generally been used for the synthesis of general furans (**Scheme 190**).[268] First, the classical approaches, which involve the (i) cyclocondensation of dicarbonyl compounds (ii), substitution/functionalization of the existing furan ring (iii), Diels-Alder-retro-Diels-Alder reaction and (iv), ylide-addition reactions and second, the metal-catalyzed cycloisomerization of alkyne (v-vii) and allene (viii)-containing compounds.[269] The scope of these approaches is limited when applied to the synthesis of furancarboxylates and furanylketones.



Scheme 190

A vast majority of the routes to multiply substituted furans have involved cyclization approaches starting from acyclic precursors. Several modification of classical cyclocondensation of 1,4-dicarbonyl compounds (Paal–Knorr synthesis and the Feist–Benary synthesis etc) have emerged,[270] yet there are some limitations, including the difficulty in accessing furans that contain sensitive groups and the inability to provide furans with high flexibility in their substitution pattern.[270c-d]

The methods based on electrophilic substitution or functionalization of existing furan precursors are typically not general. For example, derivatization of furans *via* electrophilic substitution is somewhat restricted due to the low stability of furans under acidic and aerobic conditions.[271]

An alternative method involving metalation of furan derivatives followed by quenching with various electrophiles is, however, mostly limited to α-substitution. For β-substitution, it requires the presence of the directing or blocking group. It is also limited to base stable furans.[272] Halogn-metal exchange protocol has limitation with regard to the availability of the halofurans and intolerance to reactive groups such as ester and keto already present.[273]

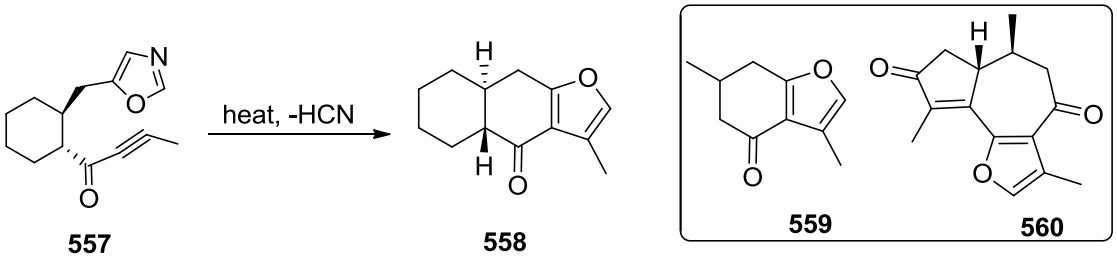
5.1.4.1. Synthesis of functionalized furancarboxylic acid ester and furanyl ketones from activated acetylenes

A good number of furan carboxylates and furanyl ketones have been synthesized from activated alkynes using different approaches.[274]

5.1.4.2. Diels-Alder-retro Diels-Alder reactions approach

Diels-Alder-retro Diels-Alder reactions have been used in the synthesis of natural products containing functionalized furans.[275]For example, the oxazole **557** (**Scheme 191**) connected to an acetylenic dienophile, on heating underwent an intramolecular tandem Diels-Alder-retro Diels-Alder reaction with extrusion of HCN to furnish the

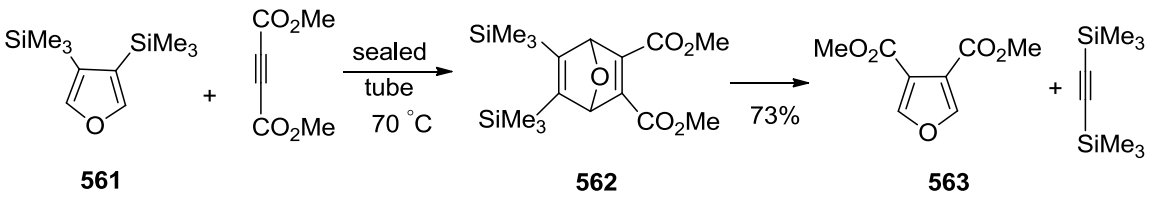
functionalized furan **558**. One advantage of this approach is its high regioselectivity because of the geometrical constraints to intramolecular Diels-Alder reaction. Naturally occurring furanoterpene evodone **559**[275a] and furanoditerpene gnididione **560**[275b] containing a β-keto functionality were synthesized in this manner.



557 **558** **559** **560**

Scheme 191

3,4-Bis(trimethylsilyl)furan **561** (**Scheme 192**) with σ-electron donating trimethylsilyl groups at the β-positions, make the furan ring a better diene. As a result, 3,4-disubstituted furan **563** was produced through a tandem Diels-Alder - retro Diels-Alder reaction via **562**.[276]

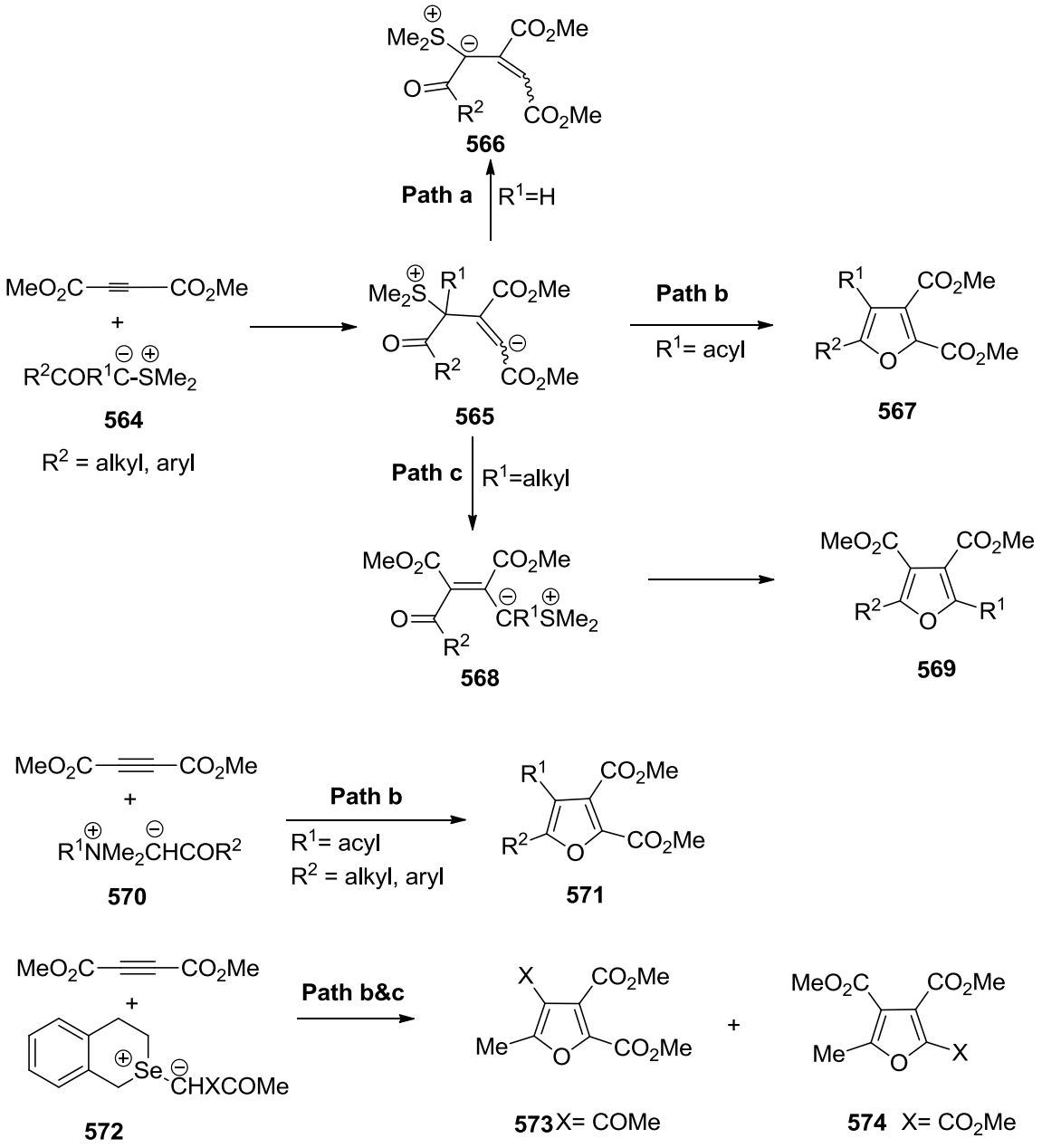


561 **562** **563**

Scheme 192

5.1.4.3. Ylide approach

The carbonyl-stabilised sulphonium ylides, ammonium ylides and cyclic selenonium *exo*-ylides react with DMAD to afford furan 3,4- and 2,3-dicarboxylic acid esters along with rearranged products.[277] Sulphonium ylides **564** (**Scheme 193**) have been reported to react with DMAD in three different ways.

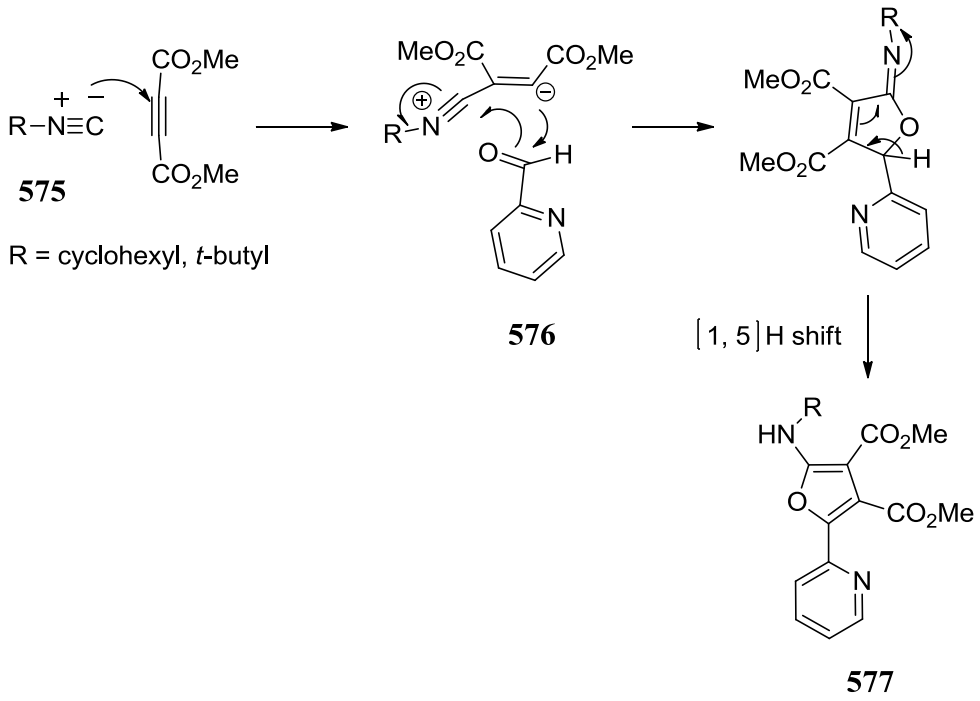


Scheme 193

Thus, addition of the carbanion centre of the ylide **564** to the triple bond formed an intermediate betaine **565**, which underwent a formal [1,3] hydrogen migration to form an ylide **566,** (path a, R^1 = H), cyclisation with loss of dimethyl sulphide to give a furan-2,3-dicarboxylate **567** (path b, R^1 = acyl) and a formal [1,3] acyl migration in **565** to give an ylide **568** followed by cyclization and loss of dimethyl sulphide to give a furan-3,4-dicarboxylate **569** [path c, R^1 = alkyl]. The ammonium ylides **570** reacted with

DMAD in a manner analogous to path (b) to give furan-2,3-dicarboxylate **571**, but in moderate yield. The selenium ylide **572** reacted with DMAD to give two kinds of tetrasubstituted furans **573** (X = COMe) and **574 (**X = CO_2Me) in 51% and 31% yields, respectively.

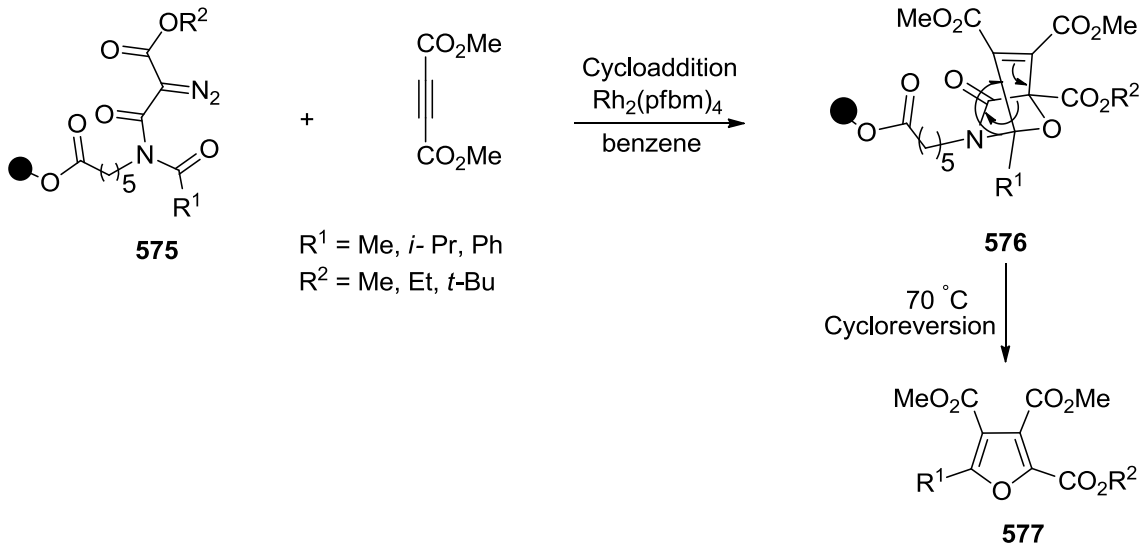
Maghsoodlou and coworkers[278] reported a one-pot multicomponent reaction for the synthesis of polysubstituted and functionalized 2-aminofuran 3,4-dicarboxylates **577** (**Scheme 194**) that involved the formation of an ylide intermediate. The reaction of alkyl isocyanides **575** with DMAD in the presence of pyridine-2-carboxaldehyde **576** led to the formation of stable 2-aminofuran dicarboxylates **577** in excellent yields.



Scheme 194

The polymer-supported diazoesters **575** (**Scheme 195**) obtained from esterification of Wang resin with caproic acid of *N*-acyl amino-diazoester underwent $Rh_2(pfbm)_4$-catalyzed chemoselective decomposition to form carbonyl ylide intermediate via rhodium carbenoid species. Subsequent 1,3-cycloaddition of carbonyl ylide intermediate

with DMAD afforded the cycloadducts **576.** Thermal cycloreversion of **576** in different way led to the detachment of the solid support and formation of furan tricarboxylic acid esters **577** in high yield and excellent HPLC purity.[279]



Scheme 195

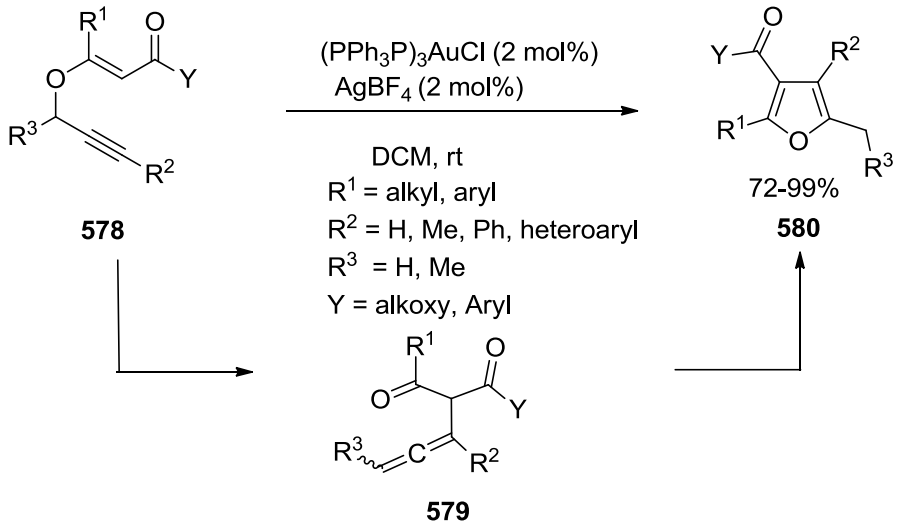
5.1.4.4. Metal-catalyzed cycloisomerization approach

A particularly effective approach is through metal-catalyzed cycloisomerization of unsaturated acyclic precursors using Rh(I), Ag(I), Au(III), Pd(0/II), Fe(III), Cu(I), and Sn(II) etc, which usually proceeds under rather mild conditions (**Scheme 190**).[268,269] Metal-catalyzed cycloisomerization of or alkynyl (v-vii) or allenyl (viii**, Scheme 190**) substrates has been generally used to prepare alkyl, aryls di- and trisubstituted furans, while tetra-substituted, particularly the functionalized furans are not readily accessed.[269] Furthermore, alkynes are typically considered to be more attractive starting materials than allenes, since practical routes to allenes that contain sensitive functional groups are very limited.[280]

A few examples of metal-catalyzed cycloisomerization for the synthesis of 3- or 2,3-difunctionalized furans are known which involve cycloisomerization of

functionalized vinyl ethers (viii, **Scheme 190**).The functionalized vinyl ethers are generally obtained by Michael addition of alcohols to activated acetylenes.

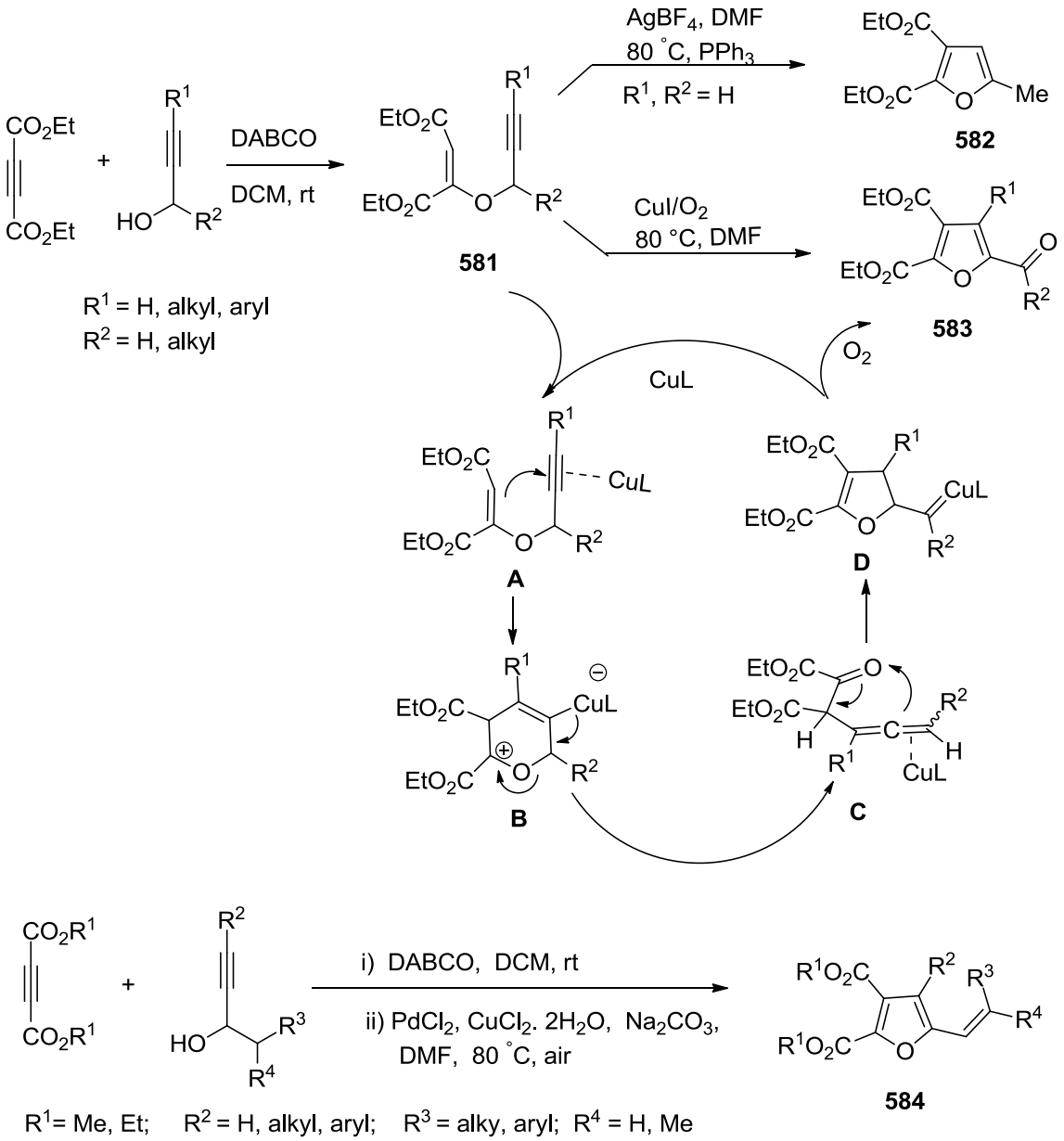
A cascade reaction involving propargyl-oxy-Cope rearrangement and heterocyclization was employed by Kirsch and co-workers[281] to synthesize tri- and tetrasubstituted furans using the propargyl vinyl ethers **578**. The 2,3-allenyl ketone intermediates **579** (**Scheme 196**) obtained from [3,3]-sigmatropic rearrangement of the propargyl vinyl ethers **578**, underwent Au(I)-catalyzed cycloisomerization to generate the tetrasubstituted furans **580**.



Scheme 196

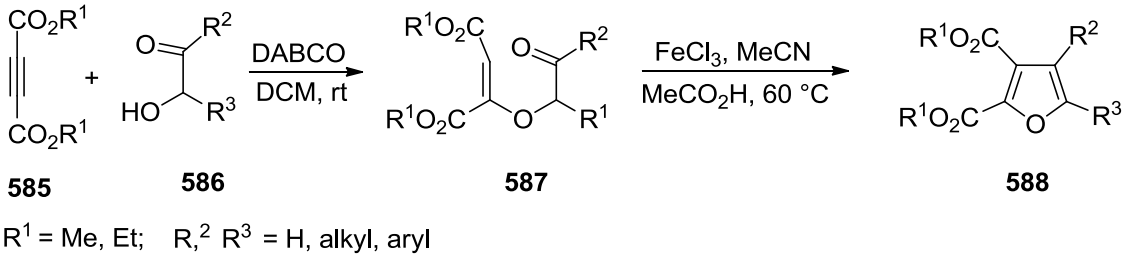
Jiang and coworkers[282] reported CuI/O_2, $AgBF_4/PPh_3$ and $PdCl_2/CuCl_2.2H_2O$-catalyzed cyclization of propargyl vinyl ethers **581** for regiospecific synthesis of functionalized furan-2,3-dicarboxylate **582**, **583** and **584** (**Scheme 197**) having additional aldo or keto functional group in moderate to good yields as useful synthetic intermediates for the synthesis of bioactive compounds. Thus, DABCO-promoted nucleophilic addition of propargyl alcohol to electron-deficient alkynoates formed the

vinyl propargyl ethers **581**. A 6-*endo-dig* attack of the enol ether onto copper (I)-alkyne complex **A** resulted in the formation of intermediate **B**, which collapsed into the allenic ketone **C**. The allenic ketone **C** was converted to the carbene complex **D.** In the presence of a copper catalyst and air, the carbene complex **D** underwent sequential dehydrogenation and carbene oxidation to give **583.**



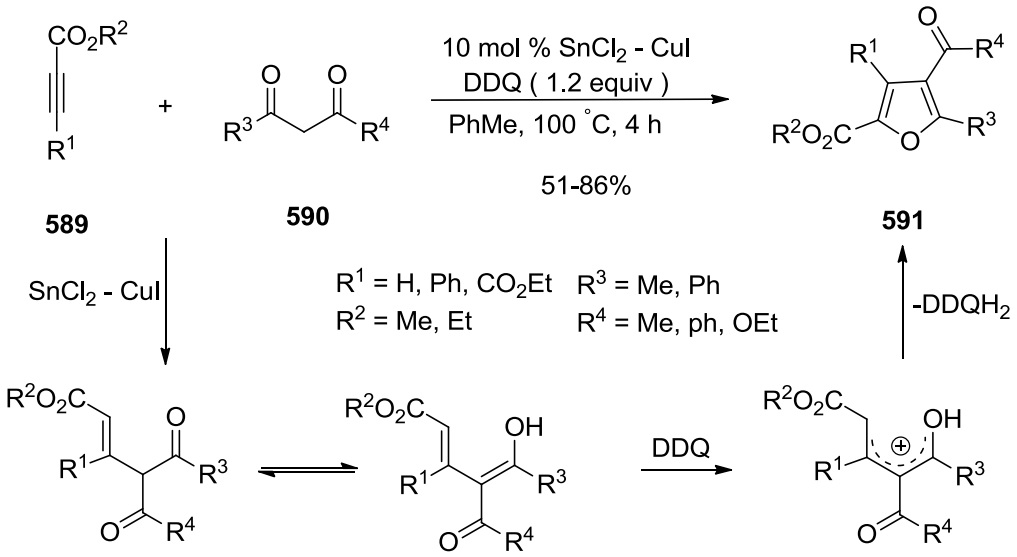
Scheme 197

Cao et al.[283] presented a one-pot domino process for the synthesis of the polysubstituted furan dicarboxylates **588** (**Scheme 198**) through $FeCl_3$-catalyzed cyclizations of the maleates **587** prepared *in- situ* through nucleophilic addition of 3-hydroxybutan-2-ones derivatives **586** to the alkynes acetylene **585** in the presence of DABCO.



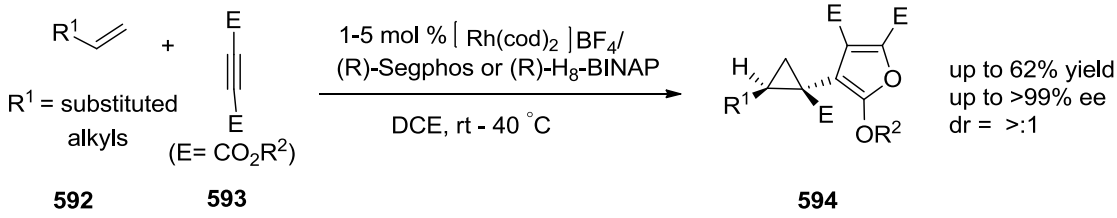
Scheme 198

The active methylene acetylene adducts have also found interesting applications in the synthesis of functionalized furans. Thus, Jiang and coworkers[284] reported a synthesis of polyfunctional furans **591** (**Scheme 199**) from alkynoates **589** and 1.3-dicarbonyl compounds **590.** The key synthesis involved Sn (II) and Cu (I)-catalyzed addition of the dicarbonyl compound **590** to the alkynoates **589** followed by dehydrogenation of the adduct with DDQ.



Scheme 199

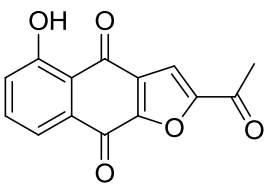
Tanaka and coworkers[285] reported that a cationic chiral rhodium (I)/Segphos or H_8-BINAP-complex catalyzed cotrimerization of electron rich monoenes **592** (**Scheme 200**) and electron deficient dialkyl acetylenedicarboxylates **593** led to the formation of functionalized furanylcyclopropanes **594** with excellent enantioselectivity and perfect diastereoselectivity.



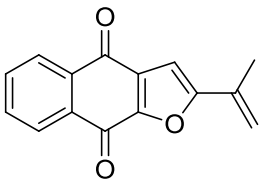
Scheme 200

5.1.5. Furanonapthoquinones

Furanonaphthoquinones have attracted much attention during the past few decades because their many derivatives occur in nature [286] (**Fig. 34**) and show biological activities.[287]



2-Acetyl-5-hydroxynaphtho[2,3-b]furan-4,9-dione

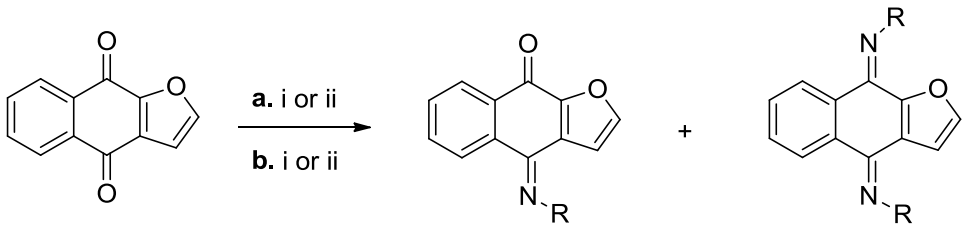


2-Isopropenylnaphtho [2,3-b]furan-4,9-dione

Fig. 34 Naturally occurring furanonapthoquinones

Many natural substituted naphtho[2,3-b]furan-4,9-diones have higher cytotoxic activity and their activity varies with the type of substituent on the parent naphtho[2,3-b]furan-4,9-dione.[287b-c] Due to being compounds of medicinal importance, the construction of substituted naphtho[2,3-b]furan-4,9-diones have drawn considerable attentions.[288]

Tseng et al.[289] reported that the furan fused naphthoquinone **595** (**Scheme 201**) reacted with hydroxylamines (NH_2OH, NH_2OMe) and aryl amines (NH_2-Aryl to give the corresponding oxime and mono-imine **596,** respectively in regiospecific and stereospecific manners. In the case of aryl amines, the dimine **597** were also obtained along with monoamine **596**. Compounds **596** and **597** displayed antiproliferative activity against four human carcinoma cells and the normal fibroblast cell line.

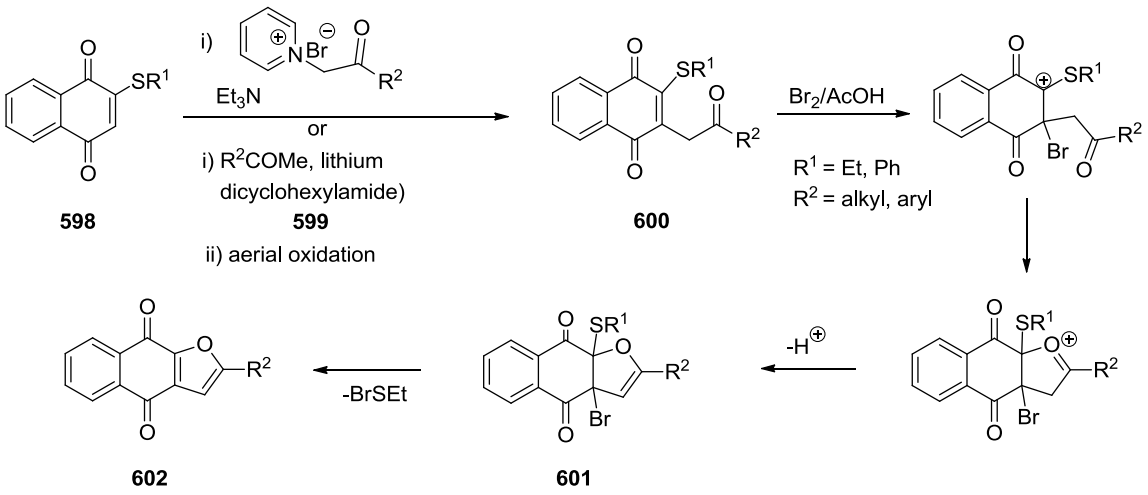


595 **596** **597**

a: (i) $HONH_2HCl$, K_2CO_3; R = OH -
(ii) $MeONH_2HCl$, K_2CO_3 R = OMe -
b: (i) Aryl-NH_2,$TiCl_4$, DCM, 10 min; R = aryl -
(ii) Aryl-NH_2,$TiCl_4$, DCM, 30 min. R = aryl R= Aryl

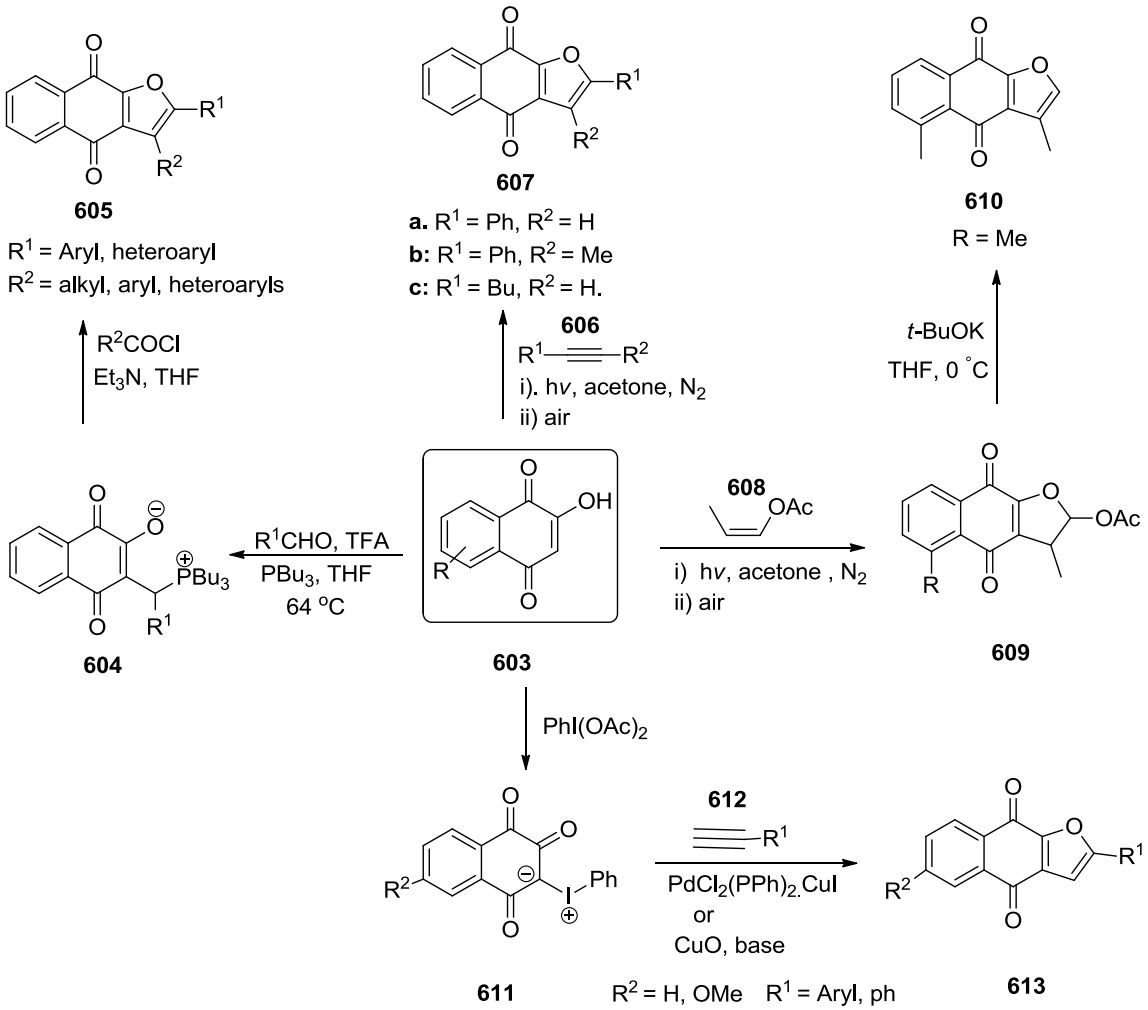
Scheme 201

Ueno and coworkers[290] reported a high yielding synthetic route to some naphtho[2,3-b]furan-4,9-dione derivatives **602** (**Scheme 202**) isolated from various plants known to show cytotoxic activity to the KB cell and HeLa cells. The 2-sulphanyl-1,4-naphthaquinone **598** on treatment with either pyridinium ylide or the lithium enolate **599** followed by aerial oxidation gave **600**, which underwent bromocyclization in the presence of bromine in acetic acid solution to **601.** Subsequent elimination of sulphinyl bromide gave naphtho[2,3-b]furan-4,9-dione **602** in good yields.



Scheme 202

Variously substituted naphtho[2,3-b]furan-4,9-diones **605, 607, 610** and **613** (**Scheme 203**) have been synthesized using 2-hydroxyl-4-naphthoquinones **603**.[291]



Scheme 203

Thus, Lin and coworkers[291a] synthesized many polysubstituted furanonaphthoquinones **605** (**Scheme 203**) by intramolecular Wittig reaction of the phosphorus zwitterions **604** derived from **603** with acid chlorides in high yields.

The naphtho[2,3-blfuran-4,9-diones **607** (**Scheme 203**) were directly obtained by regioselective [3+2] photocycloaddition of **603** to alkynes **606** in good to high yields.[291b] The 2,3-Dihydronaphtho[2,3-b]furan-2,4-dione **610** was obtained by regioselective [3+2] photocycloaddition of **603** to the alkene **608** and subsequent treatment of **609** in the presence of either DDQ or potassium butoxide.[291b] Treatment of 3-phenyliodonio-1,2,4-trioxo-1,2,3,4-tetrahydronaphthalenides **611,** derived from **603,** with terminal acetylenes **612** in the presence of a bis(triphenylphosphine)palladium chloride-cuprous iodide catalyst or cuprous oxide in the presence of *N*-methylpiperidine or pyridine base furnished the 2-substituted naphtho[2,3-b]furan-4,9-diones **613** in moderate to good yields.[291c]

5.2. Statement of the problem

From the foregoing account, it is obvious that functionalized furans especially those having halo, keto and/or ester groups particularly at the β-positions are important building blocks for the synthesis of more complex natural and synthetic bioactive furans, a library of other potentially useful furans and non-furanoid molecules.

However, such furans are not easily accessible. There are very few reported methods for the preparation of β-chlorofurans, which have their own limitation with regard to the nature of other substituents, substitution pattern and yield.

Classical approaches such as cyclocondensation of dicarbonyl compounds (Paal–Knorr synthesis and Feist–Benary furan synthesis) and their modified versions still have some limitations, including the difficulty in accessing functionalized furans that contain

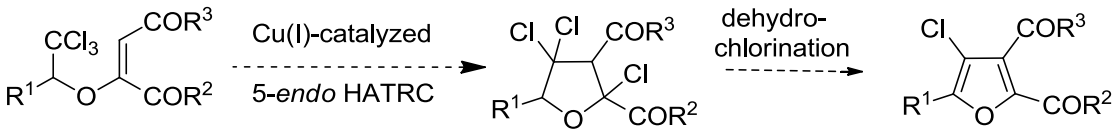
sensitive functional groups and the inability to provide furans with high flexibility with regard to the substituents and substitution pattern. The functionalization of existing furan ring *via* electrophilic aromatic substitution is somewhat restricted due to low stability of furans under acidic and aerobic conditions, and thus is limited to base stable furans. The halogen–magnesium exchange or lithiation followed by electrophilic substitution are useful in special cases and the former depends on the availability of the halofurans.

The β-silylated furans used for the synthesis of β-functionalized furans by Diels-alder-retro- Diels-alder approach are not so active as dienes. They require highly reactive dienophiles to undergo Diels-Alder cycloadditions. The carbonyl-stabilised sulphonium, selenium and ammonium ylides react with DMAD non-regioselectively to give mixtures of functionalized furans including rearranged side products.

The metal-catalyzed cycloisomerizations of alkynyl or allenyl substrates have been generally used to prepare di- and trisubstituted furans bearing alkyl and aryl substituents, while tetrasubstituted furans are not readily prepared. The widely used metal-catalyzed cycloisomerization reactions are generally not useful for the synthesis of functionalized β-chlorofurans. A few β-halofurans obtained by the former methods (**Scheme 175**) are limited to those bearing aryl groups as the other substituents. The furan ring did not incorporate the halogen atom as well as functional group which can be potentially exploited for further synthetic purposes. The synthetic utility of furans having such versatile functional groups, as chloro, keto and/or ester in the same molecule would increase manifold, especially when the functional groups occupy the β-position. However, methods for synthesis of functionalized β-chlorofurans are scarcely reported.

This laboratory reported synthesis of 3,4-di- and 2,3,4-trisubstituted β-chlorofurans using Cu (I)-catalyzed chlorine atom transfer radical cyclization as the

key step. However, these were simple alkyl or aryl substituted β-chlorofurans lacking other functional groups. The experience of this laboratory in the synthesis of β-chlorofurans led us to envisage a protocol for the synthesis of 2,3,4-tri- and tetrasubstituted furans containing an ester and/or keto functional groups at the C-2 and C-3 positions as well as a chlorine atom at C-4 position by Cu (I)-catalyzed one step *5-end-trig* radical cyclization-aromatization of functionalized 2,2,2-trichloroethyl vinyl ethers. There was also an element of curiosity in putting this approach to test because Cu (I)-catalyzed 5-*endo* radical cyclization of vinyl ethers has not been reported so far. The proposed synthetic plan is shown below in **Scheme 204**. It was expected that the known chemistry could be easily extended to the synthesis of the unknown vinyl ether cyclization precursors.



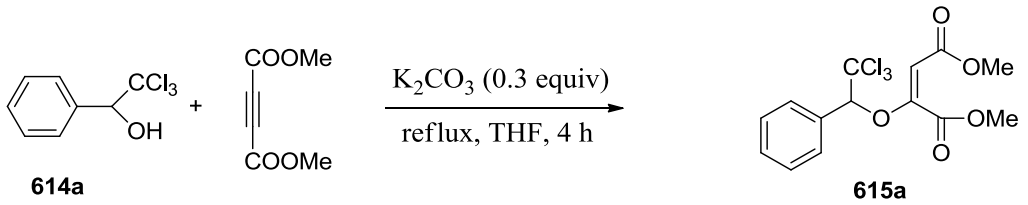
Scheme 204

5.3. Results and Discussion

5.3.1. Preparation of an HATRC precursor, dimethyl 2-(2,2,2-trichloro-1-phenyl)ethoxymaleate 615a

With this idea, an HATRC precursor dimethyl 2-(2,2,2-trichloro-1-phenylethoxy)maleate **615a** (**Scheme 205**) was thought to be prepared by Michael addition of 1-phenyl-2,2,2-trichloroethanol **614a** to DMAD relying on the well known addition of alcohol to DMAD.[282,292] This precursor was preferred over the commercially available unsubstituted simpler 2,2,2-trichloroethanol with a view to check the feasibility

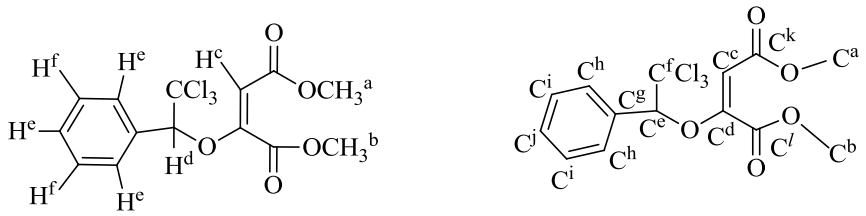
of the Michael addition of a relatively hindered secondary alcohol so that a broad furan synthesis with variable substituents could be developed. 1-Phenyl-2,2,2-trichloroethanol **131a** was easily prepared by nucleophilic addition of $CHCl_3$ to benzaldehyde[293] in the presence of DBU, as reported in the literature.[294] The reaction of the carbinol **614a** with DMAD in equivalent proportions in THF in the presence of a catalytic amount of K_2CO_3 under reflux for 4 h indeed furnished the trichloroethyl vinyl ether **615a**.



614a 615a

Scheme 205

The crude product **615a,** thus obtained was purified by column chromatography and characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry.



A B

Fig. 34. **^{1}H NMR and ^{13}C NMR assignments for the structure 615a**

The ^{1}H NMR spectrum of **615a** (**Fig**. **257**) was compatible with its structure. It showed two singlets at δ 3.63 and 3.91 ppm integrating for three protons each, which were attributed to the CH_3 protons H^a and H^b (**Fig. 34, Structure A**), respectively of the two methyl ester groups. It displayed two more singlets at δ 5.07 and 5.42 ppm integrating for one proton each, which were attributed to the olefinic CH proton H^c and

methine proton H^d, respectively. The two multiplets at δ 7.43-7.47 and δ 7.57-7.60 ppm integrating for three and two protons, respectively were attributed to the aromatic protons H^e and H^f, respectively.

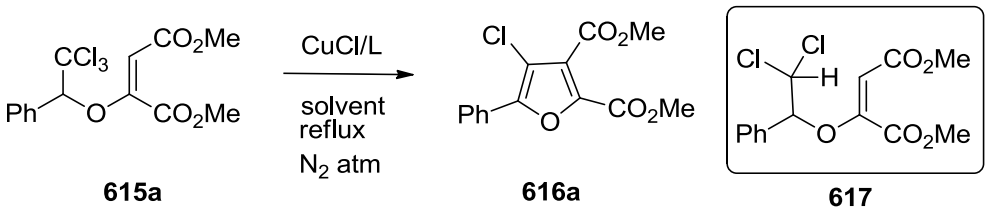
The *E*-geometry was supported by chemical shift (δ) of the vinylic proton H^c, which was found in agreement with that reported in the literature for 2-alkoxymaleates.[295]

In proton-decoupled ^{13}C NMR spectrum of **615a** (**Fig. 258**), the two signals at δ 51.6 and 53.0 ppm were assigned to the two methyl carbons C^a and C^b (**Fig. 34**, **Structure B**), respectively of the two ester groups. The three downfield signals at δ 89.0, 97.6 and 98.0 ppm were attributed to the vinylic carbon C^c, the methine carbon C^e and the quaternary CCl_3 carbon C^f, respectively. The three signals at δ 128.4, 129.3 and 130.3 ppm were assigned to the aromatic CH carbons C^h, C^j and C^i, respectively. The four downfield low intensity signals at δ 130.8, 158.4, 162.8 and 165.2 ppm were assigned to the quaternary carbons of the phenyl ring C^g, the vinyl carbon C^d and the carbonyl carbons C^k and C^l, respectively. These assignments were supported by DEPT-135 spectrum also. IR spectrum of the vinyl ether **615a** showed a strong absorption at 1729 cm^{-1} due to the C=O of the esters groups. It showed a strong absorption at 1223 cm^{-1} due to the C-O single bond stretching. HRMS spectrum of this compound showed $[M + Na]^+$ peak at m/z 388.9721, which exactly matched with the calculated value of 388.9721 for the formula $C_{14}H_{13}Cl_3O_5Na$.

5.3.2. Chlorine atom transfer radical cyclization of dimethyl 2-(2,2,2-trichloro-1-phenyl)ethoxymaleate 615a: Optimization of reaction conditions

Next, the reaction of the vinyl ether **615a** (**Scheme 206**, **Table 13**) with varying amounts of CuCl was performed in different solvents in the presence of commercially

available ligands such as bpy, TMEDA and PMDETA in order to optimize the reaction conditions. The effect of solvent was also looked into. The progress of the reaction was monitored by TLC and also by recording ^{1}H NMR spectra of the aliquots taken from time to time. The yield of the product and the amount of the catalyst used were regarded as significant parameters for the optimization. It was pleasantly noted that in all the cases where the reaction occurred, it proceeded beyond the cyclization step to afford the aromatic 4-chlorofuran **616a** (**Scheme 206**) probably by double dehydrochlorination of the initial cyclization product promoted by the basic ligand.[44] This feature of the reaction enhanced the synthetic value of the proposed scheme. The results are compiled in **Table 13**.



615a **616a** **617**

Scheme 206

Table 13. CuCl/Ligand catalyzed 5-*endo* chlorine atom transfer radical cyclization-aromatization of 615a[a]

S. No.	CuCl (mol %)	Ligand	CuCl/Ligand (mol ratio)	Solvent[b]	Time (h)	Yield of **616a** (%)
1	120	bpy	1:1	DCE	18	69
2	120	bpy	1:1	benzene	24	75
3	55	TMEDA	1:2	benzene	18	81
4	70	PMDETA	1:1	benzene	20	80

[a] All he reactions were performed with 1 mmol of **615a** at reflux temperatures under a N_2 atmosphere.

[b] Reaction mixture was heterogeneous in benzene

To begin with, the vinyl ether **615a** was treated with a catalytic amount of copper (I) chloride and bpy (40 mol% of each), the most commonly employed catalytic system in HATRC reaction, in DCE at reflux under a nitrogen atmosphere, a suitable reaction condition for HATRC reactions experienced by this and other laboratories. The reaction was found to be successful in the cyclization of the vinyl ether **615a**. However, the reaction was sluggish and required more than stoichiometric amount of the catalyst (120 mol%) for completion (**S. No. 1, Table 13**). TLC of the reaction mixture showed two spots and ^{1}H NMR of the crude product showed the presence of two compounds in nearly 90:10 ratio. The crude product was purified by column chromatography using neutral alumina to obtain a colorless solid as the major product and a very small amount of a yellow liquid. The characterization of the solid compound by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry showed that it was the 4-chlorofuran **616a** (69% yield) instead of the expected α-chlorotetrahydrofuran. The ^{1}HNMR and ^{13}C NMR of the yellow liquid showed it to be a mixture of the reduced starting material **617** and the 4-chlorofuran **616a**. The former was formed probably due to hydrogen atom abstraction by the intermediate radical from the solvent DCE.

With the aim to prevent the reduction of the starting material, the solvent DCE was replaced by a very poor hydrogen atom donor solvent with benzene. The reaction of the vinyl ether **615a** in benzene at reflux was heterogeneous but it succeeded in preventing the reduction of the starting material to **617** and the yield of the product **616a** was also found to increase to 75% (**S. No. 2**, **Table 13**). However, the reaction still required more than stoichiometric amount (120 mol %) of the catalyst. The longer reaction time (24 h) was also disconcerting.

In order to reduce the catalyst loading and the reaction time, it was considered to test some other ligands known to be more effective in HATRC reactions. In this regard,

the inexpensive and easily available ligand TMEDA (2 equiv with respect to CuCl) was found to be the most effective. The reaction completed in lesser time (18 h) and with lower catalyst loading (55 mol%) giving the product **616a** in 81% yield (**S. No. 3**). Moreover, the dark red color developed during the reaction could be easily removed to a large extent by adding ethyl acetate to the reaction mixture followed by washing with brine. In the case of bpy, the color of the reaction mixture turned black which could not be washed out by brine. Treatment of this solution with aqueous ammonia removed the color of the solution almost completely. The solid crude product obtained by evaporating this solution was found to be almost pure by ^{1}H NMR. The other ligand PMDETA, which was also tested, was found not as effective as TMEDA in terms of the amount of the catalyst (70 mol%) and reaction time (20 h) (**S. No. 4**).

Thus, the reaction conditions (**S. No. 3**) using 55 mol% CuCl/TMEDA (1:2 mol ratio) in benzene under reflux was regarded as the best optimized conditions in terms of the yield of the product, amount of the catalyst and cleanliness of the reaction for cyclization-aromatization of vinyl ether **615a** to **616a**.

The structure of **616a** was established by ^{1}H and ^{13}C NMR and IR spectroscopy and mass spectrometry.

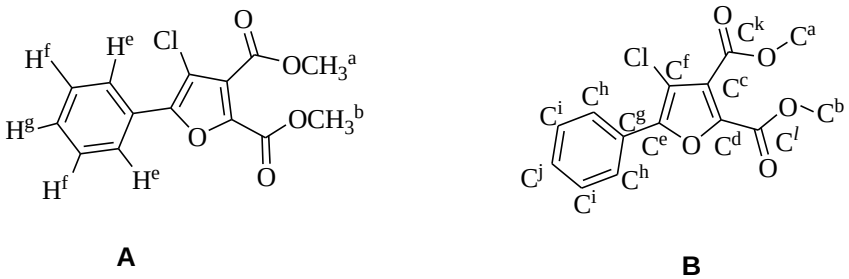


Fig. 35 ^{1}H NMR and ^{13}C NMR assignments for the structure of 616a

Thus, ^{1}H NMR spectrum of **616a** (**Fig. 291**) showed two singlets at δ 3.94 and 3.98 ppm integrating for three protons each, which were attributed to the methyl protons H^{a} and H,^{b} (**Fig. 35**, **Structure A**), respectively of the methyl ester groups. It showed a multiplet at δ 7.43-7.50 and a doublet at δ 8.01 ppm with a coupling constant of 7.2 Hz, integrating for three and two protons, respectively. The multiplet was assigned to the aromatic *meta* and *para* protons H^{f} and H^{g} and the doublet to the *ortho* protons H^{e}. The disappearance of the signals for the vinylic proton H^{c} and methine proton H^{d} in the ^{1}H NMR of the starting material **615a** (**Fig. 35. Structure A**) and the downfield shifts of the signals of the aromatic protons and methyl protons of the ester groups indicated the formation of the aromatic furan ring in which the oxygen lone pair was part of the aromatic system.

The ^{13}C NMR and DEPT-135 NMR spectra were also compatible with the structure of furan **616a** (**Fig 292**). The ^{13}C NMR spectrum showed two signals at 52.6 and 53.0 ppm, which were attributed to the methyl carbons C^{a} and C^{b} (**Fig. 35**, **Structure B**), respectively of the ester groups. The three signals at δ 111.8 126.0 and 126.3 ppm were attributed to the quaternary carbons C^{f}, C^{c} and C^{d}, respectively of the furan ring. The three signals at δ 127.4, 129.1, and 135.9 ppm were attributed to the CH carbons of the benzene ring C^{i}, C^{h} and C^{j}, respectively. The four signals at δ 140.0, 149.6, 157.4 and 161.6 ppm were attributed to the quaternary carbons C^{g}, C^{e}, C^{k} and C^{l}, respectively. The disappearance of signals due to vinylic, methine and CCl_3 carbons of the starting material **615a** and appearance of three new signals in downfield region of the ^{13}C spectrum of **616a** strongly suggested the formation of the furan ring. The IR spectrum of the product **616a** showed a strong absorption at 1737 cm^{-1} and a medium absorption at 1069 cm^{-1} due to the C=O stretching in methyl ester and C-O single bond stretching, respectively. The HRMS spectrum of this compound showed $[M+Na]^{+}$ peak at m/z

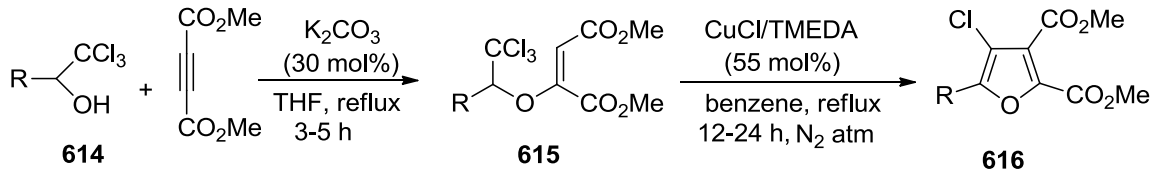
317.0178, which is within the acceptable limit of deviation from the calculated value of 317.0187 for the formula $C_{14}H_{11}ClO_5Na$.The furan structure of the product **616a** was also supported by single crystal X-ray diffraction spectroscopy of a similar derivative (vide infra).

5.3.3. Generalization of the scheme: Synthesis of other 4-chlorofurans 616

The generality of the above approach to 4-chlorofurans **616** (**Scheme 207**) was shown by preparing a variety of 1-susbstituted 2,2,2-trichloroethanols **614** by DBU-catalyzed nucleophilic addition[293] of $CHCl_3$ to aliphatic or aromatic aldehydes or by treating the aldehydes with sodium trichloroacetate.[294] The 1-substituted 2,2,2-trichloroethyl vinyl ethers **615** (**Table 14**) were prepared by Michael addition of the trichloromethyl carbinols **614** thus obtained to DMAD (1equiv) in dry THF in the presence of K_2CO_3 (0.3 equiv) under reflux for 3-5 h[282,292] The ^{1}H NMR of the crude products obtained after simple filtration of reaction mixture and evaporation of the solvent showed formation of one isomer exclusively (aryl substituted) or predominantly (alkyl substituted). However, the other isomer was too less to be isolated either by column chromatography or by recrystallization (DCM-*n*-hexane). The structures of all the Michael adducts **615** were established by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and supported by mass spectrometry. The (*E*)-stereochemistry was assigned to them by comparing the values of the ^{1}H NMR chemical shifts (δ) of the olefinic protons with the ones reported in the literature[295] for the olefinic protons of structurally analogous dimethyl 2-alkoxymaleates, having (*E*)-geometry. The olefinic protons in the vinyl ethers **615** were found to resonate in δ 5.11–6.03 ppm range, which were in agreement with the

chemical shifts range assigned to the dimethyl 2-alkoxymaleates. For the (Z)-isomers (or dimethyl 2-alkoxyfumarates), these chemical shifts values were well above δ 6.0 ppm.

The vinyl ethers **615** were treated with 0.55 equiv of CuCl and 1.1 equiv of TMEDA in benzene at reflux under a nitrogen atmosphere for 12-24 h. The expected 5-*endo* chlorine atom transfer radical cyclization and dehydrochlorination occurred smoothly and regioselectively to form the tetrasubstituted functionalized 4-chlorofurans **616** (**Scheme 207**). Usual work up of the reaction mixture and purification by column chromatography or recrysatallization afforded the products **616** in good yields (67-82%). The details are shown in **Table 14**.



Scheme 207

The reaction time taken for complete conversion of vinyl ethers **615** into furans **616** were in the order *p*-$O_2NC_4H_4$ < Ph < alkyl which was in accordance with the ease of dehydrochlorination to give the aromatic furan ring. The methodology was found to be fairly general for the synthesis of tetrasubstituted 4-chlorofuran-2,3-dicarboxylates with good flexibility with regard to the substituents at the C-5 position. Since a large number of aldehydes are commercially available and the synthesis of vinyl ether cyclization precursors was easy, a variety of alkyl, aryl, heteroaryls substituents at the C-5 positions could be introduced without any problem

Table 14. Synthesis of functionalized 4-chlorofurans 616 by CuCl/TMEDA-catalyzed chlorine atom transfer 5-*endo* radical cyclization-aromatization of vinyl ethers 615

S. No.	Trichloromethyl carbinols **614** R	Vinyl ether **615**[a]		4-Chlorofuran **616**[b]	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1	a: Ph	4	82	18	81
2	b: 4-MeC_6H_4	4	80	18	71
3	c: 2-ClC_6H_4	5	70	24	67
4	d: 3-ClC_6H_4	4	78	18	73
5	e: 4-ClC6H4	4	80	16	75
6	f: 4-BrC_6H_4	4	82	18	71
7	g: 4-$MeOC_6H_4$	4	80	16	75
8	h: 4-$O_2NC_6H_4$	4	79	12	76
9	i: 2-pyridyl	4	80	16	75
10	J: *n*-Et	4	78	24	80
11	k: *i*-Pr	4	75	24	82

[a] Prepared by performing the reaction in 10 mmol scale in THF at reflux using K_2CO_3 (3 mmol)

[b]Prepared by taking vinyl ethers (1 mmol), CuCl/TMEDA (1:2 mol ratio)(55 mol%) in benzene at reflux under a nitrogen atmosphere.

. The structure of these previously unknown furans **616** were established by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and mass spectrometry. The characteristic spectral data of vinyl ethers **615** and chlorofurans **616** were similar to those of the vinyl ether **615a** and the chlorofuran **616a**, respectively as described earlier, with the expected differences due to variation in the α-substituent. The ^{1}H and ^{13}C NMR data of **616** were

also compared and found to be in agreement with the values reported in the literature[282-283] for some similarly nonchlorinated functionalized furans. The structures of the chlorofurans were also supported by single crystal X-ray diffraction spectrometry of the *p*-tolyl derivative **616b**. The ORTEP diagram is shown in **Figure 36**.

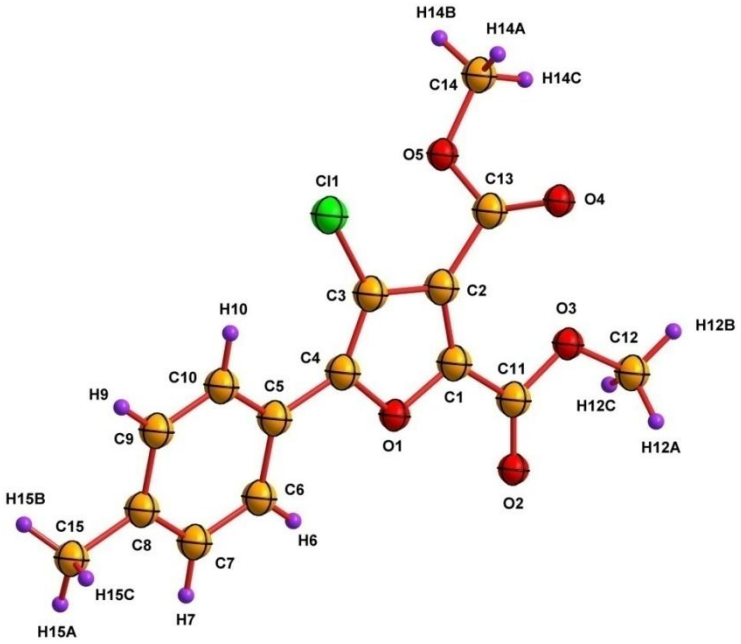
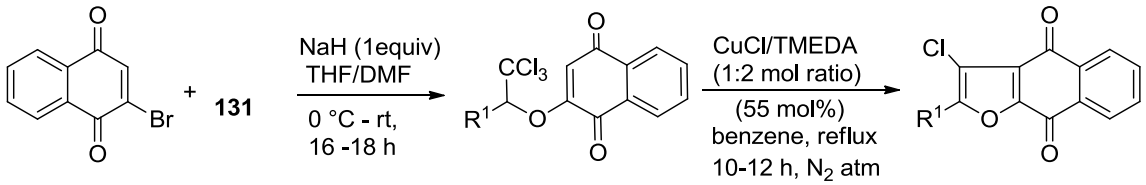


Fig. 36 ORTEP diagram of the dimethyl 4-chloro-5-*p*-tolylfuran-2,3-dicarboxylate 616b

The scope of the reaction appears to be quite broad as the vinyl ether cyclization precursors with variable substituents on the C=C double bond may be prepared in other ways also. This would give access to 4-chlorofurans having variable functional groups at the C-2 and/or C-3 positions. The feasibility of this approach was demonstrated by preparing two 4-chlorofuranonapthoquinones**.** As mentioned in **Section 5.1.5**, furanonapthoquinones are biologically significant natural products. Thus, the previously unknown vinylic ether precursors **619a,b** (**Scheme 208**) were prepared in 76 and 78% yields, respectively by nucleophilic substitution reaction of 2-bromo-1,4-napthoquinone **618** with sodium salt of 1-substituted 2,2,2-trichloroethanols **614a** and **614j** using a method reported in the literature[296] for similar reaction. The solid crude products

obtained after work up were purified by column chromatography using neutral alumina. The structures were established by ^{1}H NMR, ^{13}C NMR and IR spectroscopic data which were similar to those described earlier for **615a** and **615j** with the expected differences, and mass spectrometry.

The vinyl ethers **619a** and **619b** (**Scheme 208**) on CuCl/TMEDA-catalyzed HATRC under the usual optimized conditions and purification of the crude products thus obtained by column chromatography furnished the 4-chlorofuranonapthoquinones **620a** and **620b** in 76 and 83% yields, respectively.



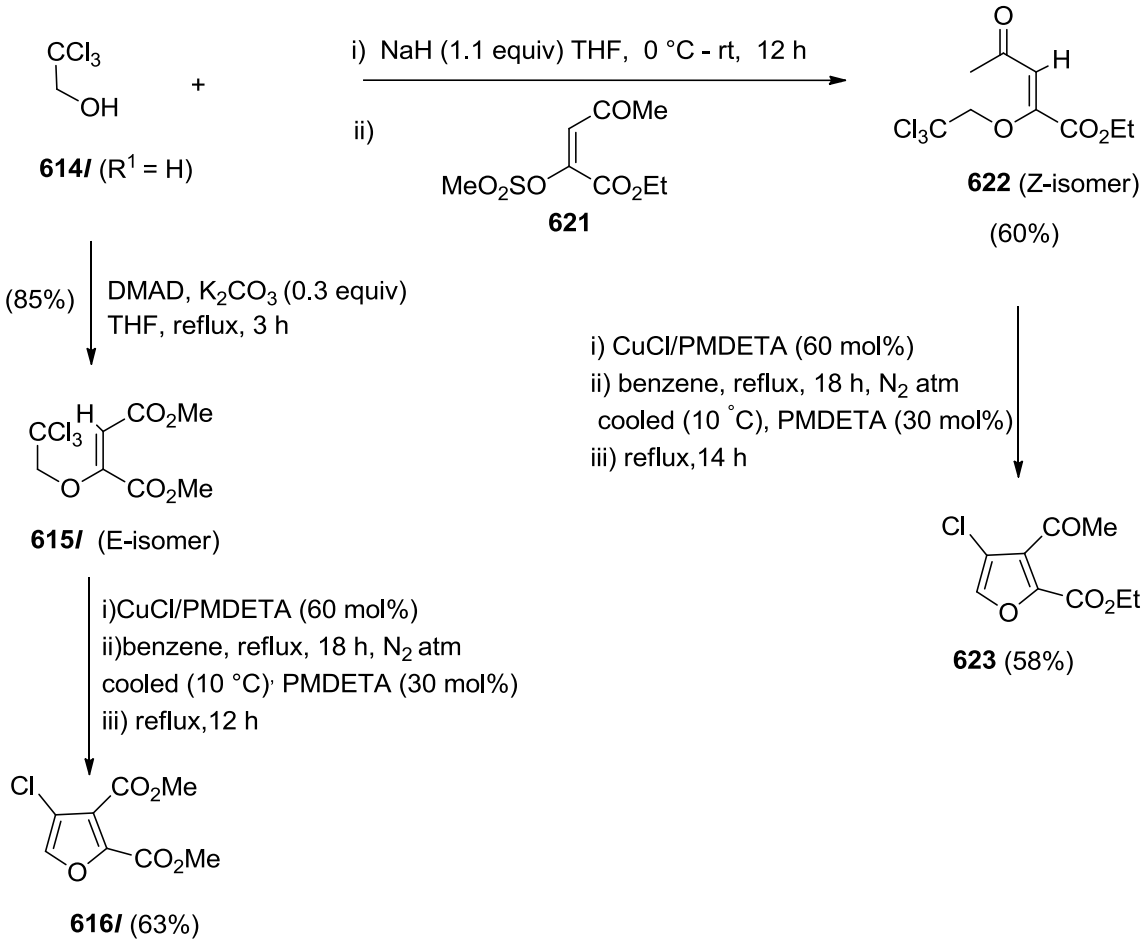
618	R^1	Time (h)	619	Time (h)	620
a:	Ph	18	76	10	76
b:	Et	16	78	12	83

Scheme 208

The structures of previously unknown furans **620** were established by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and mass spectrometry. The spectroscopic data were compared and found to be in agreement with those of similar non chlorinated compound reported in the literature.[290-291]

In an attempt to extend the scope of the present methodology to the synthesis of trisubstituted functionalized 4-chlorofurans, commercially available 2,2,2-trichloroethanol **614*l*** (R^1 = H, **Scheme 209**) was used to prepare the vinyl ethers **614*l*** and **622**. The previously unknown vinyl ether **615*l*** was obtained by the reaction of trichloroethanol **614*l*** with DMAD in THF in the presence of a catalytic amount of K_2CO_3 under reflux for 3 h as shown as mentioned earlier. Work up by filtration and purification of the crude product by column chromatography on neutral alumina furnished the vinyl ether **615*l*** as a single isomer in high yield (85%). The structure and

E-geometry was established by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and mass spectrometry. The olefinic CH proton resonated at δ 5.33 ppm which was in the range of chemical shift assigned in the literature for the vinylic protons of the (*E*)-isomers of dimethyl 2-alkoxymaleates.[295]



Scheme 209

The previously unknown vinyl ether **622** (**Scheme 209**) was obtained by nucleophilic substitution reaction of the vinyl mesylate **621** with sodium salt of trichloroethanol using a method reported in the literature for the substitution reaction of vinyl mesylates with alcohols.[297] Treatment of sodium salt of 2,2,2-trichloroethyl carbinols **614*l*** and ethyl 2-(methylsulfonyloxy)-4-oxopent-2-enoate **621** in THF at room temperature for 8 h followed by simple workup and purification by column

chromatography on neutral alumina column furnished the vinyl ether **622** in good yield (60%). The structure of **622** was established by ^{1}H NMR, ^{13}C NMR and IR spectroscopic data which were similar to those described earlier for **615a** with expected differences, and mass spectrometry. As against the *E*-configuration of the other vinyl ether **615*l***, this vinyl ether appears to have *Z*-configuration. The Z-configuration was assigned to **622** on the basis of the chemical shift of δ 6.33 of the vinylic CH proton which was in the range of the chemical shifts assigned in the literature[295] to the vinylic protons of 2-alkoxyfumarates.

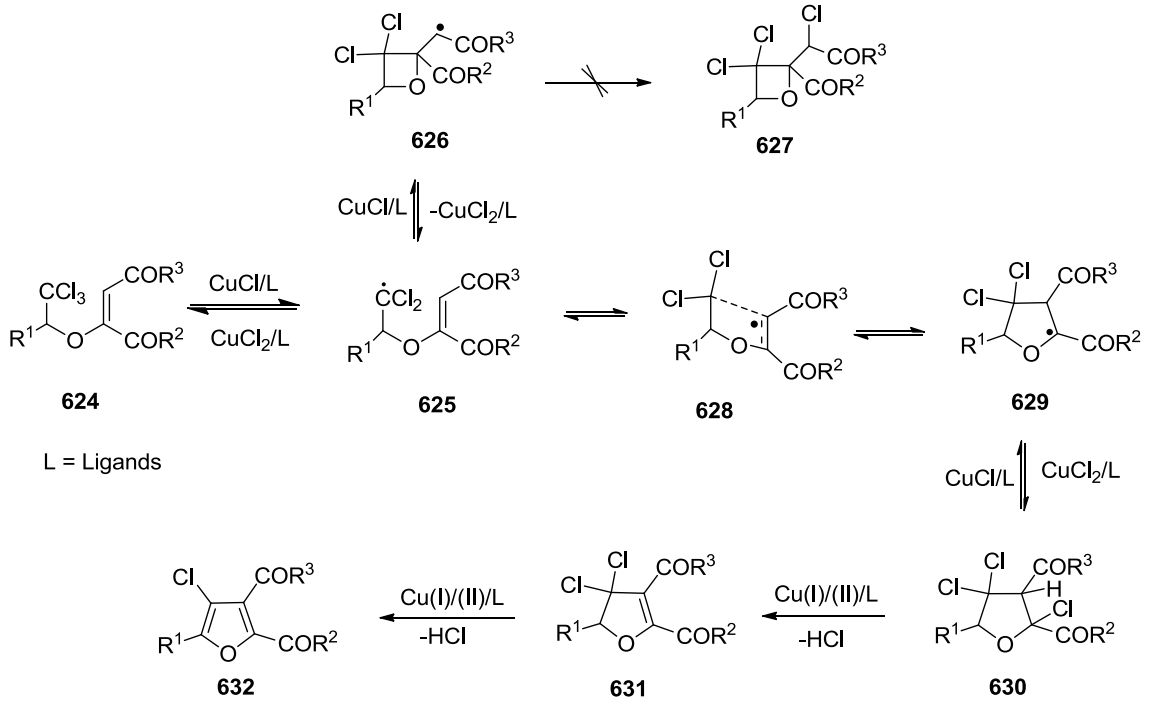
The vinyl ether **615*l*** (**Scheme 209**) did not undergo the expected 5-*endo* cyclization to completion on treatment with CuCl/TMEDA catalyst even after prolonged heating (24 h) with large excess of the catalyst (1 equivalent) . Only 23% of the product **616*l*** and 67% of the unreacted starting material were isolated by column chromatography using neutral alumina. With a little modification, the ligand PMDETA was found to be more effective than TMEDA in this case. Thus, the vinyl ethers **615*l*** was initially heated with 60 mol% of CuCl/PMDETA (1:1mol ratio) in benzene at reflux for 18 h which was followed by addition of an additional amount (30 mol%) of PMDETA into the cooled reaction mixture and resuming the heating at reflux for 6 h. This modification led to the completion of the reaction avoiding unnecessary use of excess CuCl. Usual work up of the reaction mixture and purification by column chromatography gave the tri-substituted 4-chloro furan **616*l*** in good yield (63%). The vinyl ether **622** on a similar two stage treatment with CuCl/PMDETA (60 mol%) for 18 h and with PMDETA (30 mol%) for 8 h furnished the trisubstituted 4-chlorofuran **623** in 58% yield. Probably in these cases, the dehydrochlorination was not as facile as in the case of tetrasubstituted 4-chlorofurans due to the absence of the substituent at C-5 position, thus requiring an additional amount of the basic ligand. The structures of **616*l***

and **623** were supported by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and mass spectrometry.

The functionalized 4-chlorofurans **616**, **620** and **623** were found to be stable when stored as neat at low temperatures as against alkyl and aryl substituted 3-chlorofurans which were reported to be stable in solution in hydrocarbon solvents, particularly when stored as dilute solutions.[10b]

5.3.4. Mechanistic study

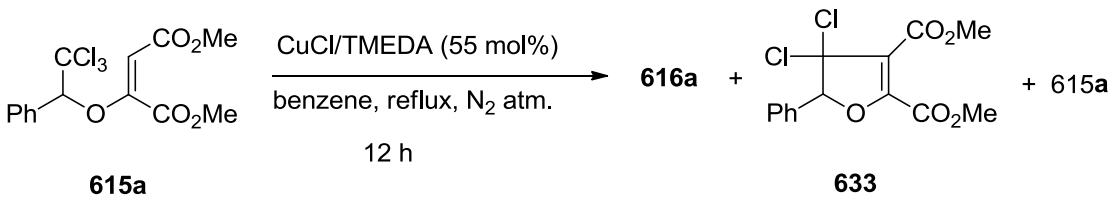
The following straight forward mechanism involving 5-*endo-trig* chlorine atom transfer radical cyclization of the trichloroethyl vinyl ethers **624** (**Scheme 210**) to the α-chlorotetrahydrofuran **630** followed by two successive dehydrochlorinations promoted by the basic ligand was proposed for the formation of the 4-chlorofurans.



Scheme 210: Proposed mechanism for the formation of 4-chlorofurans

Such ligand- promoted dehydrochlorination in some Cu (I)-catalyzed HATRC reactions has been observed earlier where bpy promoted the elimination.[44] The dehydrochlorination of the α-chlorotetrahydrofuran **630** was expected to be particularly facile due to the presence of the active α-chloroether unit in it. α-Chloroethers are known to undergo dehydrochlorination easily.[298] Similarly, the dehydrochlorination of the dihydrofurans **631** should occur easily due to formation of the aromatic furan products.

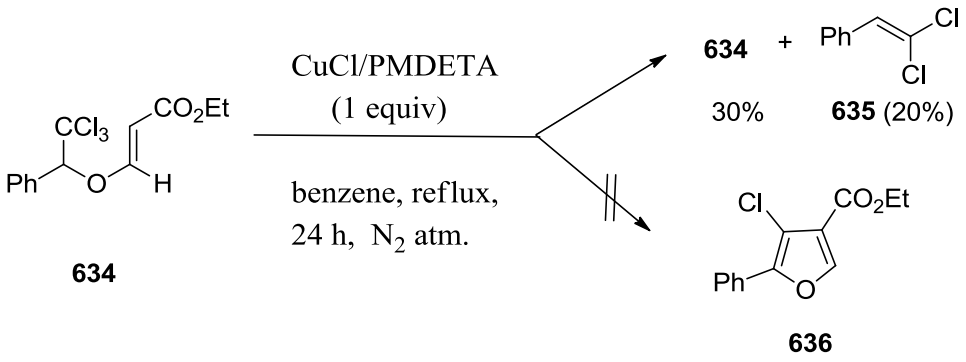
The formation of the dihydrofuran intermediate **631** (**Scheme 210**) was indicated by quenching a reaction before completion of the reaction and isolating the dihydrofuran. Thus, the trichloroethyl vinyl ether **615a** (**Scheme 211**) was treated with CuCl/TMEDA (55 mol%) in refluxing benzene under the optimized reaction conditions. The reaction was quenched after 12 h instead of 18 h required for completing it, and worked up. Column chromatography of the crude product on neutral alumina column using a mixture of ethyl acetate in *n*-hexane (5-15%, v:v) as the solvent for elution gave a mixture containing the 4-chlorofuran **616a**, a small amount of the dihydrofuran **633** and the starting material **615a.** The new dihydrofuran product **633** was characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry.



Scheme 211

No product **627** (**Scheme 210**) arising from *4-exo* cyclization could be detected in any of the cyclization reactions. Although the 4-*exo-trig* cyclization is kinetically preferred according to Beckwith-Baldwin's rule,[37,39] it is highly reversible due to high strain in the 4-membered ring. Such products are formed in special cases when the

radical intermediates such as **626** initially formed by 4-*exo* cyclization are particularly stabilized by substituents especially bulky ones to discourage the competing 5-*endo* cyclization. 5-*Endo* radical cyclizations are kinetically not favored but lead to the formation of thermodynamically more stable products due to relatively less ring strain in the 5-membered ring. Therefore, under equilibrating reaction conditions, 5-*endo* products are predominantly or exclusively formed.[42] In the present case, the relatively high reaction temperature (refluxing benzene) might also have promoted reversibility of the 4-*exo* cyclization leading to the formation of the 5-*endo* cyclization product. The preference for the formation of 5-*endo* product at higher temperatures has been observed earlier.[207,299] 5-*Endo* cyclization was expected to be further facilitated due to greater stabilization of the radical intermediate **629** by captodative effect[208] than the simple stabilization of the radical **626** by only one ester group. This view was supported by the fact that the trichloroethyl vinyl ether monoester **634** (**Scheme 212**) did not undergo 5-*endo* cyclization in the absence of an ester or a keto group to stabilize the radical intermediate initially formed by 5-*endo* cyclization by the captodative effect.

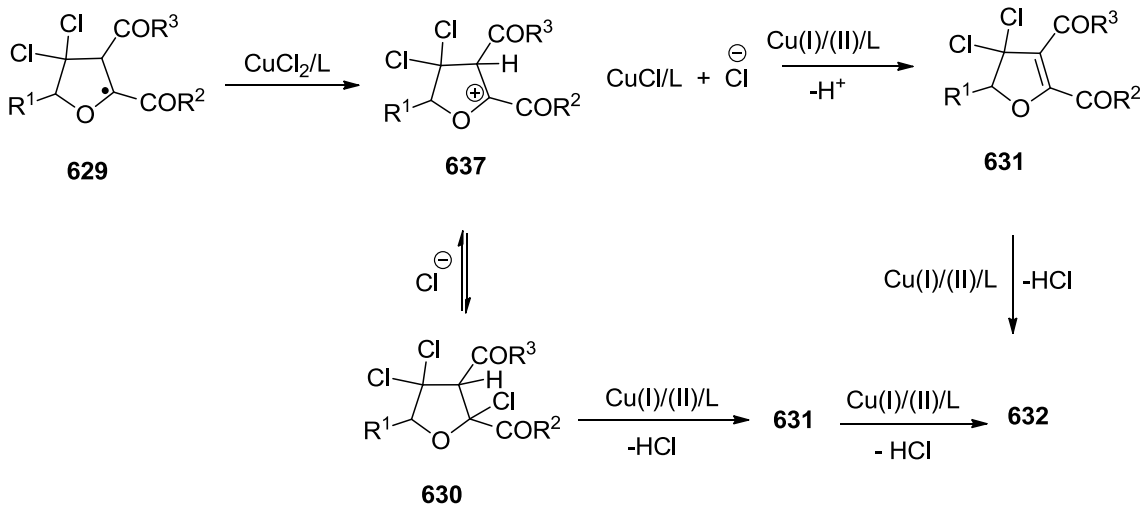


Scheme 212

The mono ester vinyl ether **634** (**Scheme 212**) was prepared by Michael addition of 2,2,2-trichloro-1-phenylethanol **615a** to ethyl propiolate in the presence of K_2CO_3 under reflux for 3 h.[292] The *E*-geometry was assigned to **634** on the basis of the coupling constant (*J*) of 12.9 Hz of the olefinic proton.[295] Treatment of **634** in refluxing benzene

even with a large amount of CuCl/TMEDA (1 equiv) for a long time (24 h) gave nearly 60% of the starting material **634,** nearly 10% of the elimination product **635** and some unidentifiable complex mixture on column chromatography of the crude product on neutral alumina column. No 5-*endo* cyclization product **636** was isolated or detected. Using PMDETA in the place of TMEDA under the same reaction conditions produced higher amount of the elimination product **635** (20%), nearly 30% of the starting material **634** and an unidentifiable complex mixture. The elimination product **635** could have arisen by fragmentation of **634** by C-O bond cleavge.[300]

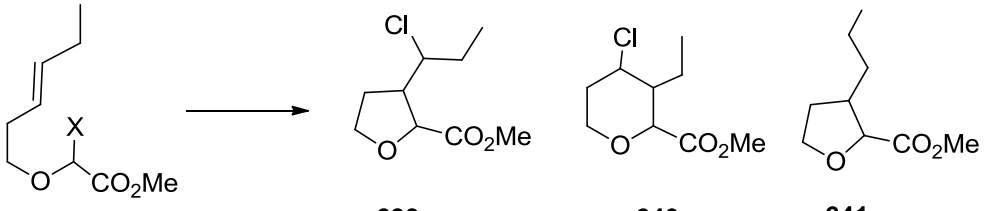
Since the radicals are known to be oxidized to carbocations by redox active metal ions such as Cu (II),[211] the radical **629** might be oxidized to the carbocation **637** (**Scheme 213**) by Cu(II) complex formed in this reaction. This carbocation may reversibly combine with the chloride ion to produce the α-chlorotetrahydrfuran intermediate **630** or undergo fast deprotonation to give the dihydrofuran intermediate **631** directly.



Scheme 213

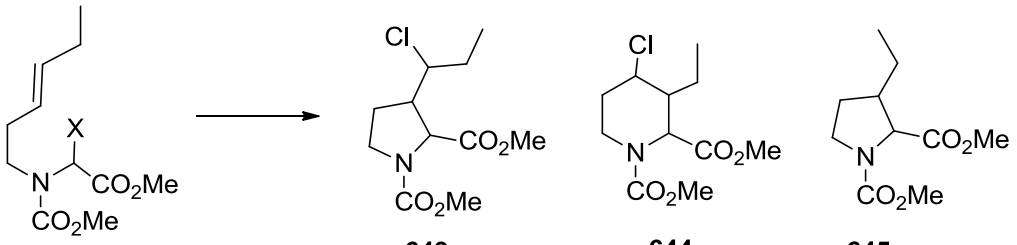
The formation of this type of the captodative carbocation in which the cationic carbon is linked to a stabilizing alkoxy or amino group as well as the destabilizing ester

group is well documented.[28,216,] Speckamp, Hiemstra and coworkers[28,216] studied the cyclization of α-substitued O-homoallylic glycolic acid esters, such as **638** and α-substitued *N*-methoxycarbonyl-*N*-homoallylic glycine esters, such as **642** (**Scheme 214**).



638 **639** **640** **641**

X	Reagents	Yield (%)	Yield (%)	yield (%)
OAc	$SnCl_4$	-	62	-
SPh	Bu_3SnH/AIBN	-	-	77
Cl	CuCl/bpy	87	-	-



642 **643** **644** **645**

X	Reagents	Yield (%)	Yield (%)	yield (%)
OAc	$SnCl_4$	-	80	-
SPh	Bu_3SnH/AIBN	-	-	93
Cl	CuCl/bpy	78	2	-

Scheme 214

They observed that these compounds underwent both cationic and radical cyclization depending on the reaction conditions. While $SnCl_4$ promoted reaction of the acetates, such as **638** (X = OAc) and **642** (X = OAc) occurred exclusively by 6-*endo* cyclization of a carbocation intermediate to give pyrans, such as **640** and piperidines, such as **644**, respectively,[216,220a,301] the reaction of chlorides, such as **638** (X = Cl) and **642** (X = Cl) with CuCl/bpy occurred exclusively by 5-*exo* cyclization of the captodative radical

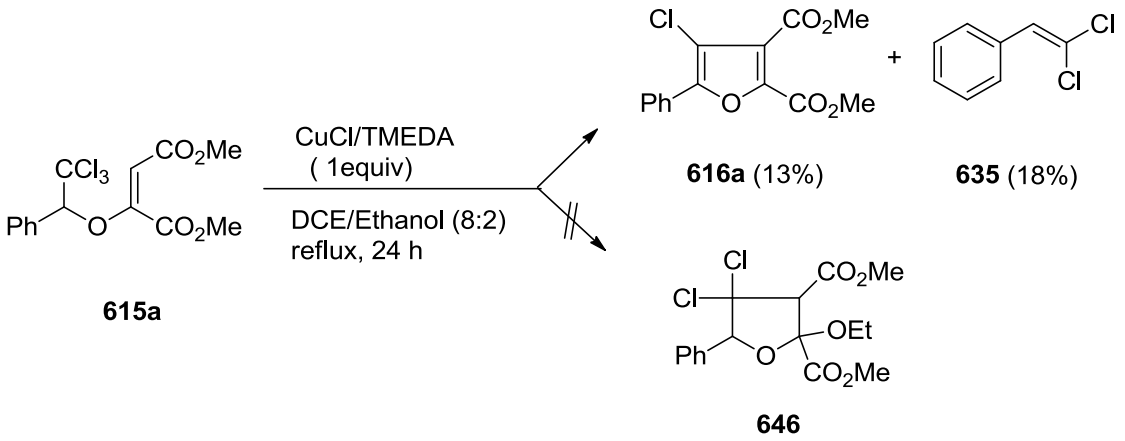
intermediate to afford tetrahydrofurans, such as **639** and pyrrolidines, such as **643**, respectively. In the CuCl/bpy-catalyzed reactions of a few other derivatives, the 6-*endo* products corresponding to **640** and **644** were also formed as minor products.[27,36,216,220b]

A comparison of the regiochemistry of the CuCl/bpy-catalyzed reactions with a truly Bu_3SnH/AIBN-mediated radical cyclization of the corresponding α-phenyl thio derivatives **638** (X = SPh) and **642** (X = SPh), wherein only 5-*exo* cyclization to **641** and **645** was observed, as well as the $SnCl_4$-promoted truly cationic reactions, wherein exclusively 6-*endo* cyclization occurred, led the authors to conclude that in CuCl/bpy-catalyzed reactions, the major 5-*exo* cyclization occurred through a radical mechanism where as the minor 6-*endo* cyclization occurred through a carbocationic mechanism.[302,217] The latter being promoted by Lewis acid action of the copper complex. Though they realized that the minor 6-*endo* product in the CuCl/bpy-catalyzed reactions of the α-chloroglycolate derivatives most likely arose through a truly radical mechanism, the carbocationic mechanism could not be excluded in view of their observation on the effect of the ligands. They observed that in CuCl/bpy catalyzed reaction of methyl α-chlorohomoallylic glycolate, replacement of the ligand bpy with 6,6′-dimethyl-2,2′-bipyridine reversed the regioseletivity of the reaction from predominantly 5-*exo* to exclusively 6-*endo* giving the corresponding pyran derivative in good yield (**Scheme 31**, **chapter 1**). They attributed this ligand effect to the higher Lewis acidity of the copper complex of the latter ligand than the CuCl/bpy complex, thus promoting the cationic 6-*endo* cyclization.[28]

In the present study, the regioselectivity of the reaction could not provide any clue about involvement or otherwise of the cationic intermediate **637**. It is highly unlikely for the copper complex to act as a Lewis acid, if at all it works like one, on the starting trichloroethyl vinyl ether substrate **624** (**Scheme 210**) in view of instability of a

dichloroalkyl carbocation as well as the documented radical chemistry of the trichloromethyl substrates in the Cu (I)-catalyzed HATRC, HATRA and ATRP reactions. Carbocation formation in the radical-polar crossover reactions has been reported to occur at a later stage as in some 5-*endo* cyclization of *N*-vinyltrichloroacetamides (haloenamides).[42b]

The carbocation **637** might arise before or after the formation of the α-chlorotetrahydrofuran intermediate **630** or both by single electron transfer from the captodative radical to Cu (II) complex, or by Lewis acid action of the copper complex on **630** leading to the heterolysis of C-Cl bond or both. Irrespective of the stage at which it might arise, at present we have no evidence for its involvement or otherwise in the reaction. Attempts to trap the carbocation with ethanol in the reaction of **615a** in DCE/ethanol (4:1 ratio) in the presence of 1 equivalent of CuCl and TMEDA for 24 h failed.[42b] Separation of the crude product by column chromatography furnished small amounts of the furan **616a** and 2,2-dichlorovinyl)benzene **635** (**Scheme 215**) in 2:3 ratio as determined by ^{1}H NMR along with unidentified complex mixture probably arising by decomposition of the starting material. The expected acetal **646** could not be isolated.



615a

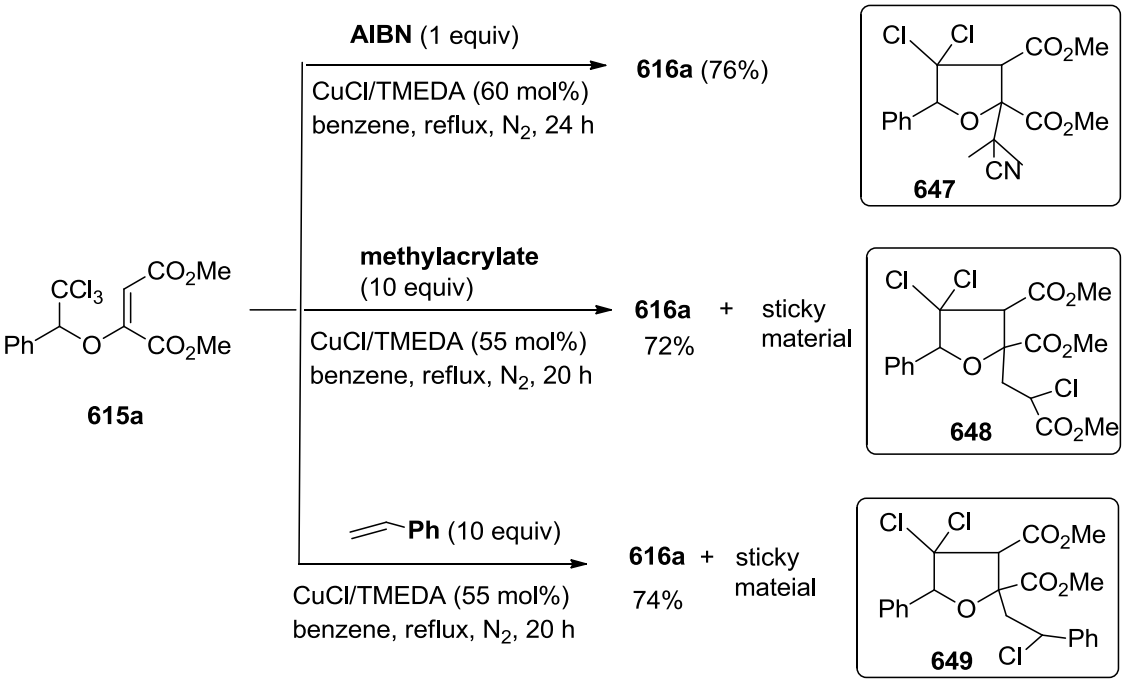
616a (13%)

635 (18%)

646

Scheme 215

Similarly attempts to trap the captodative radical **629** in the reaction of **615a** by IBN radical, styrene and methyl acrylate met with failure. In these cases only the chlorofuran **616a** was isolated by column chromatography in nearly 76, 72 and 74%, yields respectively. The expected radical coupling product **647** or the alkene radical addition products **648** or **649** (**Scheme 216**) could not be isolated or detected in the crude reaction mixture.



Scheme 216

However, the trapping experiment did not exclude the involvement of these intermediates in the reaction. Probably their intermolecular reactions were slower than the other reactions leading to the formation of the dihydrofuran **631.**

5.4. Conclusion

The present chapter describes a single step method for the synthesis of tri- and tetrasubstituted 2,3-difunctionalized 4-chlorofurans from readily accessible

trichloromethyl carbinols in good overall yields. It involves tandem *5-endo* radical cyclization of 2,2,2-trichloroethyl vinyl ethers obtained easily by the reaction of trichloromethyl carbinols with DMAD or functionalized vinylic halides/pseudo halides. The success of the disfavored 5-*endo* cyclization was attributed to the formation of the captodatively stabilized radical intermediate in the cyclization step and relatively high reaction temperature. Although a radical mechanism nicely explained the formation of the products, radical polar cross over mechanism through other routes including the oxidation of the captodative radical intermediate to a cation by Cu (II) could not be excluded. The present method of 4-chlorofuran synthesis is applicable to the synthesis of a variety of 4-chlorofurans with ester group at C-2 position and an ester or keto group at the C-3 position. The C-5 position may have an alkyl, aryl,or heteroaryl substituent or may be kept unsubstituted. Furanonapthoquinones were also accessible by this methodology. The furans thus prepared are potential synthetic intermediates for accessing valuable aliphatic, alicyclic and aromatic compounds.

Although high catalyst loading is a point of concern, the present methodology for the synthesis of functionalized β-chlorofurans is still attractive in view of inexpensive and easily accessible starting materials and short route.

5.5. Experimental

5.5.1. General preparative procedures

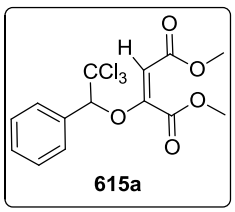
All the trichloromethy carbinols **614a-k** were prepared by the reaction of aldehydes with chloroform in the presence of catalytic amounts of DBU[293] or by reaction of aldehydes with trichloroacetic acid in DMSO as reported in the literature.[294] 2-Bromo-1,4-napthoquinone[303] **618** was prepared by known procedures.

5.5.1.1. Preparation of 2,2,2-trichloroethyl vinyl ether 615a-*l*

These were prepared by Michael addition of 2,2,2-trichloroethylcarbinols **614a-*l*** to DMAD following a method reported in the literature[282,293] for Michael addition of alcohols to DMAD.

General procedure: A suspension of the 2,2,2-trichloroethalnols **614a-*l*** (10 mmol), DMAD (1.420 g, 10 mmol) and K_2CO_3 (0.424 g, 3 mmol) in dry THF (40 mL) was heated at reflux. The progress of the reaction was monitored by TLC, which indicated completion of the reaction by disappearance of the starting organic material after 3-5 h (**Table 14**). After completion of the reaction, the reaction mixture was cooled and evaporated under reduced pressure, the residual mass was treated with diethyl ether or ethyl acetate (150 mL) and filtered. The filtrate was washed with water (2x20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to obtain the crude adducts which on purification by column chromatography on a small pad of neutral alumina using a *n*-hexane/ethylacetate mixture (95:5-90:10, v:v) as solvent for elution afforded the trichloroethyl vinyl ethers **615a-*l*** in (75-85%) high yields.

Dimethyl 2-(2,2,2-trichloro-1-phenylethoxy)maleate ***615a:***

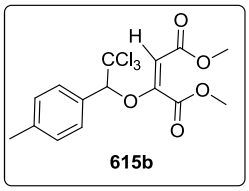


615a

White crystals, mp 120 ˚C (DCM-*n*-hexane), gives positive Beilstein's test for halogens; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.63 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 5.07 (s, 1H, CH), 5.42 (s, 1H, CH), 7.43-7.47 (m, 3H, CH), 7.57-7.60 (m, 2H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.6 (CH_3), 53.0 (CH_3), 89.0 (CH), 97.6 (CH), 98.0 (C), 128.4 (CH), 129.3 (CH), 130.3 (CH), 130.8 (C), 158.4 (C), 162.8 (C), 165.2 (C) ppm; IR (KBr): ν_{max} 2950(w), 1729(s), 1633(s), 1443(m), 1383(m), 1223(s), 1183(s), 1150(s), 1041(m), 832(m),

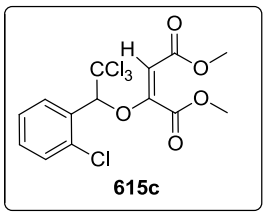
782(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{13}Cl_3O_5Na$ 388.9721, found 388.9721.

Dimethyl 2-(2,2,2-trichloro-1-p-tolylethoxy)maleate ***615b****:*



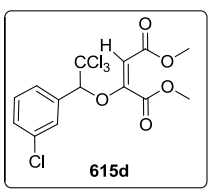
White crystals, mp 114 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.37 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 5.07 (s, 1H, CH), 5.39 (s, 1H, CH), 7.23 (d, 2H, *J* = 8.1 Hz, CH), 7.46 (d, 2H, *J* = 8.1 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3 (CH_3), 51.6 (CH_3), 53.1 (CH_3), 89.1 (CH), 97.5 (CH), 98.3 (C), 127.9 (C) 129.1 (CH), 129.2 (CH), 140.5 (C), 158.5 (C), 162.9 (C), 165.4 (C) ppm; IR (KBr): ν_{max} 2948(w), 1729(s), 1636(s), 1438(w), 1213(s), 1155(s), 1026(m), 830(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{15}Cl_3O_5Na$ 402.9865, found 402.9877.

Dimethyl 2-(2,2,2-trichloro-1-(2-chlorophenyl)ethoxy)maleate ***615c****:*



Colorless crystals, mp 94 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.63 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 5.11 (s, 1H, CH), 6.03 (s, 1H, CH), 7.34-7.48 (m, 3H, CH), 7.79 (dd, 1H, *J* = 7.2, 2.1 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.8 (CH_3), 53.2 (CH_3), 83.9 (CH), 97.3 (CH), 97.7 (C), 127.4 (CH) 129.2 (C), 129.7 (CH), 129.8 (CH), 131.7 (CH), 135.5 (C) 158.1 (C), 162.8 (C), 165.3 (C) ppm; IR (KBr): ν_{max} 2956(w), 1750(s), 1721(s), 1633(s), 1438(m), 1376(m), 1327(m), 1211(s), 1150(s), 1034(m), 825(m), 784(m), 754(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_4O_5Na$ 422.9331, found 422.9341.

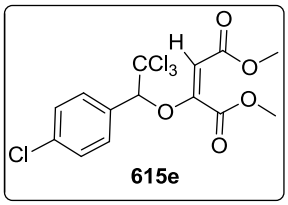
Dimethyl 2-(2,2,2-trichloro-1-(3-chlorophenyl)ethoxy)maleate ***615d:***



Colorless crystals, mp 107 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.64 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 5.09 (s, 1H, CH),

5.39 (s, 1H, CH), 7.34-7.49 (m, 3H, CH), 7.58 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.7 (CH_3), 53.1 (CH_3), 88.2 (CH), 97.6 (C), 98.0 (CH), 127.5 (CH), 129.3 (CH), 129.7 (CH), 130.6 (CH), 132.9 (C), 134.4 (C), 158.1 (C), 162.6 (C), 165.1 (C) ppm; IR (KBr): ν_{max} 3103(w), 1727(s), 1632(s), 1574(m), 1476(m), 1437(s), 1380(s), 1220(s), 1145(s), 1034(m), 820(m), 763(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_4O_5Na$ 422.9331, found 422.9345.

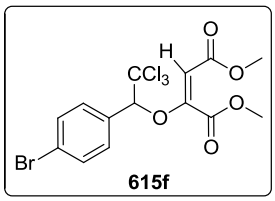
Dimethyl 2-(2,2,2-trichloro-1-(4-chlorophenyl)ethoxy)maleate ***615e****:*



615e

Colorless crystals, mp 116 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.66 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 5.08 (s, 1H, CH), 5.42 (s, 1H, CH), 7.44 (d, 2H, *J* = 8.4 Hz, CH), 7.55 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.8 (CH_3), 53.1 (CH_3), 88.3 (CH), 97.8 (C), 98.0 (CH), 128.8 (CH) 129.5 (C) 130.7 (CH), 136.6 (C), 158.2 (C), 162.7 (C), 165.1 (C) ppm; IR (KBr): ν_{max} 2998(w), 1745(s), 1632(s), 1494(m), 1442(m), 1375(m), 1216(s), 1154(s), 1023(m), 830(s), 775(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_4O_5$ Na 422.9331, found 422.9146.

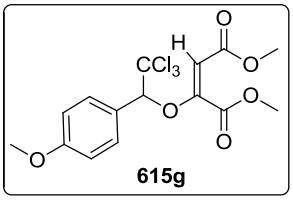
Dimethyl 2-(1-(4-bromophenyl)-2,2,2-trichloroethoxy)maleate ***615f****:*



615f

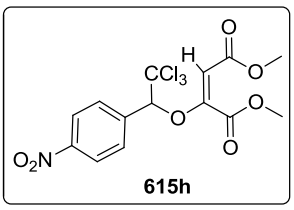
Colorless crystals, mp 117 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.64 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 5.06 (s, 1H, CH), 5.39 (s, 1H, CH), 7.46 (d, 2H, *J* = 8.4 Hz, CH), 7.59 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.8 (CH_3), 53.2 (CH_3), 88.4 (CH), 97.7 (C), 98.0 (CH), 125.0 (C) 130.0 (C) 130.9 (CH), 131.8 (CH), 158.2 (C), 162.7 (C), 165.1 (C) ppm; IR (KBr): ν_{max} 3088(w), 1745(s), 1721(s), 1631(s), 1492(w), 1440(m), 1375(m), 1340(m), 1215(s), 1154(s), 1020(m), 865(w), 772(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}BrCl_3O_5Na$ 466.8810, found 466.8826.

Dimethyl 2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethoxy)maleate ***615g****:*



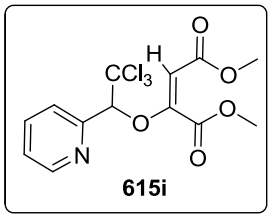
Colorless crystals, mp 104 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.61 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 5.07 (s, 1H, CH), 5.38 (s, 1H, CH), 6.94 (d, 2H, *J* = 8.4 Hz, CH), 7.50 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.7 (CH_3), 53.1 (CH_3), 55.2 (CH_3), 88. 9 (CH), 97.5 (CH), 98.6 (C), 113.8 (CH), 122.7 (C), 130.7 (CH), 158.5 (C), 161.0 (C), 162.9 (C), 165.4 (C) ppm; IR (KBr): ν_{max} 3025(w), 1752(s), 1709(s), 1633(s), 1515(m), 1442(m), 1374(m), 1309(m), 1256(m), 1212(s), 1150 (s), 1027(m), 831(m), 752(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{15}Cl_3O_6Na$ 418.9809, found 418.9826.

Dimethyl 2-(2,2,2-trichloro-1-(4-nitrophenyl)ethoxy)maleate ***615h:***



Light yellow crystals, mp 144 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.64 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 5.09 (s, 1H, CH), 5.55 (s, 1H, CH), 7.82 (d, 2H, *J* = 8.7 Hz, CH), 8.30 (d, 2H, *J* = 8.7 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.9 (CH_3), 53.3 (CH_3), 87.8 (CH), 97.1 (C), 98.7 (CH), 123.5 (CH), 130.6 (CH), 137.8 (C), 149.1 (C) 159.8 (C), 162.5 (C), 164.9 (C) ppm; IR (KBr): ν_{max} 2921(w), 1747(s), 1721(s), 1635(s), 1525(m), 1438(m), 1349(m), 1144(s), 1030(m), 957(m), 826(m), 779(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_3NO_7$ Na 433.9565, found 433.9572.

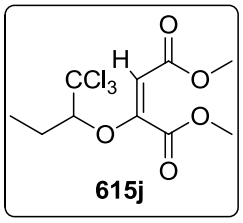
Dimethyl 2-(2,2,2-trichloro-1-(pyridin-2-yl)ethoxy)maleate ***615i:***



Reddish liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.62 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 5.16 (s, 1H, CH), 5.63 (s, 1H, CH), 7.37 (dd, 1H, *J* = 7.2, 5.1 Hz, CH), 7.72-7.84 (m, 2H, CH), 8.68 (d, 1H, *J* = 4.5 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.8 (CH_3), 53.2 (CH_3), 89.9 (CH),

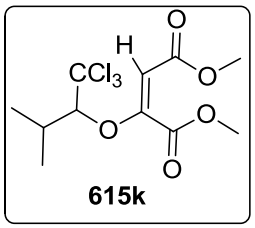
96.9 (C), 98.0 (CH), 123.4 (CH), 124.9 (CH), 137.1 (CH), 149.2 (CH), 151.7 (C), 158.3 (C), 162.8 (C), 164.4 (C) ppm; IR (KBr): ν_{max} 3106 (w), 1721(s), 1644(w), 1593(m), 1517(s), 1438(m), 1345(s), 1303(s), 1129(s), 1073(m), 859(m), 801(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{12}Cl_3NO_5Na$ 389.9672, found 389.9673.

Dimethyl 2-(1,1,1-trichlorobutan-2-yloxy)maleate ***615j****:*



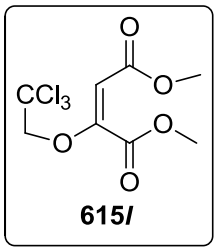
Colorless liquid, gives positive Beilstein's test for halogens; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.11 (t, 3H, J = 7.5 Hz, CH_3), 1.89-2.04 (m, 1H, CH_2), 2.25-2.31 (m, 1H, CH_2), 3.70 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.49 (dd, 1H, J = 9.6, 2.1 Hz, CH), 5.48 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.1 (CH_3), 24.6 (CH_2), 51.8 (CH_3), 53.0 (CH_3), 89.2 (CH), 96.5 (CH), 99.2 (C), 161.1 (C), 163.1 (C), 165.9 (C) ppm; IR (KBr): ν_{max} 2983(m), 1753(s), 1716(s), 1632(s), 1440(m), 1368(m), 1273(m), 1152(s), 1036(m), 785(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{13}Cl_3O_5Na$ 340.9709, found 340.9721

Dimethyl 2-(1,1,1-trichloro-3-methylbutan-2-yloxy)maleate ***615k****:*



Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.00 (d, 3H, J = 6.9 Hz, CH_3), 1.08 (d, 3H, J = 6.9 Hz, CH_3), 2.43-2.48 (m, 1H, CH), 3.57 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 4.38 (d, 1H, J = 3.3 Hz, CH), 5.37 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.7 (CH_3), 22.2 (CH_3), 30.9 (CH), 51.3 (CH_3), 52.6 (CH_3), 90.4 (CH), 95.9 (CH), 98.9 (C), 161.0 (C), 162.7 (C), 165.4 (C) ppm; IR (KBr): ν_{max} 2959(m), 1752(s), 1722(s), 1633(s), 1440(w), 1366(s), 1205(m), 1146(s), 1039(m), 823(w), 764(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{11}H_{15}Cl_3O_5Na$ 354.9885, found 354.9877.

Dimethyl 2-(2,2,2-trichloroethoxy)maleate ***615l***:



615*l*

Colorless solid, mp 82-84 ˚C (DCM-*n*-hexane), gives positive Beilstein's test for halogens; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.74 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 4.43 (s, 2H, CH_2), 5.34 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.9 (CH_3), 53.2 (CH_3), 79.4 (CH_2), 93.3 (C), 96.4 (CH), 159.2 (C) 162.7 (C), 165.3 (C) ppm; IR (KBr): ν_{max} 3096(w), 2955(w), 1756(s), 1712(s), 1630(s), 1438(m), 1373(s), 1209(s), 1164(s), 1082(w), 1041(m), 852(m), 734(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_9Cl_3O_5Na$ 312.9409, found 312.9408.

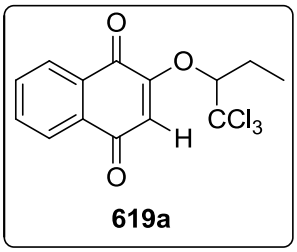
5.5.1.2. Preparation of 2,2,2-trichloroethyl vinyl ethers 619a and 619b

These were prepared by nucleophilic substitution reaction of 2-bromo-1,4-napthoquinone with 2,2,2-trichloroethanols **614a** and **614j** according to a method reported in the literature[296] for a similar reaction of 2-bromo-1,4-napthoquinone with other alcohols.

To a suspension of NaH (0.48 g, 0.01 mol, 60% dispersion in mineral oil) in dry THF/DMF (25 mL, 4:1 v/v) was added a solution of the trichloroethanol **614a** (2.254 g, 0.01 mol) or **614j** (1.775 g, 0.01 mol) in dry THF (10 mL) drop wise at 0˚C over 15 min duration. The mixture was stirred at 0 ˚C for another 30 min and then 2-bromo-1,4-naphthoquinone **618** (2.370 g, 0.01 mol) was added into the suspension. The ice bath was then removed and the mixture was stirred at room temperature (25-30 ˚C). The progress of the reaction was monitored by TLC, which indicated the completion of the reaction by disappearance of the starting material after 18 h (16 h in the case of **614j**). The volatiles were removed under reduced pressure and water (20 mL) was added to the residual mass. The resulting suspension was extracted with ethylacetate (2×50 mL) and the combined solvent extract was washed with brine (2×20 mL), dried (Na_2SO_4), filtered and

evaporated under reduced pressure. Purification of the residual mass by column chromatography on a small pad of neutral alumina using *n*-hexane/ethyl acetate mixture (98:1%, v/v) afforded the pure trichloroethyl vinylic ethers **619a** (2.905 g, 76 %) or **619j** (2.60 g, 78%) as yellow solids.

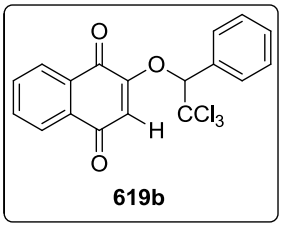
*2-(1,1,1-Trichlorobutan-2-yloxy)naphthalene-1,4-dione **619a**:*



619a

Yellow crystals, mp 110 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (t, 3H, *J* = 7.5 Hz, CH_3), 2.11-2.22 (m, 1H, CH_2), 2.33-2.39 (m, 1H, CH_2), 4.82 (dd, 1H, *J* = 8.4, 2.1 Hz, CH), 6.42 (s, 1H, CH), 7.75-7.77 (m, 2H, CH), 8.07-8.10 (m, 1H, CH), 8.14-8.17 (m, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.4 (CH_3), 24.5 (CH_2), 88.7 (CH), 99.5 (C), 112.6 (CH), 126.1 (CH), 126.8 (CH), 131.1 (C), 131.6 (C), 133.6 (CH), 134.3 (CH), 159.3 (C), 179.1 (C), 184.9 (C) ppm: IR (KBr): ν_{max} 3067(w), 1690(s), 1653(s), 1612(s), 1587(m), 1238(m), 1206(s), 1052(m), 1022(w), 819(m), 745(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{11}Cl_3O_3$ Na 354.9665, found 354.9666.

*2-(2,2,2-Trichloro-1-phenylethoxy)naphthalene-1,4-dione **619b**:*



619b

Yellow solid, mp 101 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.60 (s, 1H, CH), 6.02 (s, 1H, CH), 7.42-7.44 (m, 3H, CH), 7.65 (d, 2H, *J* = 6 .0 Hz, CH), 7.71-7.74 (m, 2H, CH), 7.99-8.03 (m, 1H, CH), 8.13-8.16 (m, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 88.3 (CH), 98.3 (C), 113.1 (CH), 126.0 (CH), 126.5 (CH), 128.3 (CH), 129.3 (CH), 130.3 (CH), 130.8 (C), 131.0 (C), 131.4 (C), 133.4 (CH), 134.1 (CH), 157.0 (C), 178.7 (C), 184.2 (C) ppm; IR (KBr): ν_{max} 3061(w), 1689(m), 1656(s), 1609(s), 1330(w), 1243(m),

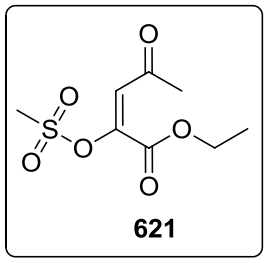
1210(m), 1064(w), 1036(m), 1006(m), 820(s), 775(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{18}H_{11}Cl_3O_3Na$ 402.9668, found 402.9666.

5.5.1.3. Preparation of the trichloroethyl vinyl ether 622

Previously unknown ethyl 2-(methylsulfonyloxy)-4-oxo-2-enoate **621** was prepared in (1.227 g, 52%) yield by following a procedure reported in the literature[297a] and used as such in the preparation of **622** by a method similar to that used for the preparation of the 1,4-napthoquinone derivatives **618** with slight modifications.

To a suspension of NaH (0.48 g, 0.01 mol, 60% dispersion in mineral oil) was added a solution of the 2,2,2-trichloroethanol **614*l*** (1mL, 1.494 g, 0.01 mol) in dry THF (10 mL) drop wise at 0˚C over 15 min duration. The mixture was stirred at 0 °C for another 30 min and then ethy 2-(methylsulfonyloxy)-4-oxo-2-enoate **621** (2.360 g, 0.01 mol) was added in one lot and the reaction mixture was stirred at room temperature for 12 h. The crude product obtained after work up as described above, was further purified by column chromatography on a small pad of neutral alumina using *n*-hexane/ethyl acetate mixture (95:5, v:v) as the solvent for elution to get the vinyl ether **622** in (1.70 g, 60 % yield) as a colorless liquid.

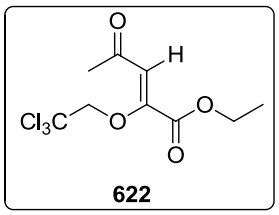
*(E)-Ethyl 2-(methylsulfonyloxy)-4-oxopent-2-enoate **621**:*



621

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, 3H, J = 7.1 Hz, CH_3), 2.40 (s, 3H, CH_3CO), 3.37 (s, 3H, CH_3S), 4.26 (q, 2H, J = 7.1 Hz, CH_2), 6.75 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (CH_3), 31.2 (CH_3), 40.3 (CH_3), 63.0 (CH_2), 126.3 (CH), 141.0 (C), 161.7 (C), 195.9 (C) ppm. IR (KBr): ν_{max} 2924(w), 1731(s), 1667(s), 1603(m), 1236(s), 1136(m), 1131(s), 1044 (m), 972(m), 823(m), 724(m) cm^{-1}.

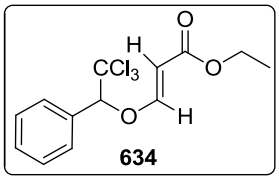
(Z)-Ethyl 4-oxo-2-(2,2,2-trichloroethoxy)pent-2-enoate ***622****:*



622

Colorless liquid, gives positive Beilstein's test for halogens; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, 3H, *J* = 7.1 Hz, CH_3), 2.53 (s, 3H, CH_3), 4.33 (q, 2H, *J* = 7.1 Hz, CH_2), 4.77 (s, 2H, CH_2), 6.33 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 32.0 (CH_3), 62.7 (CH_2), 82.3 (CH_2), 95.4 (C), 118.2 (CH), 150.4 (C), 162.6 (C), 197.7 (C) ppm. IR (KBr): ν_{max} 2924(w), 1732(s), 1668(s), 1603(m), 1236(s), 1136(s), 1045m), 824(m), 724(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_{11}Cl_3O_4Na$ 310.9615, found 310.9615.

(E)-Ethyl 3-(2,2,2-trichloro-1-phenylethoxy)acrylate ***634****:*



634

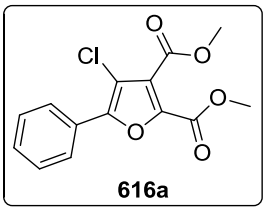
It was prepared according to the procedure described under section 5.5.1.2 by taking 2,2,2-trichloro-1-phenylethanol **614a** (2.255 g, 10 mmol), ethyl propiolate (0.910 g, 1.01 mL, 10 mmol) and K_2CO_3 (0.424 g, 3 mmol) in THF (40 mL) and heating at reflux for 3 h. The crude product obtained after work up was purified by column chromatography on a small pad of neutral alumina using a *n*-hexane/ethyl acetate mixture (95:5, v:v) as the solvent for elution to give the vinyl ether **634** (2.750 g, 85%) as a white crystalline, mp 89 ˚C (DCM-*n*-hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, 3H, *J* = 7.2 Hz, CH_3), 4.11 (q, 2H, *J* = 7.2 Hz, CH_2), 5.32 (s, 1H, CH), 5.35 (d, 1H, *J* = 12.9 Hz, CH), 7.42-7.44 (m, 2H, CH), 7.52-7.58 (m, 3H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2 (CH_3), 60.0 (CH_2), 91.4 (CH), 98.7 (C), 100.5 (CH), 128.2 (CH), 129.5 (CH), 130.1 (CH), 132.1 (C), 159.7 (CH), 166.9 (C) ppm; IR (KBr): ν_{max} 2993(w), 1694(s), 1637(s), 1383(m), 1317(m), 1215(m), 1123(s), 1037(m), 974(m), 780(m), 744(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{13}Cl_3O_3Na$ 344.9823, found 344.9822.

5.5.2. Preparation of the functionalized 4-chlorofurans: Chlorine atom transfer radical 5-*endo* cyclization of 2,2,2-trichloroethyl vinyl ethers.

5.5.2.1. Preparation of the tetra-substituted 4-chlorofurans 616a-k and 620a-b

A flame-dried two-necked round-bottom flask was charged with CuCl (0.055g, 0.55 mmol), TMEDA (0.2 mL, 0.128 g, 1.10 mmol) and degassed dry benzene (40 mL). An atmosphere of nitrogen was created inside the flask using Schlenk technique. The suspension was stirred for 10 minutes at room temperature (25-30 ˚C) and trichloroethyl vinyl ether **615a-k** or **619a-b** (1 mmol) was added to it. The reaction mixture was degassed again by applying vacuum and refilled with the N_2 gas. The mixture was heated at reflux with stirring and the progress of the reaction was monitored by TLC. After completion of the reaction as indicated by disappearance of the starting vinyl ether (10-24 h), the reaction mixture was cooled and diluted with ethyl acetate (100 mL). The resulting mixture was washed with brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. In case the organic extract was dark in color, the organic extract was also washed with aqueous ammonia solution (20 mL) prior to drying and evaporating. The solid thus obtained was recrystalized from DCM-*n*-hexane or diethylether-*n*-hexane at room temperature (low temperature in case needed). In the cases where the crude product was a liquid or could not be crystallized by the above process, it was purified by column chromatography on a small pad of neutral alumina using *n*-hexane/ethyl acetate mixture (90:10 to 80:20%, v/v) as the solvent for elution to obtain tetrasusbtituted 4-chlorofuran in good to high yields (67-83%).

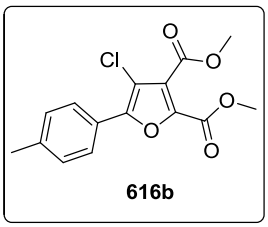
Dimethyl 4-chloro-5-phenylfuran-2,3-dicarboxylate ***616a***:



616a

Colorless crystals, mp 58 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 7.43-7.50 (m, 3H, CH), 8.01 (d, 2H, *J* = 7.2 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6 (CH_3), 53.0 (CH_3), 111.8 (C), 126.0 (C), 126.3 (C), 127.4 (CH), 129.1 (CH), 135.9 (CH), 140.0 (C), 149.6 (C), 157.4 (C), 161.6 (C) ppm; IR (KBr): ν_{max} 2954(w), 1737(s), 1640(w), 1599(w), 1538(w), 1484(w), 1444(m), 1315(s), 1272(m), 1233(s), 1170(s), 1069(m), 797(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{11}ClO_5Na$ 317.0187, found 317.0178.

Dimethyl 4-chloro-5-p-tolylfuran-2,3-dicarboxylate ***616b****:*



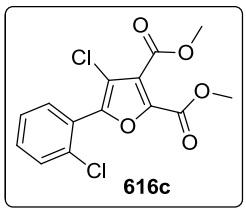
616b

Colorless crystals, mp 46 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 7.18 (d, 2H, *J* = 7.8 Hz, CH), 7.78 (d, 2H, *J* = 7.8 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4 (CH_3), 52.5 (CH_3), 52.9 (CH_3), 110.7 (C), 124.8 (C), 126.1 (CH), 126.4 (C), 129.4 (CH), 139.4 (C), 140.2 (C), 151.0 (C), 157.5 (C), 161.8 (C) ppm; IR (KBr): ν_{max} 2955(w), 1740(s), 1598(w), 1548(w), 1492(m), 1446(m), 1380(w), 1309(s), 1231(m), 1199(s), 1167(m), 1068(m), 989(m), 824(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{13}ClO_5Na$ 331.0339, found 331.0344.

X-ray crystal structure of 616b

Formula sum: $C_{15}H_{13}ClO_5$, Formula weight: 308.7 g/mol; Crystal system: triclinic; Space group: P -1 (2); Unit cell dimensions: a = 7.170(3) Å b = 9.128(4) Å c = 11.218(5) Å α = 98.826(7)° β = 90.908(7)° γ = 92.801(7)°; Cell volume = 724.43(50) $Å^3$, Z = 2; Density calculated = 1.41512 g/cm^3; R_{All} = 0.0688. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989265).

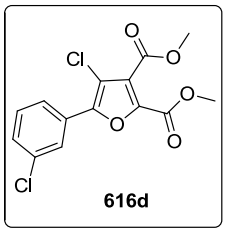
Dimethyl 4-chloro-5-(2-chlorophenyl)furan-2,3-dicarboxylate ***616c***:



616c

Colorless crystals, mp 66 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3H, CH_3), 4.0 (s, 3H, CH_3), 7.35-7.47 (m, 2H, CH), 7.50-7.55 (m, 2H, CH,) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.7 (CH_3), 53.0 (CH_3), 114.6 (C), 125.0 (C), 126.0 (C), 126.7 (CH), 130.3 (CH), 131.7 (CH), 131.9 (CH), 134.2 (C), 141.2 (C), 149.8 (C), 157.4 (C), 161.7 (C) ppm; IR (KBr): ν_{max} 2951(w), 1731(s), 1596(w), 1555(w), 1437(m), 1310(s), 1228(m), 1205(m), 1164(m), 1051(m), 763(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}Cl_2O_5$ Na 350.9797, found 350.9797.

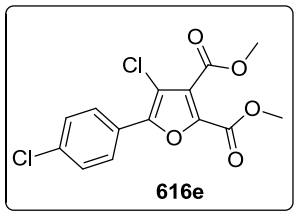
Dimethyl 4-chloro-5-(3-chlorophenyl)furan-2,3-dicarboxylate ***616d****:*



616d

Colorless crystals, mp 51 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 7.41 (d, 2H, *J* = 5.1 Hz, CH), 7.91 (t, 1H, *J* = 3.8 Hz, CH), 7.99 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6 (CH_3), 53.0 (CH_3), 111.8 (C), 124.2 (CH), 126.3 (C), 126.4 (CH), 127.5 (CH), 130.1 (C), 131.6 (C), 132.0 (CH), 140.0 (C), 149.6 (C), 157.4 (C), 161.5 (C) ppm; IR (KBr): ν_{max} 2956(w), 1746(s), 1643(m), 1595(w), 1440(m), 1313(s), 1209(m), 1072(m), 993(m), 780(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}Cl_2O_5Na$ found 350.9797, found 350.9787.

Dimethyl 4-chloro-5-(4-chlorophenyl)furan-2,3-dicarboxylate ***616e***:

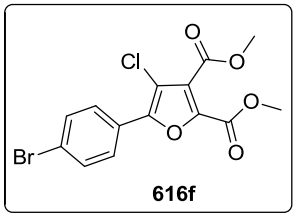


616e

Colorless crystals, mp 58 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 7.37 (d, 2H, *J* = 8.4 Hz, CH), 7.87 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6 (CH_3), 53.0 (CH_3), 111.8 (C), 126.0 (C), 126.3 (C), 127.4 (CH), 129.1 (CH), 135.9 (C), 140.0 (C), 149.6 (C), 157.4 (C), 161.6 (C) ppm; IR (KBr): ν_{max} 3011(w), 1738(s), 1659(w), 1591(m), 1478(m), 1440(m), 1312(s), 1238(m),

1206(m), 1176(m), 1070(m), 830(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}Cl_2O_5$ Na found 350.9797, found 350.9807.

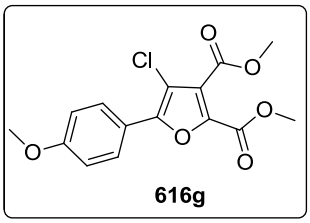
Dimethyl 5-(4-bromophenyl)-4-chlorofuran-2,3-dicarboxylate ***616f****:*



616f

Colorless crystals, mp 57 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.91 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 7.57 (d, 2H, *J* = 8.7 Hz, CH), 7.85 (d, 2H, *J* = 8.7 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6 (CH_3), 53.0 (CH_3), 111.4 (C), 124.1 (C), 126.25 (C), 126.33 (C), 127.4 (CH), 132.0 (CH), 140.0 (C), 149.5 (C), 157.3 (C), 161.5 (C) ppm; IR (KBr): ν_{max} 2957(w), 1728(s), 1643(w), 1590(w), 1478(m), 1437(m), 1300(s), 1232(m), 1197(m), 1068(m), 1006(m), 821(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}BrClO_5Na$ 394.9292, found 394.9298.

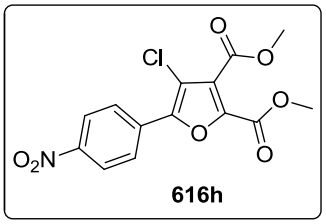
Dimethyl 4-chloro-5-(4-methoxyphenyl)furan-2,3-dicarboxylate ***616g***:



616g

White solid, mp 56 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 6.88 (d, 2H, *J* = 8.7 Hz, CH), 7.84 (d, 2H, *J* = 8.7 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.5 (CH_3), 52.9 (CH_3), 55.4 (CH_3), 109.8 (C), 114.2 (CH), 120.3 (C), 126.5 (C), 127.9 (CH), 139.1 (C), 151.0 (C), 157.6 (C), 160.8 (C), 161.9 (C) ppm; IR (KBr): ν_{max} 3001(w), 1731(s), 1603(m), 1546(w), 1493(m), 1446(m), 1300(s), 1266(s), 1235(s), 1169(m), 1075(m), 1009(m), 829(m), 795(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{13}ClO_6Na$ 347.0303, found 347.0293.

Dimethyl 4-chloro-5-(4-nitrophenyl)furan-2,3-dicarboxylate ***616h****:*

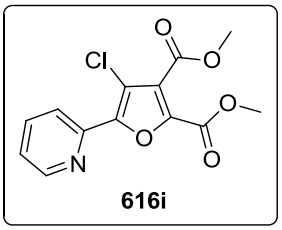


616h

Yellow crystals, mp 105 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 8.14 (d, 2H, *J* = 8.4 Hz, CH), 8.26 (d, 2H, *J* = 8.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.8 (CH_3), 53.1 (CH_3), 114.3 (C), 124.0 (CH),

126.2 (C), 126.5 (CH), 133.0 (C), 141.2 (C), 147.7 (C), 147.8 (C), 157.0 (C), 161.0 (C) ppm; IR (KBr): ν_{max} 3111(w), 1727(s), 1595(w), 1518(m), 1445(w), 1347(m), 1316(s), 1242(w), 1205(w), 1074(m), 859(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}ClNO_7Na$ 362.0056, found 362.0038.

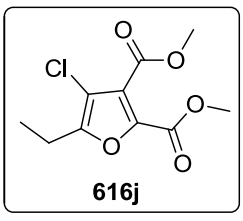
Dimethyl 4-chloro-5-(pyridin-2-yl)furan-2,3-dicarboxylate ***616i****:*



616i

Colorless crystals, mp 81 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.88 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 7.26 (t, 1H, *J* = 6.0 Hz CH), 7.75 (t, 1H, *J* = 6.0 Hz, CH), 7.94 (d, 1H, *J* = 7.8 Hz, CH), 8.70 (d, 1H, *J* = 3.6 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.7 (CH_3), 53.1 (CH_3), 114.2 (C), 121.8 (CH), 123.9 (CH.), 126.4 (C), 136.8 (CH), 140.8 (C), 146.8 (C) 149.1 (C), 150.1 (CH), 157.4 (C), 161.5 (C) ppm; IR (KBr): ν_{max} 3110 (w), 1727(s), 1643(w), 1598(w), 1520(m), 1349(m), 1316(m), 1205(m), 1174(m), 1073(m), 1024(w), 859(w) cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_{13}H_{10}ClNO_5H$ 296.0324, found 296.0320.

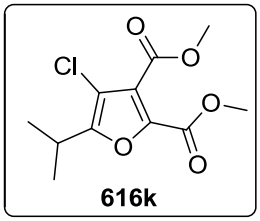
Dimethyl 4-chloro-5-ethylfuran-2,3-dicarboxylate ***616j***:



616j

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, 3H, *J* = 7.5 Hz, CH_3), 2.74 (q, 2H, *J* = 7.5 Hz, CH_2), 3.89 (s, 3H, CH_3), 3.93 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.2 (CH_3), 19.1 (CH_2), 52.2 (CH_3), 52.6 (CH_3), 111.1 (C), 124.5 (C), 139.7 (C), 156.5 (C), 157.3 (C), 161.7 (C) ppm; IR (KBr): ν_{max} 2953(m), 1734(s), 1648(w), 1603(w), 1551(m), 1442(m), 1314(s), 1252(m), 1206(m), 1167(m), 1086(m), 1023(m), 796(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{11}ClO_5Na$ 269.0195, found 269.0187.

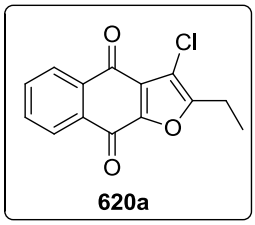
Dimethyl 4-chloro-5-isopropylfuran-2,3-dicarboxylate ***616k****:*



616k

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (d, 6H, *J* = 6.9 Hz, CH_3), 3.20 (septet, 1H, *J* = 6.9 Hz, CH), 3.89 (s, 3H, CH_3), 3.95 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.9 (CH_3), 26.3 (CH), 52.4 (CH_3), 52.8 (CH_3), 110.1 (C), 124.8 (C), 139.4 (C), 157.5 (C), 159.6 (C), 162.1 (C) ppm; IR (KBr): ν_{max} 2970(m), 1733(s), 1603(w), 1547(m), 1414(m), 1377(w), 1314(s), 1227(m), 1201(m), 1166(m), 1075(m), 1022(m), 796(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{11}H_{13}ClO_5Na$ 283.0346, found 283.0344.

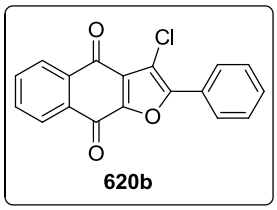
3-Chloro-2-ethylnaphtho[2,3-b]furan-4,9-dione ***620a***:



620a

Yellow crystals, mp 112 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, 3H, *J* = 7.5 Hz, CH_3), 2.87 (q, 2H, *J* = 7.5 Hz, CH_2), 7.68-6.70 (m, 2H, *J* = 3.0 Hz, CH), 8.09 (d, 2H, *J* = 3.0 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.4 (CH_3), 19.3 (CH_2), 110.4 (C), 126.6 (CH), 126.7 (C), 126.8 (CH), 131.9 (C), 132.8 (C), 133.78 (CH), 133.83 (CH), 150.0 (C), 160.7 (C), 172.4 (C), 179.3 (C) ppm; IR (KBr): ν_{max} 2930(m), 1679(s), 1587(m), 1536(m), 1458(w), 1199(m), 1063(w), 995(m), 718(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_9ClO_3Na$ 283.0122, found 283.0132.

3-Chloro-2-phenylnaphtho[2,3-b]furan-4,9-dione ***620b****:*



620b

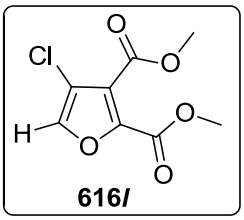
Yellow crystals, mp 127 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48–7.55 (m, 3H, CH), 7.76-7.79 (m, 2H, CH), 8.14-8.25 (m, 4H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 110.6 (C), 126.6 (CH), 126.8 (CH), 127.0 (CH), 127.2 (C), 127.7 (C), 128.9 (CH), 130.5 (CH), 132.2 (C), 133.1 (C), 133.9 (CH), 134.0 (CH), 149.8 (C), 153.9 (C), 172.6 (C), 179.4 (C) ppm; IR (KBr): ν_{max} 3067(w), 1679(s), 1587(m), 1531(w), 1480(m),

1360(m), 1216(m), 1038(w), 941(m), 766(w), cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{18}H_9ClO_3Na$ 331.0121, found 331.0132.

5.5.2.2. Synthesis of tri substituted 4-chloro furans 616*l* and 623

A flame-dried two-necked round-bottom flask was charged with CuCl (0.06 g, 0.6 mmol), PMDETA (0.12 mL, 0.103 g, 0.6 mmol) and degassed dry benzene (40 mL). An atmosphere of nitrogen was created using Schlenk technique. The suspension was stirred for 10 minutes at room temperature (25-30 ˚C) and trichloroethyl vinyl lether **615*l*** (0.292 g, 1 mmol) or **622** (0.290 g, 1 mmol) was added to it. The reaction mixture was degassed again by applying vacuum and refilled with the N_2 gas. The mixture was heated at reflux with stirring for 18 h. The heating was stopped and the reaction mixture was cooled to 5-10 ˚C. An additional amount of PMDETA (0.06 mL, 0.052 g, 0.3 mmol) was added and the reaction mixture was stirred for 10 min at the same temperature. The heating at reflux temperature was then resumed for an additional 12 h (in the case of **615*l***) or 14 h (in the case of **622**). The reaction mixture was worked up as described under section 5.5.2. but the crude products were purified by column chromatography on a small pad of neutral alumina using *n*-hexane/ EtOAc mixture (90:10 to 80:20, v/v) as the solvent for elution to obtain **616*l*** (0.138 g, 63%) as a colorless low melting solid and **623** (0.126 g, 58%) as a colorless liquid.

*Dimethyl 4-chlorofuran-2,3-dicarboxylate **616l**:*

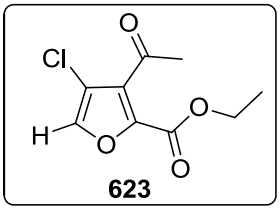


616*l*

Colorless crystals, mp 45 ˚C (DCM-*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.93 (CH_3), 3.96 (CH_3), 7.57 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.7 (CH_3), 53.0 (CH_3), 116.7 (C), 123.9 (C), 141.7 (CH), 142.6 (C), 157.3 (C), 161.5 (C) ppm; IR (KBr): ν_{max} 3147(w), 1737(s), 1594(w), 1508(m), 1442(s), 1312(m), 1279(m), 1218(m), 1170(w), 1066(m),

794(w) cm^{-1}. HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_7ClO_5Na$ 240.9871, found 240.9874.

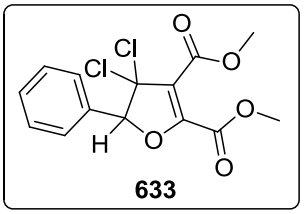
*Ethyl 3-acetyl-4-chlorofuran-2-carboxylate **623**:*



623

Colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, 3H, *J* = 7.1 Hz, CH_3), 2.57 (s, 3H, CH_3), 4.36 (q, 2H, *J* = 7.1 Hz, CH_2), 7.52 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 31.7 (CH_3), 62.0 (CH_2), 115.7 (C), 131.6 (C), 141.0 (CH), 141.7 (C), 157.2 (C), 195 (C) ppm; IR (KBr): ν_{max} 3146(w), 1722(s), 1586(m), 1503(m), 1389(m), 1293(s), 1182(s), 1118(m), 1018(m), 782(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_9ClO_5$ Na 239.0081, found 239.0082.

*Dimethyl 4-chloro-5-phenyldihydrofuran-2,3-dicarboxylate **633***:



633

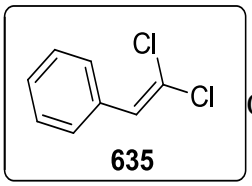
Colorless solid 40 ˚C (DCM-*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 5.80 (s, 1H, CH), 7.37-7.43 (m, 3H, *J* = 5.4 Hz, CH), 7.56 (d, 2H, *J* = 6.3 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.5 (CH_3), 52.8 (CH_3), 90.7 (CH), 95.7 (C), 125.7 (C), 128.4 (CH), 128.6 (CH), 129.5 (CH), 136.2 (C), 142.8 (C), 161.9 (C), 168.7 (C) ppm; IR (KBr): ν_{max} 2940(m), 1728(s), 1638(m), 1582(s), 1538(s), 1486(m), 1363(m), 1266(m), 1097(m), 968(m), 817(m), 761(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}ClO_5$ Na 352.9954, found 352.9954.

5.5.3. Attempted Cu (1)-catalyzed chlorine atom transfer radical cyclization of the 2,2,2-trichloro-1-phenyl ethyl vinyl ether 634

This experiment was performed by the same procedure as mentioned above under section 5.5.2 for the synthesis of the tetrasubstituted 4-chlorofurans using amount (1 equiv) of CuCl/PMDETA (1:1 mol ratio).

A flame-dried two-neck round-bottom flask was charged with CuCl (0.100 g, 1.0 mmol) and degassed benzene (40 mL) under a N_2 atmosphere using Schlenk technique. PMDETA (0.2 mL, 0.173 g, 1 mmol) was injected to this suspension and the suspension stirred for 10 minutes. Next, the vinyl ether **634** (0.323 g, 1 mmol) was added and the mixture was heated at reflux. The progress of the reaction was monitored periodically by TLC which it showed appearance of few new spots on TLC plate. The starting material did not disappear even after prolonged heating of the reaction mixture for 24 h. Then the heating was stopped. The ^{1}H NMR of the crude product obtained after the usual work up of the reaction mixture showed the formation of a mixture of products along with the unreacted starting material. The purification of the crude product by column chromatography on neutral alumina column using *n*-hexane/ethyl acetate mixture (99:01-80:20, v:v) as the solvent for the elution gave a small amount of the dichloroalkene **635** (0.035 g, 20%) and the starting material **634** (0.100 g, 30%). Other products could not be separated and purified.

*(2,2-Dichlorovinyl)benzene **635.***[72,93]



635

Colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.90 (s, 1H, olefinic CH), 7.34-7.43 (m, 3H, aromatic CH), 7.56 (d, 2H, *J* = 6.9 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 121.1 (C), 128.5 (CH), 128.6

(CH), 128.7 (CH), 133.4 (C) ppm.

5.5.4. Experiments towards attempted trapping of intermediates in the CuCl/TMEDA-catalyzed cyclization of 615a

Attempted trapping of free radical intermediate 629 with alkenes and AIBN: This experiment was performed by the same procedure as mentioned above under section 5.5.2 for the synthesis of the tetrasubstituted 4-chlorofurans. Excess amount of CuCl/TMEDA (1:2 mol ratio) (60 mol%) was used to ensure complete disappearance of the starting material **615a**. Large excess of alkenes were deliberately taken to promote the trapping of the possible radical intermediate **629**. Similarly, an excess of AIBN (1 equiv) was chosen due to involvement of IBN radical to the reduction of Cu (II) to Cu (I)-complex.

A flame-dried two-neck round-bottom flask was charged with CuCl (0.060 g, 0.6 mmol) and degassed benzene (40 mL) under a N_2 atmosphere using Schlenk technique. TMEDA (0.18 mL, 0.139 g, 1.2 mmol) was injected to this suspension and the suspension stirred for 10 minutes. Next, the vinyl ether **615a** (0.367 g, 1 mmol) and AIBN (0.137 g, 1 mmol) or styrene (1.15 mL, 1.041 g, 10 mmol) or methyl acrylate (0.9 mL, 0.861 g, 10 mmol) were added and the mixture was heated at reflux. In the case of alkenes, the formation of the polymeric material along the wall of the round bottom flask was observed. After the disappearance of the starting material as indicated by TLC, the reaction mixture was cooled and ethyl acetate (100 mL) was added. The resulting solution was washed with brine (3x25 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The purification of the

residual mass by column chromatography on a small pad of neutral alumina column using *n*-hexane/ethyl acetate mixture (90:10 to 80:20, v:v) as the solvent for elution gave the chlorofuran **616a** (0.220 g, 76%, in the case of AIBN) or (0.212 g, 72%, in the case of methyl acrylate) or (0.217 g, 74% in the case of styrene).

Attempted trapping of the carbocationic intermediate 637 with ethanol: This experiment was performed by the same procedure as mentioned for the synthesis of the tetrasubstituted 4-chlorofurans under section 5.5.2. Excess catalyst was taken to ensure complete disappearance of the starting material **615a.**

A flame-dried two-neck round-bottom flask was charged with CuCl (0.100 g, 1 mmol) and degassed dry DCE (24 mL) under a nitrogen atmosphere using Schlenk technique. TMEDA (0.20 mL, 0.173 g, 2 mmol) and vinyl ether **615a** (0.367 g, 1 mmol) were added to the suspension and stirred for 10 min. Next, ethanol (6 mL) was injected and the mixture was heated at reflux. Periodic monitoring of the reaction by TLC showed development of many spots. After disappearance of the starting material as indicated by TLC (24 h), the solvent of the reaction mixture was evaporated and ethyl acetate (100 mL) was added to the residual mass. Uusual work up gave the crude product, the ^{1}H NMR of which indicated the formation of a complex mixture of products. Attempts to separate the products by column chromatography gave a small amount of the the chlorofuran **616a** (0.038 g, 13%) and the dichloroalkene **635** (0.032 g, 18%). Other products could not be separated and purified.

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Appendix

(NMR Spectra)

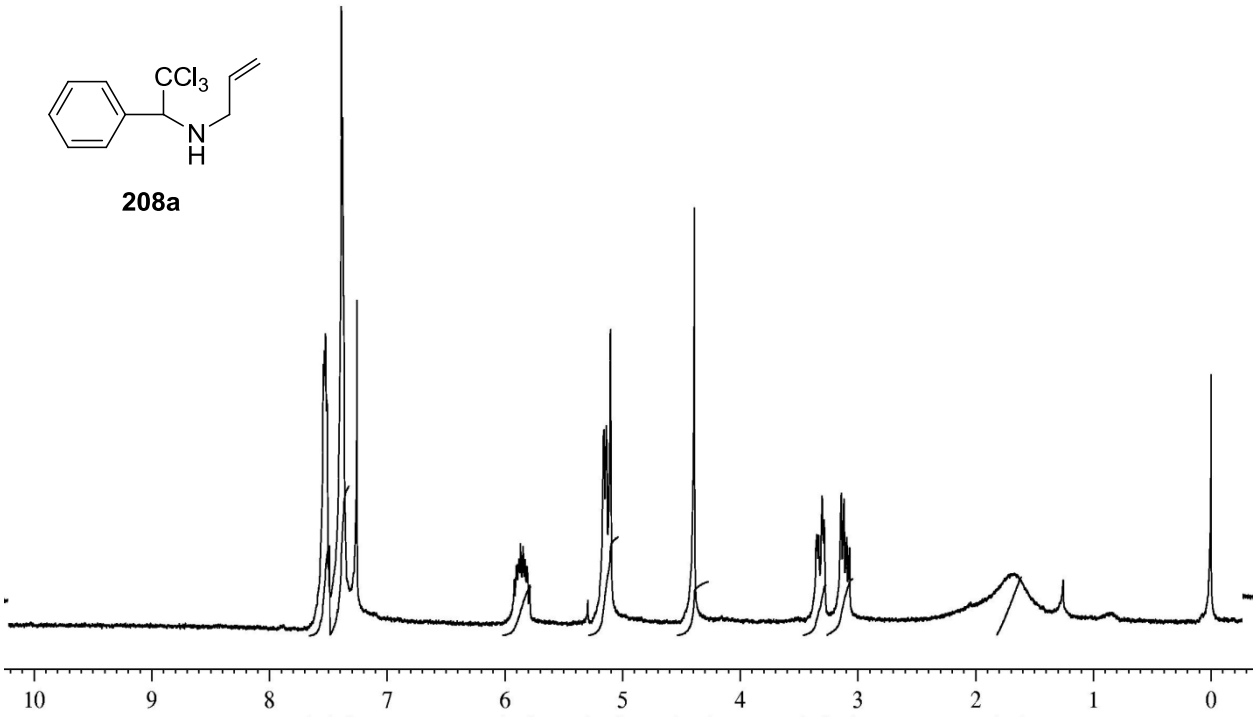


Fig. 37 ^{1}H NMR Spectrum of *N*-(2,2,2-trichloro-1-phenylethyl)prop-2-en-1-amine 208a

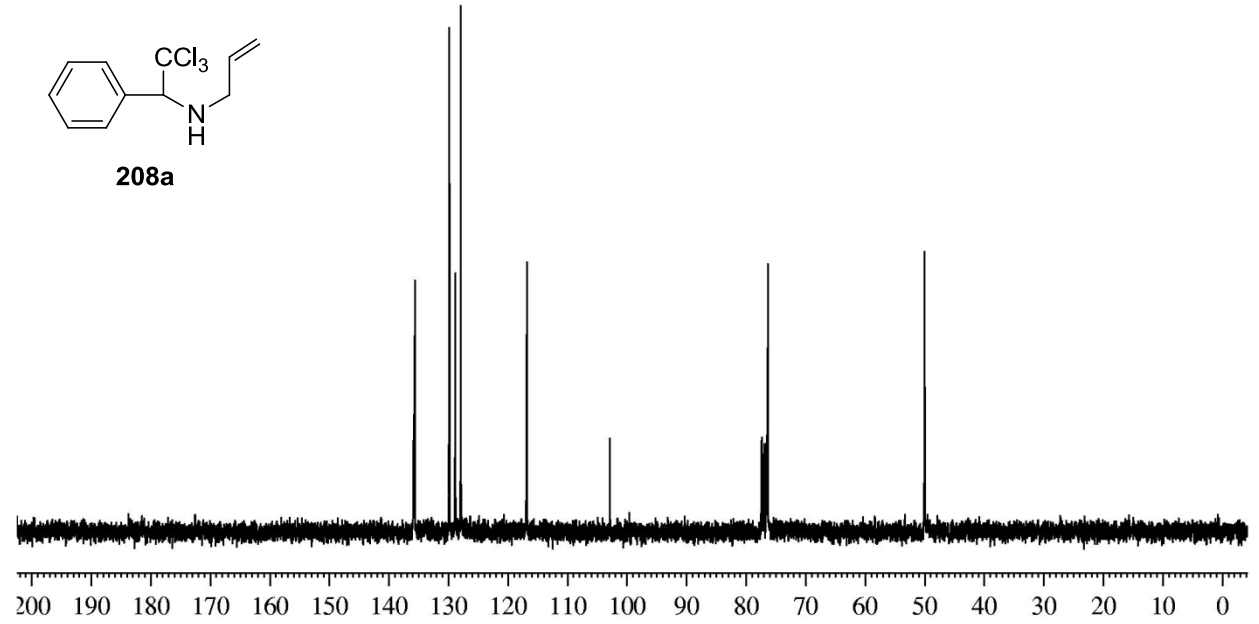


Fig. 38 ^{13}C{^{1}H} NMR Spectrum of *N*-(2,2,2-trichloro-1-phenylethyl)prop-2-en-1-amine 208a

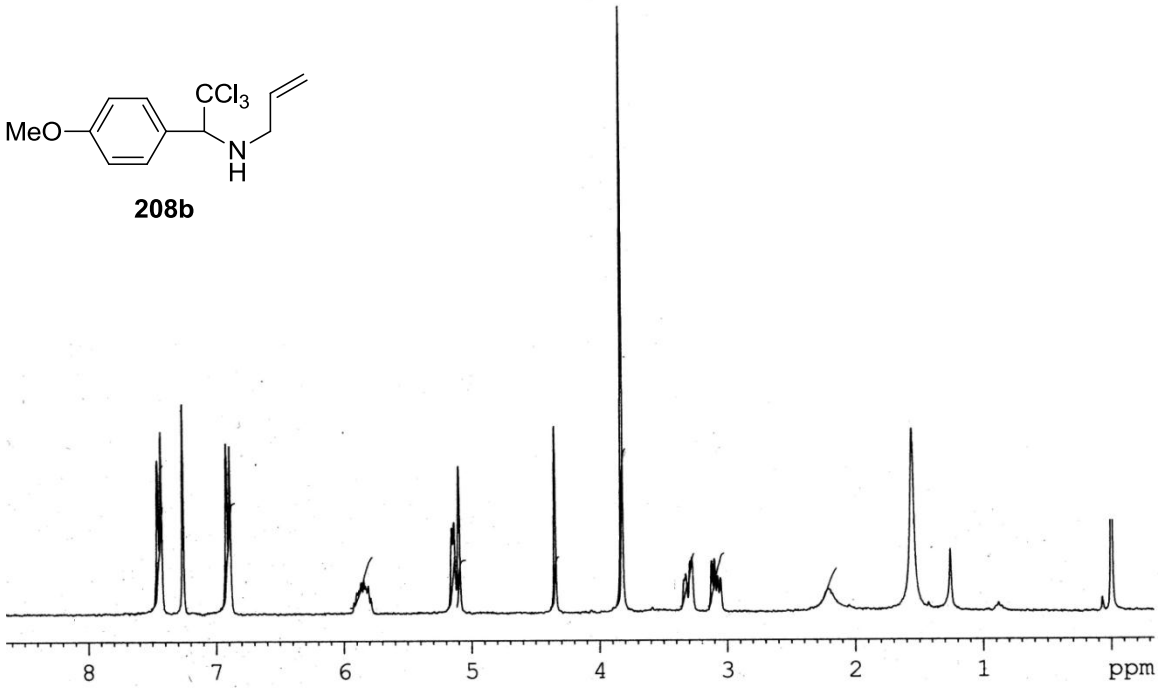


Fig. 39 ^{1}H NMR Spectrum of *N*-(2,2,2-trichloro-1-(4-methoxyphenyl)ethyl)prop-2-en-1-amine 208b

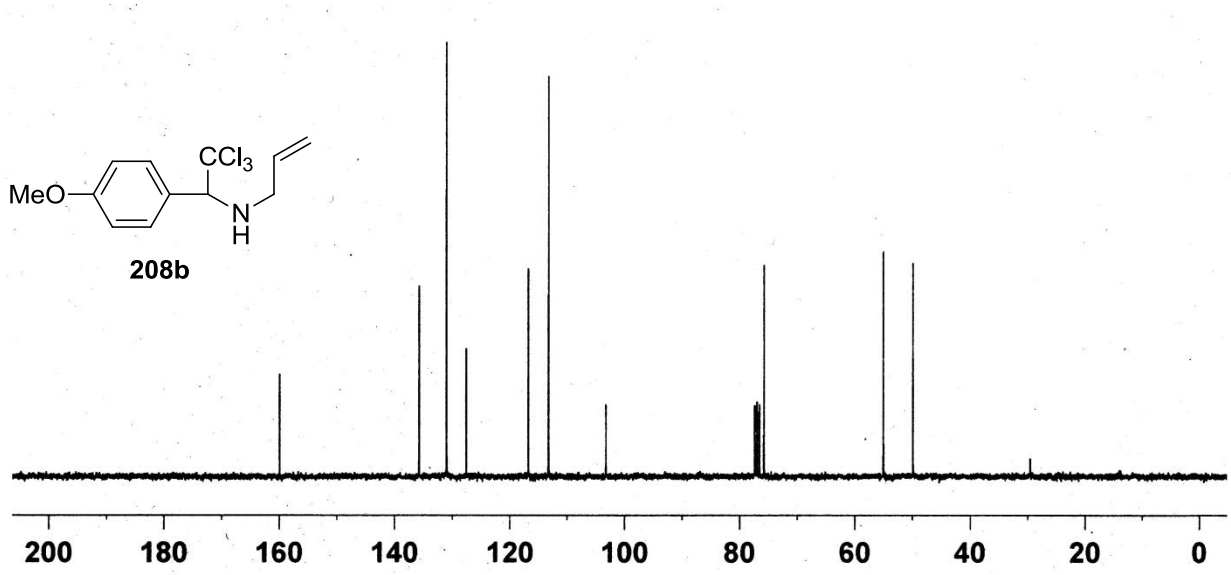


Fig. 40 ^{13}C{^{1}H} NMR Spectrum of *N*-(2,2,2-trichloro-1-(4-methoxyphenyl)ethyl)prop-2-en-1-amine 208b

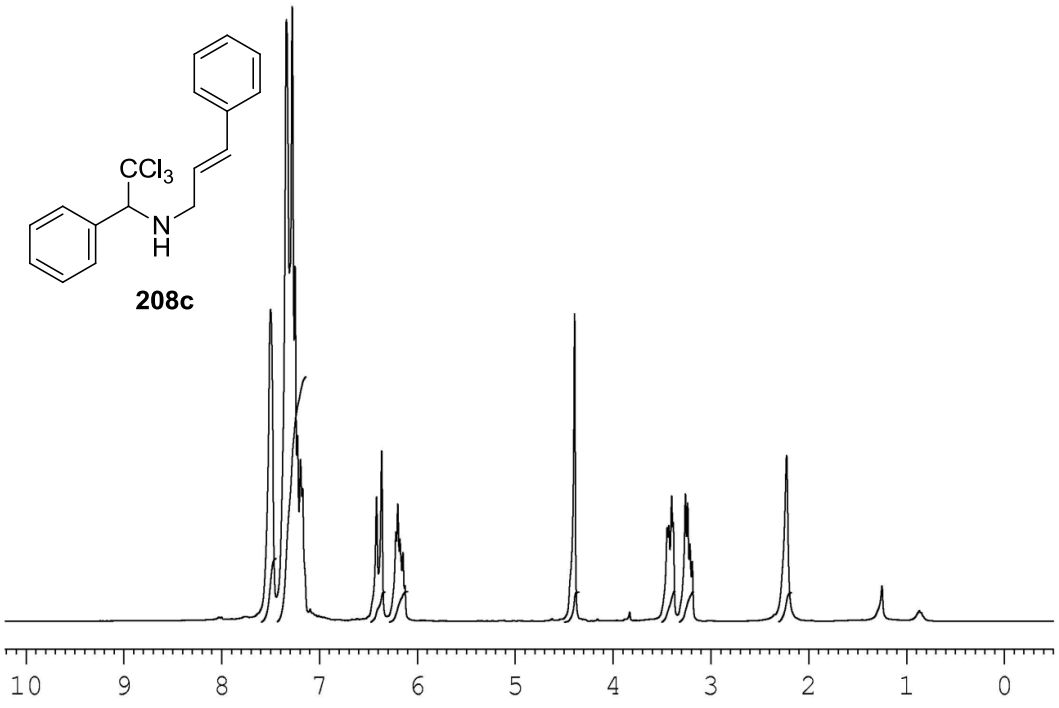


Fig. 41 ^{1}H NMR Spectrum of 3-phenyl-*N*-(2,2,2-trichloro-1-phenylethyl)prop-2-en-1-amine 208c

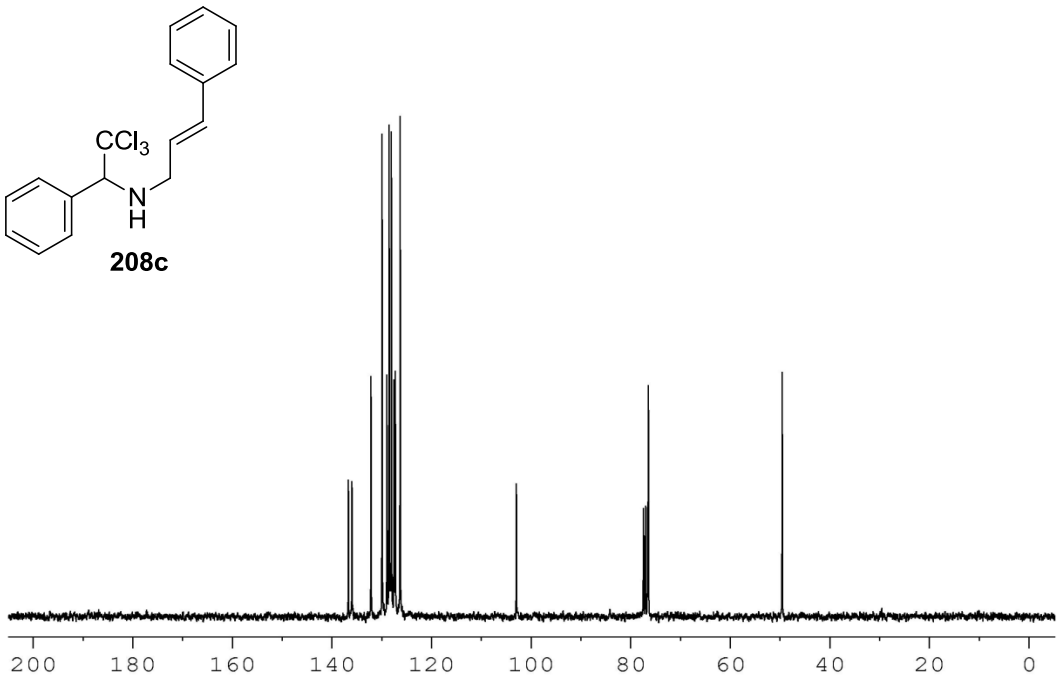


Fig. 42 ^{13}C{^{1}H} NMR Spectrum of 3-phenyl-*N*-(2,2,2-trichloro-1-phenylethyl)prop-2-en-1-amine 208c

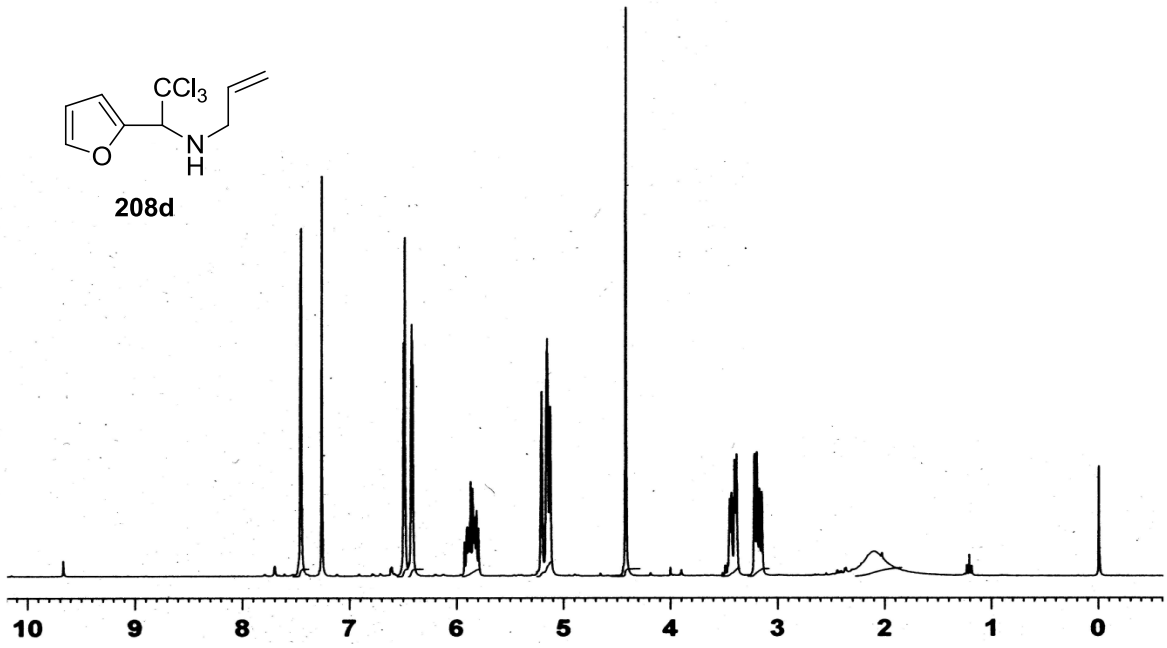


Fig. 43 ^{1}H NMR Spectrum of *N*-(2,2,2-trichloro-1-(furan-2-yl)ethyl)prop-2-en-1-amine 208d

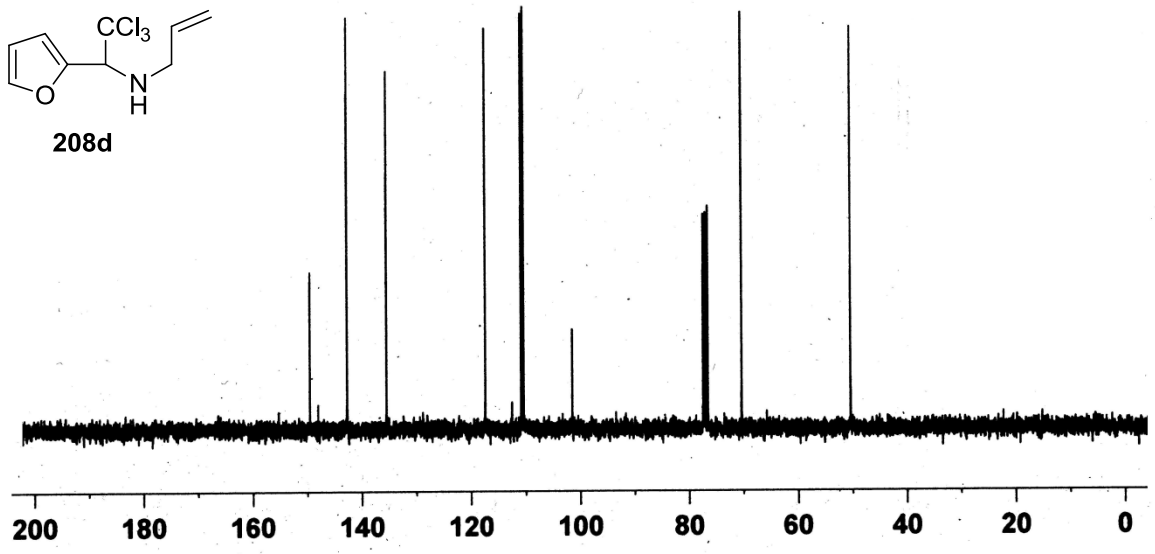


Fig. 44 ^{13}C{^{1}H} NMR Spectrum of *N*-(2,2,2-trichloro-1-(furan-2-yl)ethyl)prop-2-en-1-amine 208d

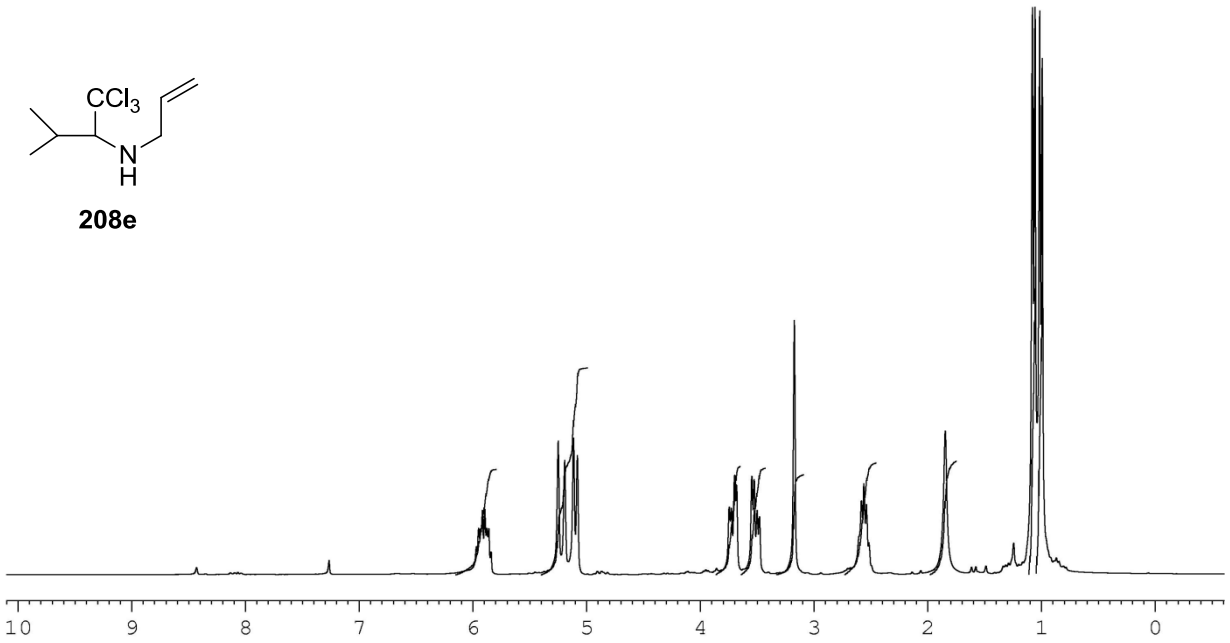


Fig. 45 ^{1}H NMR Spectrum of *N*-allyl-1,1,1-trichloro-3-methylbutan-2-amine 208e

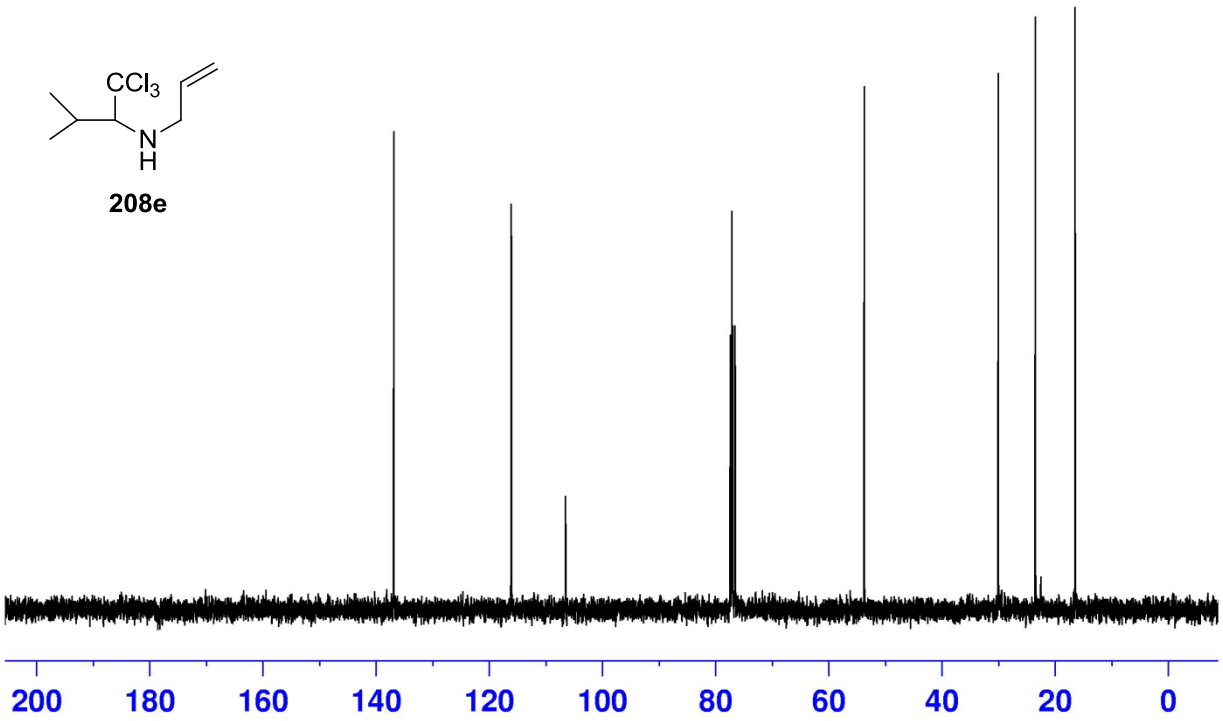


Fig. 46 ^{13}C{^{1}H} NMR Spectrum of *N*-allyl-1,1,1-trichloro-3-methylbutan-2-amine 208e

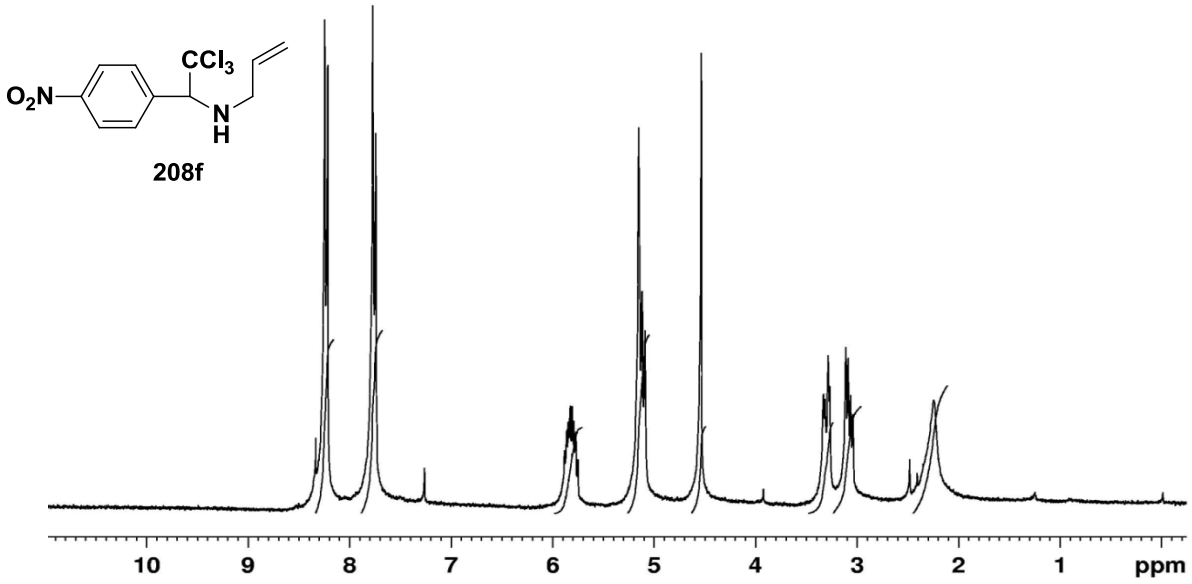


Fig. 47 ^{1}H NMR Spectrum of *N*-(2,2,2-trichloro-1-(4-nitrophenyl)ethyl)prop-2-en-1-amine 208f

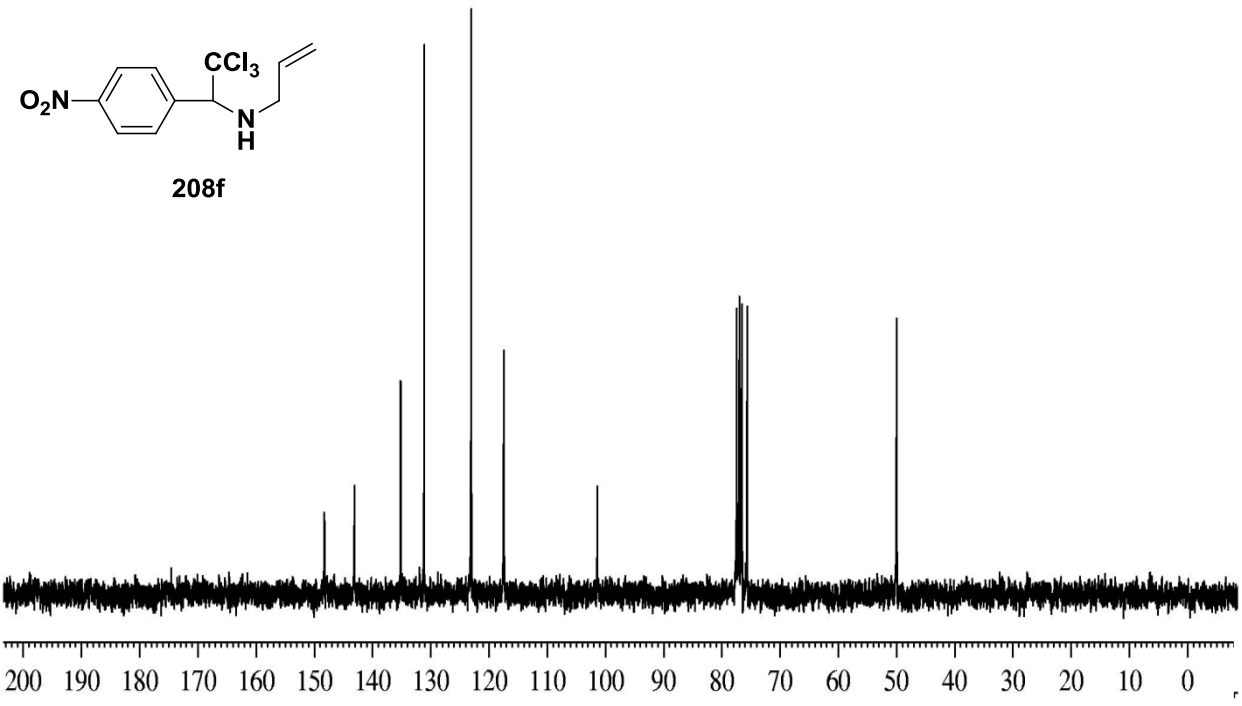


Fig. 48 ^{13}C{^{1}H} NMR Spectrum of *N*-(2,2,2-trichloro-1-(4-nitrophenyl)ethyl)prop-2-en-1-amine 208f

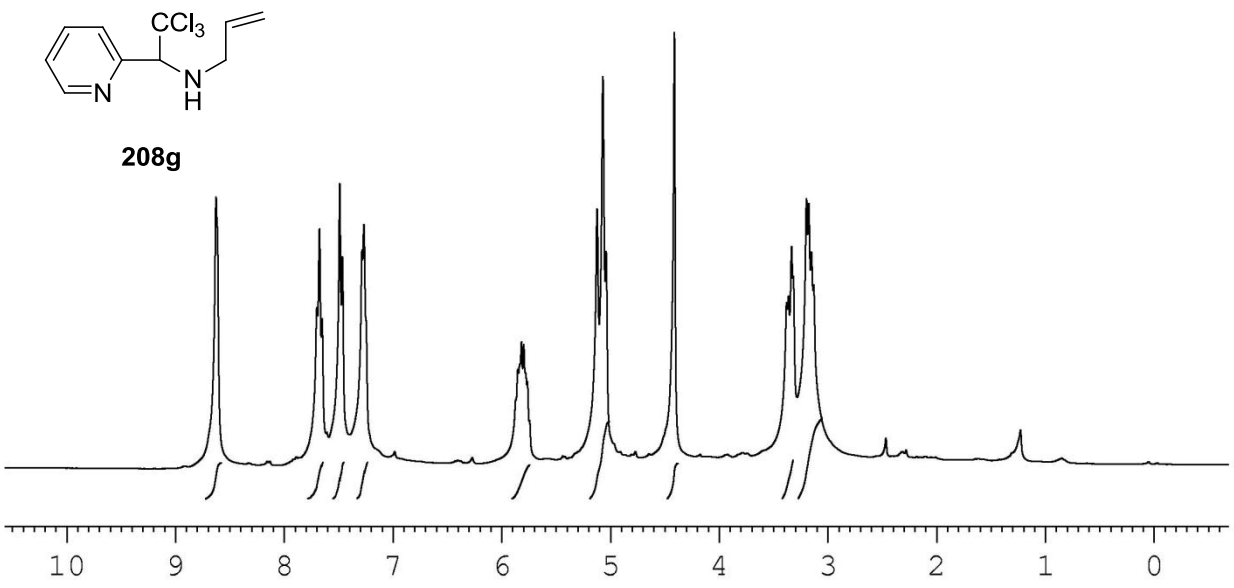


Fig. 49 ^{1}H NMR Spectrum of *N*-(2,2,2-trichloro-1-(pyridin-2-yl)ethyl)prop-2-en-1-amine 208g

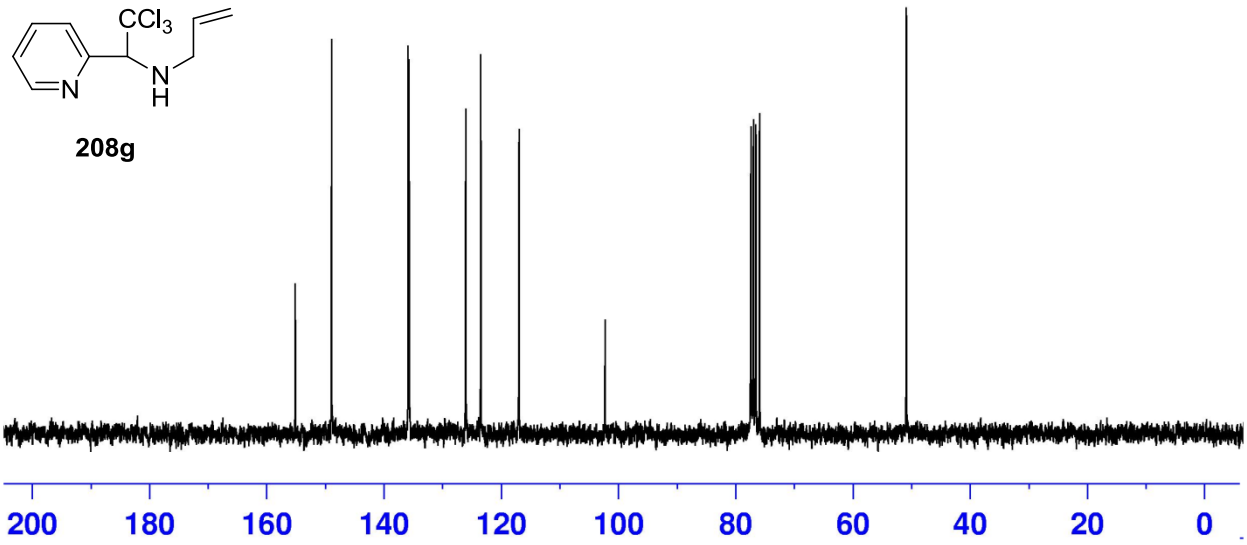


Fig. 50 ^{13}C{^{1}H} NMR Spectrum of *N*-(2,2,2-Trichloro-1-(pyridin-2-yl)ethyl)prop-2-en-1-amine 208g

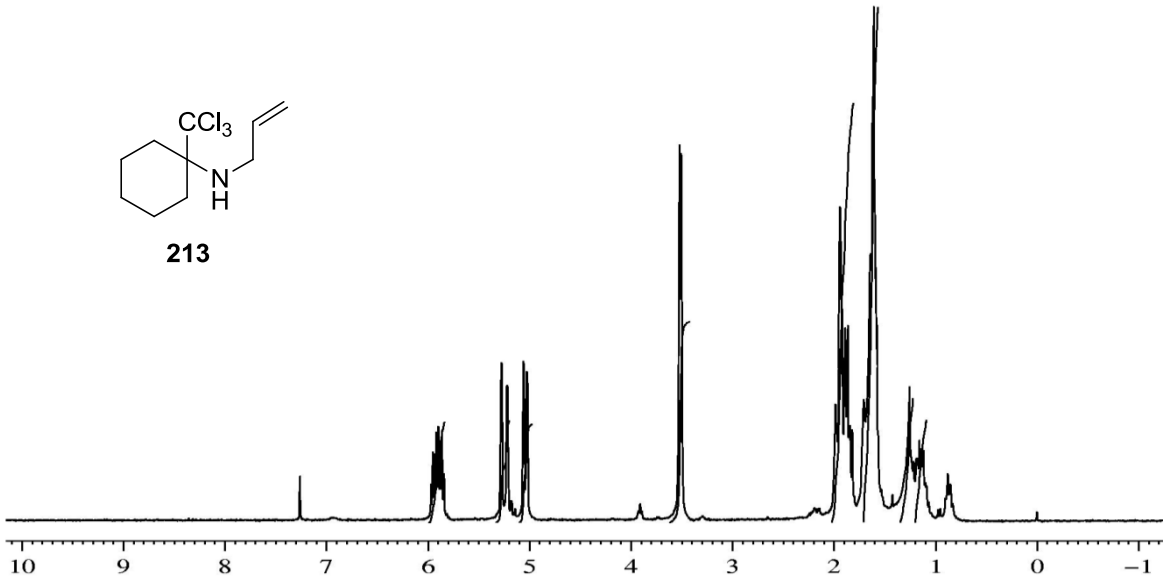


Fig. 51 ^{1}H NMR Spectrum of *N*-allyl-1-(trichloromethyl) cyclohexanamine 213

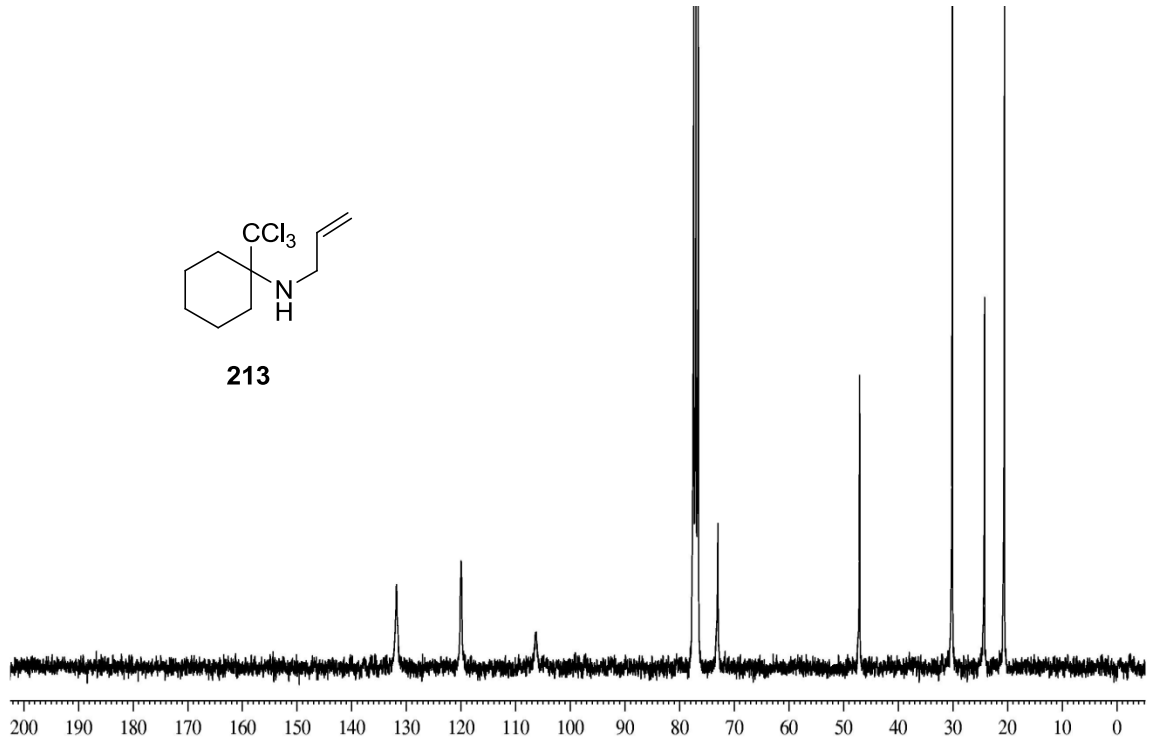


Fig. 52 ^{13}C{^{1}H} NMR Spectrum of *N*-allyl-1-(trichloromethyl) cyclohexanamine 213

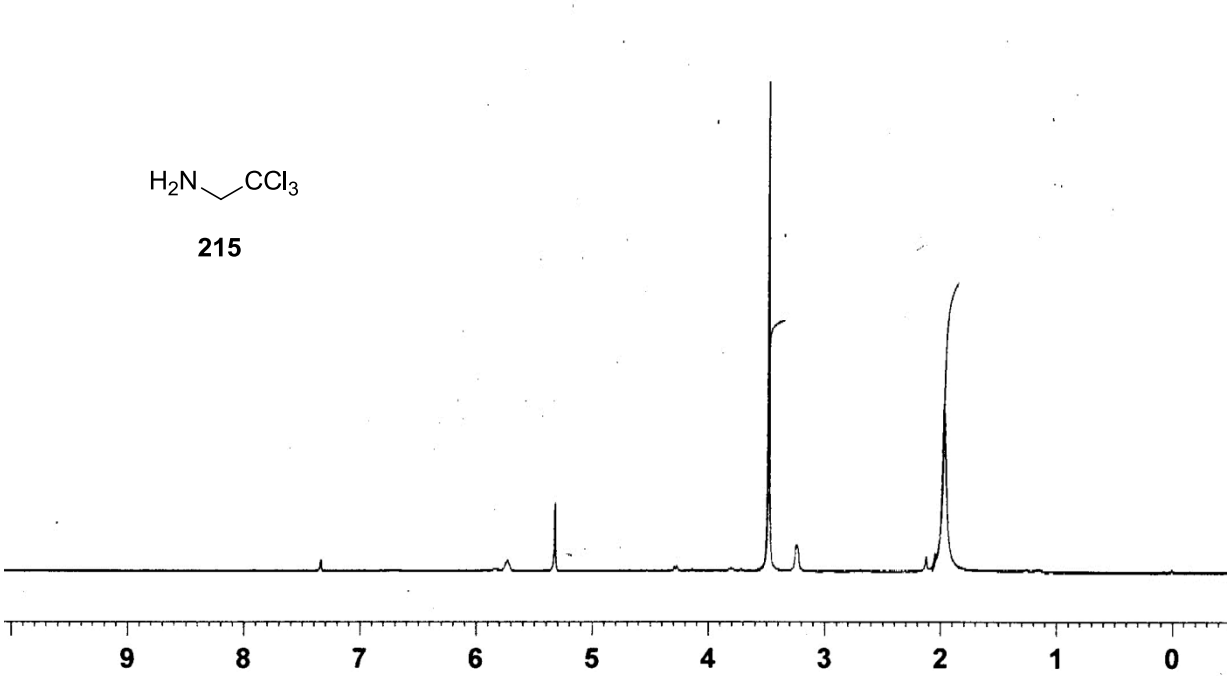


Fig. 53 ^{1}H NMR spectrum of 2,2,2-trichloroethanamine 215

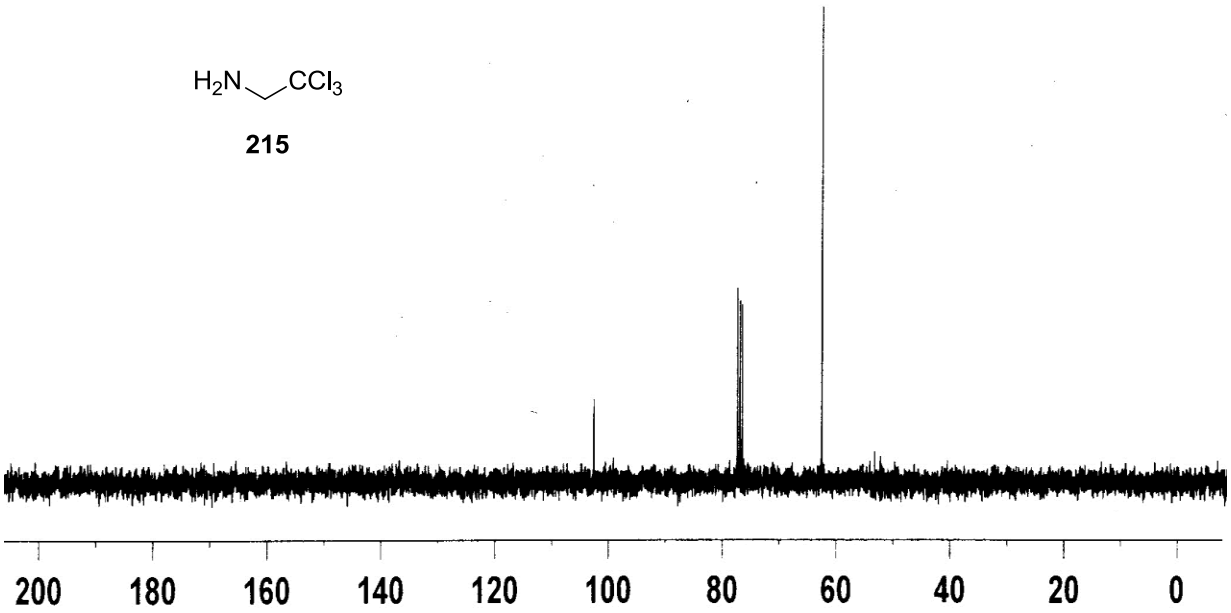


Fig. 54 ^{13}C{^{1}H} NMR spectrum of 2,2,2-trichloroethanamine 215

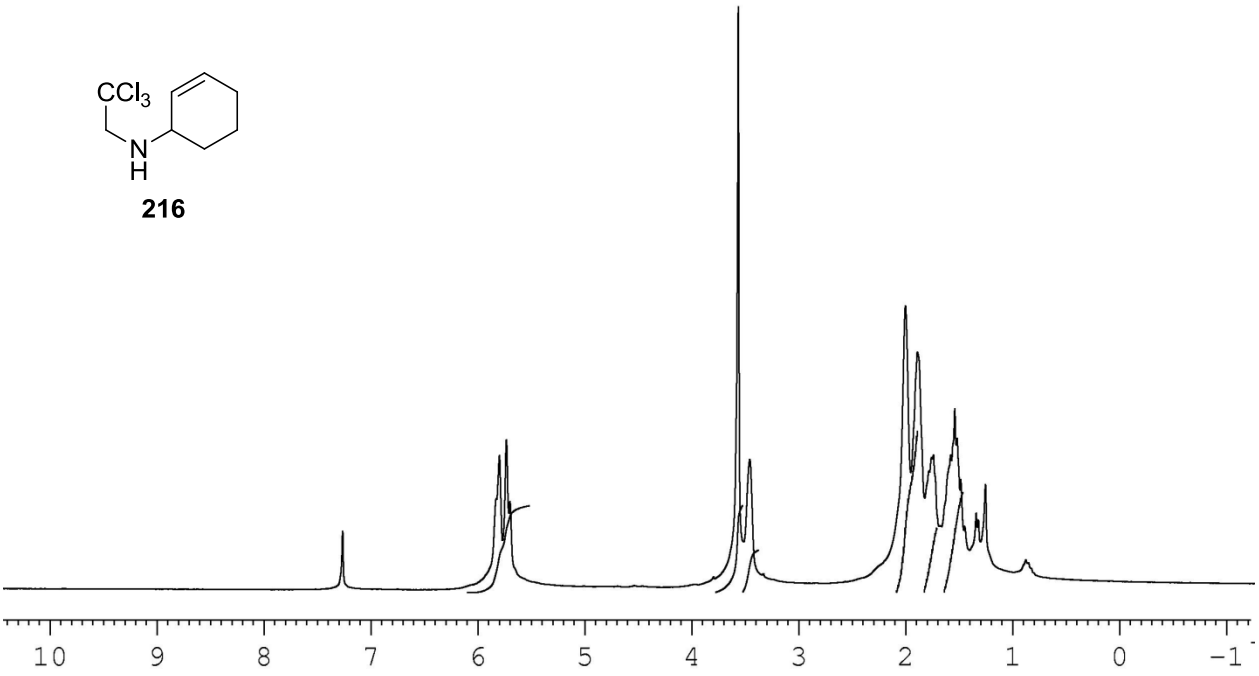


Fig. 55 ^{1}H NMR Spectrum of *N*-(2,2,2-trichloroethyl)cyclohex-2-enamine 216

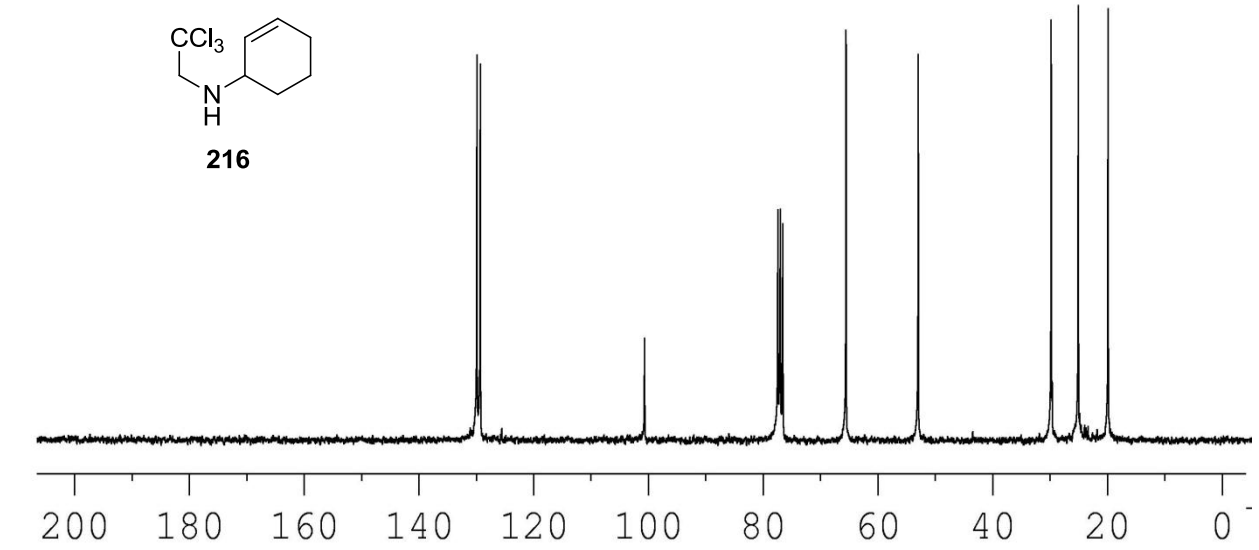


Fig. 56 ^{13}C{^{1}H} NMR Spectrum of *N*-(2,2,2-trichloroethyl)cyclohex-2-enamine 216

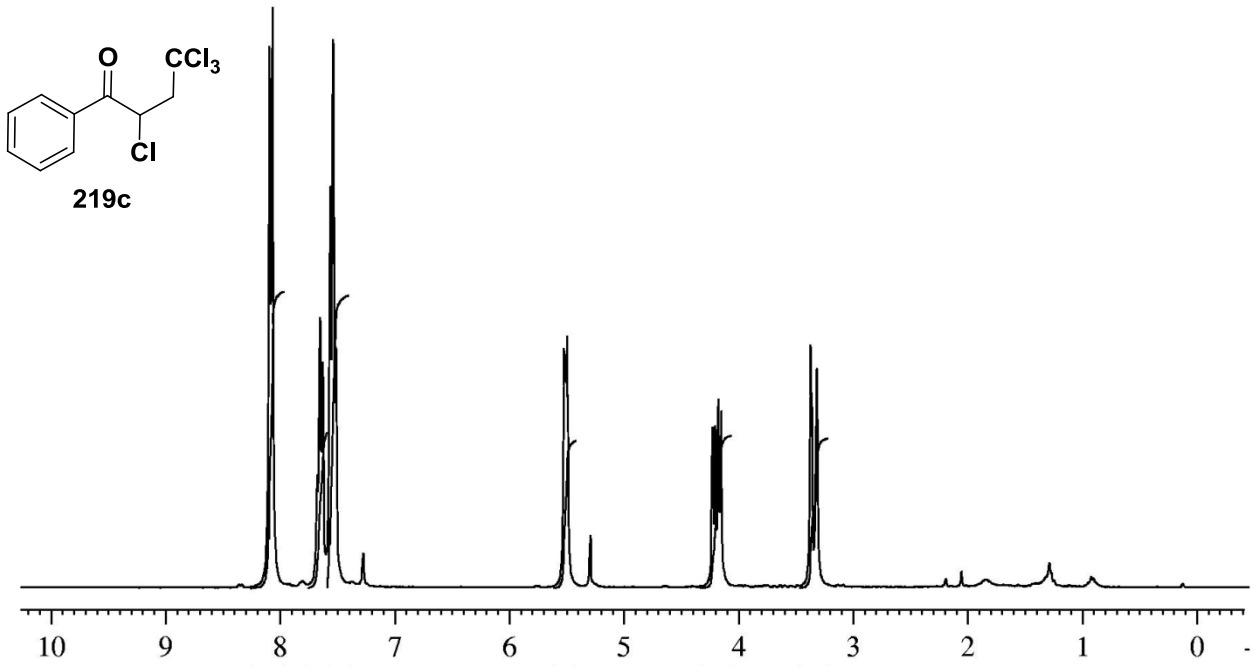


Fig. 57 ^{1}H NMR Spectrum of 2,4,4,4-tetrachloro-1-phenylbutan-1-one 219c

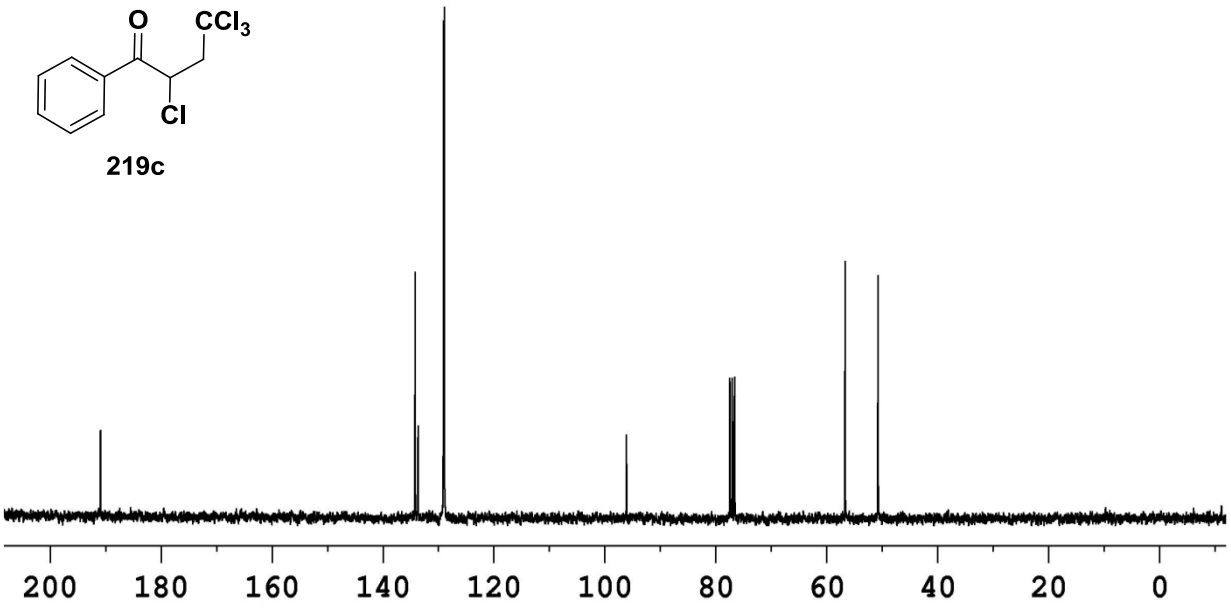


Fig. 58 ^{13}C{^{1}H} NMR Spectrum of 2,4,4,4-tetrachloro-1-phenylbutan-1-one 219c

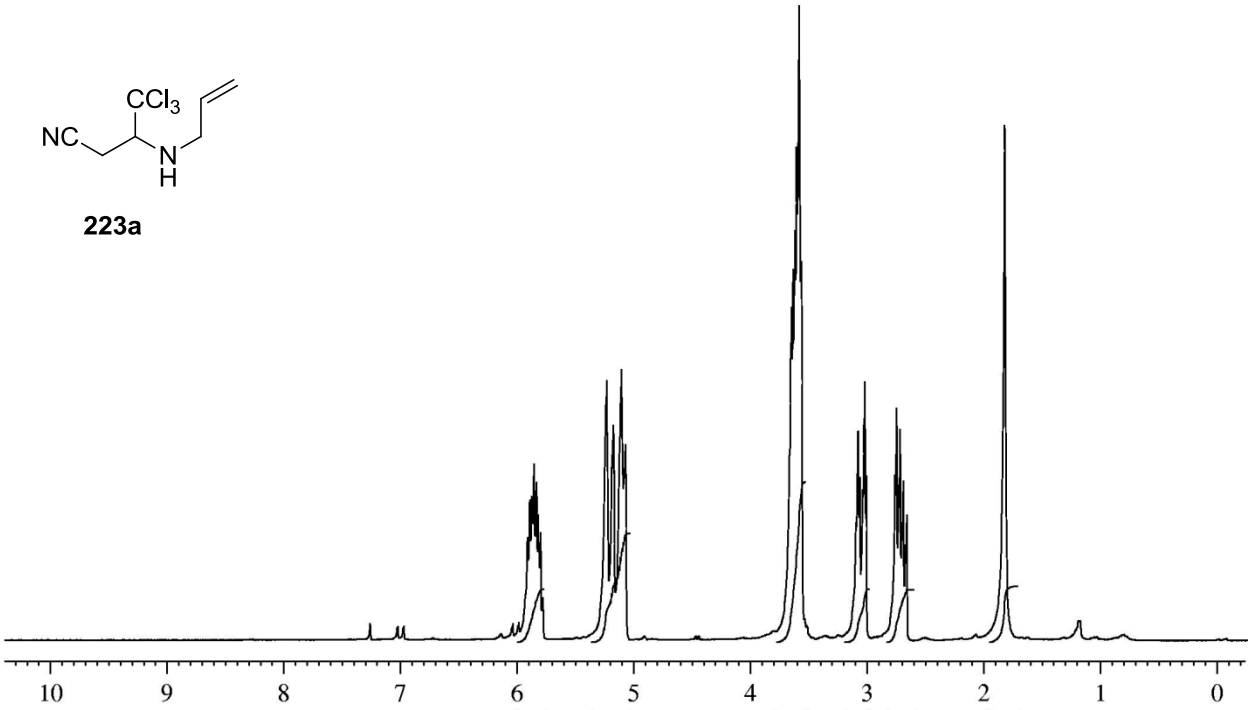


Fig. 59 ^{1}H NMR Spectrum of 3-(allylamino)-4,4,4-trichlorobutanenitrile 223a

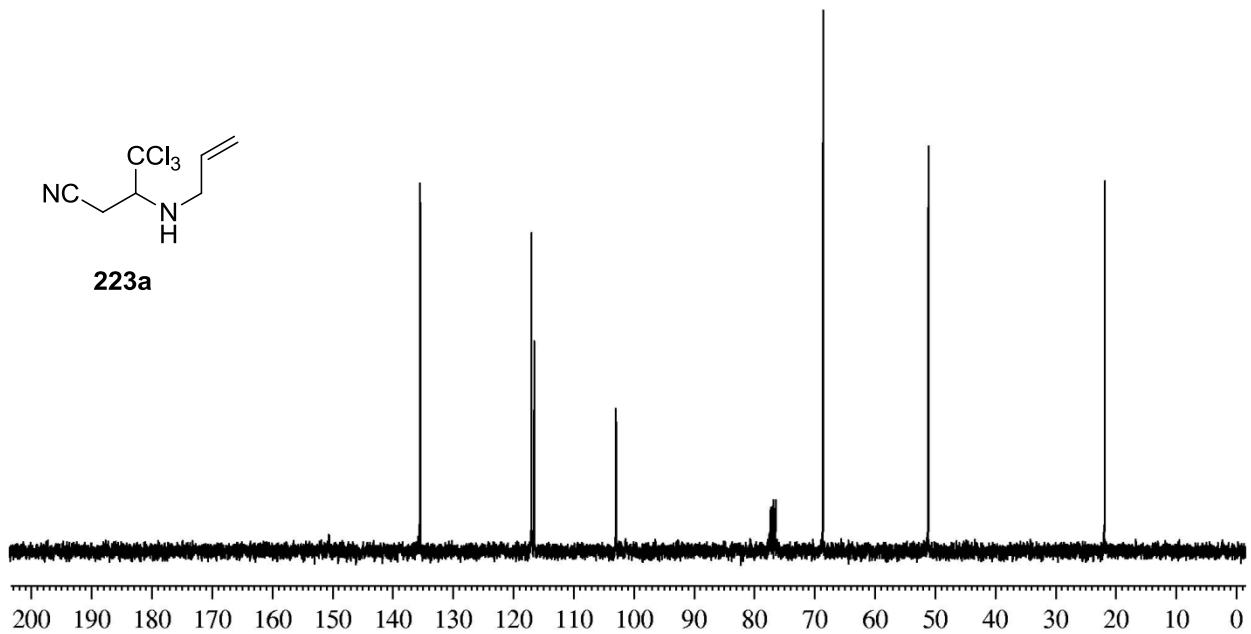


Fig. 60 ^{13}C{^{1}H} NMR Spectrum of 3-(allylamino)-4,4,4-trichlorobutanenitrile 223a

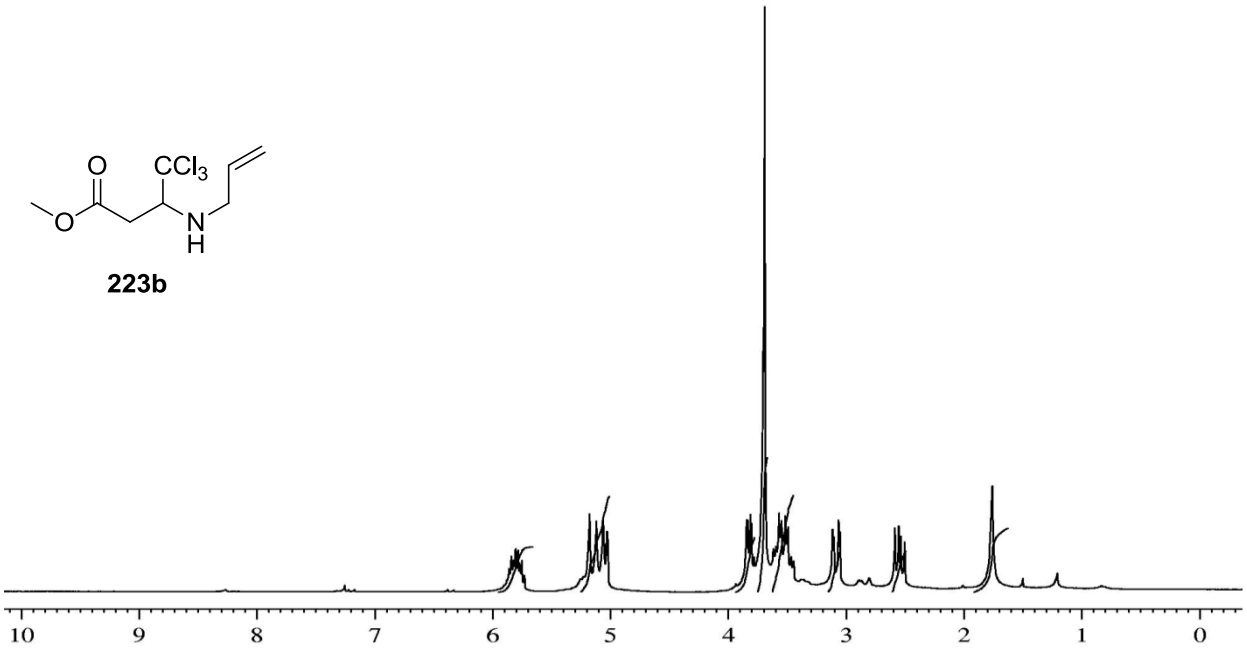


Fig. 61 ^{1}H NMR Spectrum of Methyl 3-(allylamino)-4,4,4-trichlorobutanoate 223b

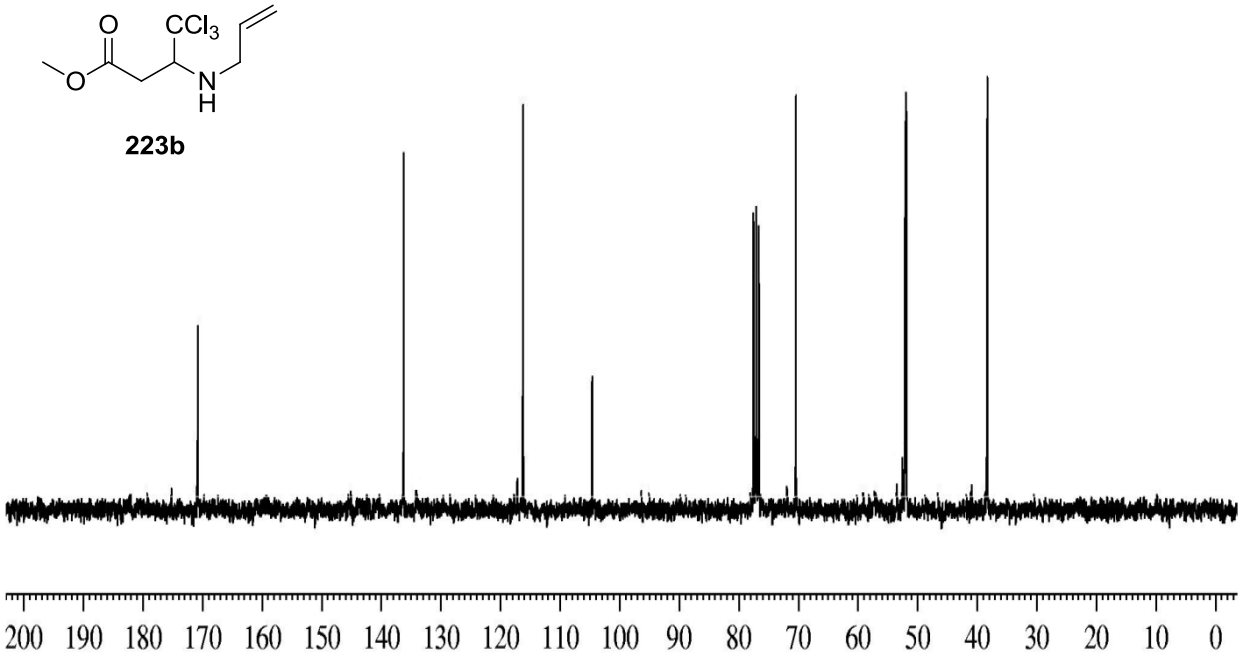


Fig. 62 ^{13}C{^{1}H} NMR Spectrum of methyl 3-(allylamino)-4,4,4-trichlorobutanoate 223b

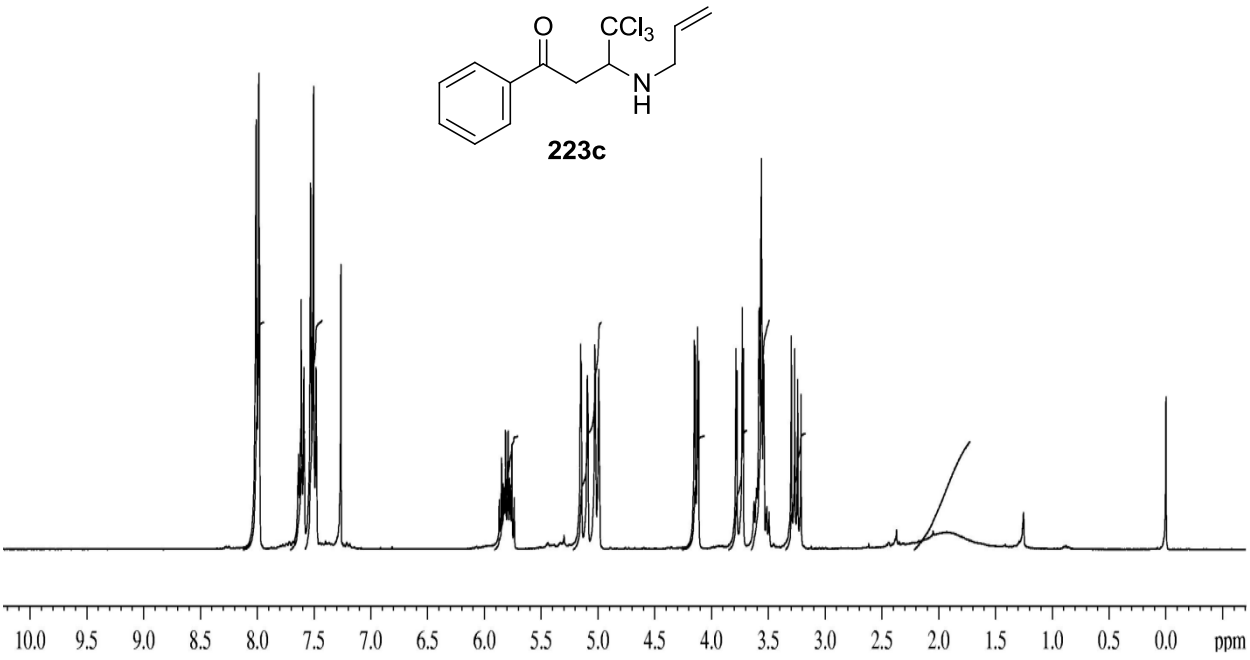


Fig. 63 ^{1}H NMR Spectrum of 3-(allylamino)-4,4,4-trichloro-1-phenylbutan-1-one 223c

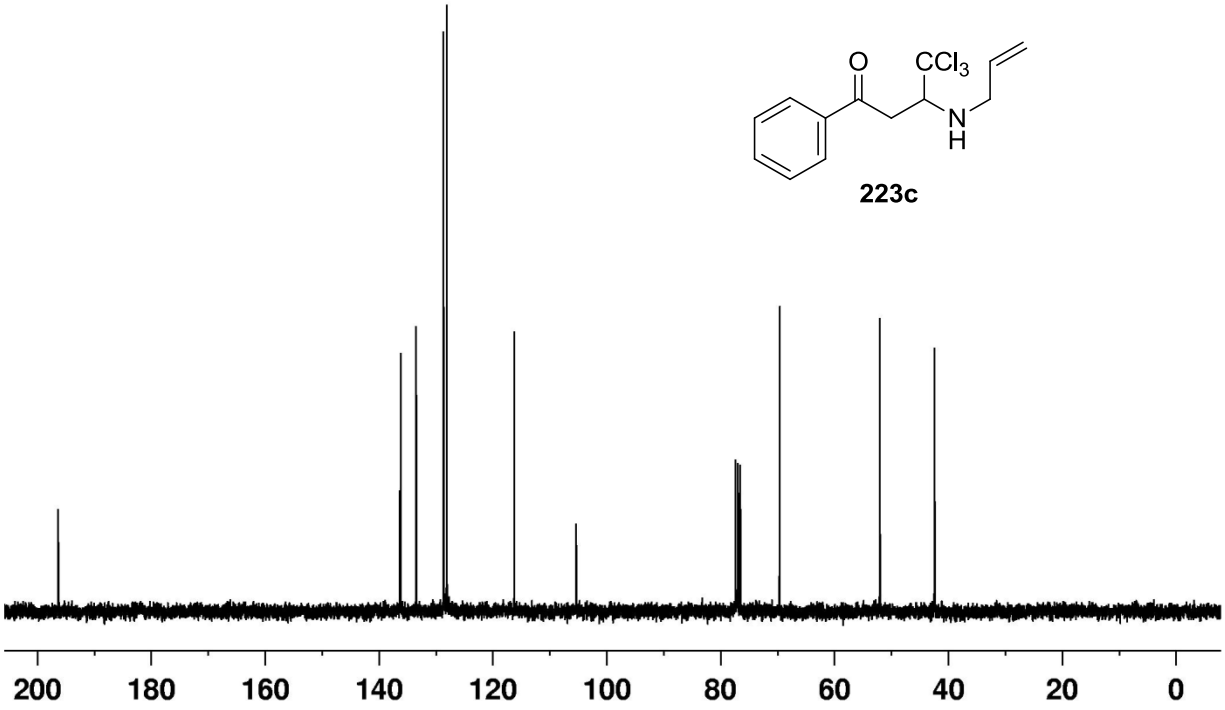


Fig. 64 ^{13}C{^{1}H} NMR Spectrum of 3-(allylamino)-4,4,4-trichloro-1-phenylbutan-1-one 223c

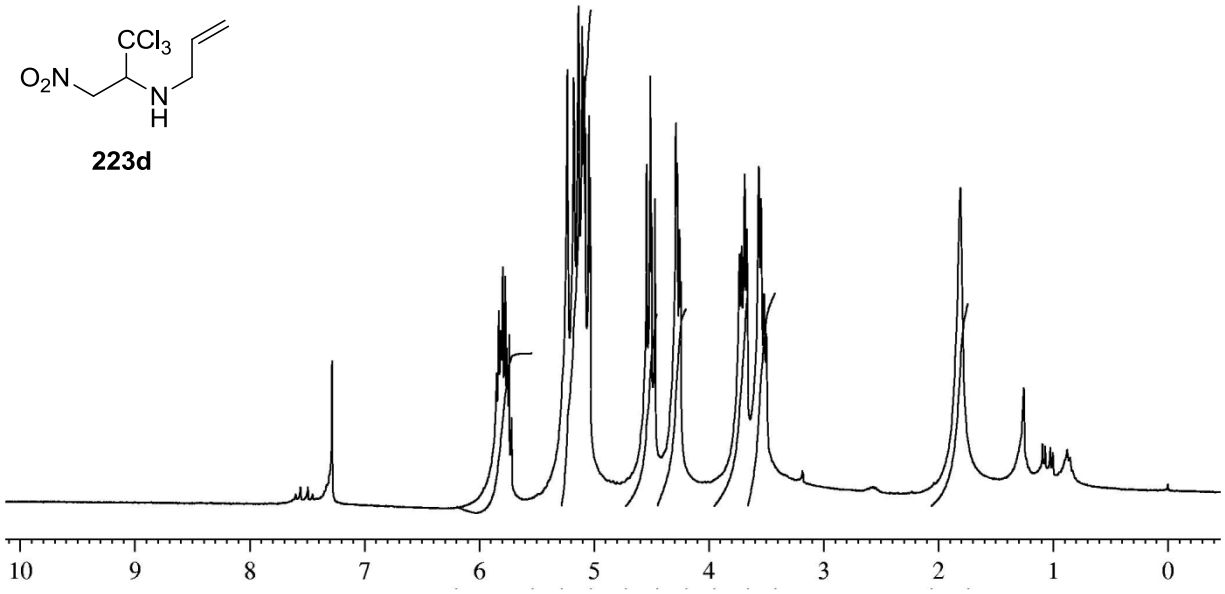


Fig. 65 ^{1}H NMR Spectrum of *N*-(1,1,1-trichloro-3-nitropropan-2-yl)prop-2-en-1-amine 223d

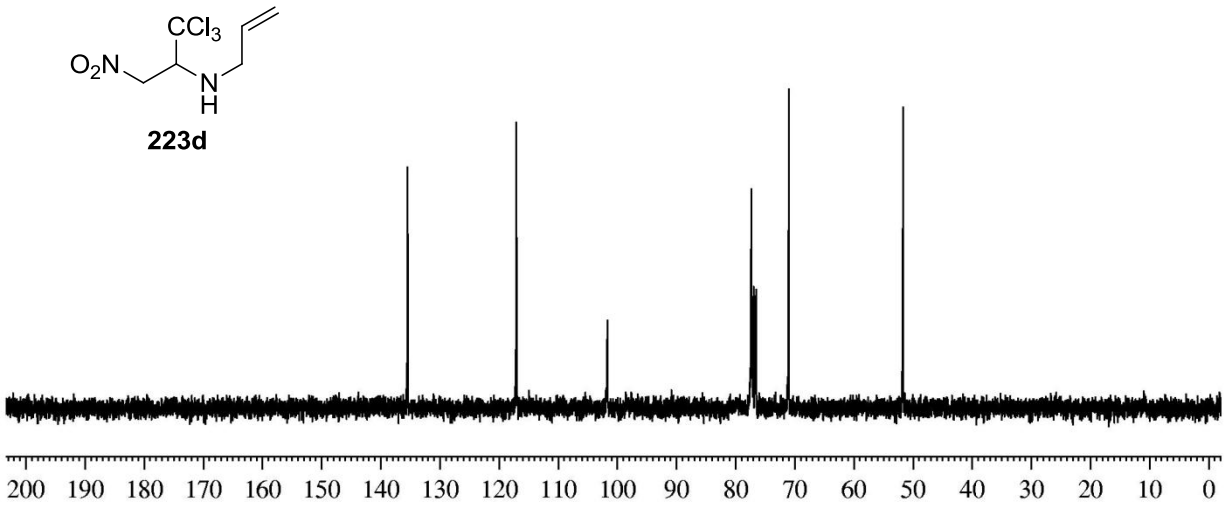


Fig. 66 ^{13}C{^{1}H} NMR Spectrum of *N*-(1,1,1-trichloro-3-nitropropan-2-yl)prop-2-en-1-amine 223d

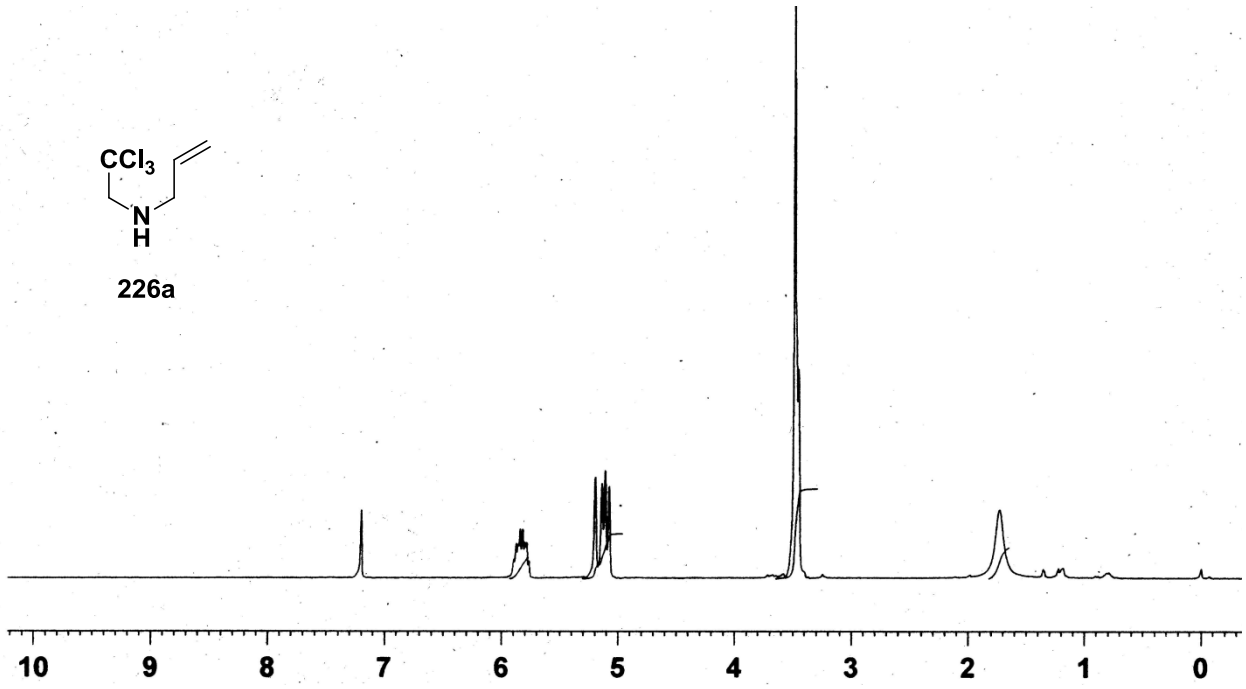


Fig. 67 ^{1}H NMR Spectrum of *N*-(2,2,2-trichloroethyl) prop-2-en-1-amine 226a

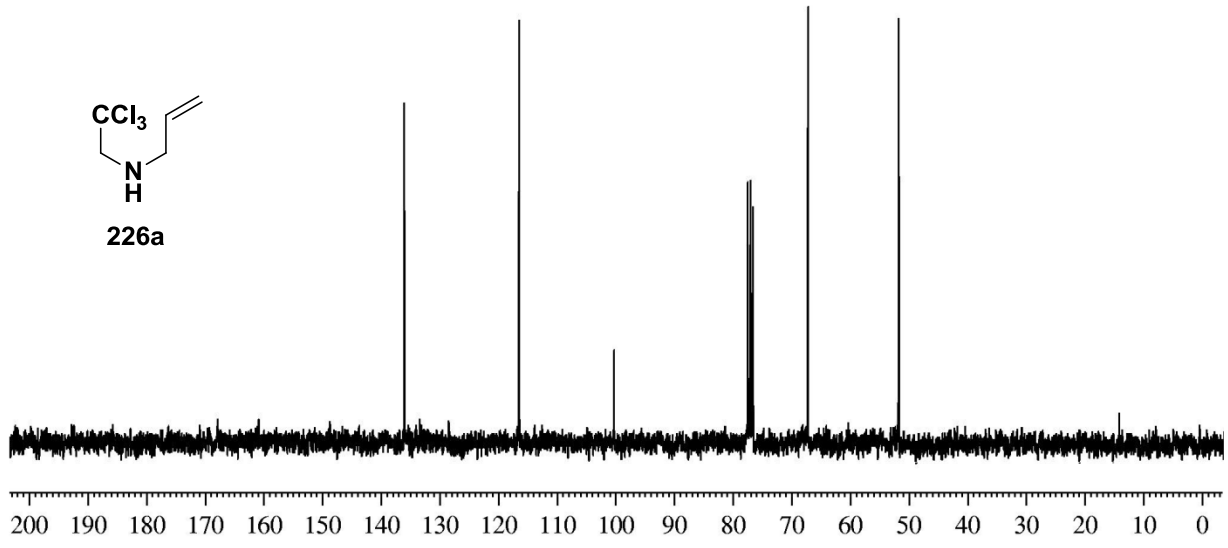


Fig. 68 ^{13}C{^{1}H} NMR Spectrum of *N*-(2, 2,2-trichloroethyl) prop-2-en-1-amine 226a

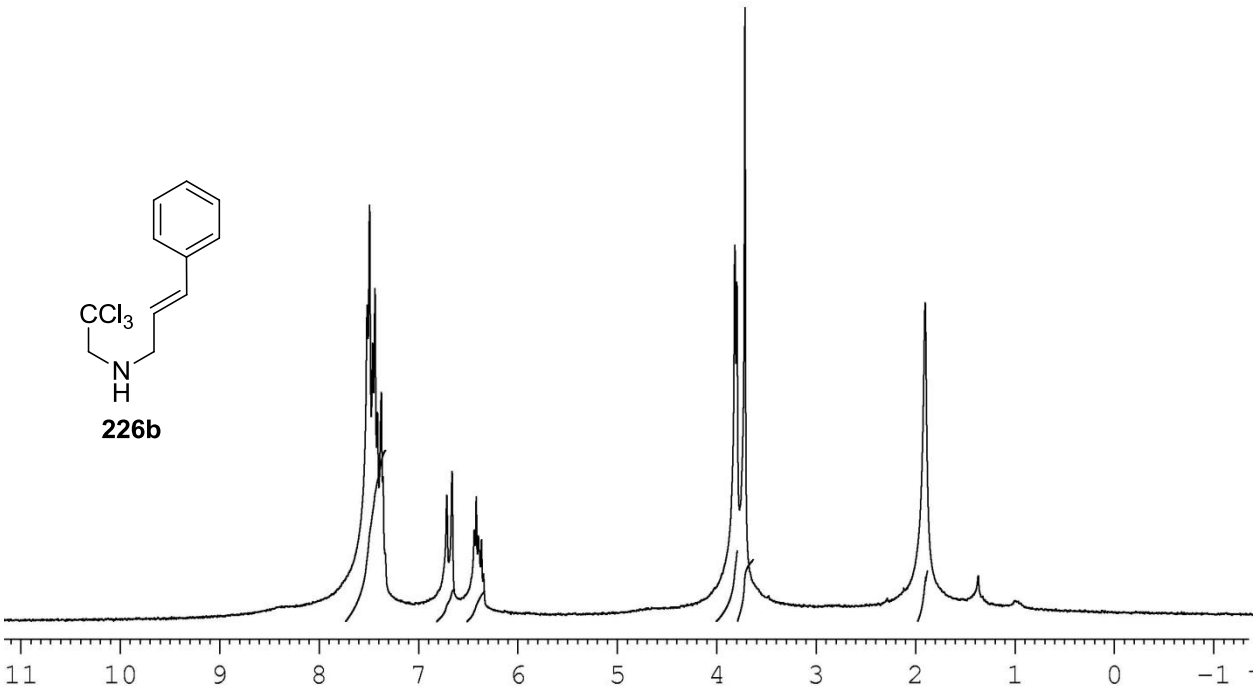


Fig. 69 ^{1}H NMR Spectrum of 3-phenyl-*N*-(2,2,2-trichloroethyl) prop-2-en-1-amine 226b

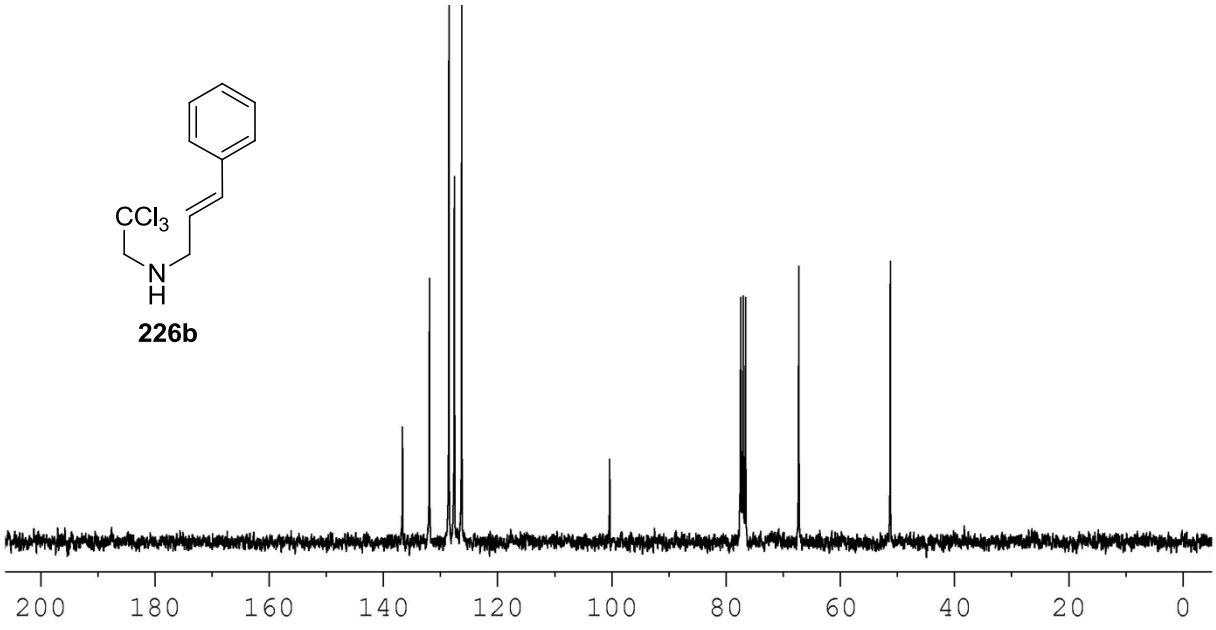


Fig. 70 ^{13}C{^{1}H} NMR Spectrum of 3-phenyl-*N*-(2,2,2-trichloroethyl) prop-2-en-1-amine 226b

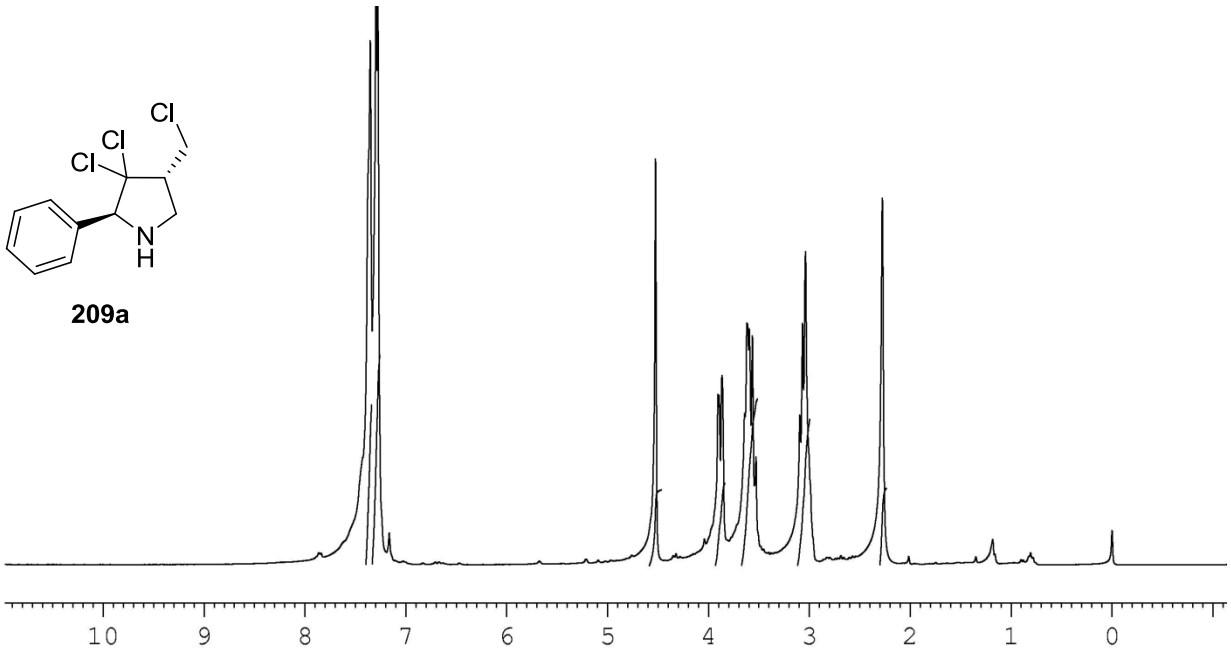


Fig. 71 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-phenylpyrrolidine 209a

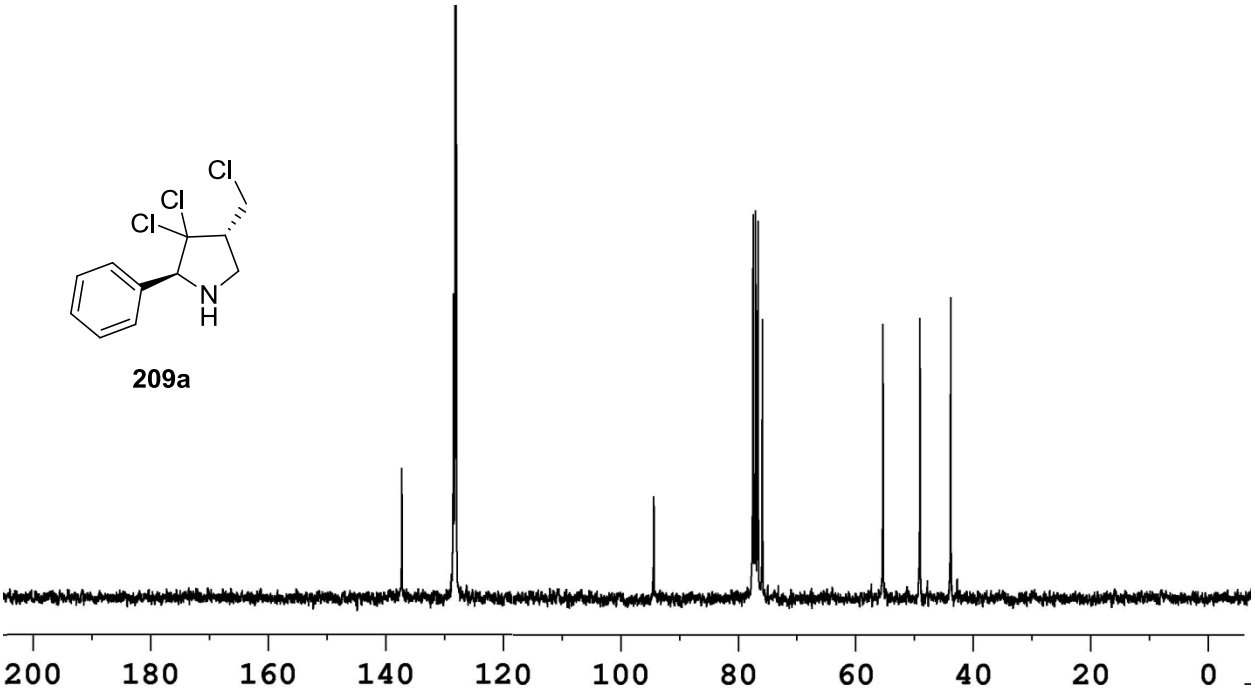


Fig. 72 ^{13}C{^{1}H} NMR spectrum of 3,3-dichloro-4-(chloromethyl)-2-phenylpyrrolidine 209a

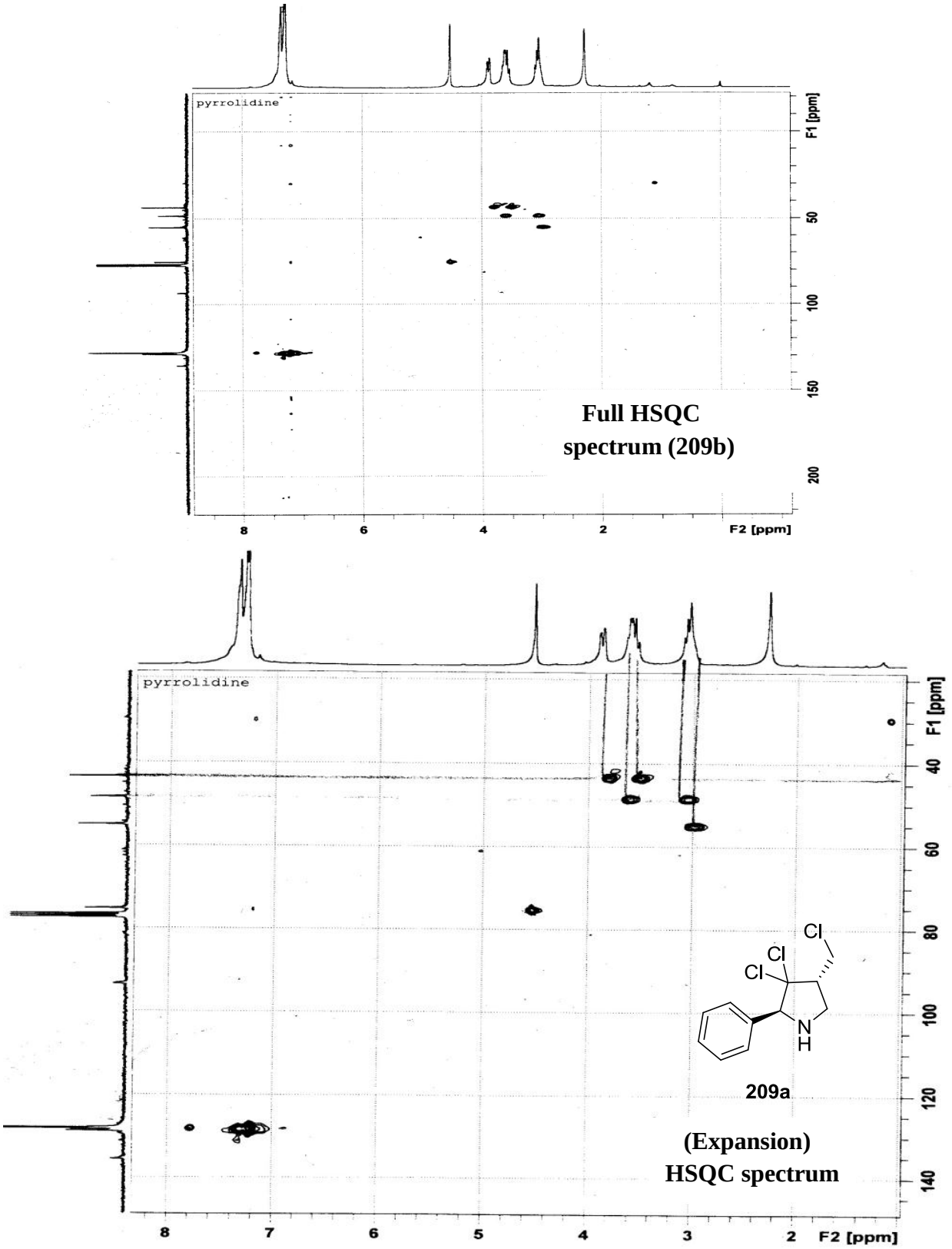


Fig. 73 HSQC Spectrum of 3,3-dichloro-4-(chloromethyl)-2-phenylpyrrolidine 209a

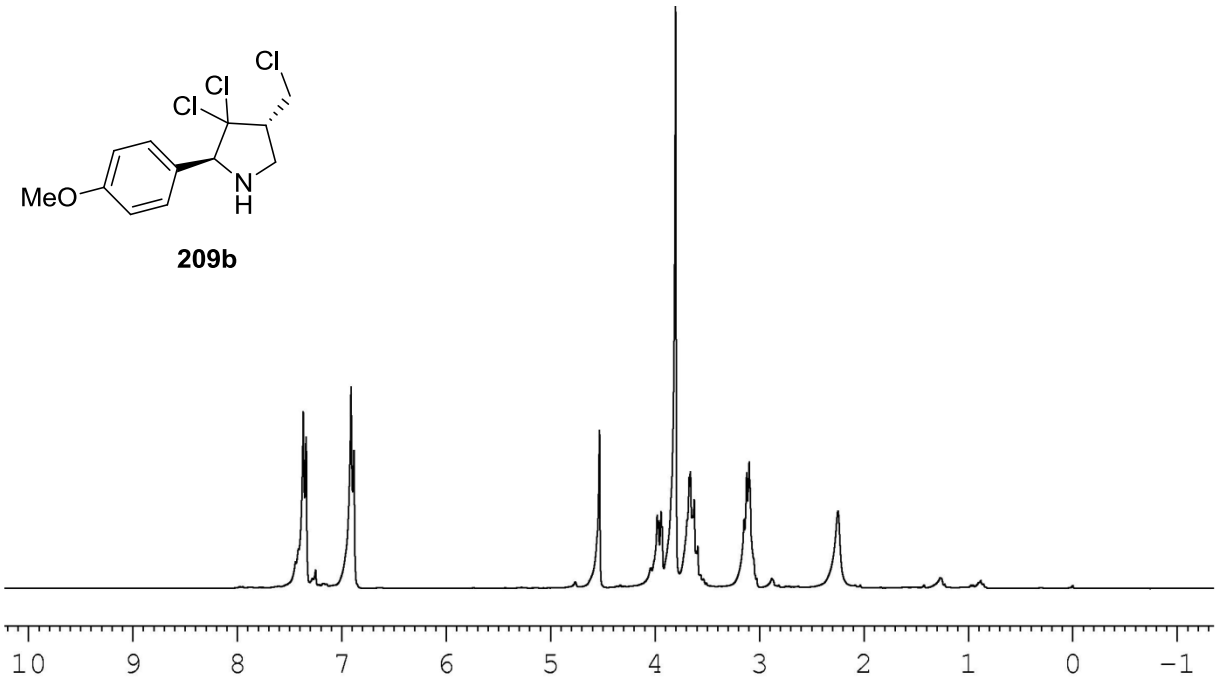


Fig. 74 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-(4-methoxyphenyl)pyrrolidine 209b

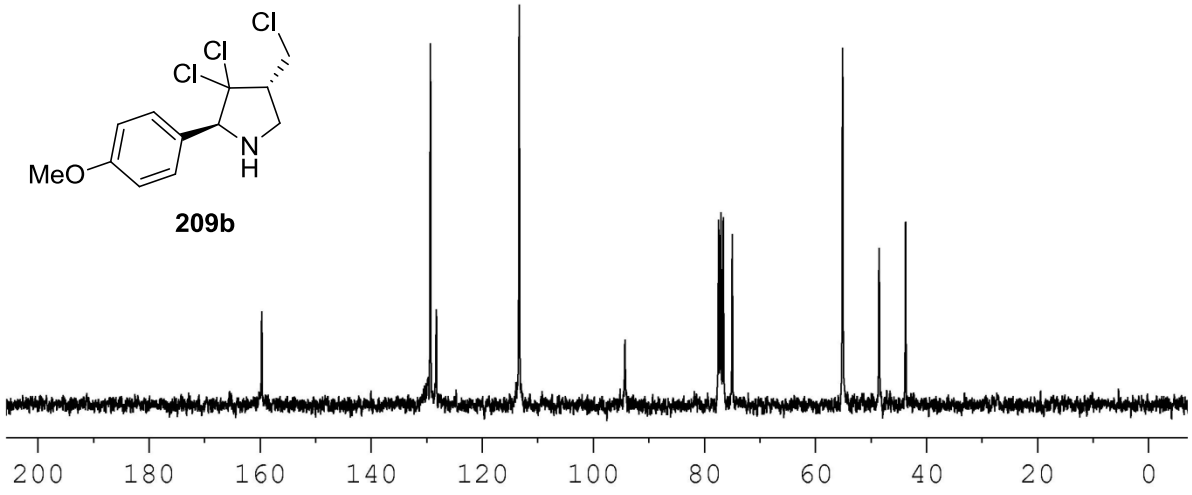


Fig. 75 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-(4-methoxyphenyl)pyrrolidine 209b

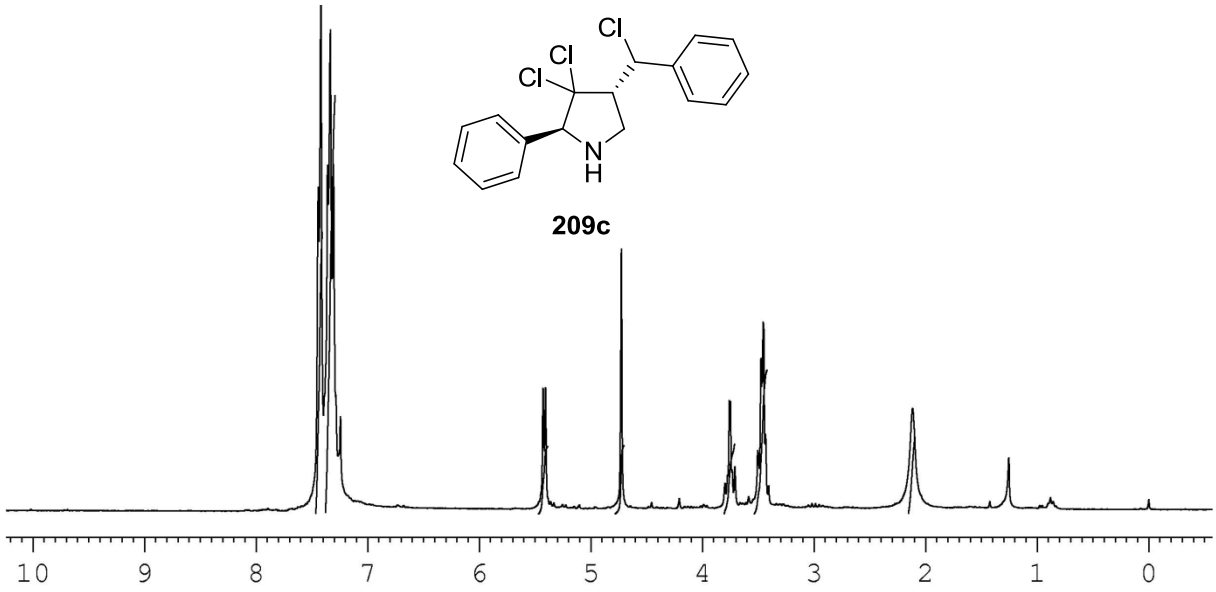


Fig. 76 ^{1}H NMR Spectrum of 3-phenyl-*N*-(2,2,2-trichloro-1-phenylethyl)prop-2-en-1-amine 209c

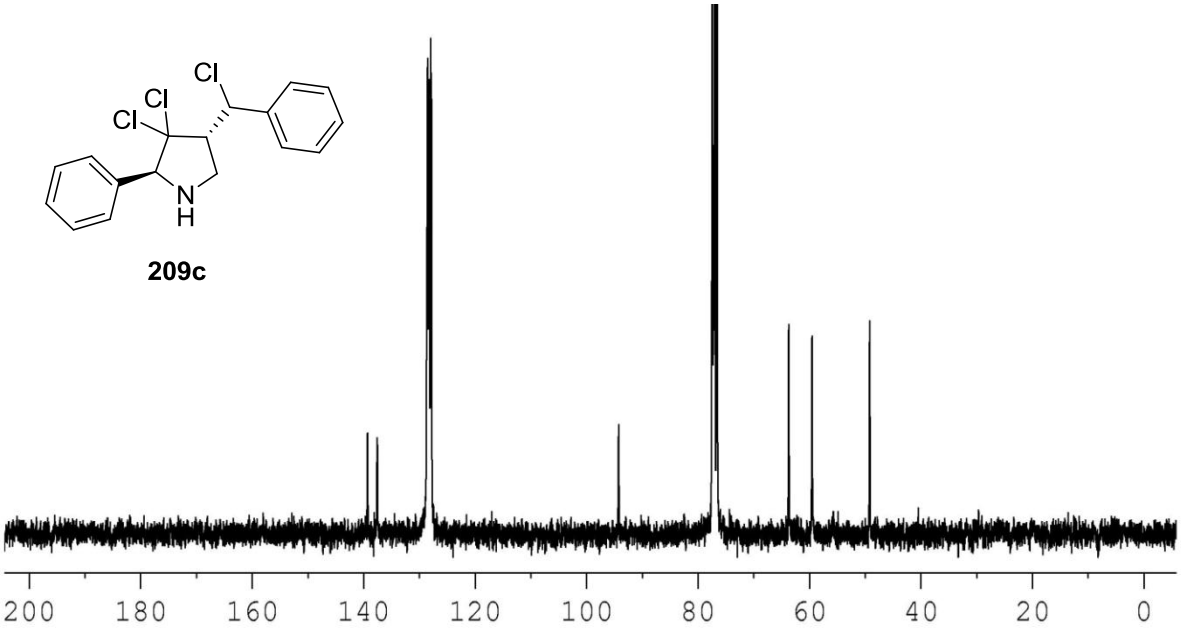


Fig. 77 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloro(phenyl)methyl)-2-phenylpyrrolidine 209c

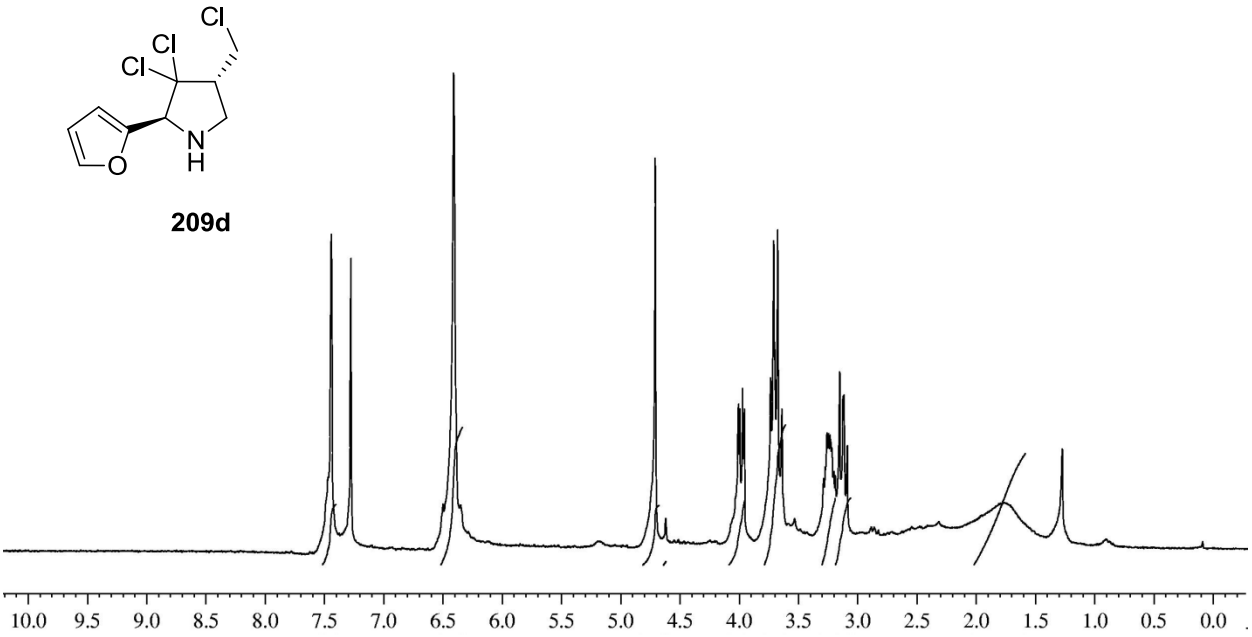


Fig. 78 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-(furan-2-yl)pyrrolidine 209d

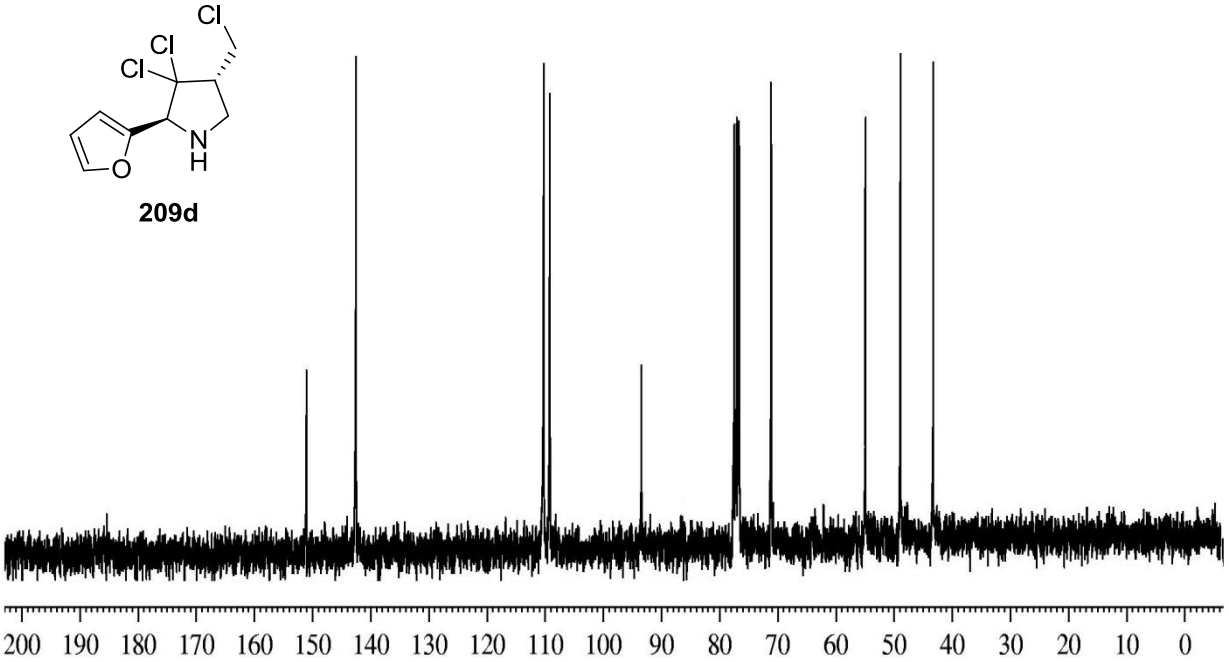


Fig. 79 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-(furan-2-yl)pyrrolidine 209d

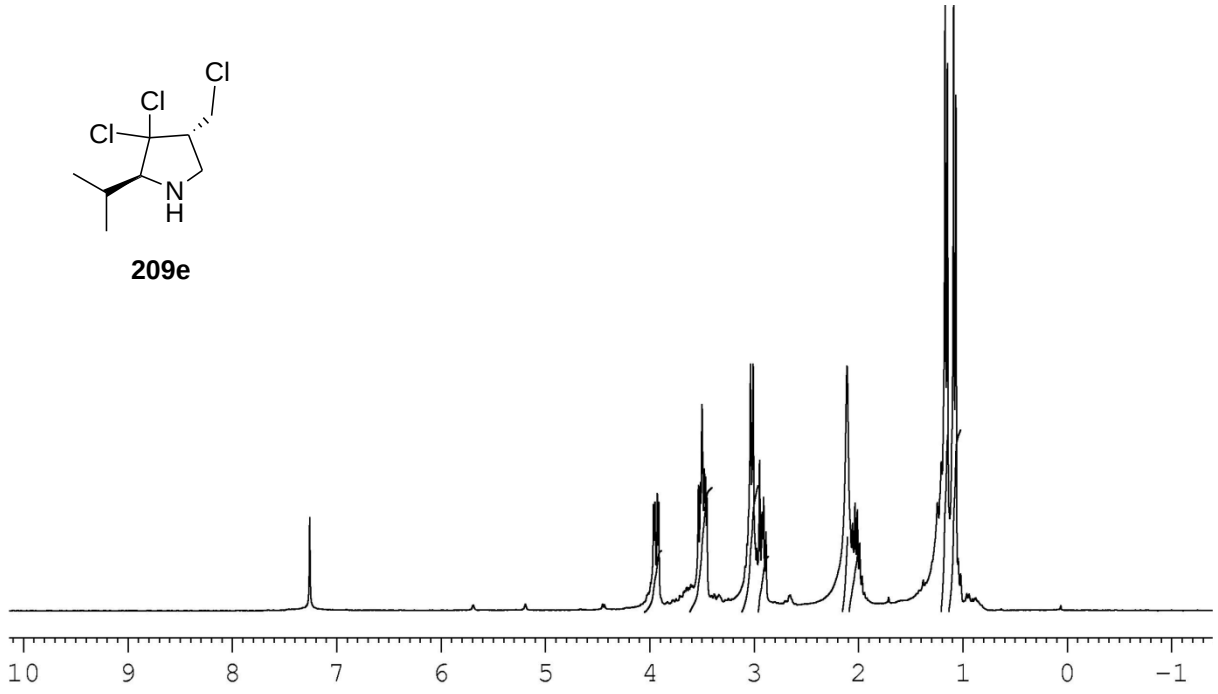


Fig. 80 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-isopropylpyrrolidine 209e

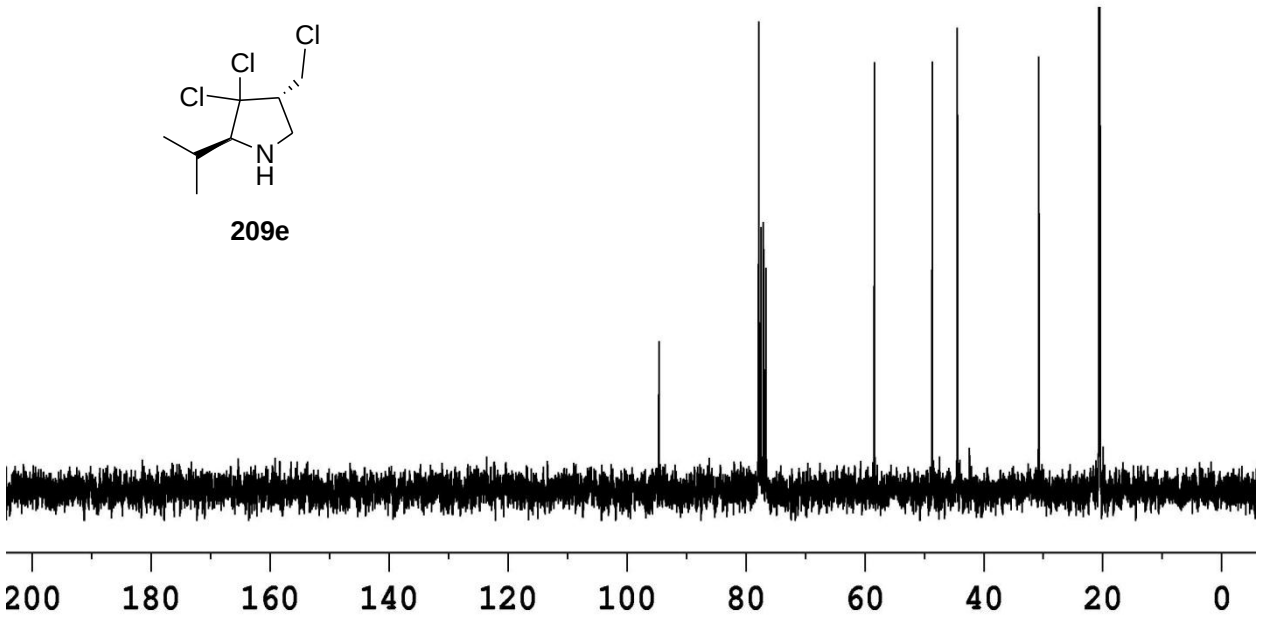


Fig. 81 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-isopropylpyrrolidine 209e

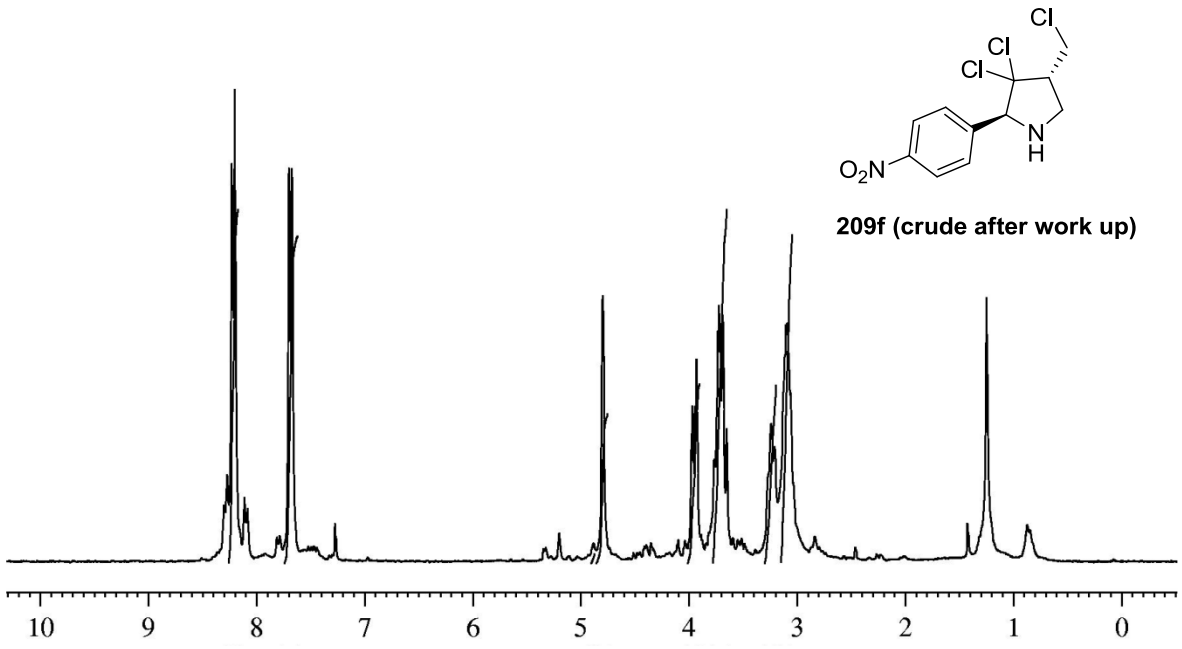


Fig. 82 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-(4-nitrophenyl)pyrrolidine 209f

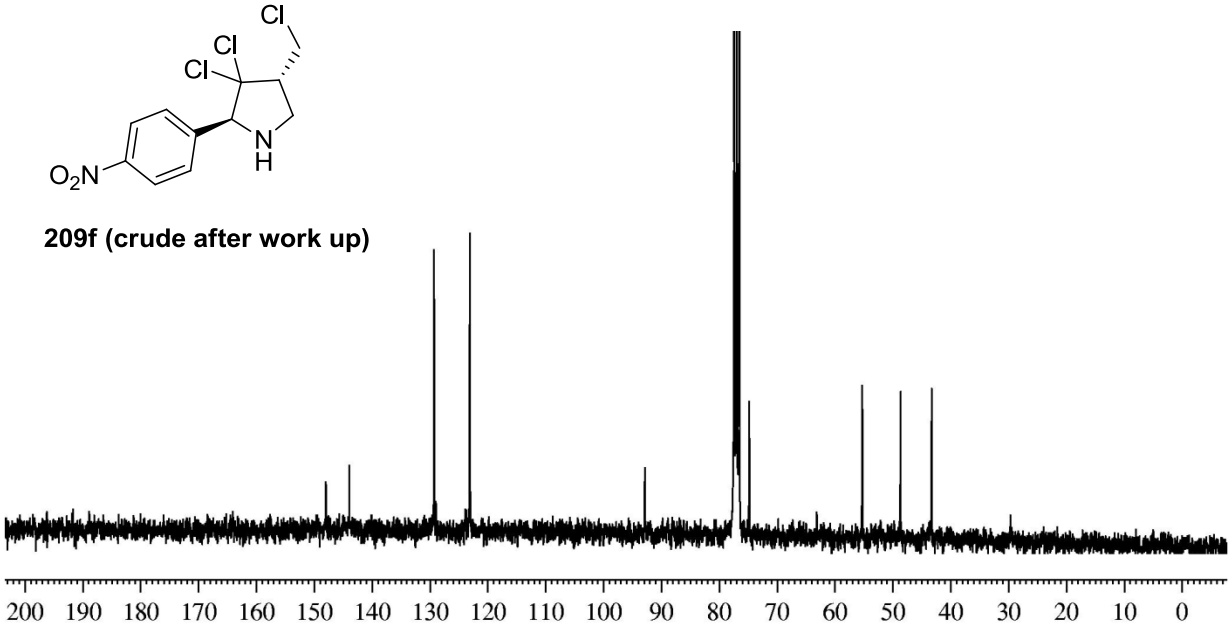


Fig. 83 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-(4-nitrophenyl)pyrrolidine 209f

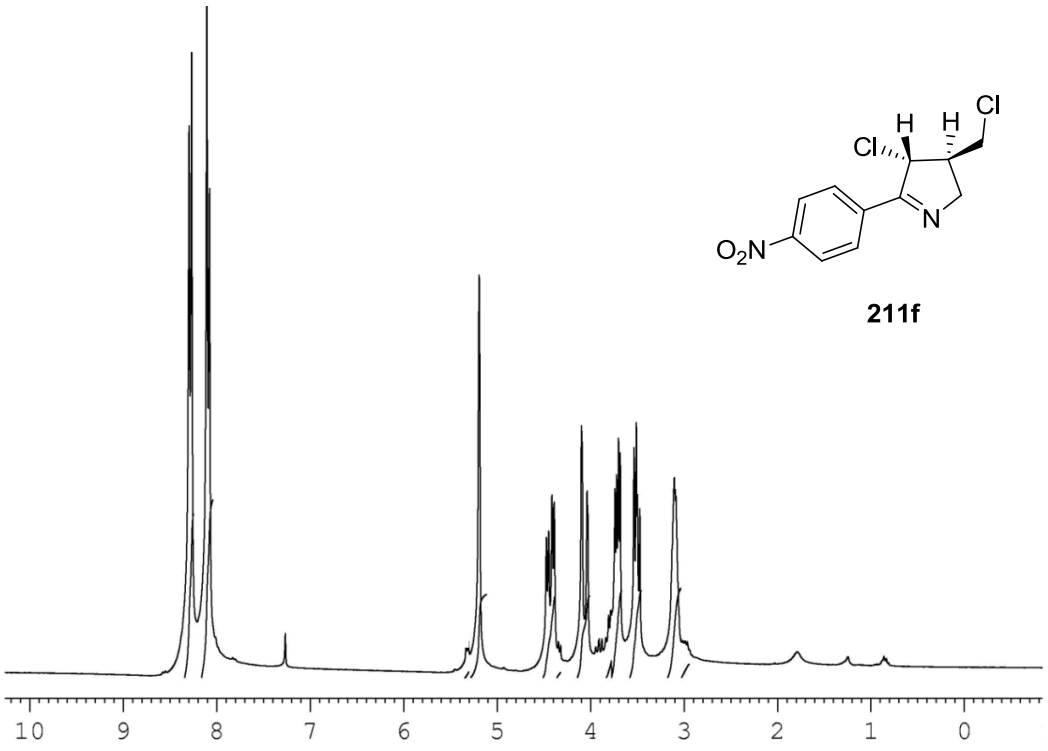


Fig. 84 ^{1}H NMR Spectrum of 4-chloro-3-(chloromethyl)-5-(4-nitrophenyl)-3,4-dihydro-2H-pyrrole 211f

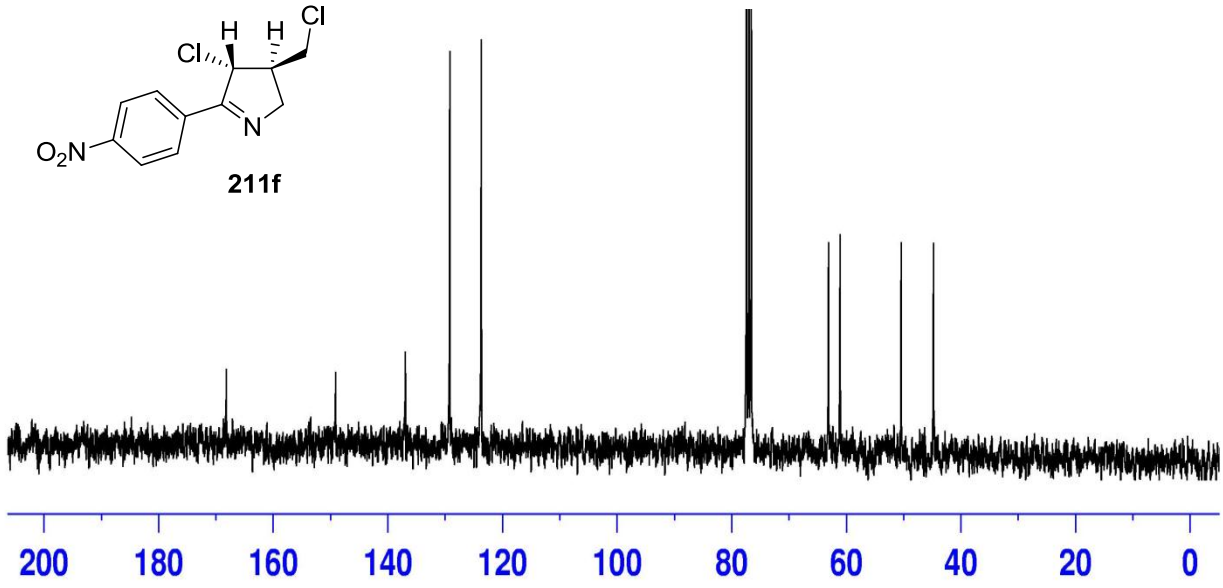


Fig. 85 ^{13}C{^{1}H} NMR Spectrum of 4-chloro-3-(chloromethyl)-5-(4-nitrophenyl)-3,4-dihydro-2H-pyrrole 211f

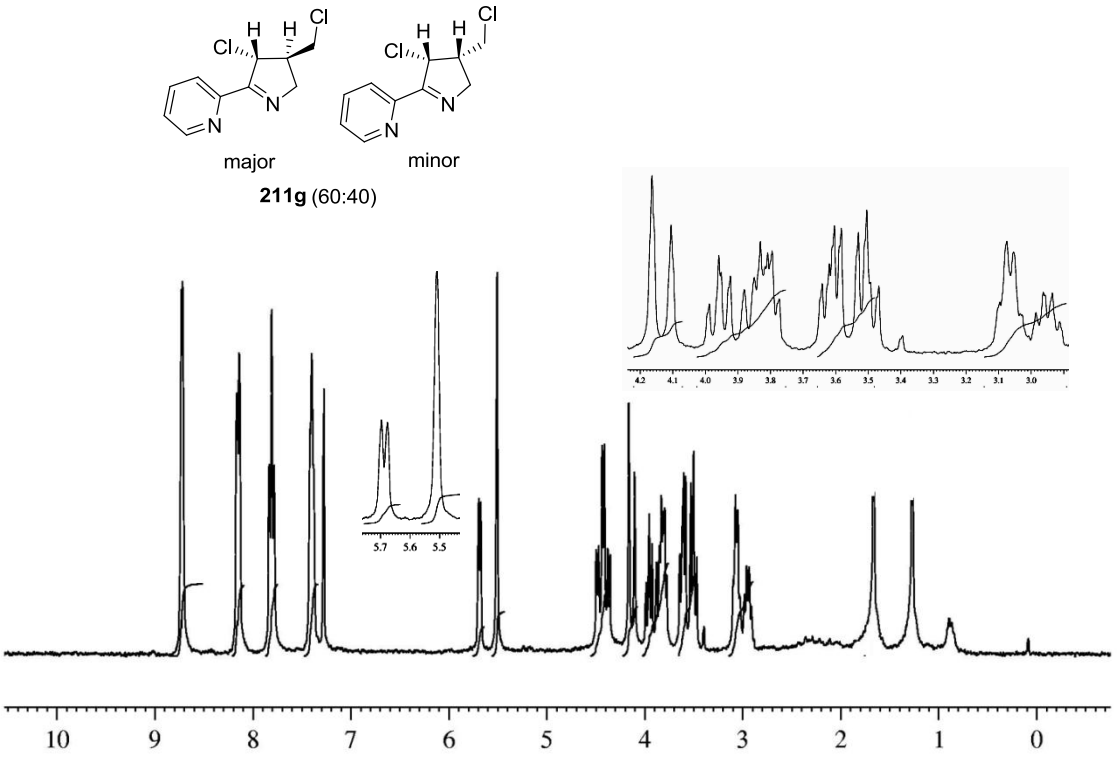


Fig. 86 ^{1}H NMR Spectrum of 2-(3-chloro-4-(chloromethyl)-4,5-dihydro-3H-pyrrol-2-yl)pyridine 211g

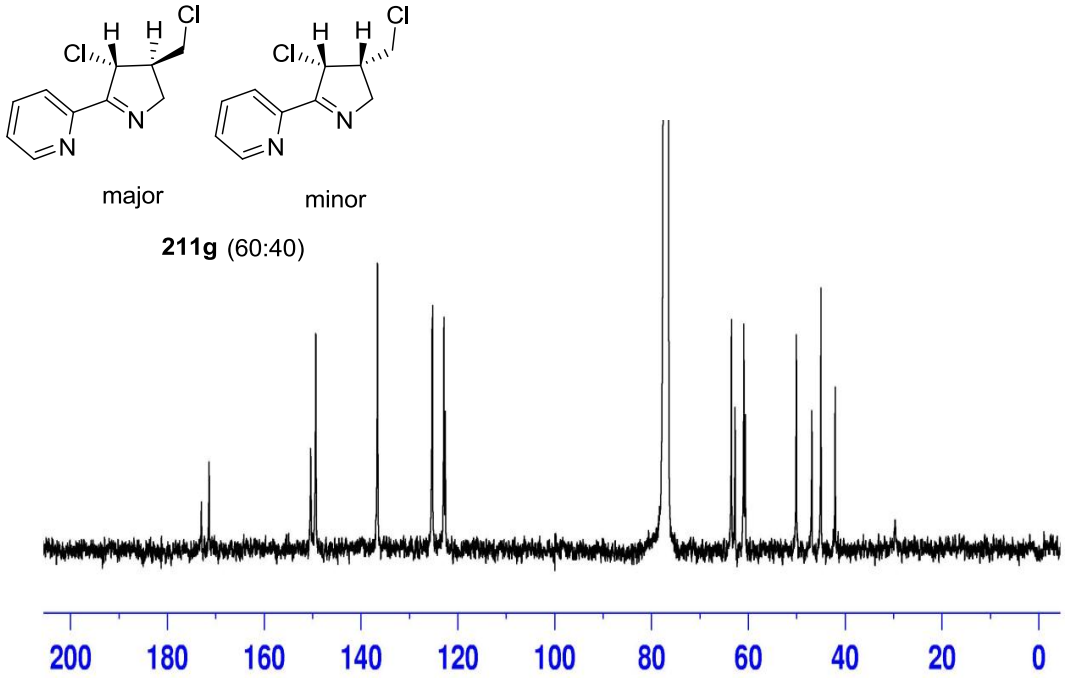


Fig. 87 ^{13}C{^{1}H} NMR Spectrum of 2-(3-chloro-4-(chloromethyl)-4,5-dihydro-3H-pyrrol-2-yl)pyridine 211g

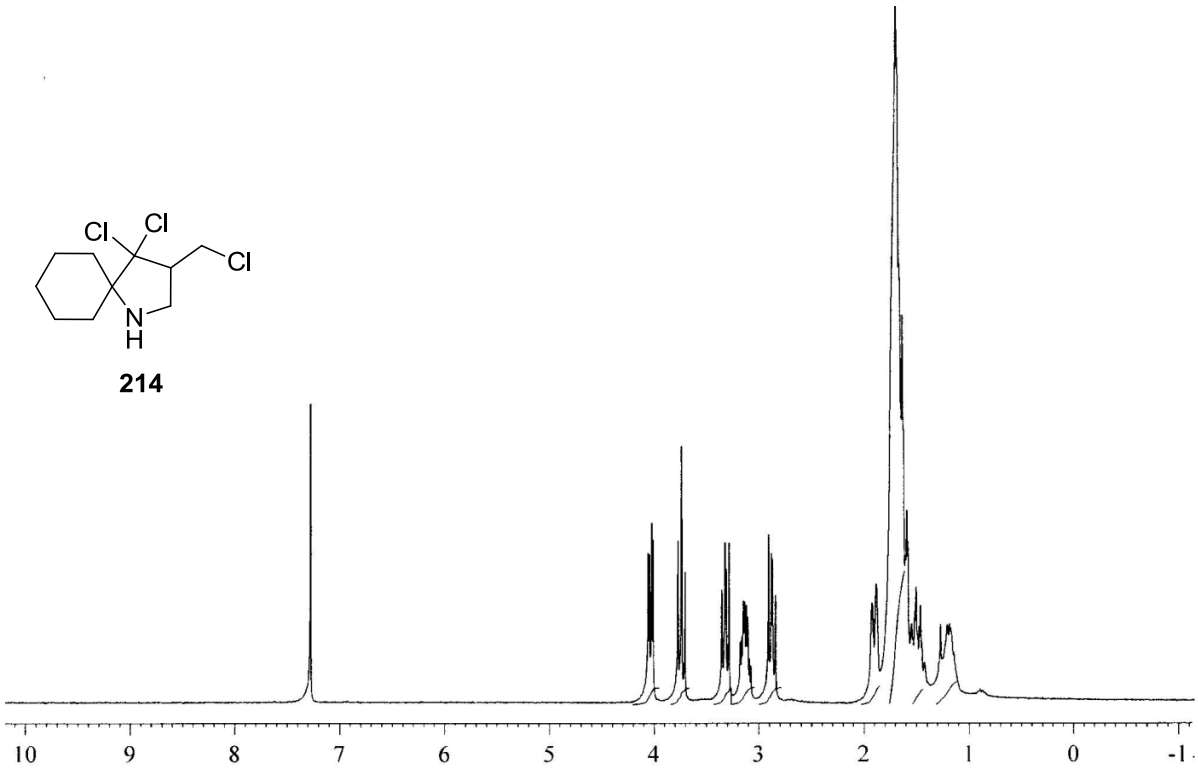


Fig. 88 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-spirocyclohexyl-pyrrolidine 214

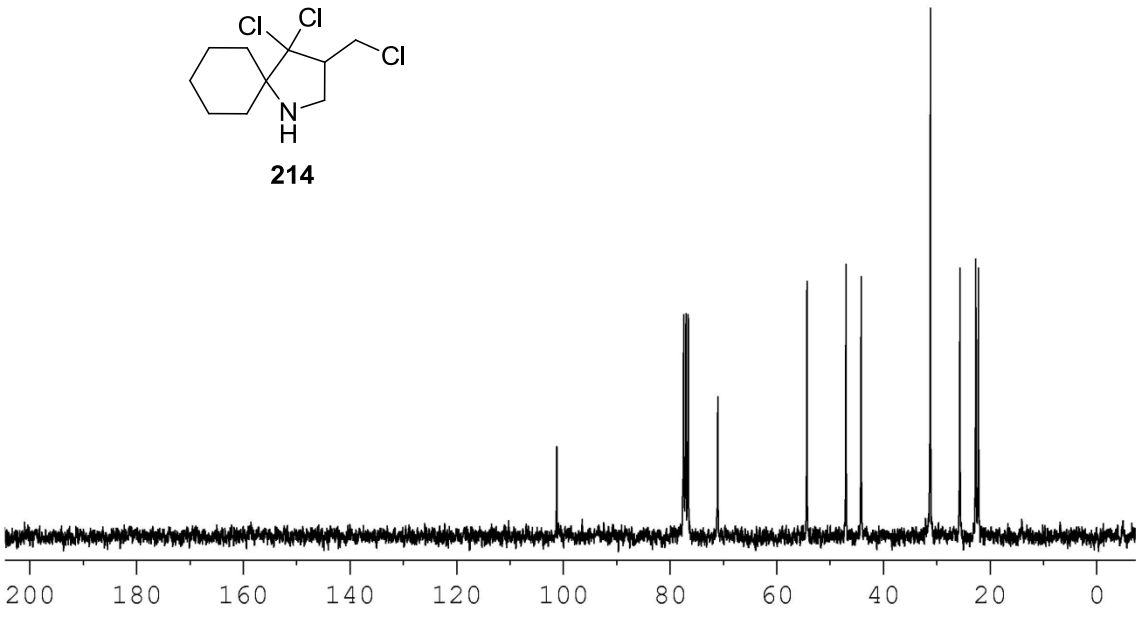
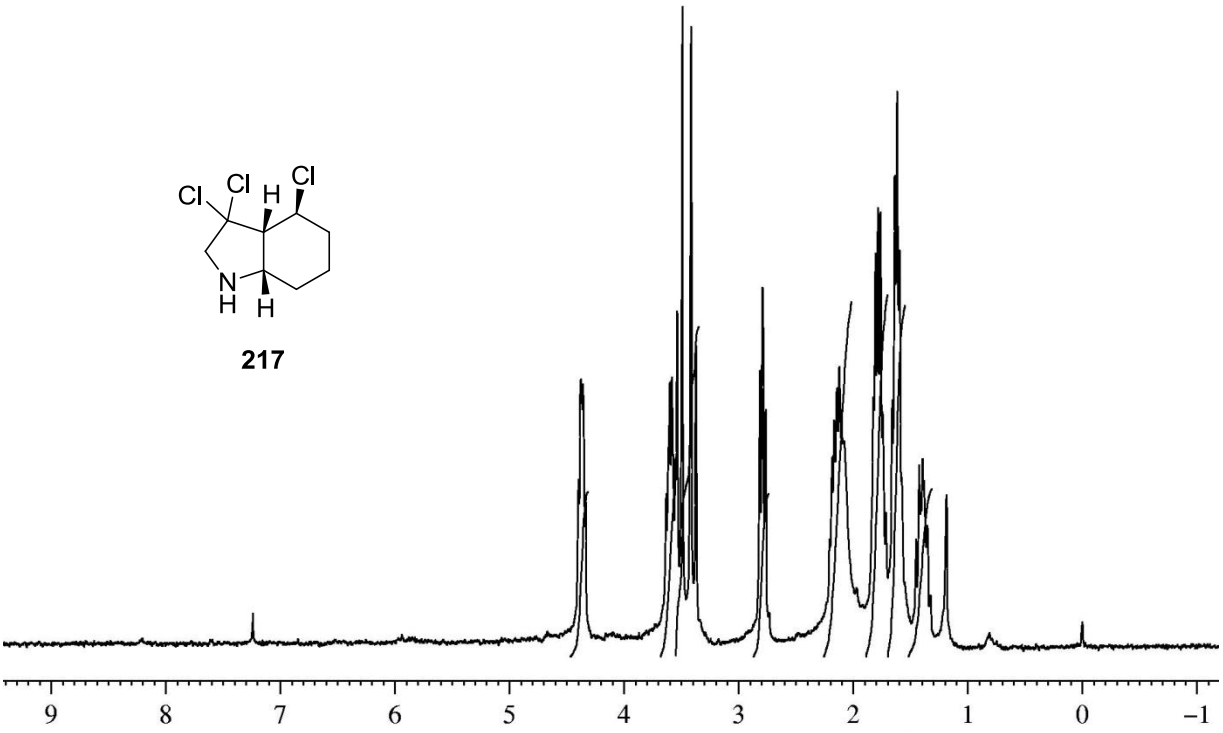
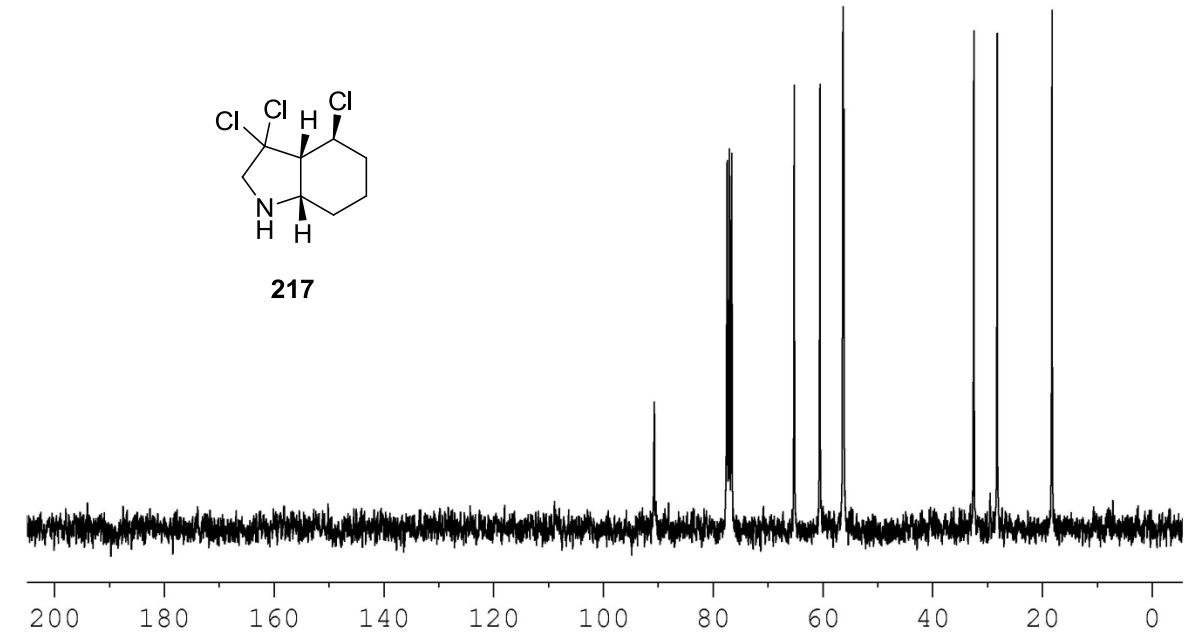


Fig. 89 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-spirocyclohexyl-pyrrolidine 214



217

Fig. 90 ^{1}H NMR Spectrum of 3,3,4-trichloro-octahydro-1H-indole 217



217

Fig. 91 ^{13}C{^{1}H} NMR Spectrum of 3,3,4-trichloro-octahydro-1H-indole 217

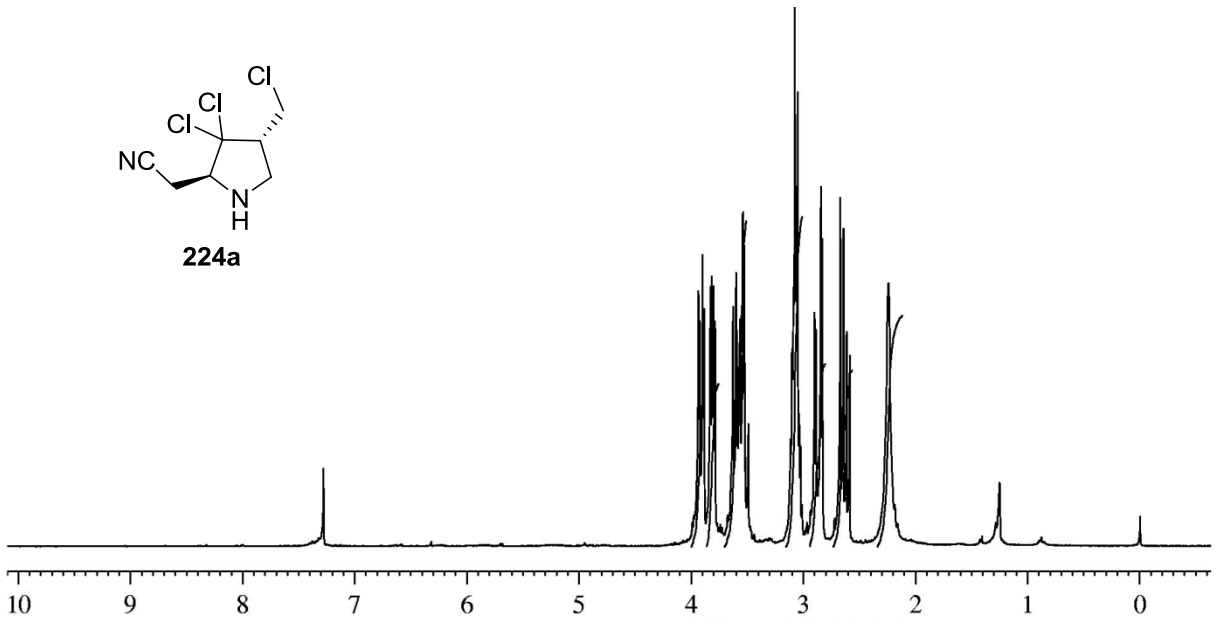


Fig. 92 ^{1}H NMR Spectrum of 2-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)acetonitrile 224a

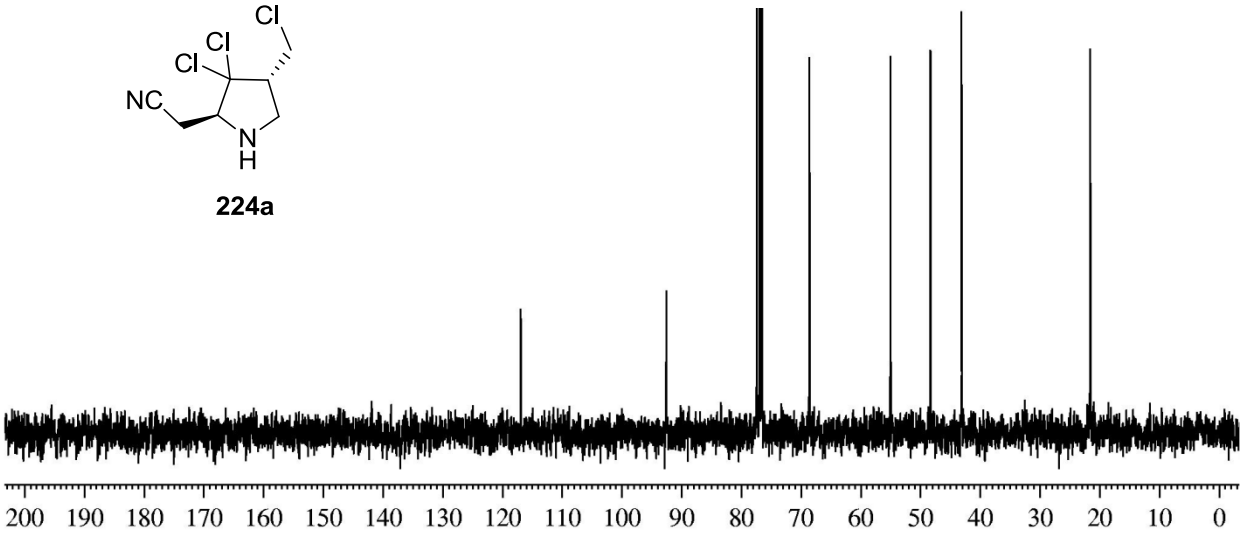


Fig. 93 ^{13}C{^{1}H} NMR Spectrum of 2-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)acetonitrile 224a

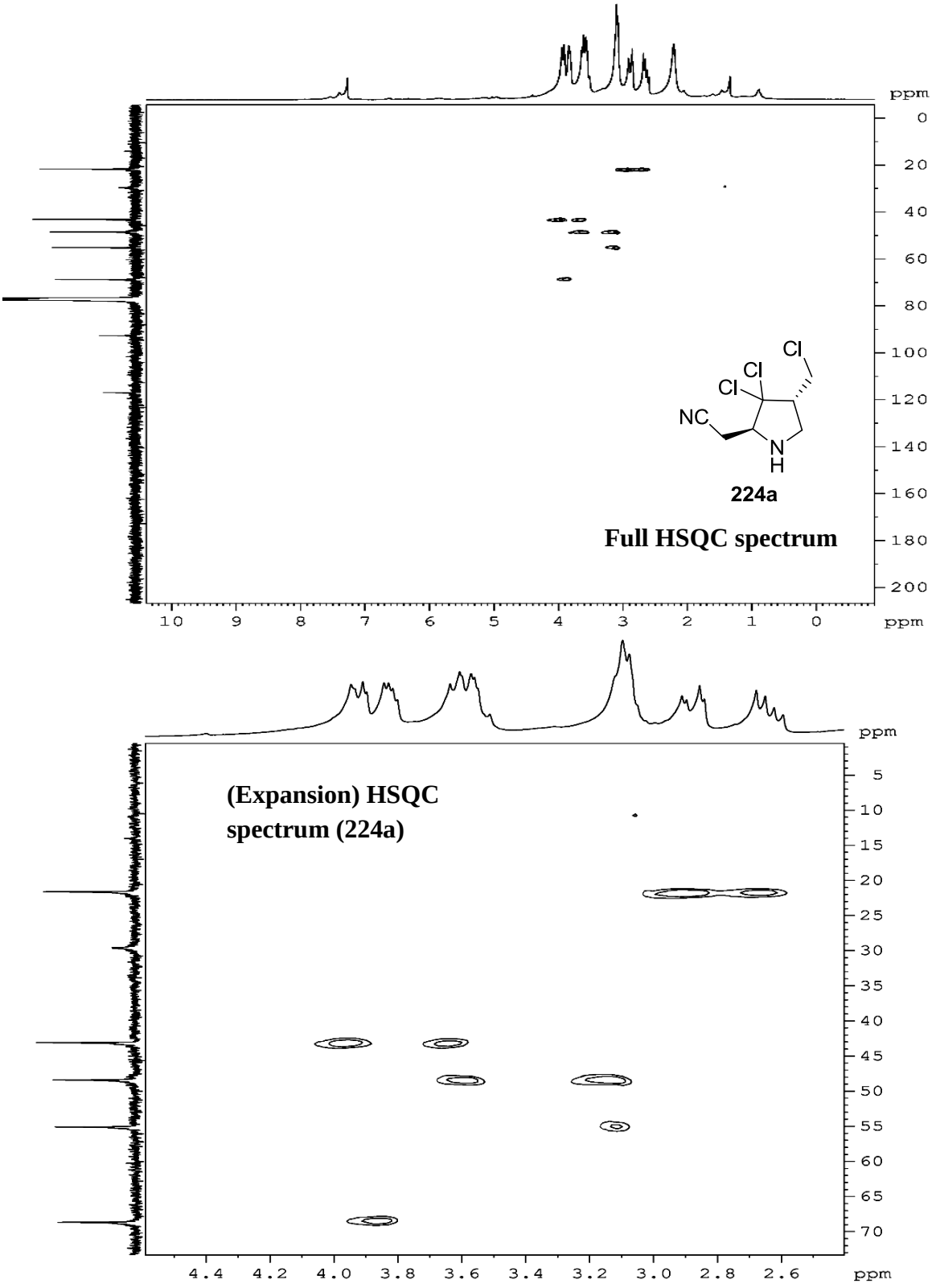


Fig. 94 HSQC Spectrum of 2-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)acetonitrile 224a

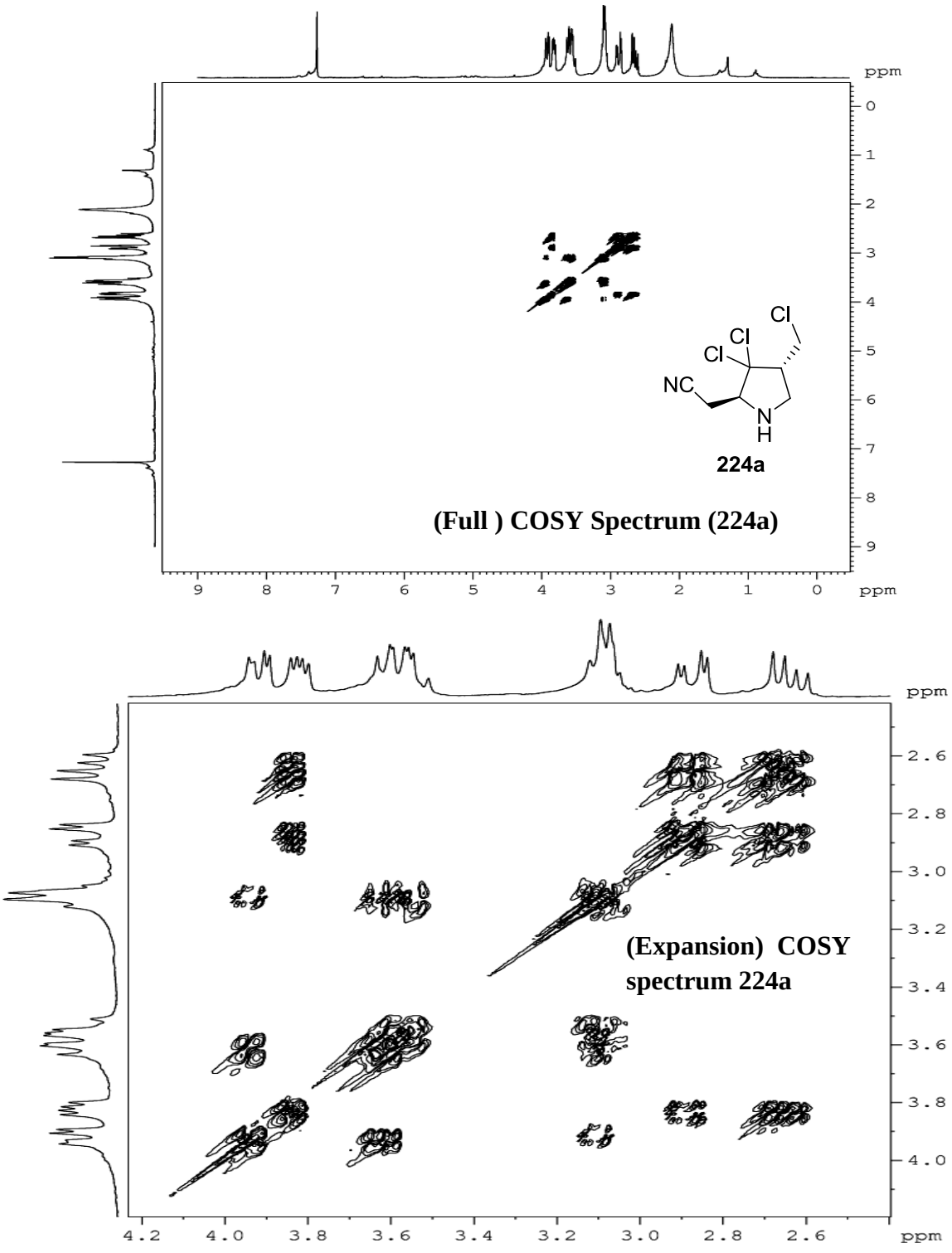


Fig. 95 ^{1}H-^{1}H COSY Spectrum of 2-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)acetonitrile 224a

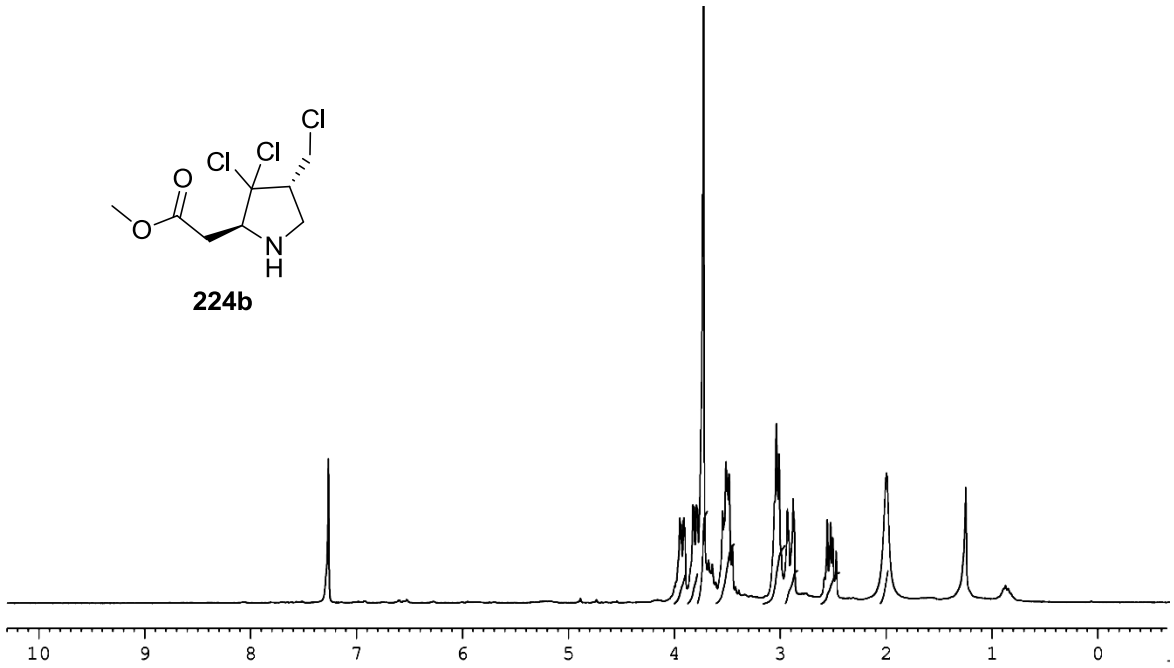


Fig. 96 ^{1}H NMR Spectrum of methyl 2-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)acetate 224b

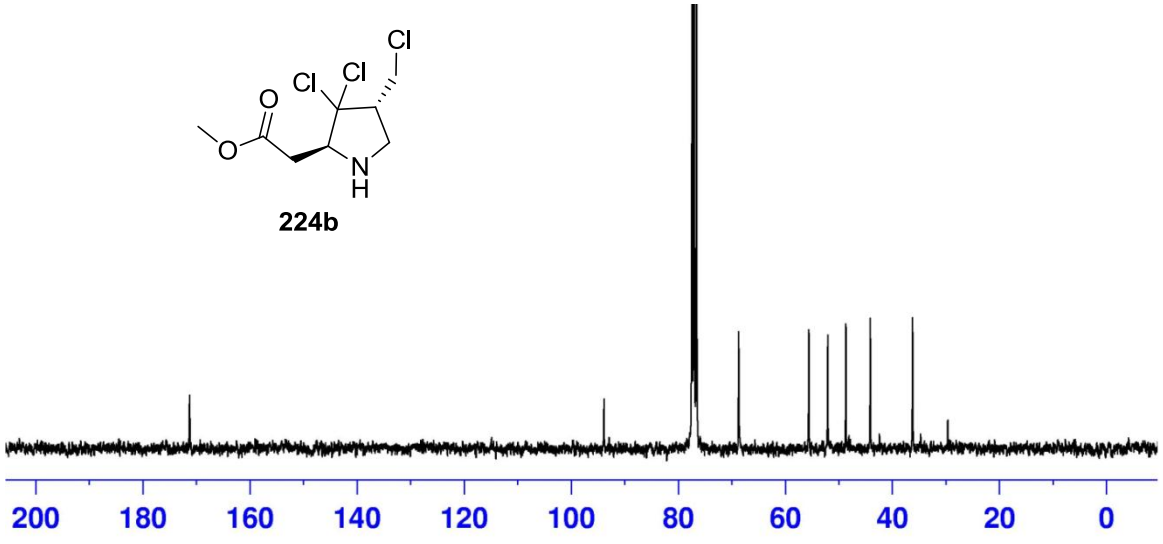


Fig. 97 ^{13}C{^{1}H} NMR Spectrum of methyl 2-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)acetate 224b

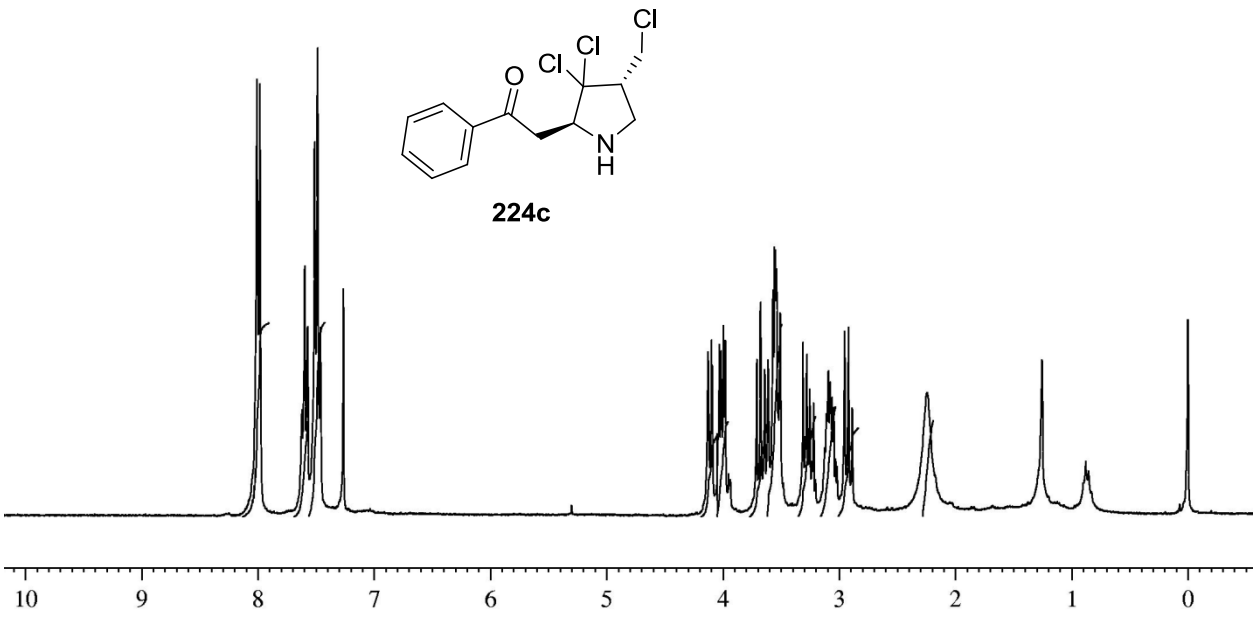


Fig. 98 ^{1}H NMR Spectrum of 2-(3,3-Dichloro-4-(chloromethyl)pyrrolidin-2-yl)-1-phenylethanone 224c

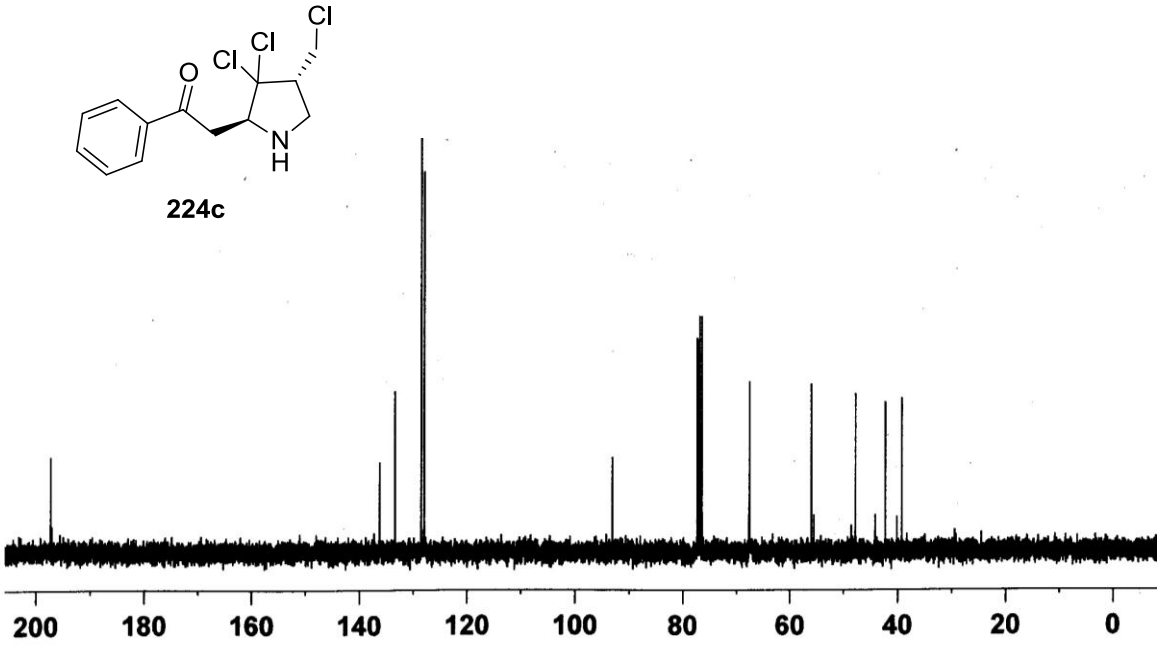


Fig. 99 ^{13}C{^{1}H} NMR Spectrum of 2-(3,3-Dichloro-4-(chloromethyl)pyrrolidin-2-yl)-1-phenylethanone 224c

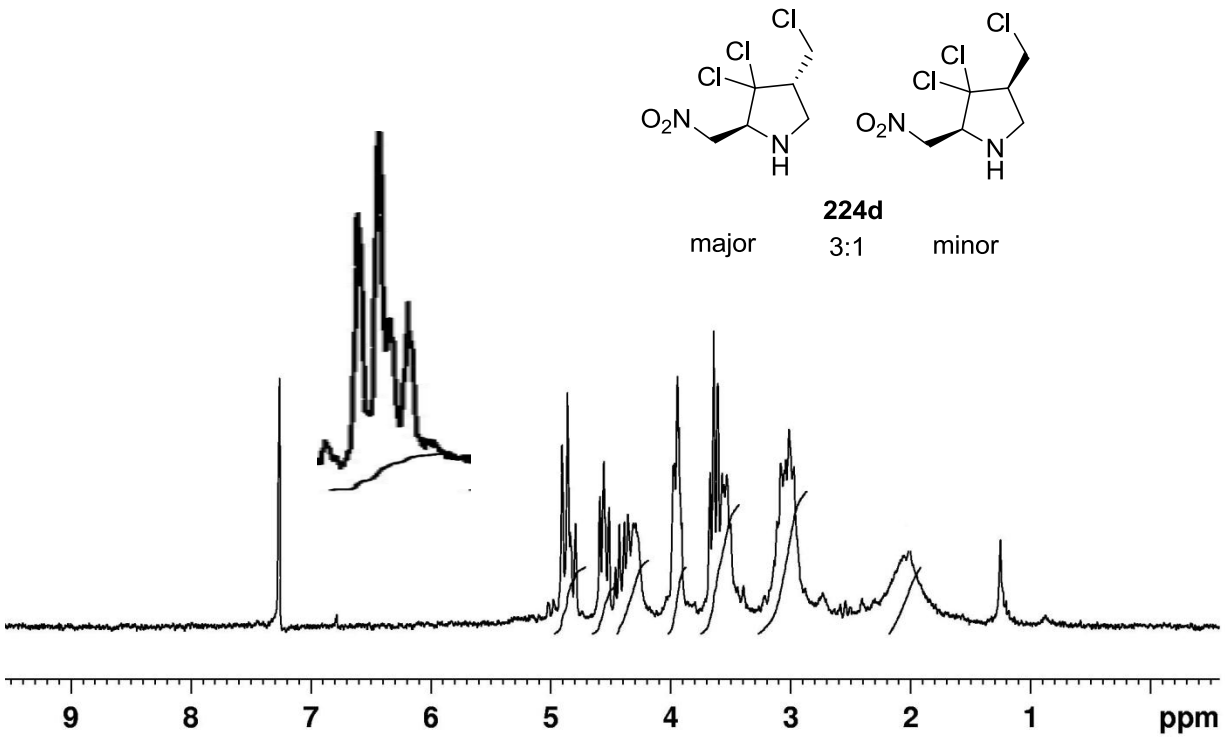


Fig. 100 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-(nitromethyl)pyrrolidine 224d

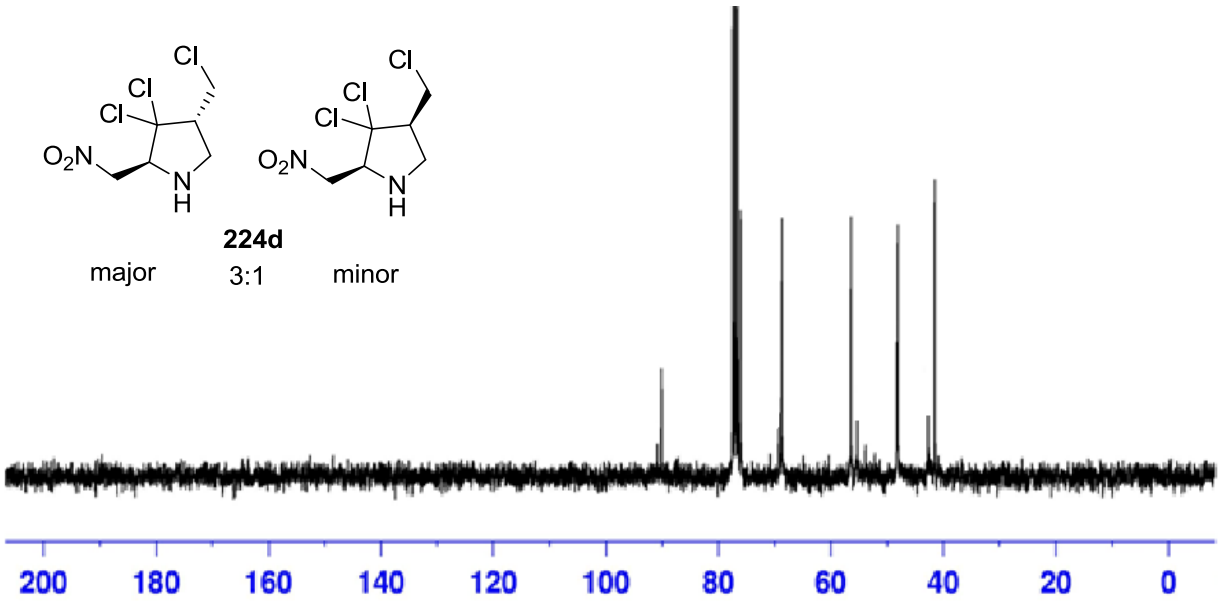


Fig. 101 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-(nitromethyl)pyrrolidine 224d

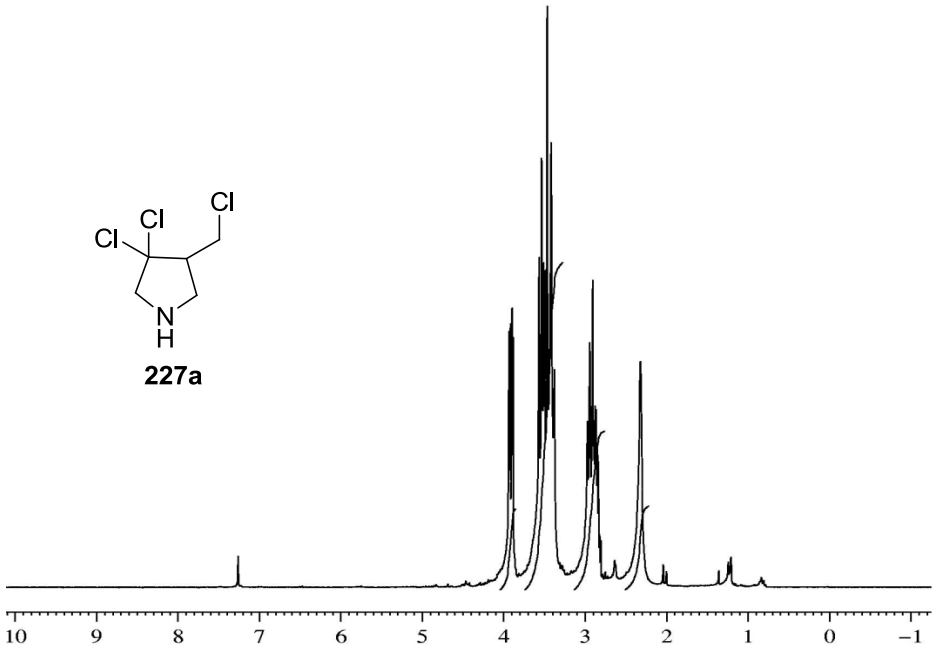


Fig. 102 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)pyrrolidine 227a

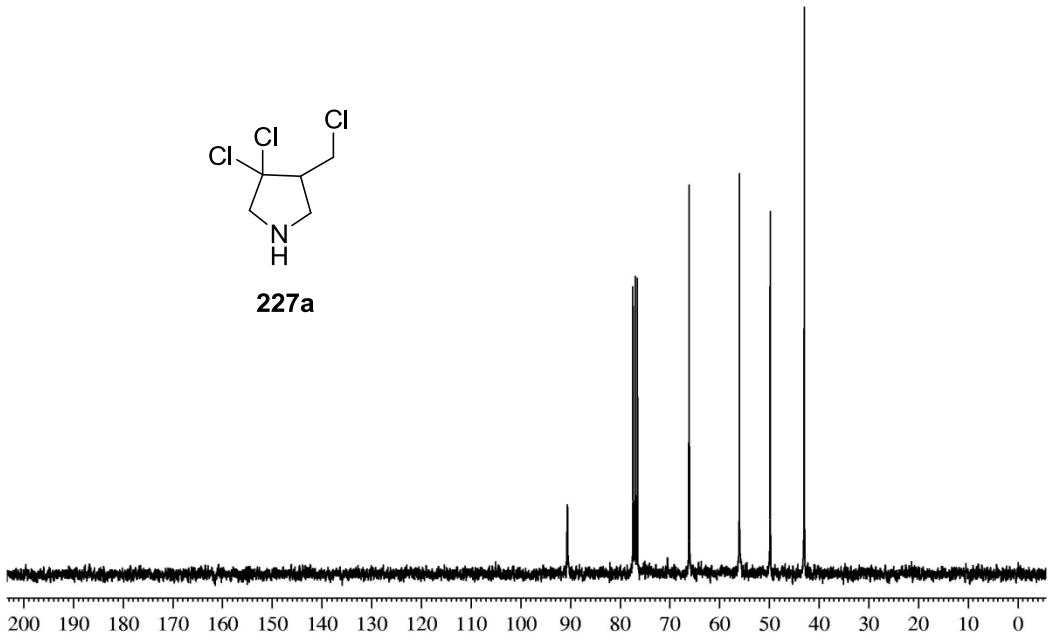


Fig. 103 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloromethyl)pyrrolidine 227a

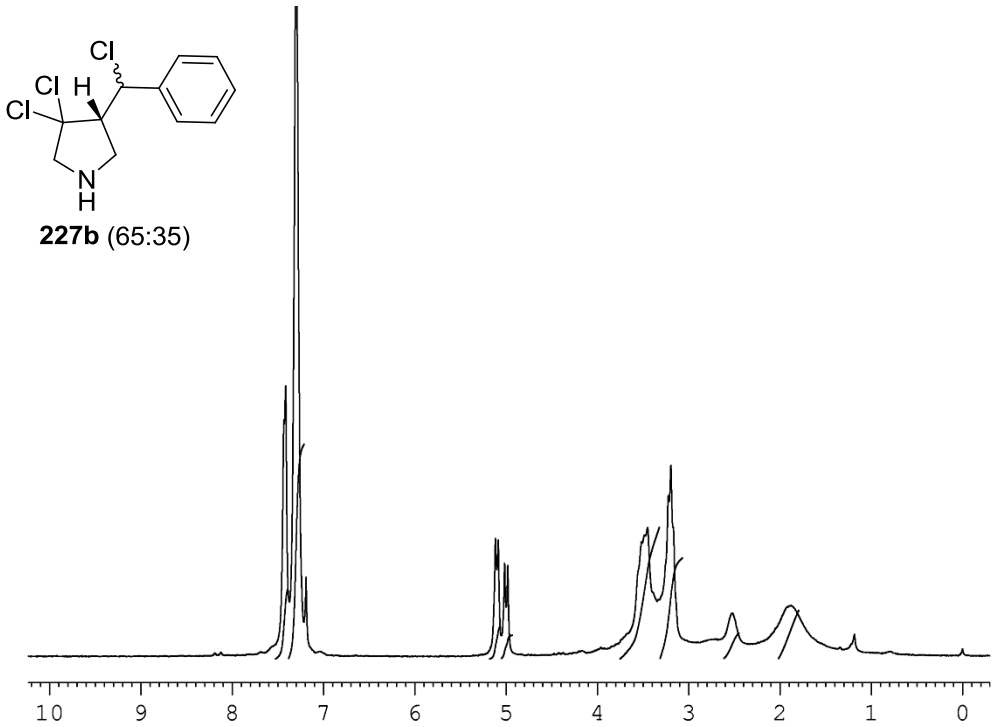


Fig. 104 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloro (phenyl)methyl) pyrrolidine 227b

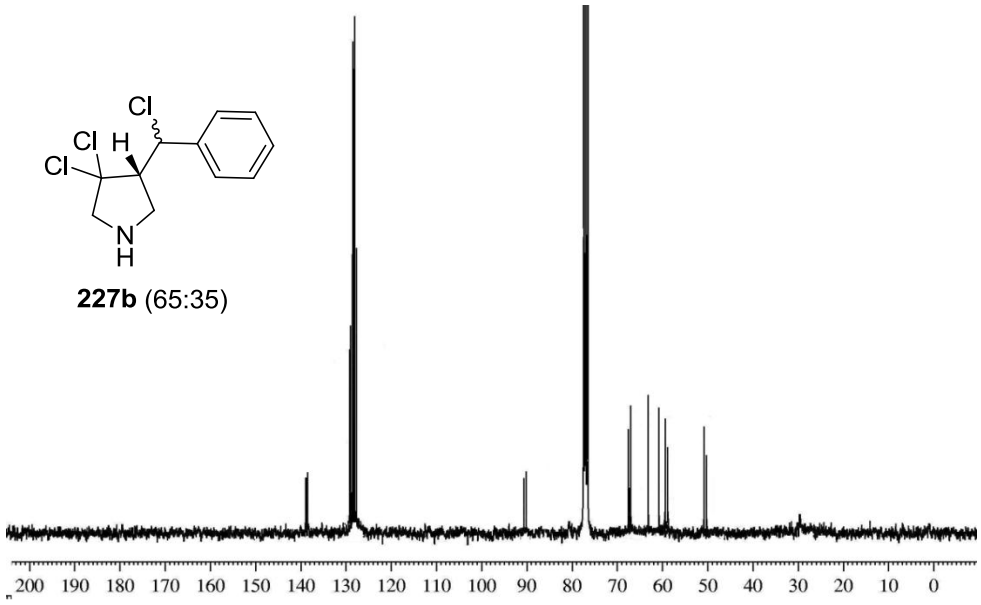


Fig. 105 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloro (phenyl)methyl) pyrrolidine 227b

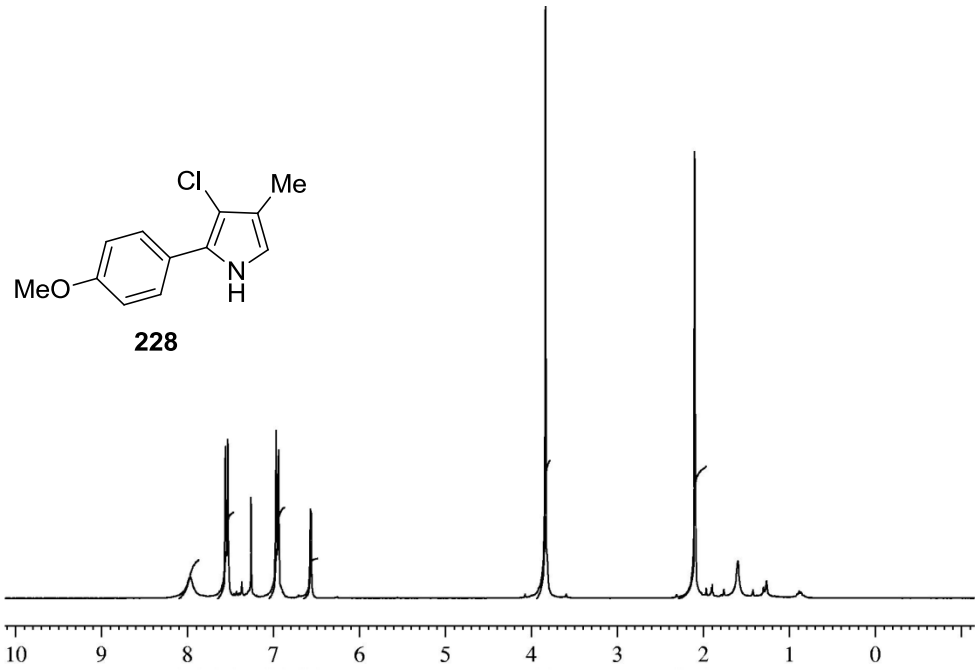


Fig. 106 ^{1}H NMR Spectrum chloro-2-(4-methoxyphenyl)-4-methyl-1H-pyrrole 228

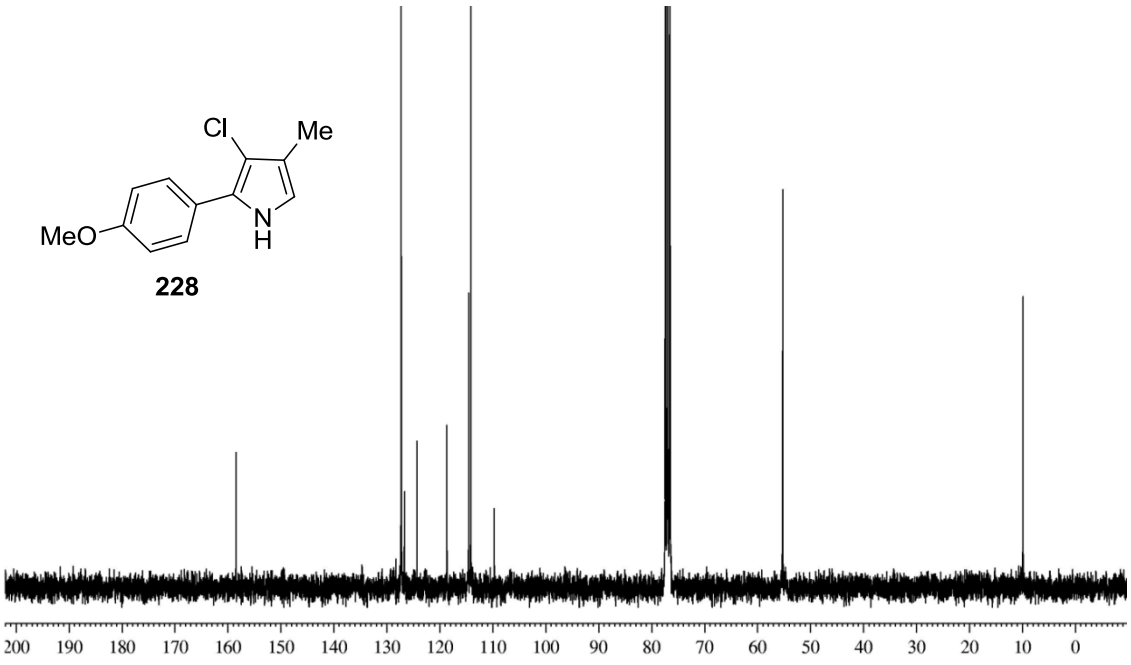


Fig. 107 ^{13}C{^{1}H} NMR Spectrum chloro-2-(4-methoxyphenyl)-4-methyl-1H-pyrrole 228

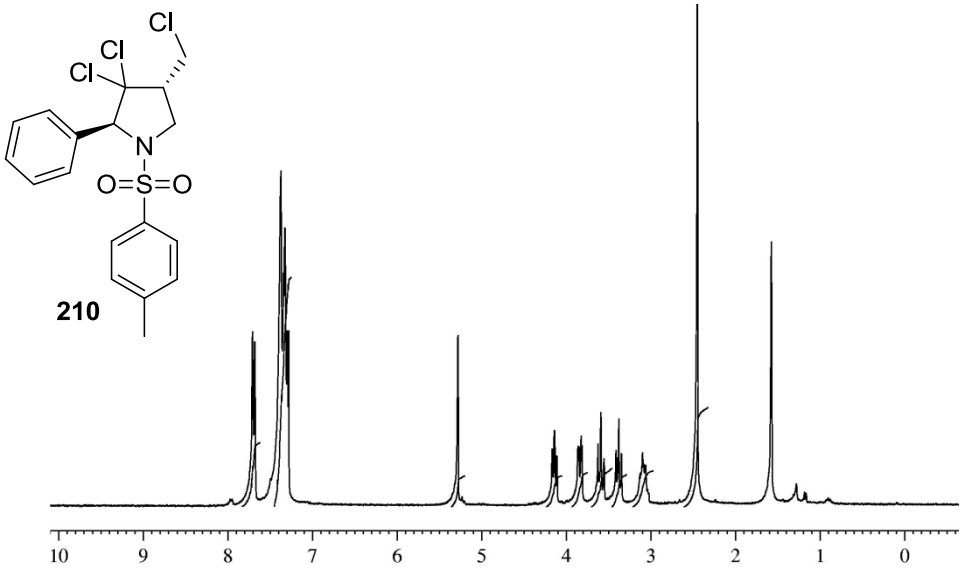


Fig. 108 ^{1}H NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-phenyl-1-tosylpyrrolidine 210

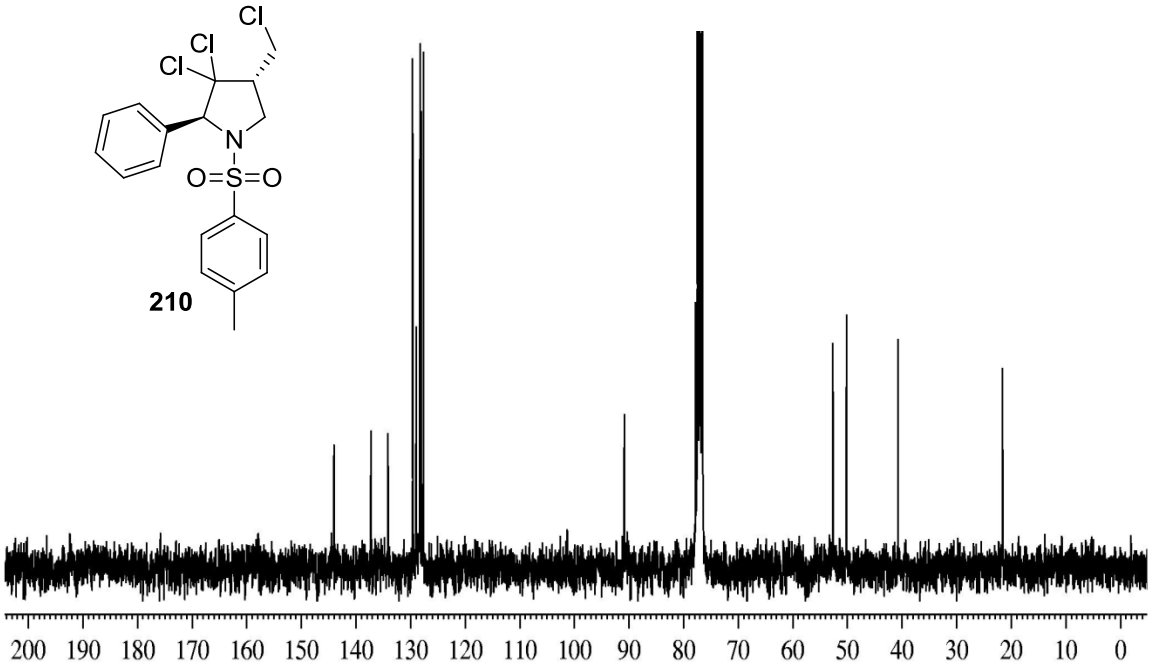


Fig. 109 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(chloromethyl)-2-phenyl-1-tosylpyrrolidine 210

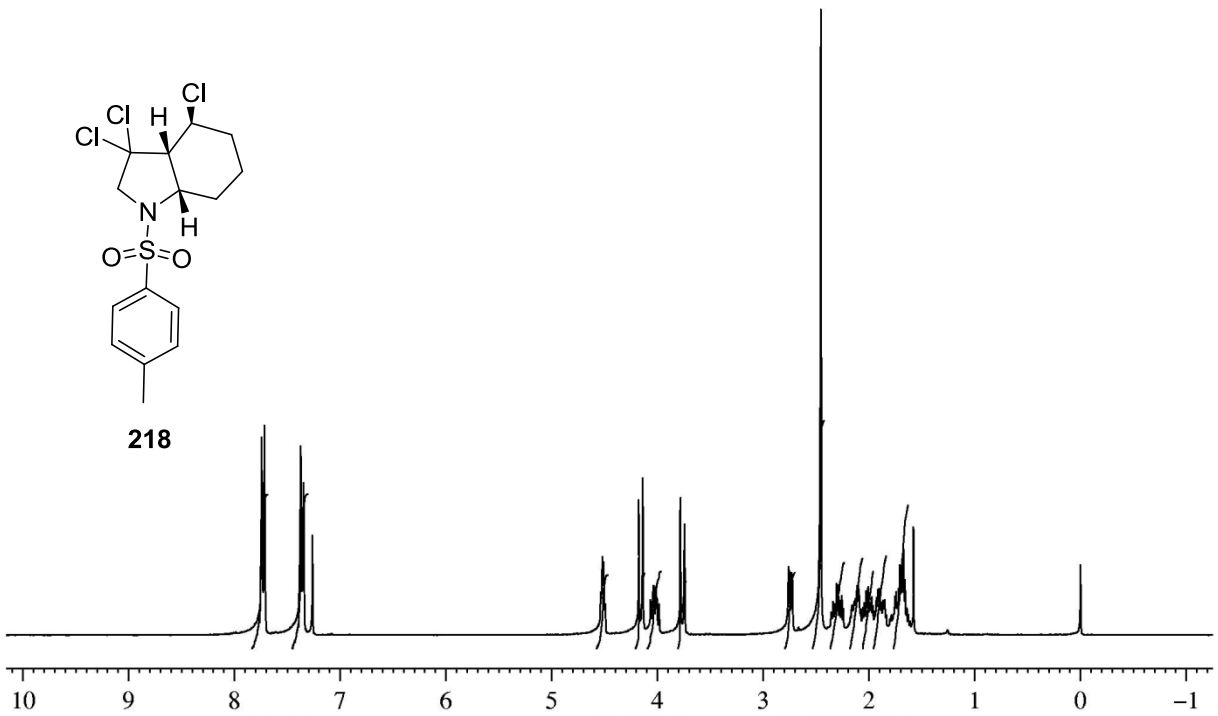


Fig. 110 ^{1}H NMR Spectrum of 3,3,4-trichloro-1-tosyloctahydro-1H-indole 218

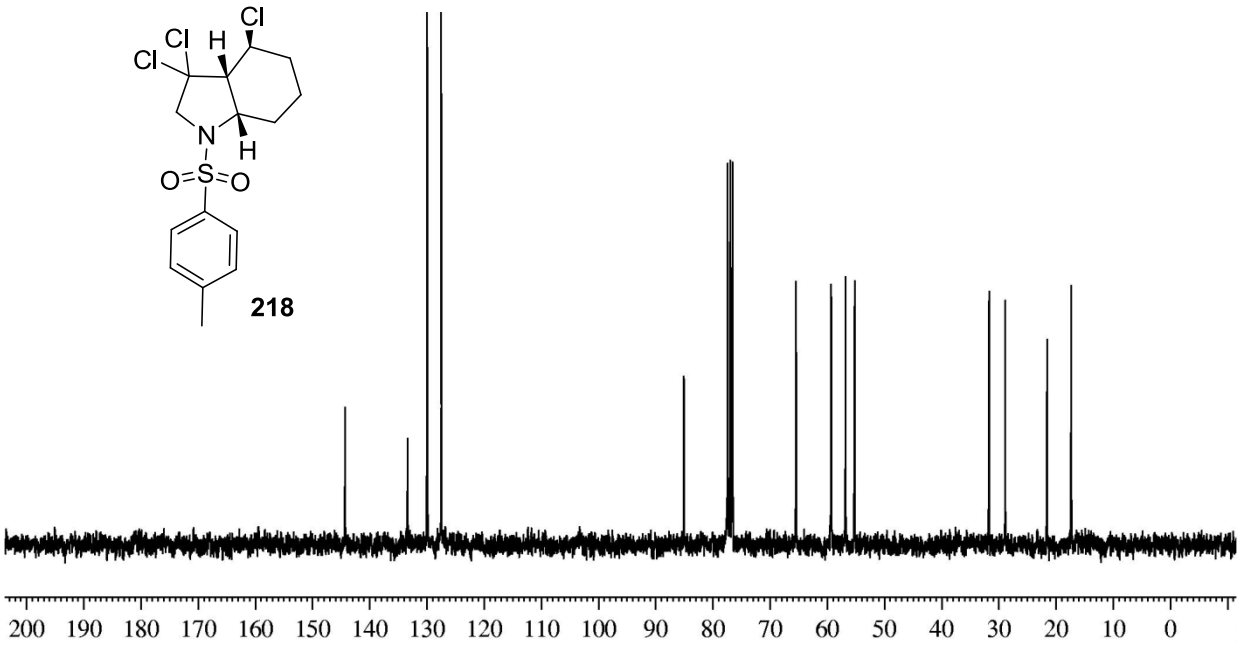


Fig. 111 ^{13}C{^{1}H} NMR Spectrum of 3,3,4-trichloro-1-tosyloctahydro-1H-indole 218

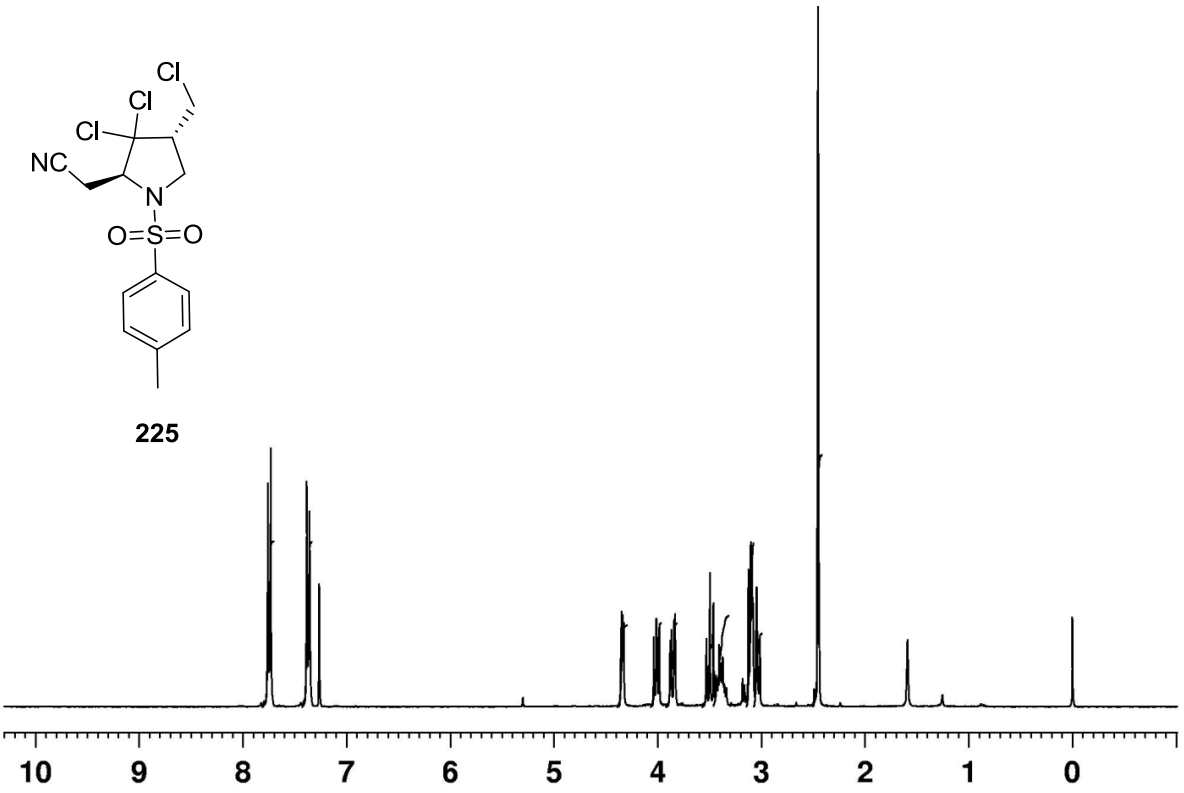


Fig. 112 ^{1}H NMR Spectrum of 2-(3,3-dichloro-4-(chloromethyl)-1-tosylpyrrolidin-2-yl)acetonitrile 225

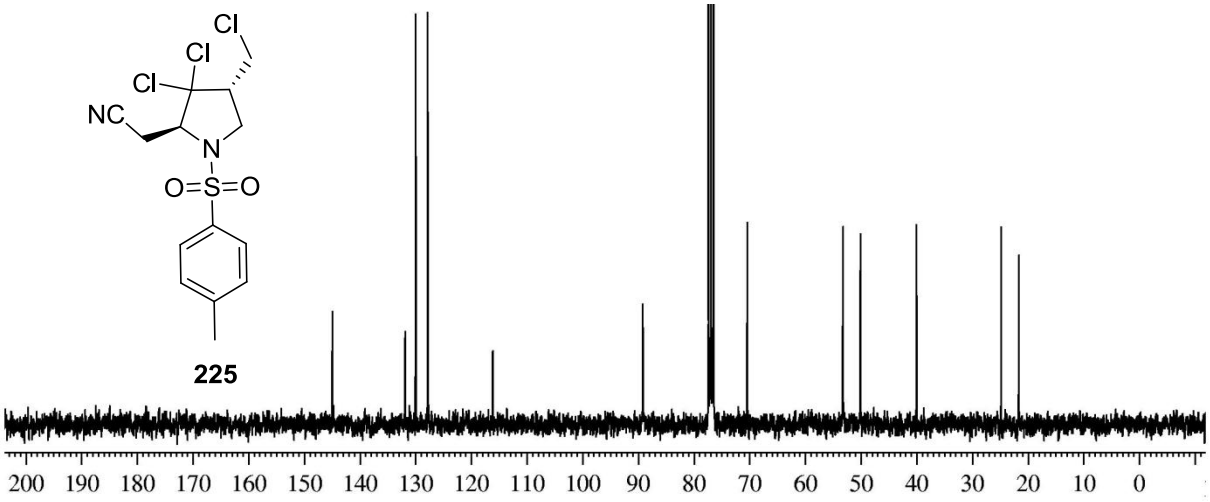


Fig. 113 ^{13}C{^{1}H} NMR Spectrum of 2-(3,3-dichloro-4-(chloromethyl)-1-tosylpyrrolidin-2-yl)acetonitrile 225

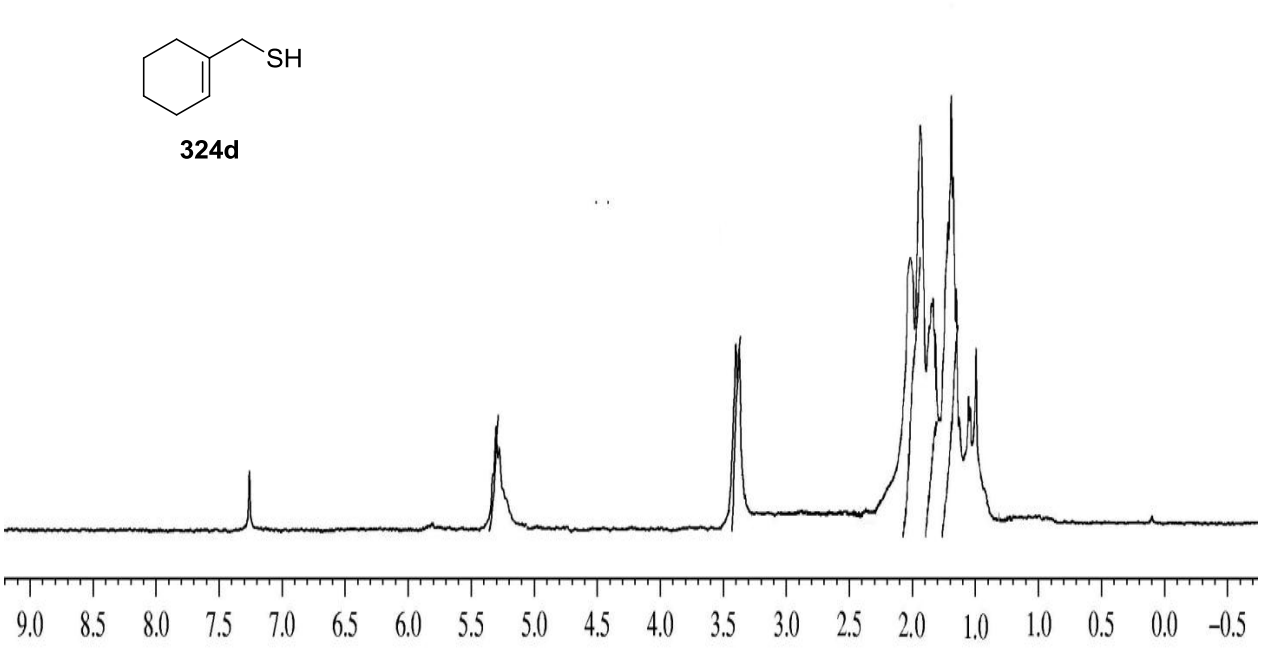


Fig. 114 ^{1}H NMR Spectrum of cyclohexenylmethanethiol 324d

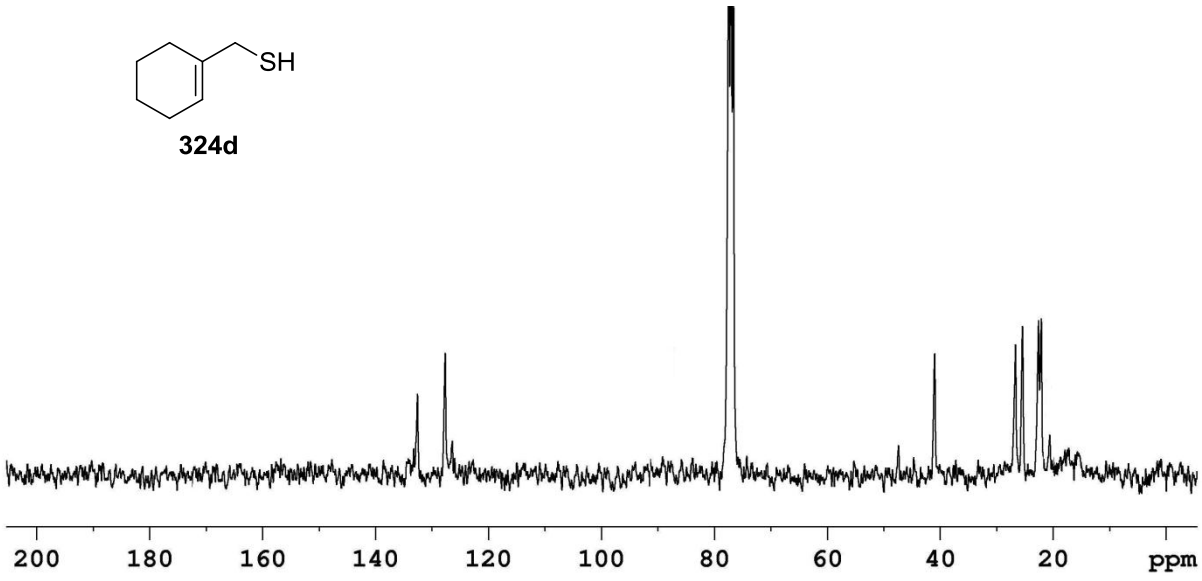


Fig. 115 ^{13}C{^{1}H} NMR Spectrum of cyclohexenylmethanethiol 324d

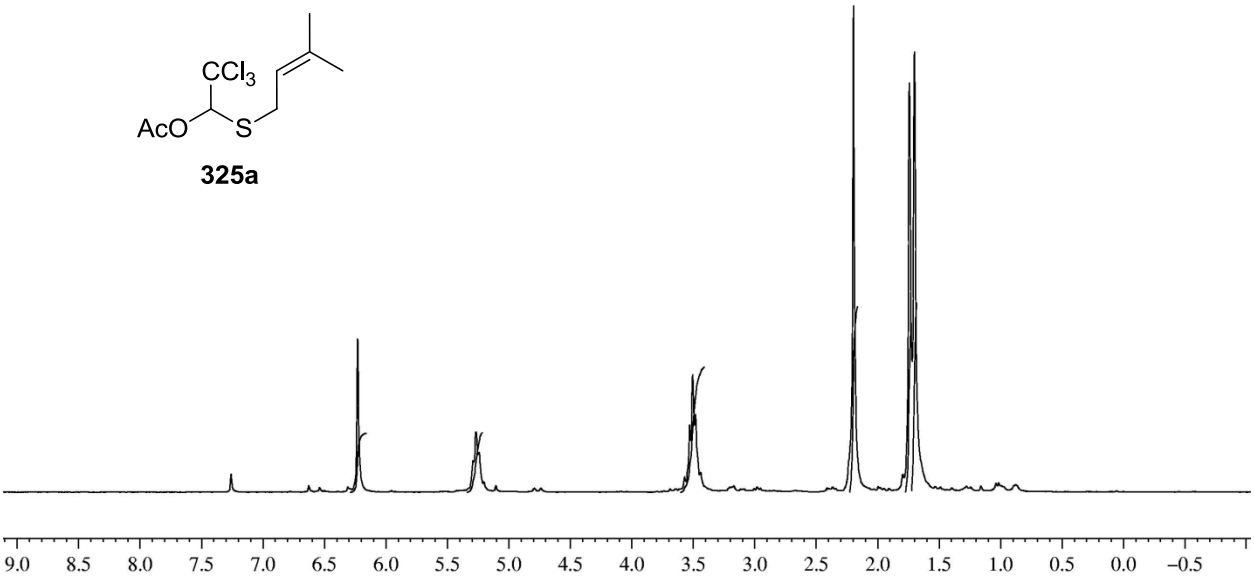


Fig. 116 ^{1}H NMR Spectrum of 2,2,2-trichloro-1-(3-methylbut-2-enylthio)ethyl acetate 325a

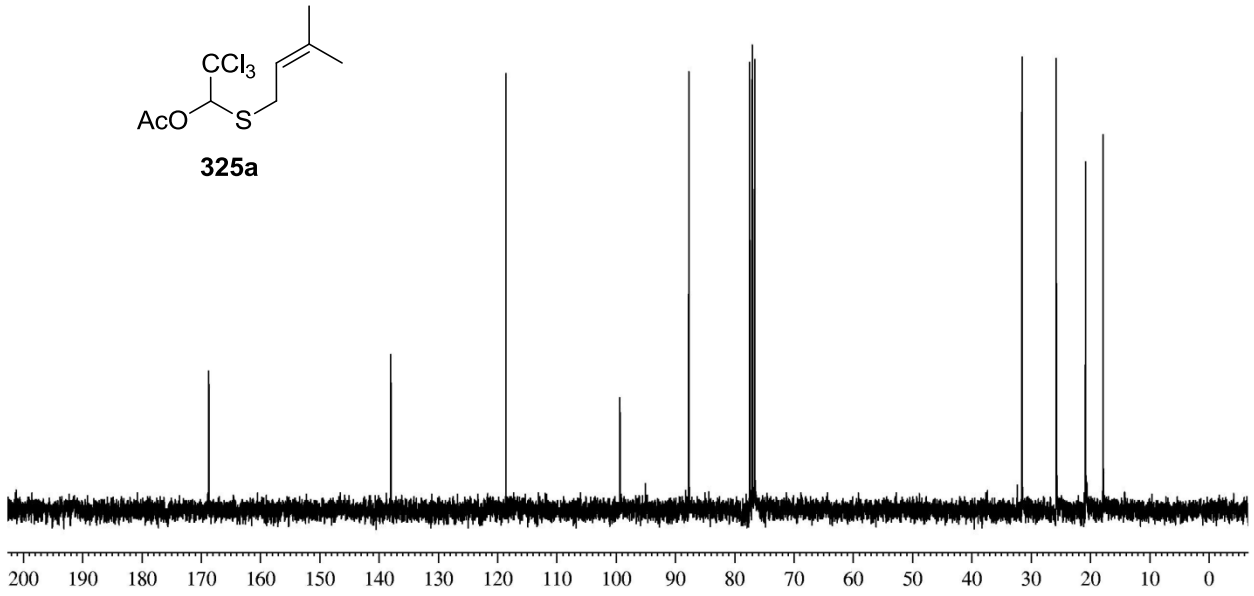


Fig. 117 ^{13}C{^{1}H} NMR Spectrum of 2,2,2-trichloro-1-(3-methylbut-2-enylthio)ethyl acetate 325a

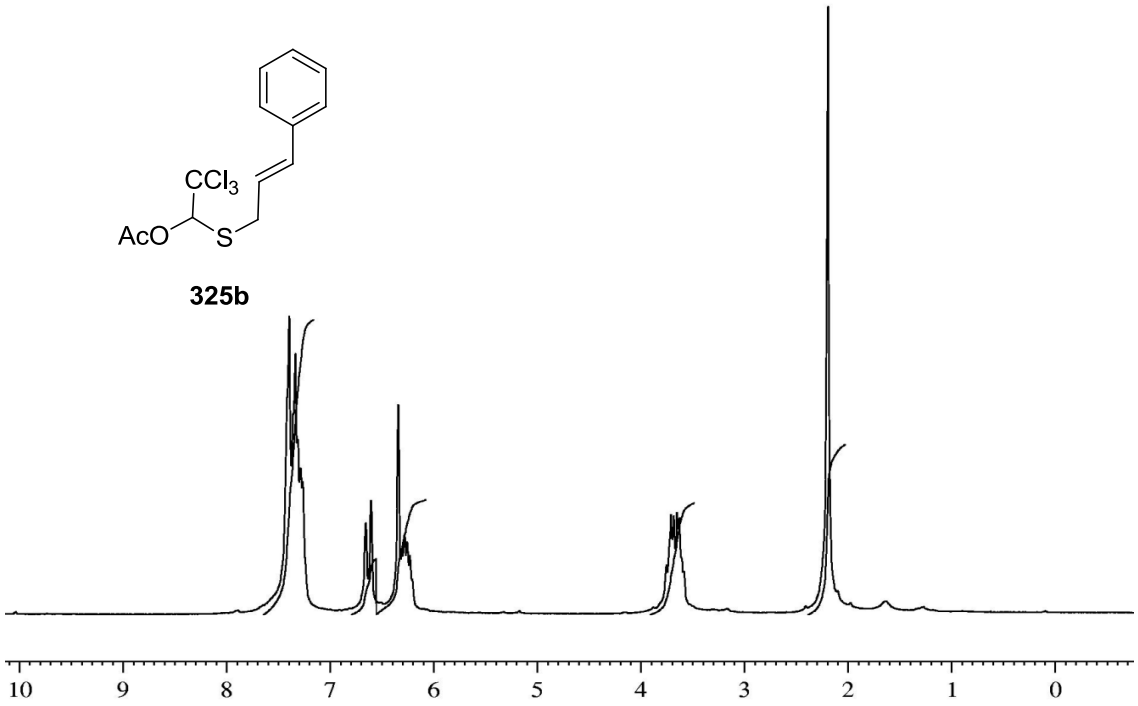


Fig. 118 ^{1}H NMR Spectrum of 2,2,2-trichloro-1-(3-phenylallylthio)ethyl acetate 325b

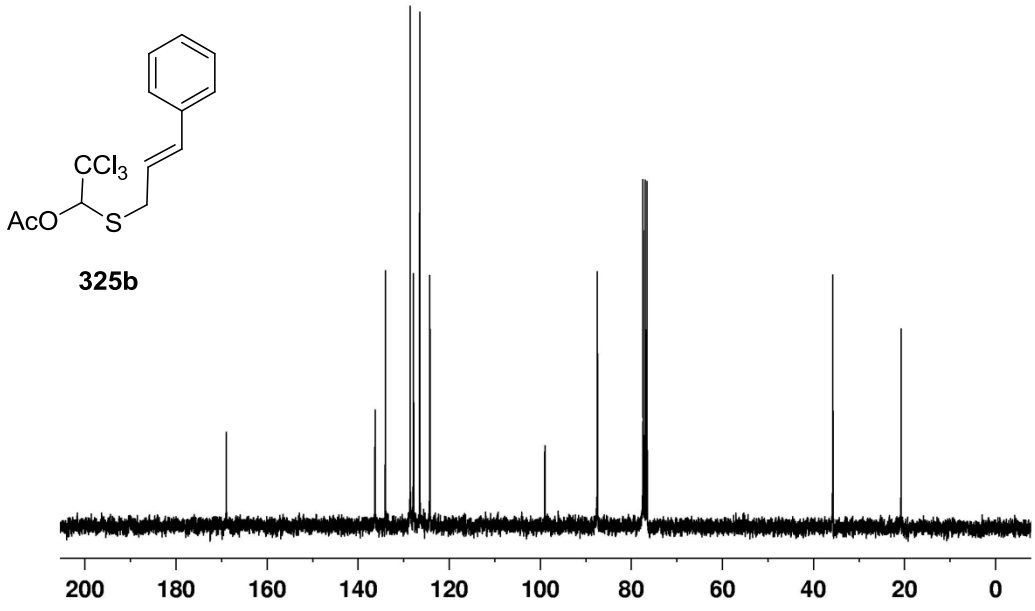


Fig. 119 ^{13}C{^{1}H} NMR Spectrum of 2,2,2-trichloro-1-(3-phenylallylthio)ethyl acetate 325b

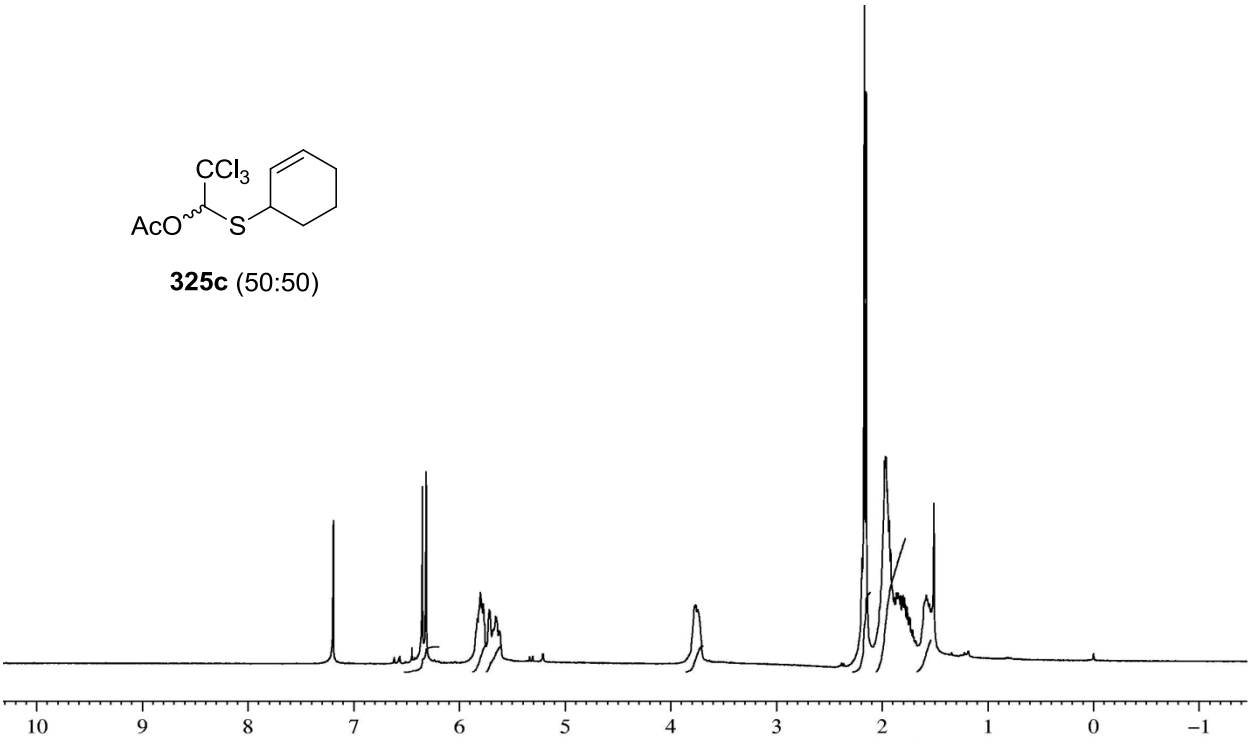


Fig. 120 ^{1}H NMR Spectrum of 2,2,2-trichloro-1-(cyclohex-2-enylthio)ethyl acetate 325c

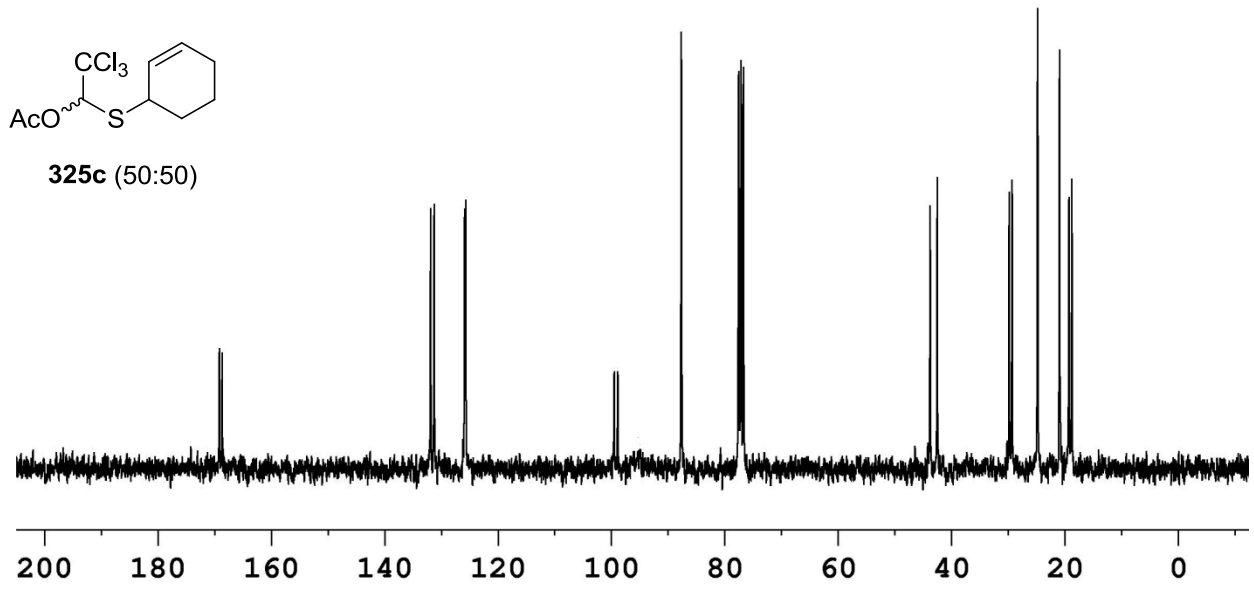


Fig. 121 ^{13}C{^{1}H} NMR Spectrum of 2,2,2-trichloro-1-(cyclohex-2-enylthio)ethyl acetate 325c

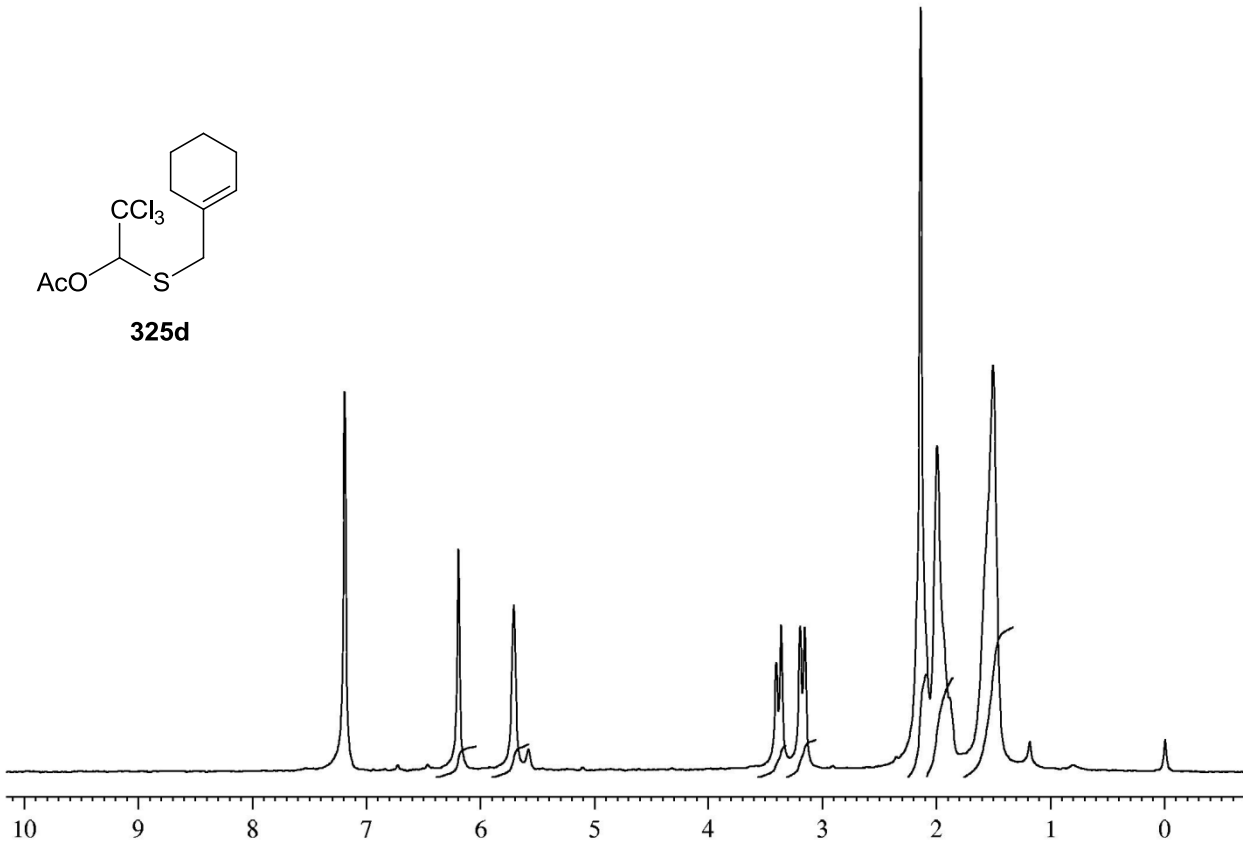


Fig. 122 ^{1}H NMR Spectrum of 2,2,2-trichloro-1-(cyclohexenylmethylthio)ethyl acetate 325d

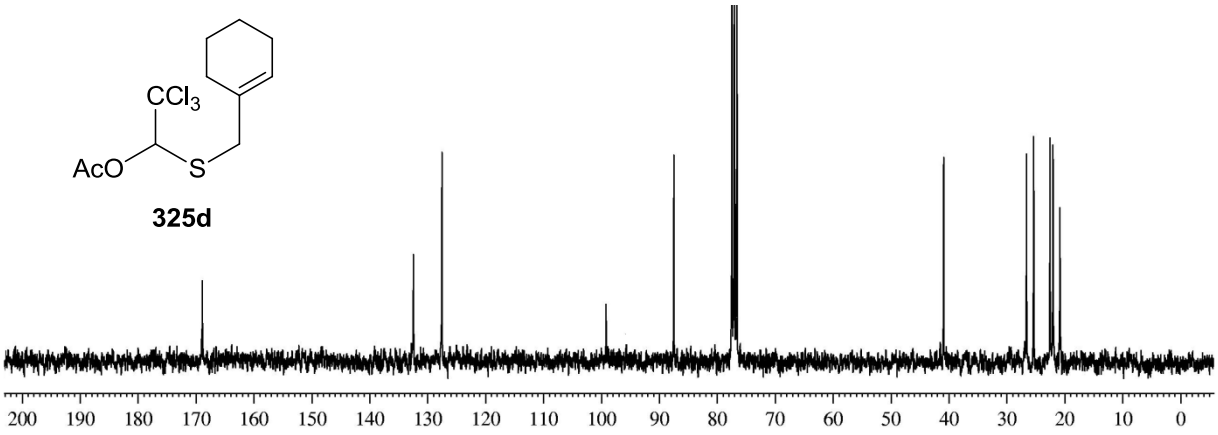


Fig. 123 ^{13}C{^{1}H} NMR Spectrum of 2,2,2-trichloro-1-(cyclohexenylmethylthio)ethyl acetate 325d

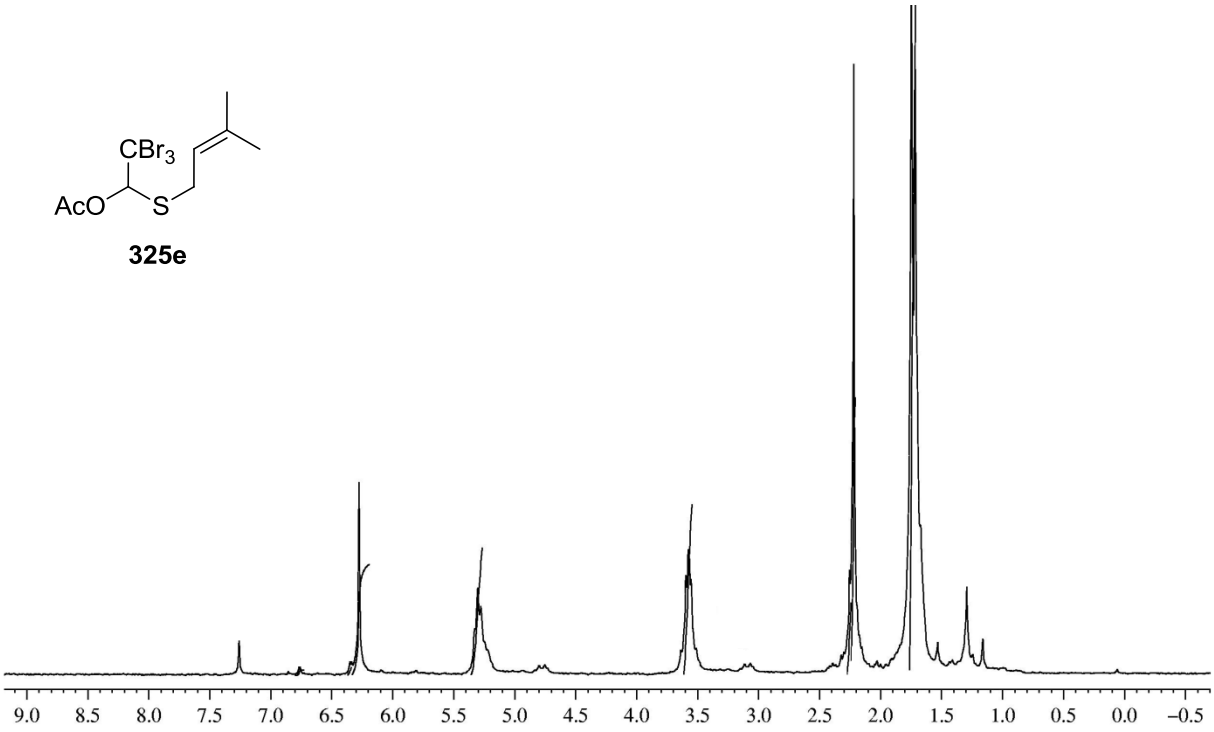


Fig. 124 ^{1}H NMR Spectrum of 2,2,2-tribromo-1-(3-methylbut-2-enylthio)ethyl 325e

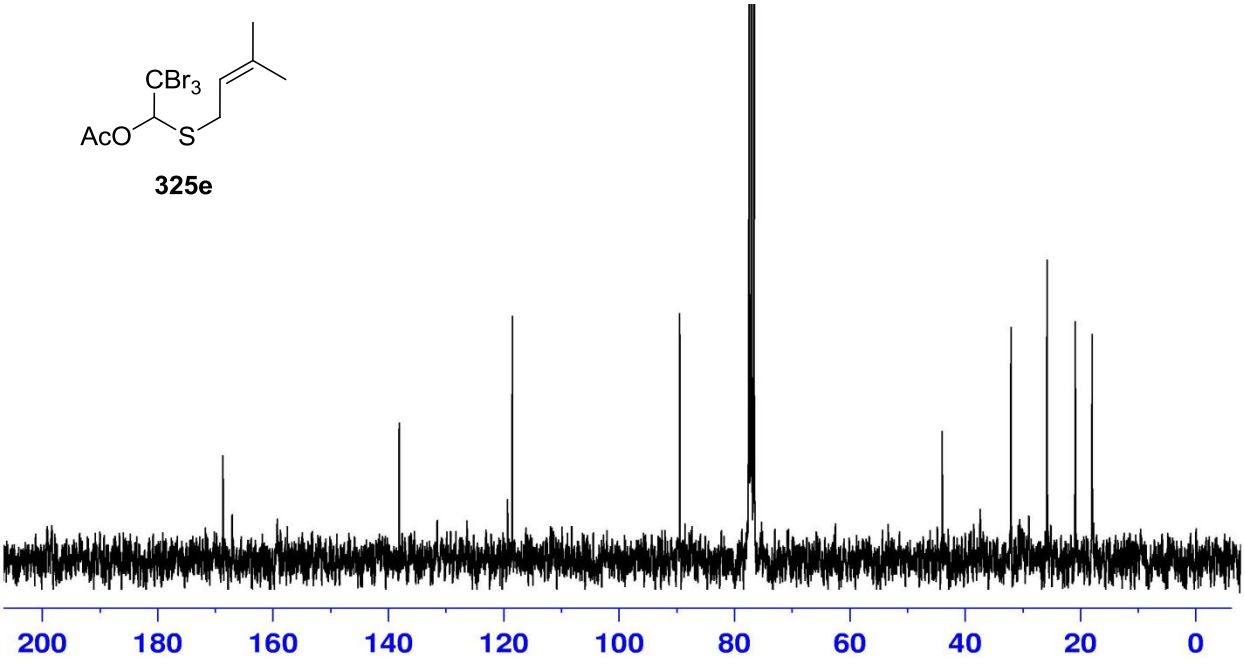


Fig. 125 ^{13}C{^{1}H} NMR Spectrum of 2,2,2-tribromo-1-(3-methylbut-2-enylthio)ethyl 325e

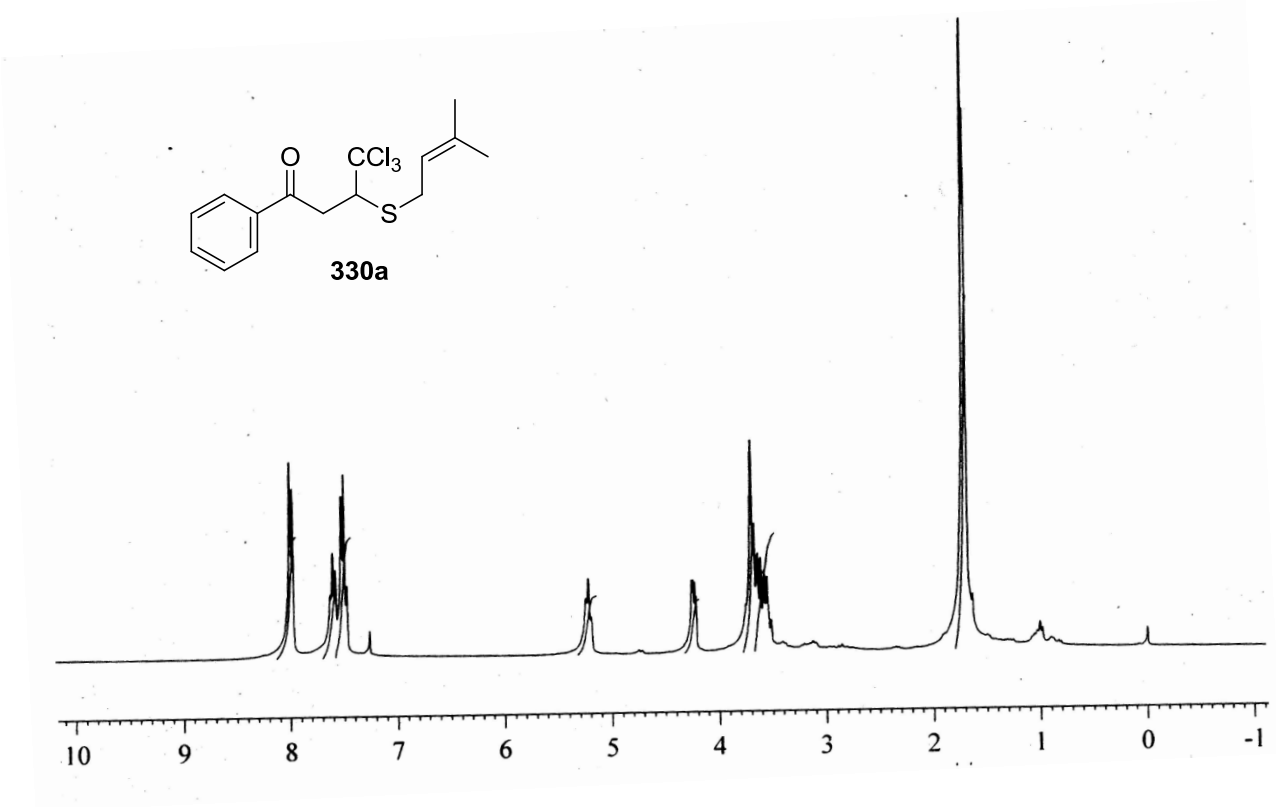


Fig. 126 ^{1}H NMR Spectrum of 4,4,4-trichloro-3-(3-methylbut-2-enylthio)-1-phenylbutan-1-one 330a

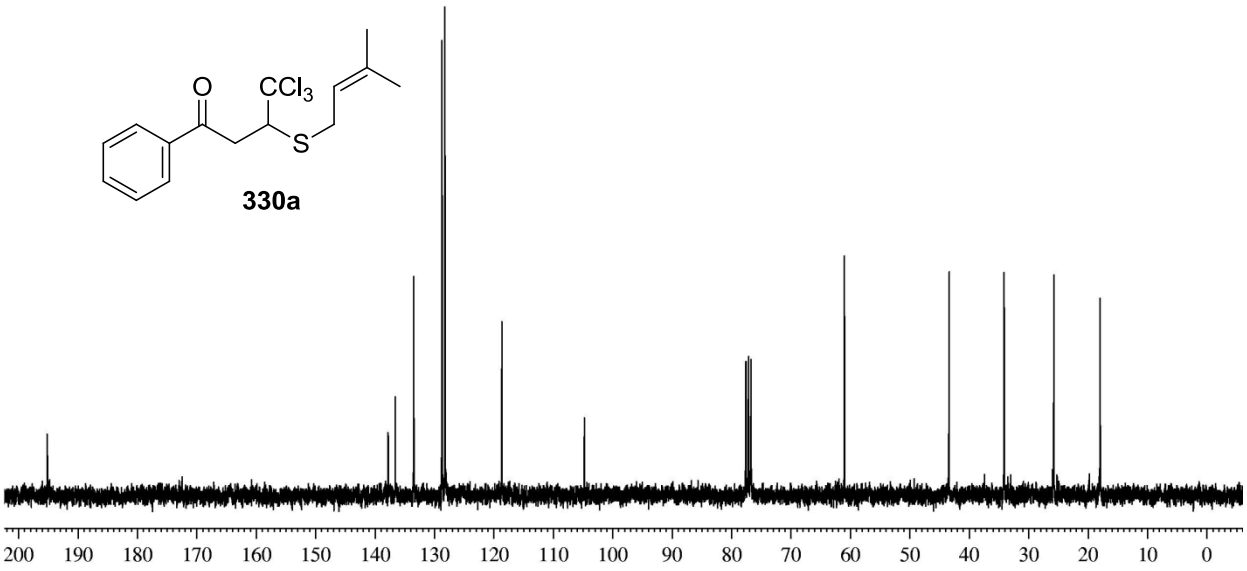


Fig. 127 ^{13}C{^{1}H} NMR Spectrum of 4,4,4-trichloro-3-(3-methylbut-2-enylthio)-1-phenylbutan-1-one 330a

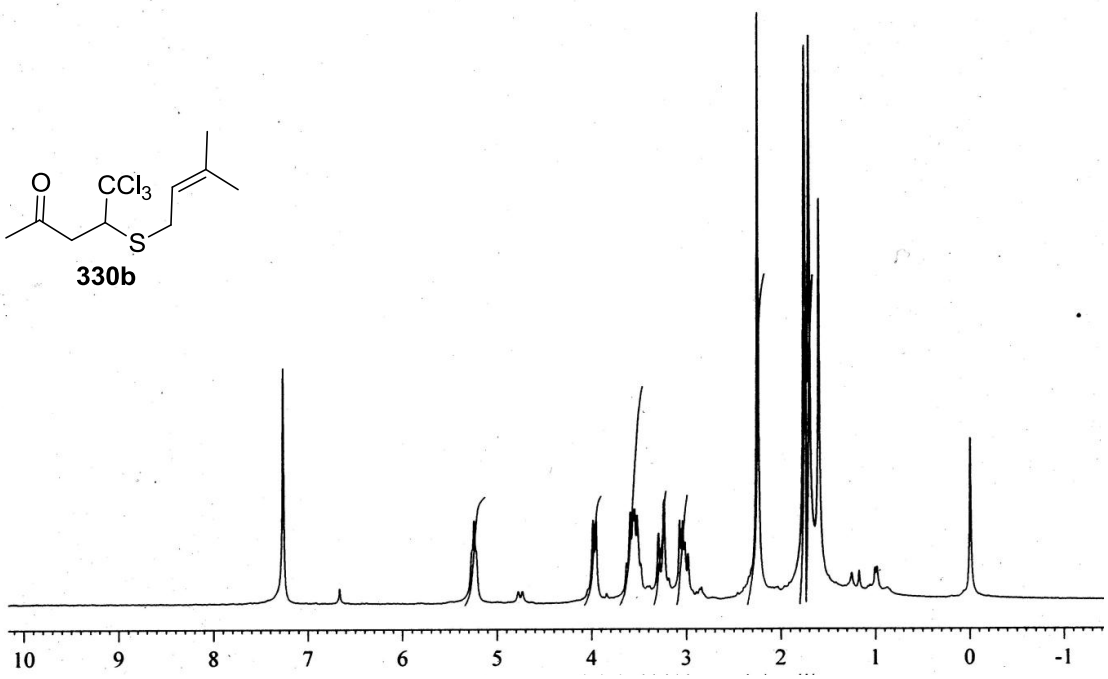


Fig. 128 ^{1}H NMR Spectrum of 5,5,5-trichloro-4-(3-methylbut-2-enylthio)pentan-2-one 330b

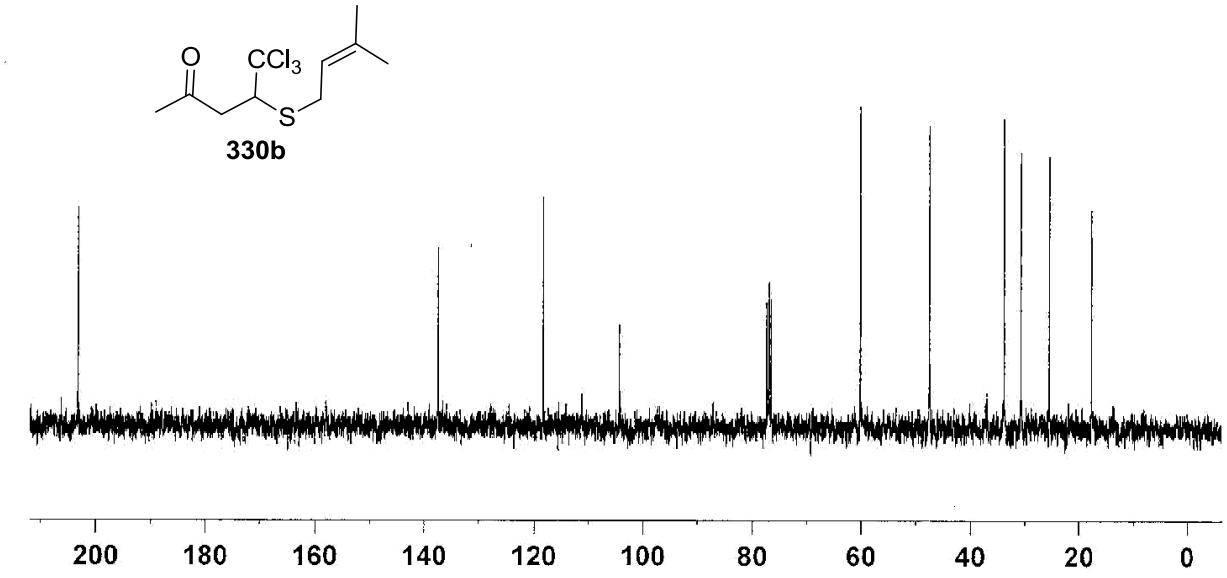


Fig. 129 ^{13}C{^{1}H} NMR Spectrum of 5,5,5-trichloro-4-(3-methylbut-2-enylthio)pentan-2-one 330b

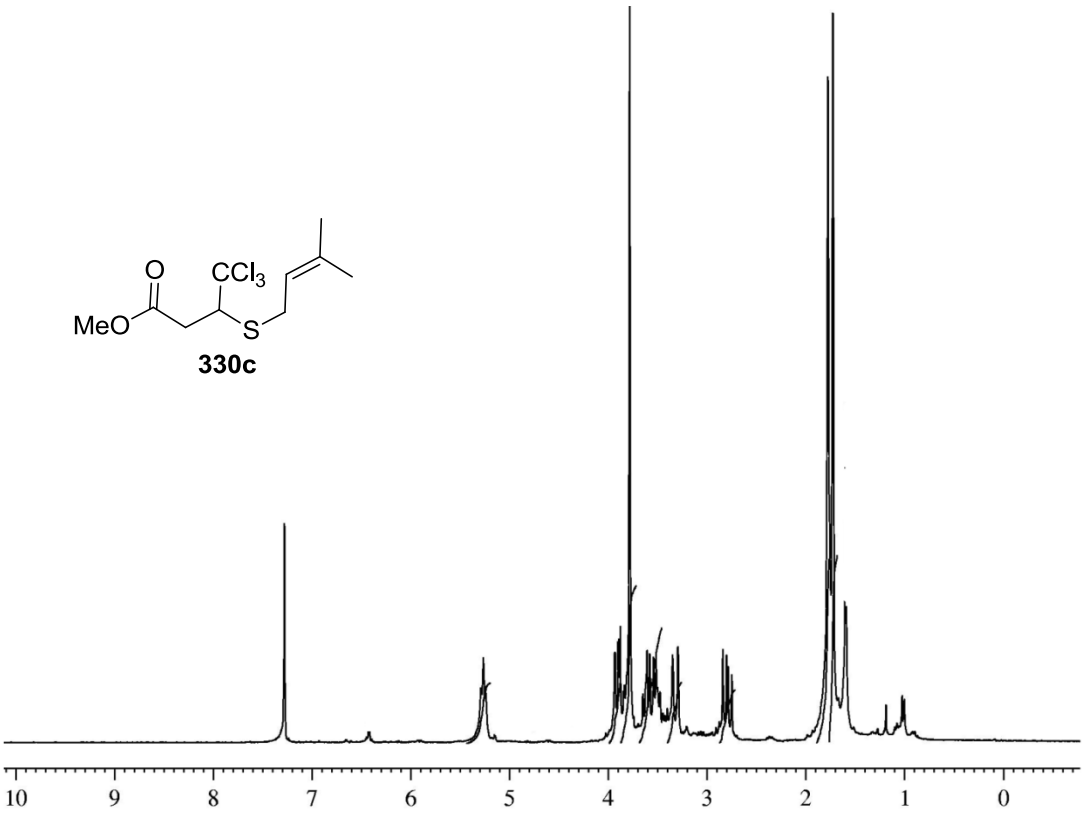


Fig. 130 ^{1}H NMR Spectrum of methyl 4,4,4-trichloro-3-(3-methylbut-2-enylthio)butanoate 330c

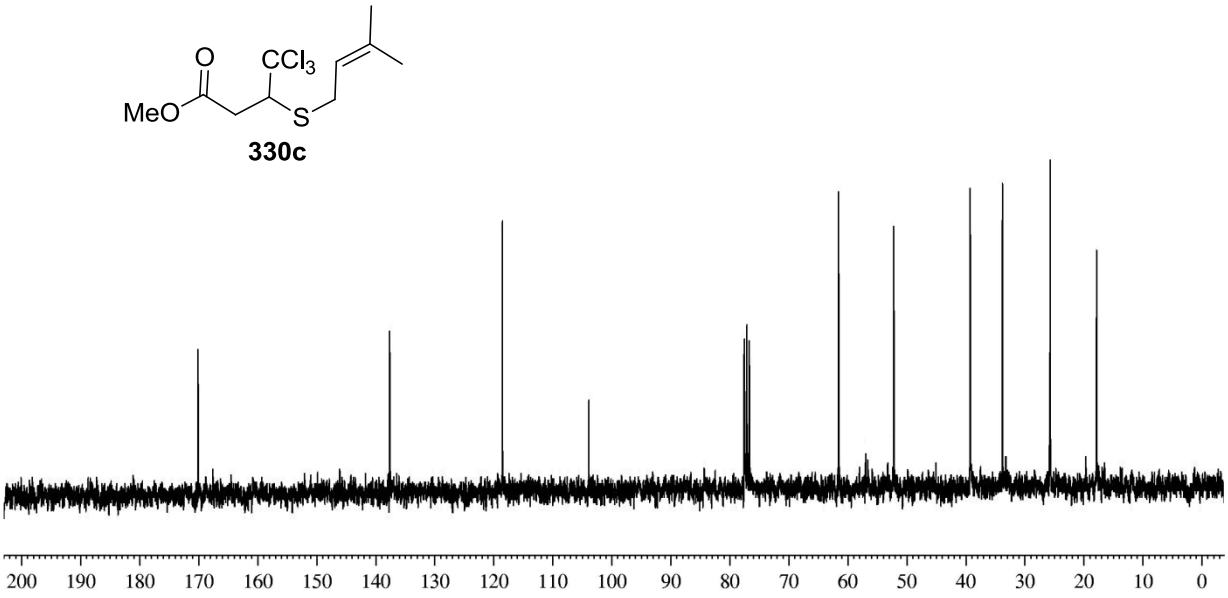


Fig. 131 ^{13}C{^{1}H} NMR Spectrum of methyl 4,4,4-trichloro-3-(3-methylbut-2-enylthio)butanoate 330c

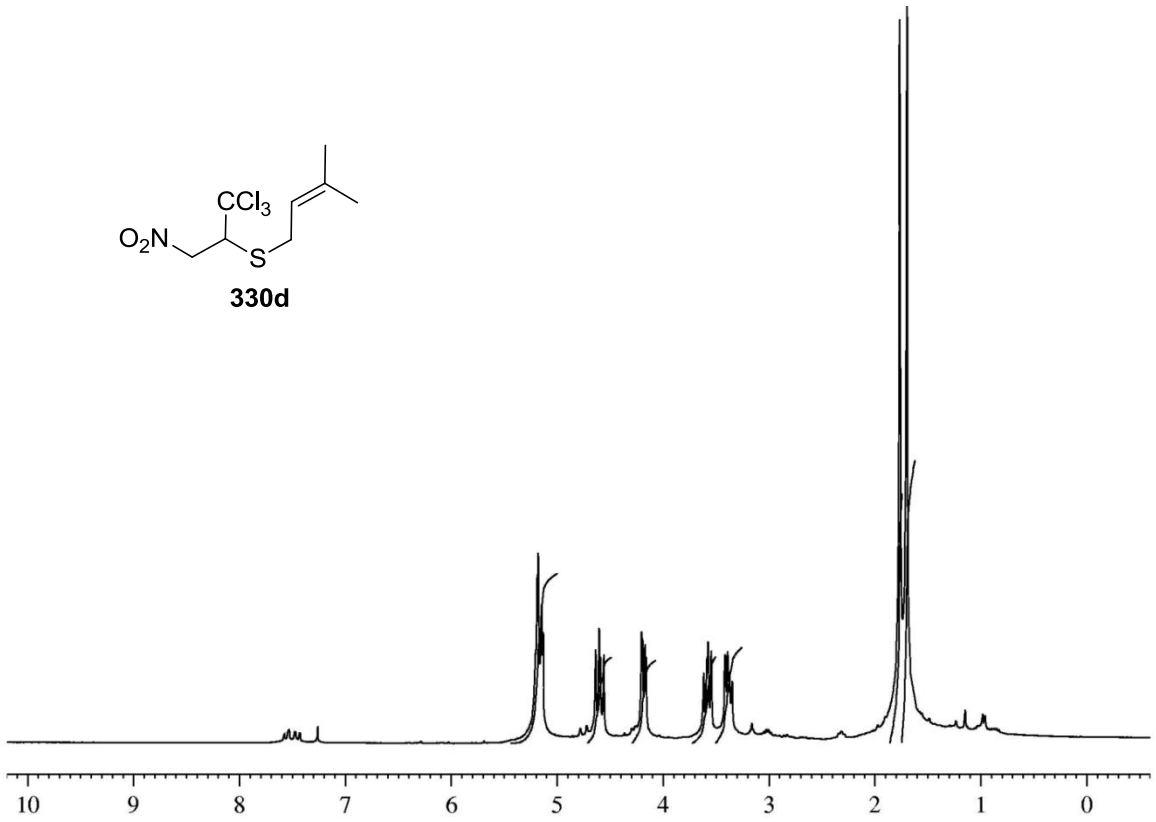


Fig. 132 ^{1}H NMR Spectrum of (3-methylbut-2-enyl)(1,1,1-trichloro-3-nitropropan-2-yl)sulfane 330d

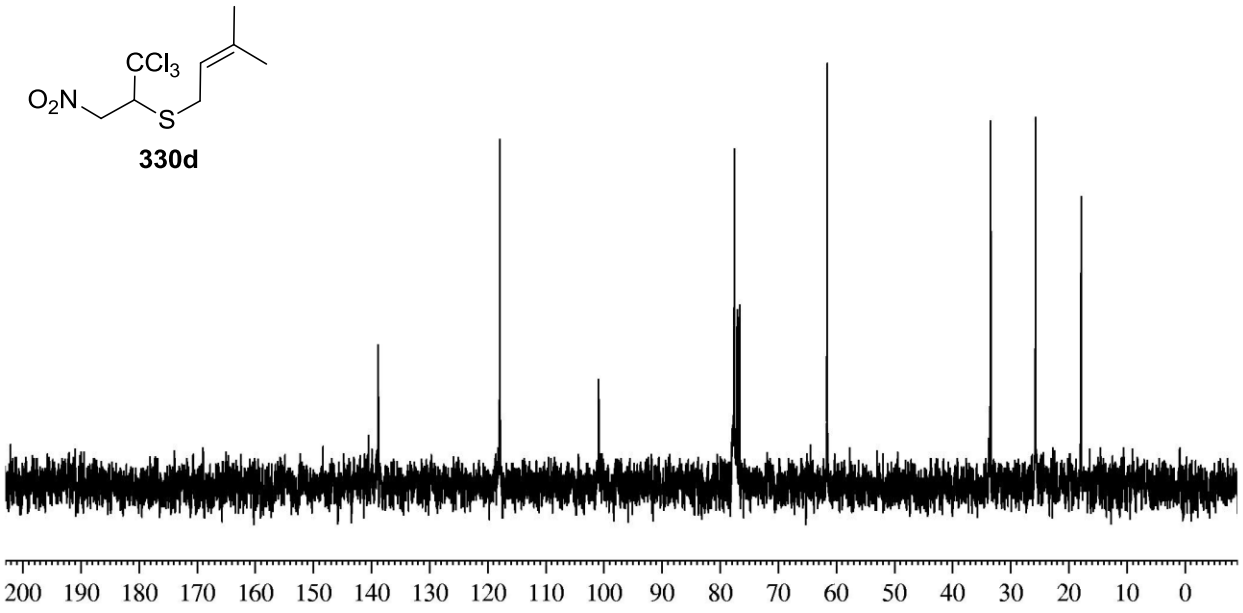


Fig. 133 ^{13}C{^{1}H} NMR Spectrum of (3-methylbut-2-enyl)(1,1,1-trichloro-3-nitropropan-2-yl)sulfane 330d

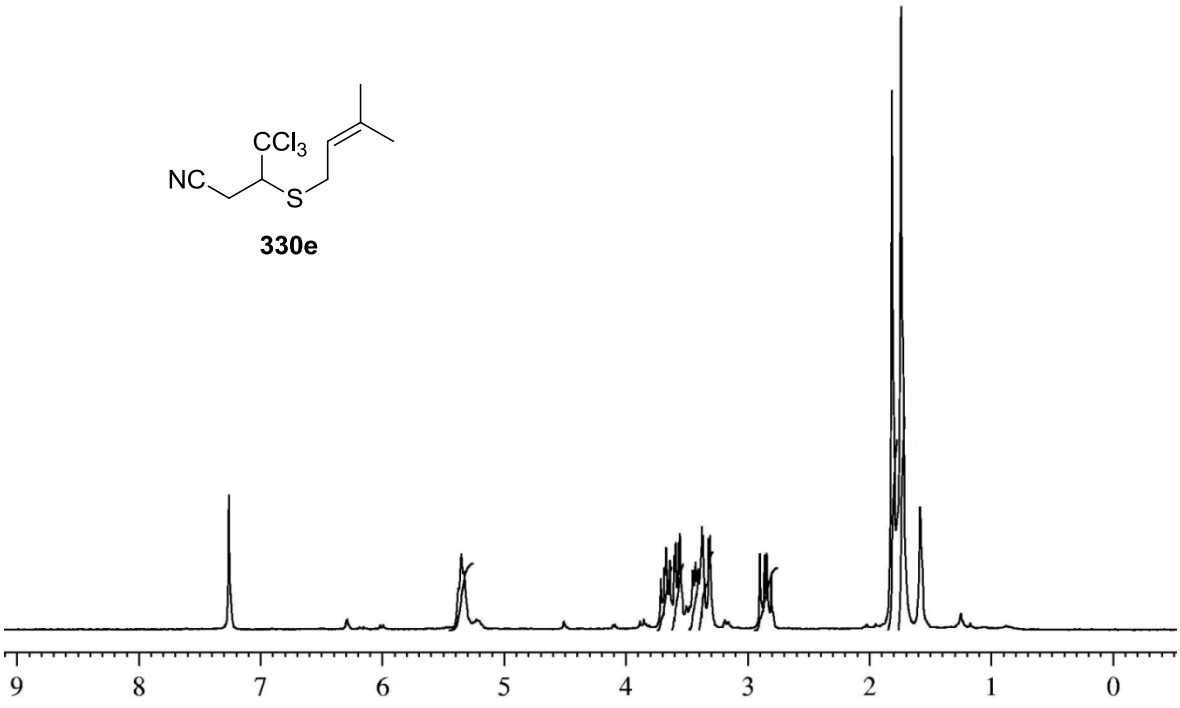


Fig. 134 ^{1}H NMR Spectrum of 4,4,4-trichloro-3-(3-methylbut-2-enylthio)butanenitrile 330e

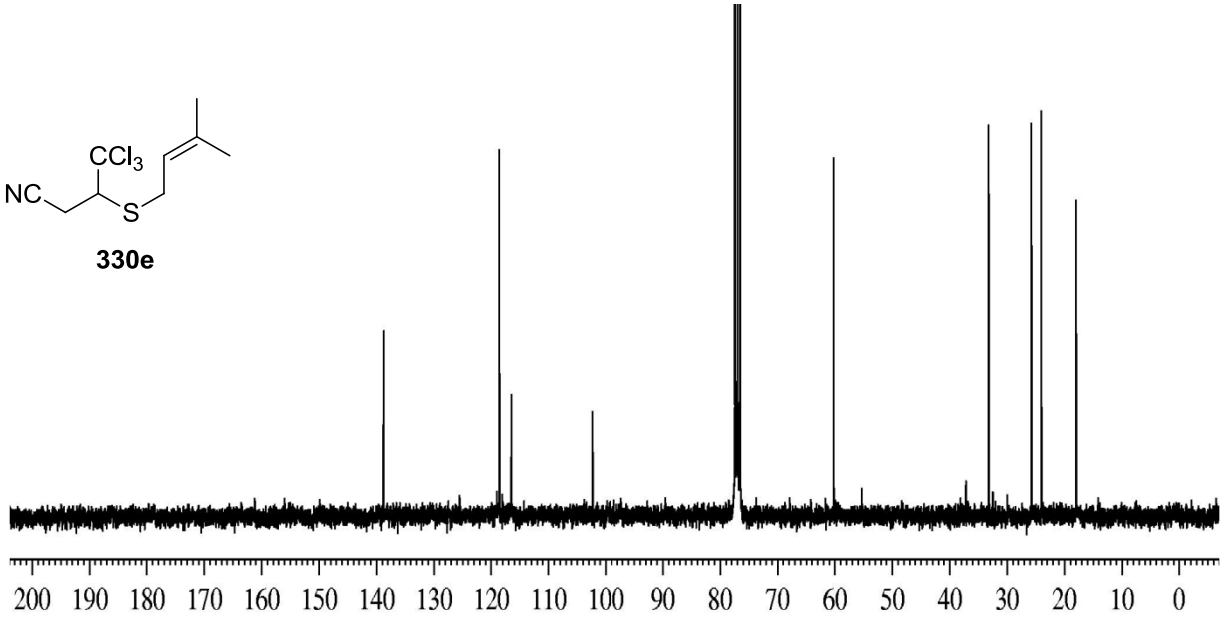


Fig. 135 ^{13}C{^{1}H} NMR Spectrum of 4,4,4-trichloro-3-(3-methylbut-2-enylthio)butanenitrile 330e

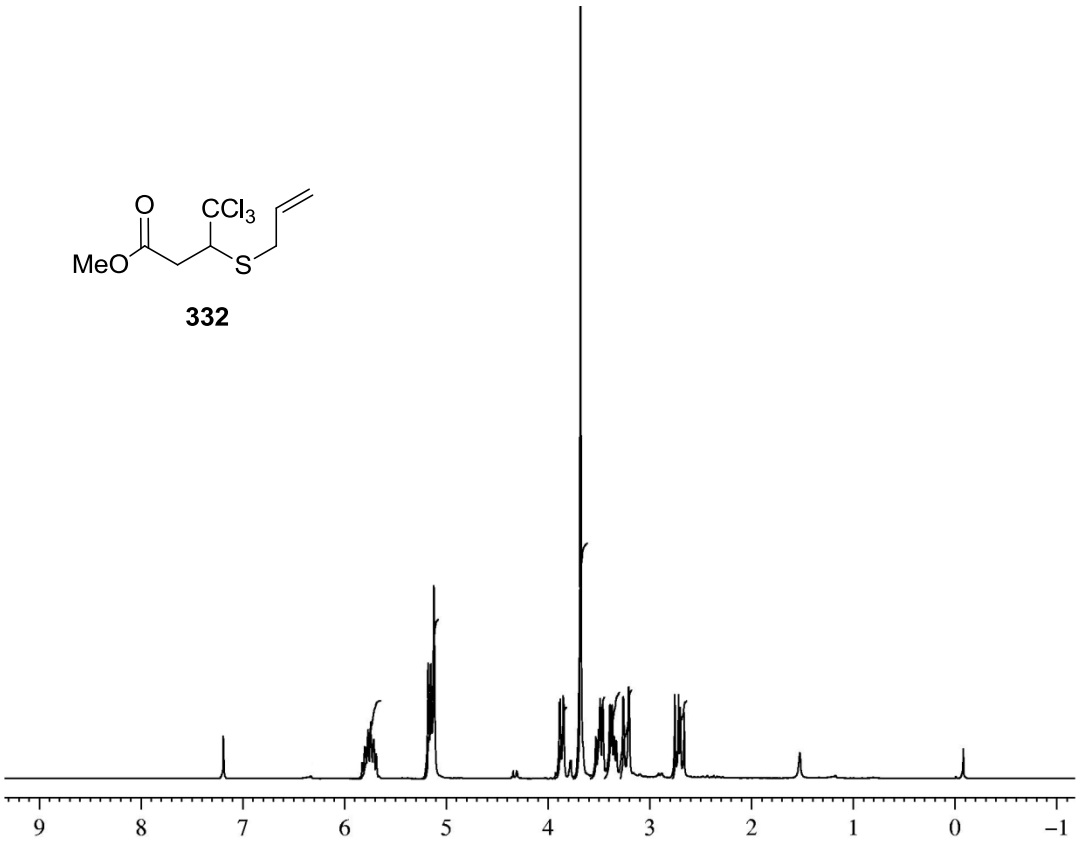


Fig. 136 ^{1}H NMR Spectrum of methyl 3-(allylthio)-4,4,4-trichlorobutanoate 332

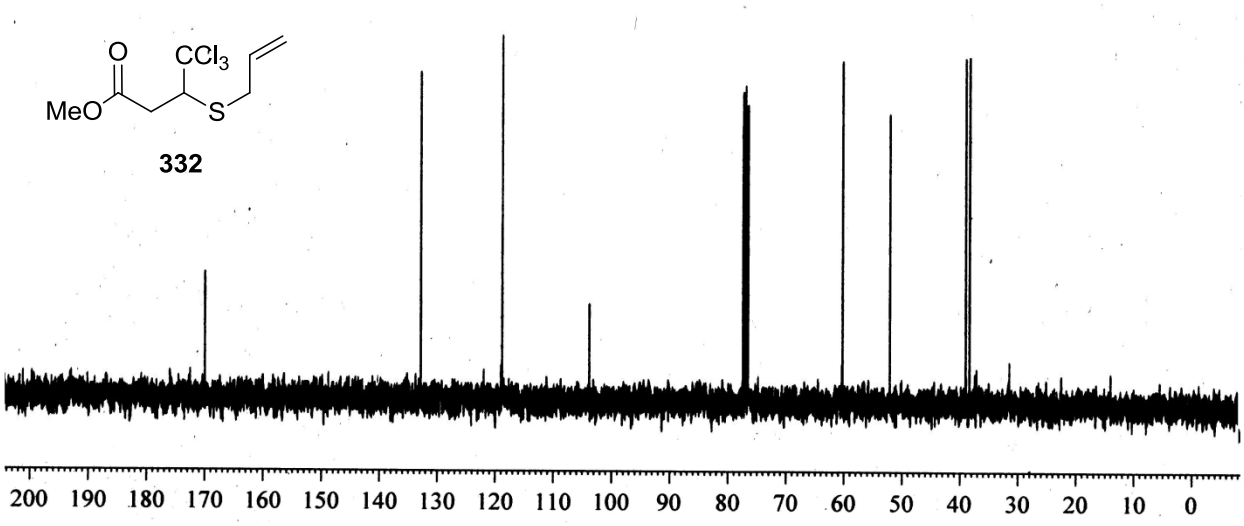


Fig. 137 ^{13}C{^{1}H} NMR Spectrum of methyl 3-(allylthio)-4,4,4-trichlorobutanoate 332

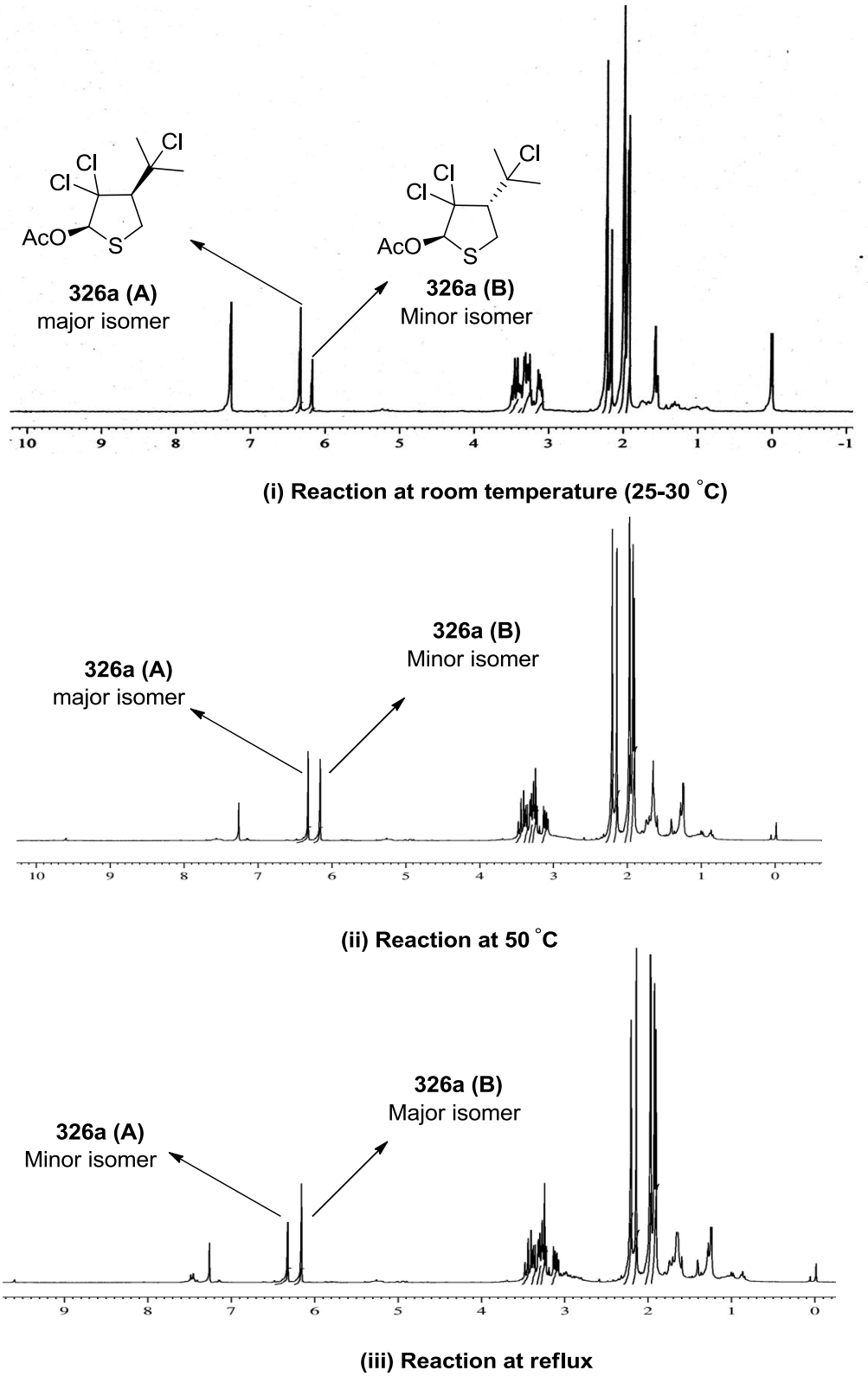


Fig. 138 Effect of temperature on diastereoselectivity of 326a

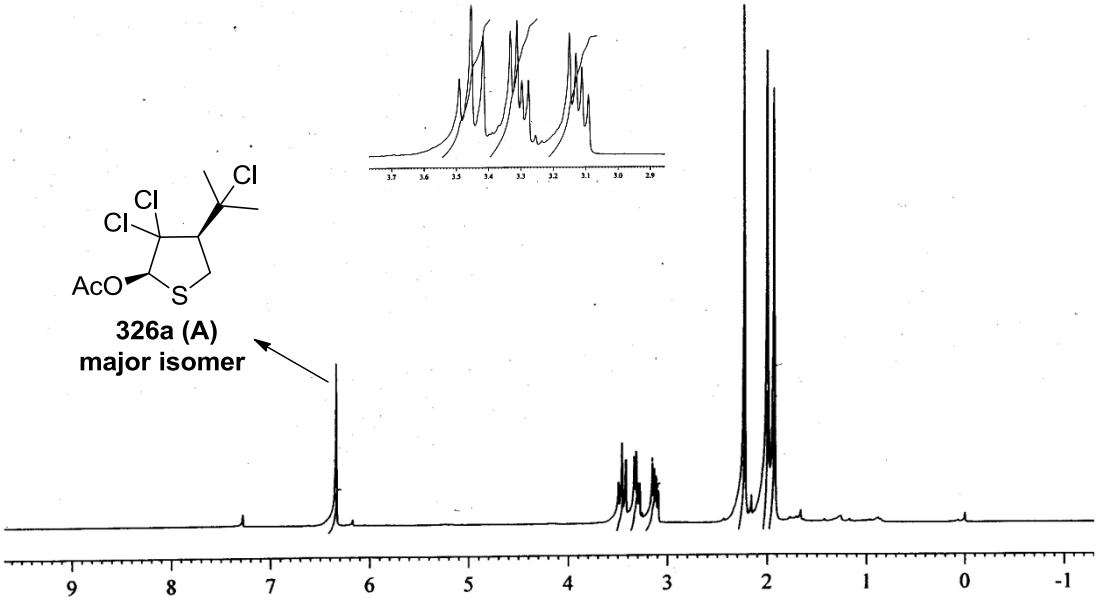


Fig. 139 ^{1}H NMR Spectrum of 3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl acetate 326a (A) (major diastereomer)

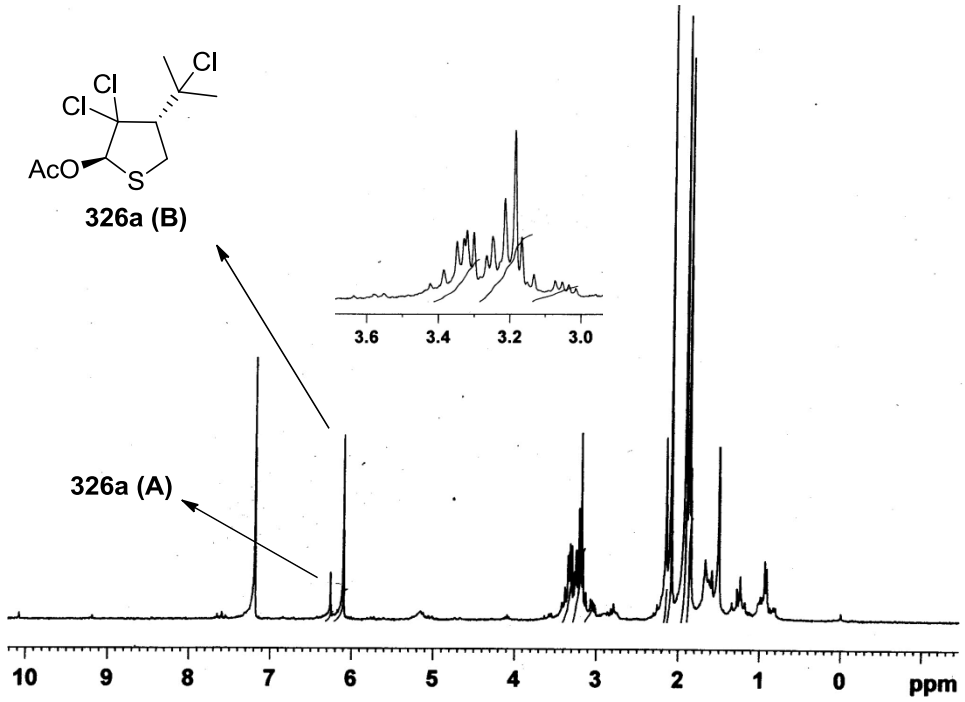


Fig. 140 ^{1}H NMR Spectrum of 3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl acetate 326a (B) in mother liquor

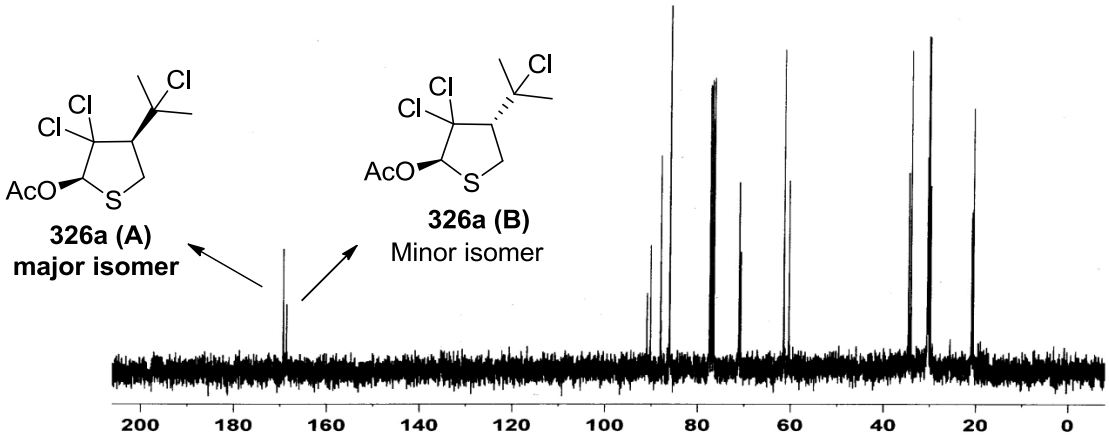


Fig. 141 $^{13}C\{^{1}H\}$ NMR Spectrum of 3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl acetate 326a (A&B) obtained after work up

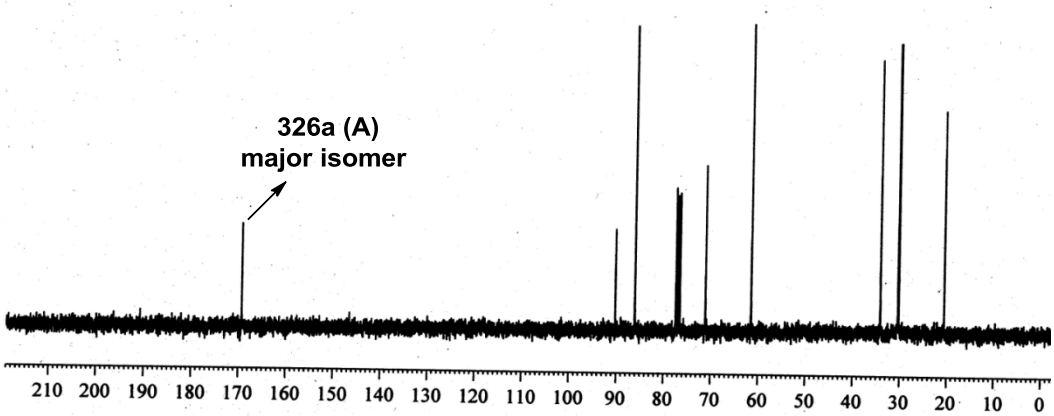


Fig. 142 $^{13}C\{^{1}H\}$ NMR Spectrum of 3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl acetate 326a (A) (major diastereomer)

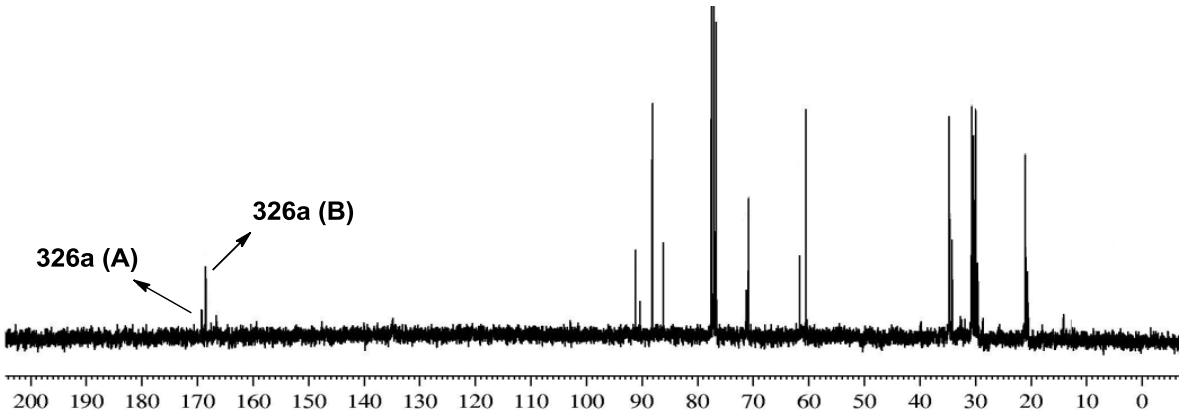


Fig. 143 $^{13}C\{^{1}H\}$ NMR Spectrum of 3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl acetate 326a (B) in mother liquor

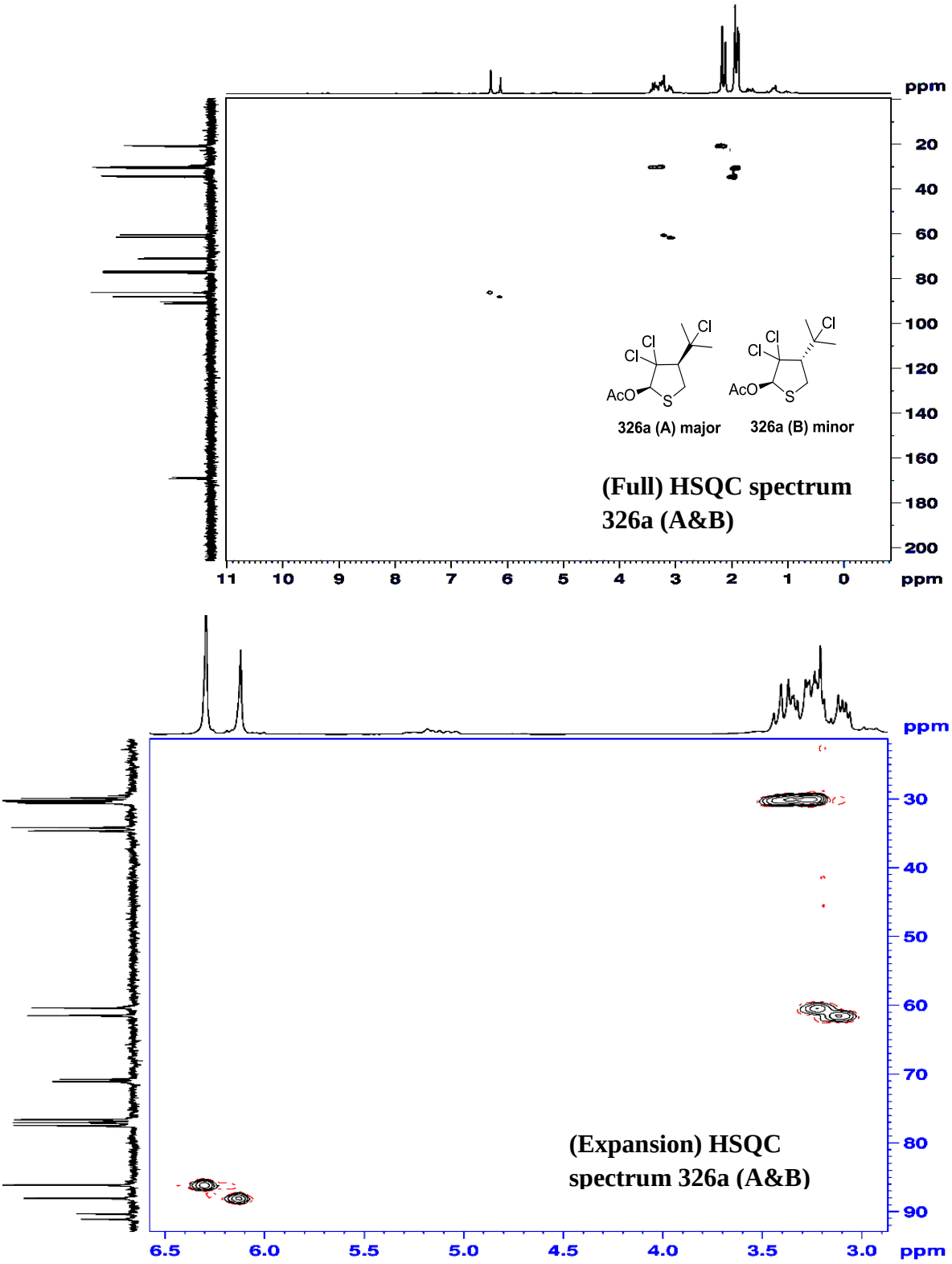


Fig. 144 HSQC NMR Spectrum of 3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl acetate 326a (A & B)

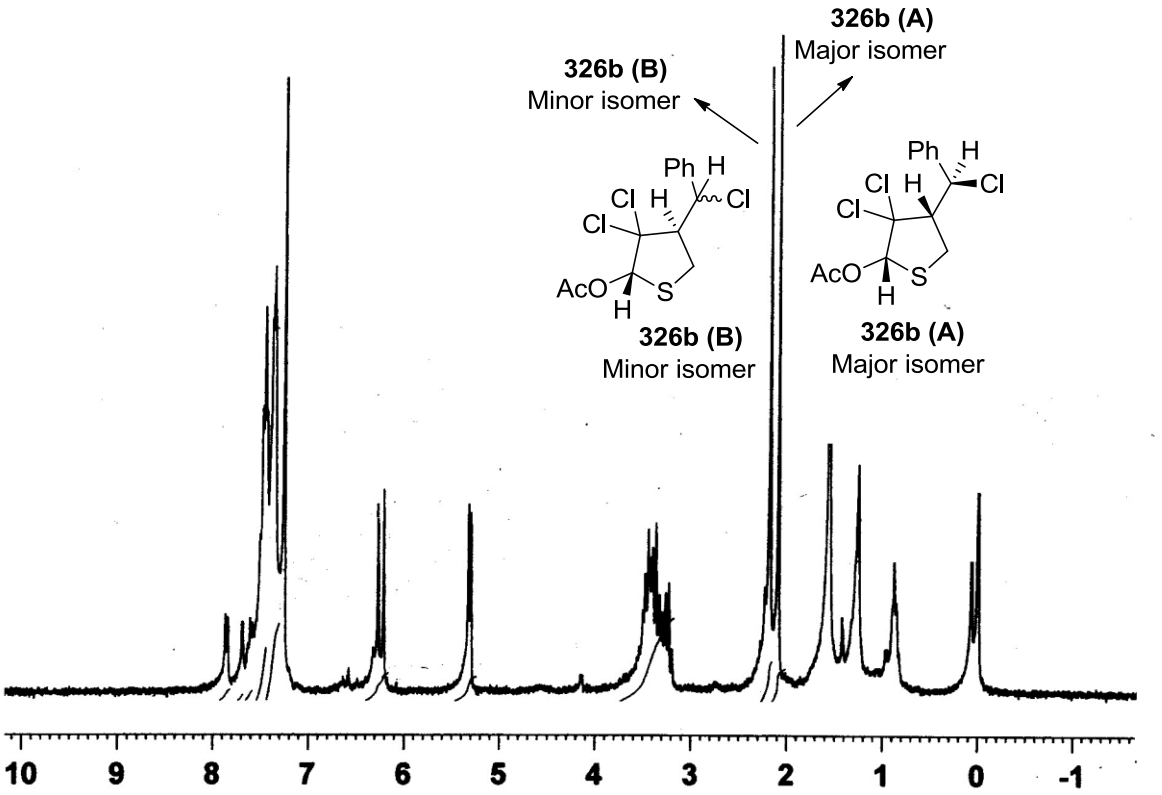


Fig. 145 ^{1}H NMR Spectrum of 3,3-dichloro-4-((S)-chloro(phenyl)methyl)-tetrahydrothiophen-2-yl acetate 326b (A & B)-(crude product)

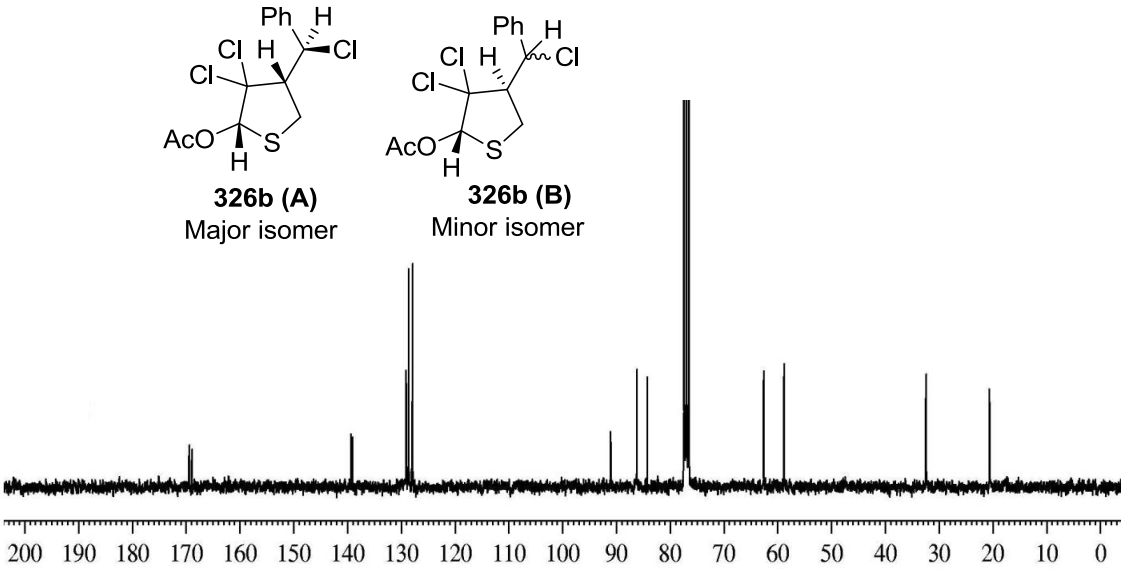


Fig. 146 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-((S)-chloro(phenyl)methyl)-tetrahydrothiophen-2-yl acetate 326b (A & B) (crude product)

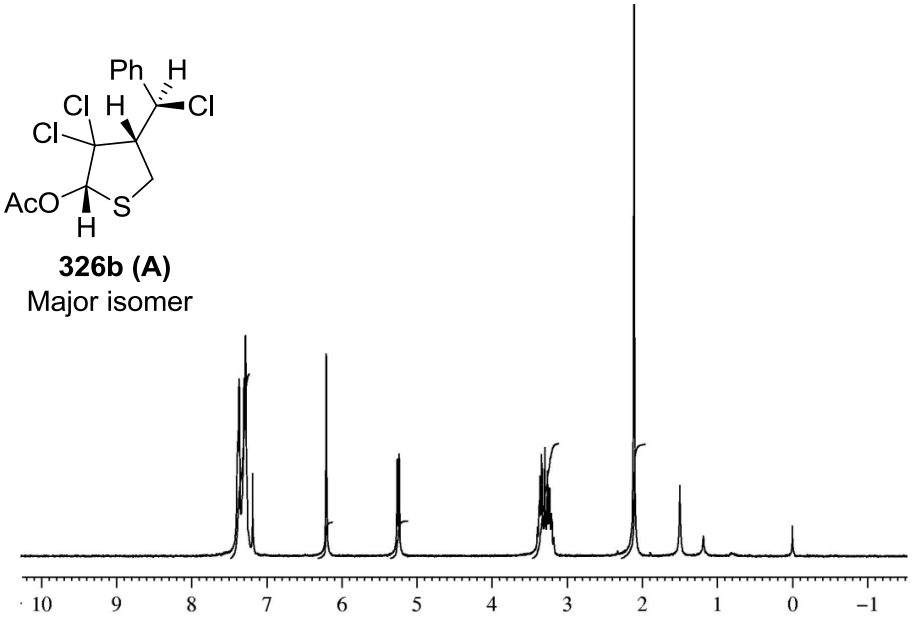


Fig. 147 ^{1}H NMR Spectrum of 3,3-dichloro-4-((S)-chloro(phenyl)methyl)-tetrahydrothiophen-2-yl acetate 326b (A)(major diastereomer)

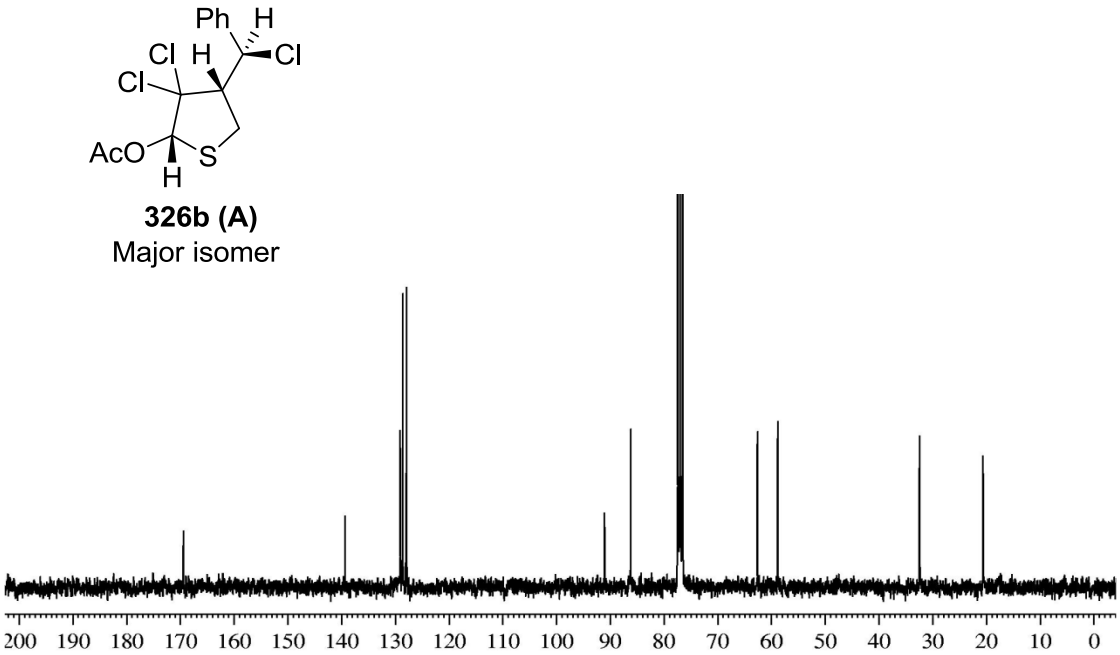


Fig. 148 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-((S)-chloro(phenyl)methyl)-etrahydrothiophen-2-yl acetate 326b (A) (major diastereomer)

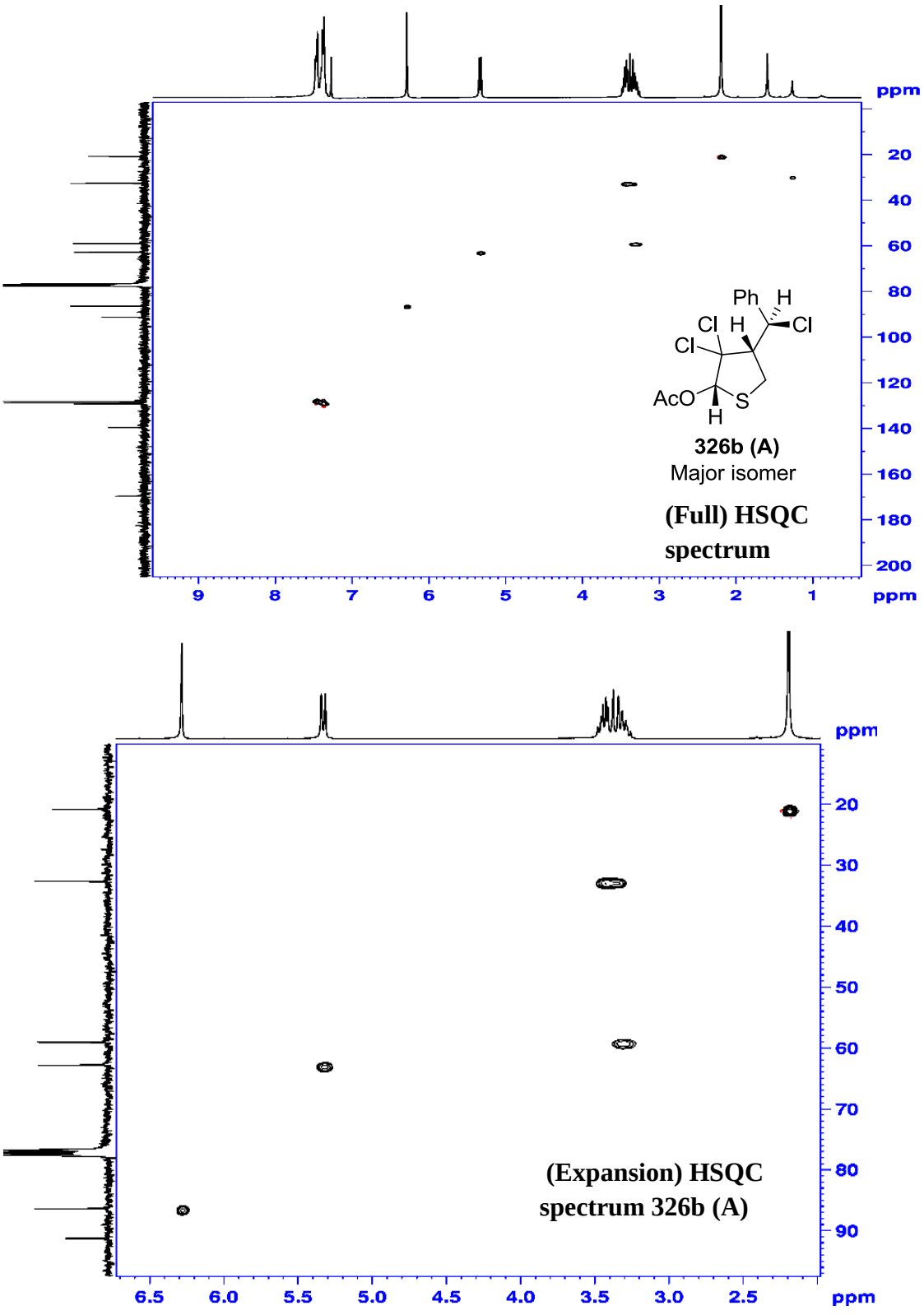


Fig. 149 HSQC Spectrum of 3,3-dichloro-4-((S)-chloro(phenyl)methyl)-tetrahydrothiophen-2-yl acetate 326b (A) (major diastereomer)

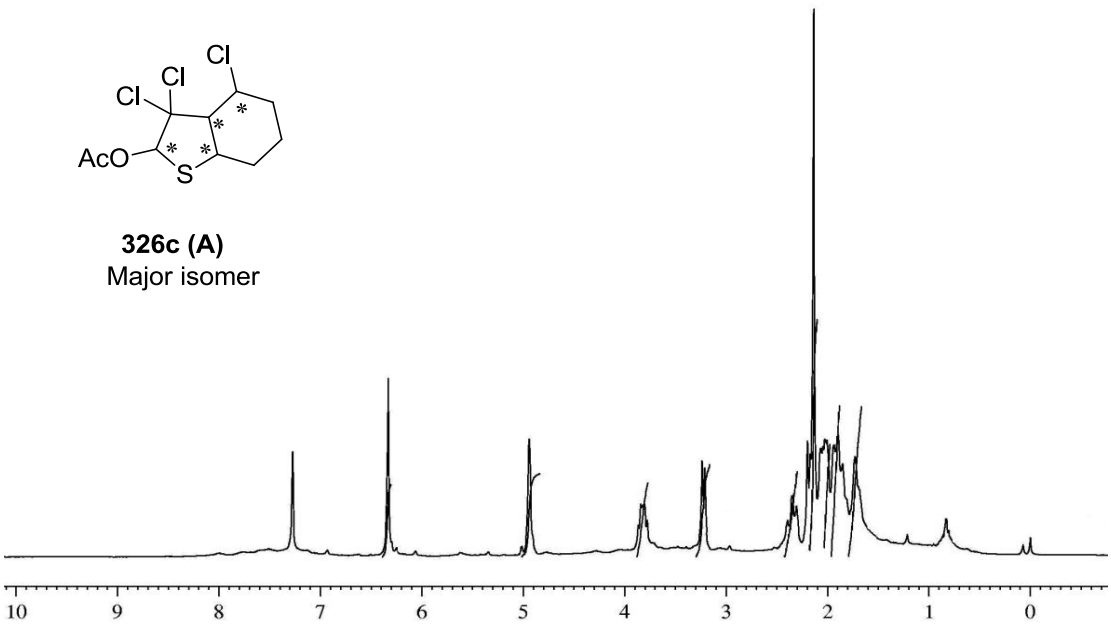


Fig. 150 ^{1}H NMR Spectrum of 3,3,4-trichloro-octahydrobenzo[b]thiophen-2-yl acetate 326c(A) (major diastereomer)

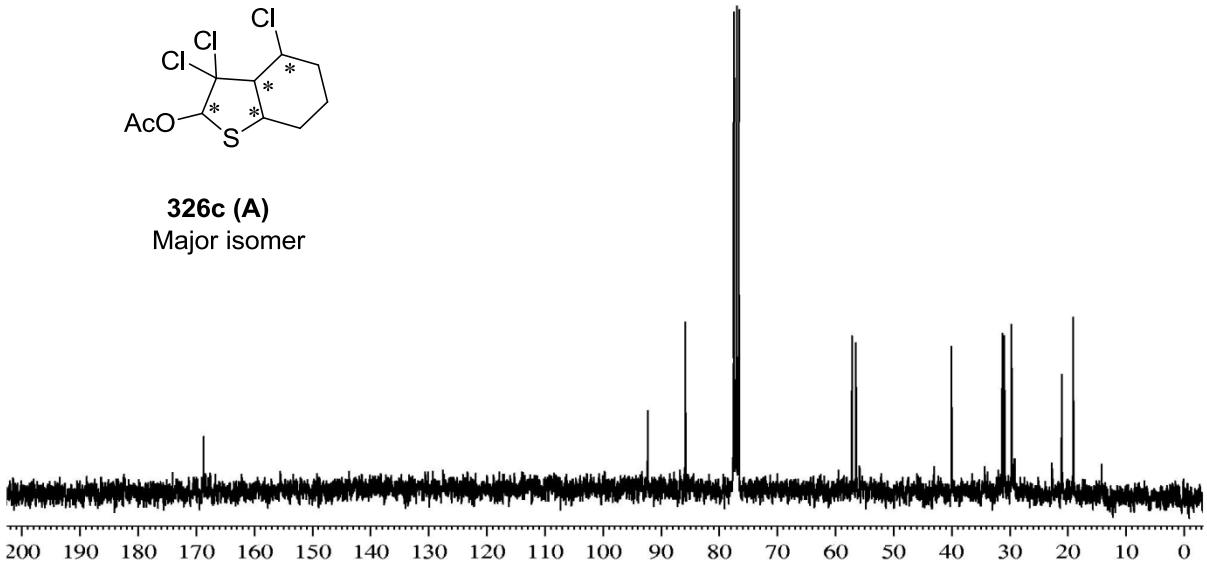


Fig. 151 ^{13}C{^{1}H} NMR Spectrum of 3,3,4-trichloro-octahydrobenzo[b]thiophen-2-yl acetate 326c (A) (major diastereomer)

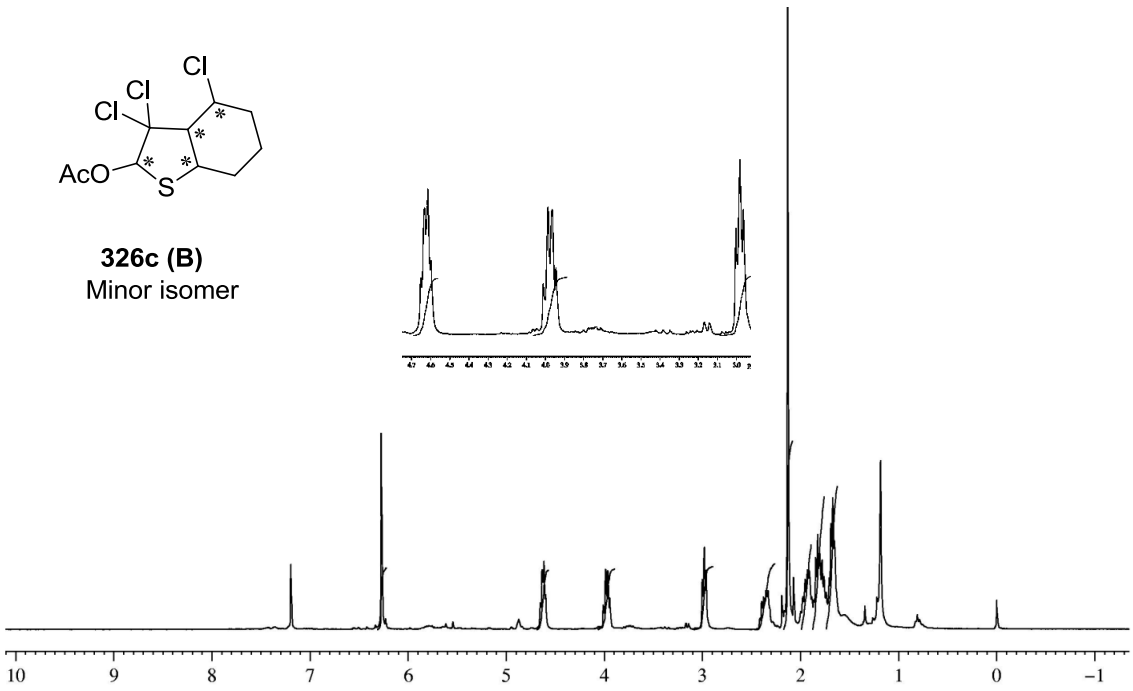


Fig. 152 ^{1}H NMR Spectrum of 3,3,4-trichloro-octahydrobenzo[b]thiophen-2-yl acetate 326c (B) (minor diastereomer)

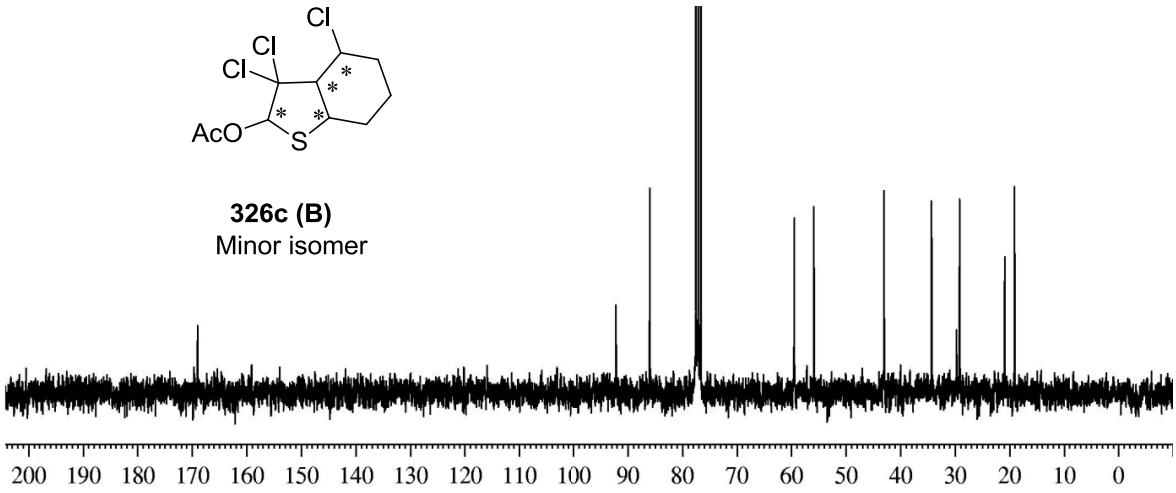


Fig. 153 ^{13}C{^{1}H} NMR Spectrum of 3,3,4-trichloro-octahydrobenzo[b]thiophen-2-yl acetate 326c (B) (minor diastereomer)

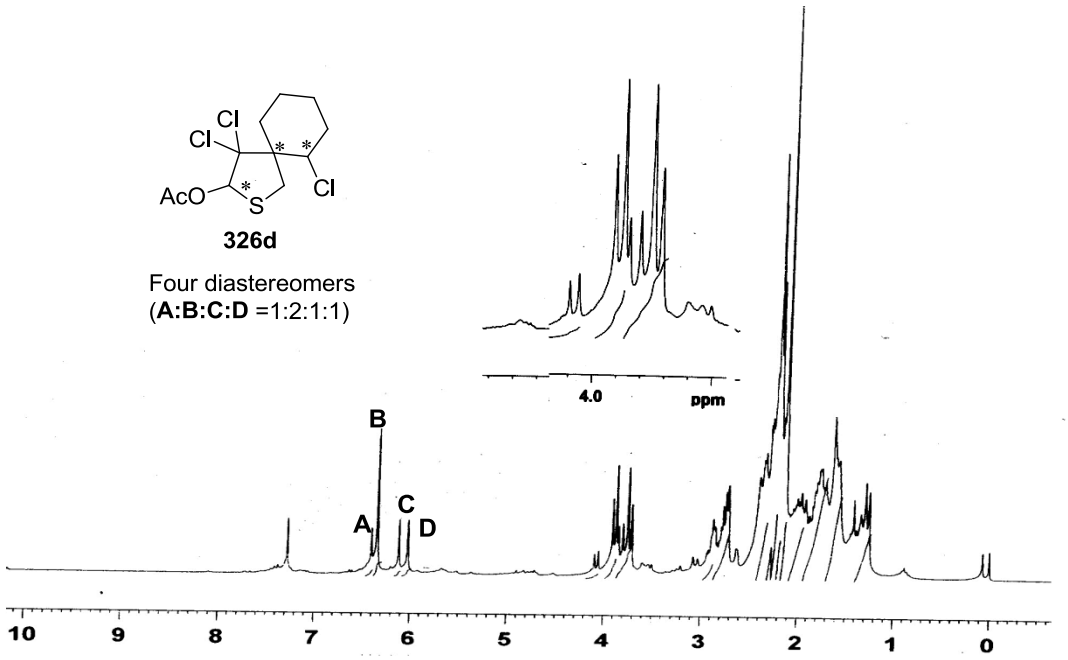


Fig. 154 ^{1}H NMR Spectrum of spiro(cyclohexyl)dihydrothiophene 326d (crude product)

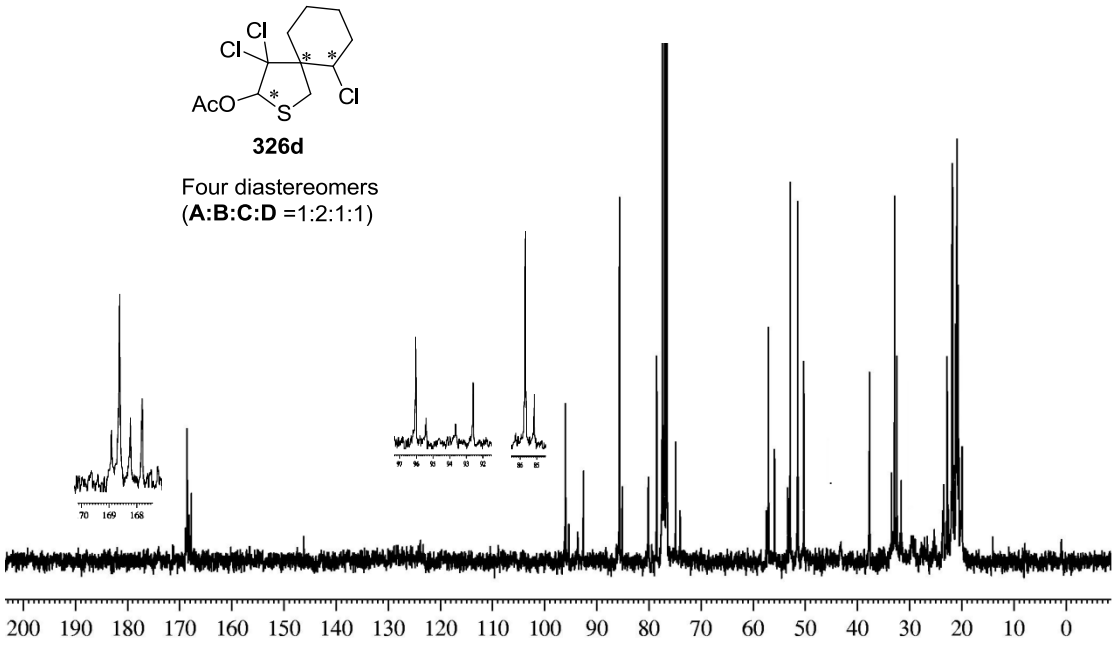


Fig. 155 ^{13}C{^{1}H} NMR Spectrum of spiro(cyclohexyl)dihydrothiophene 326d (crude product)

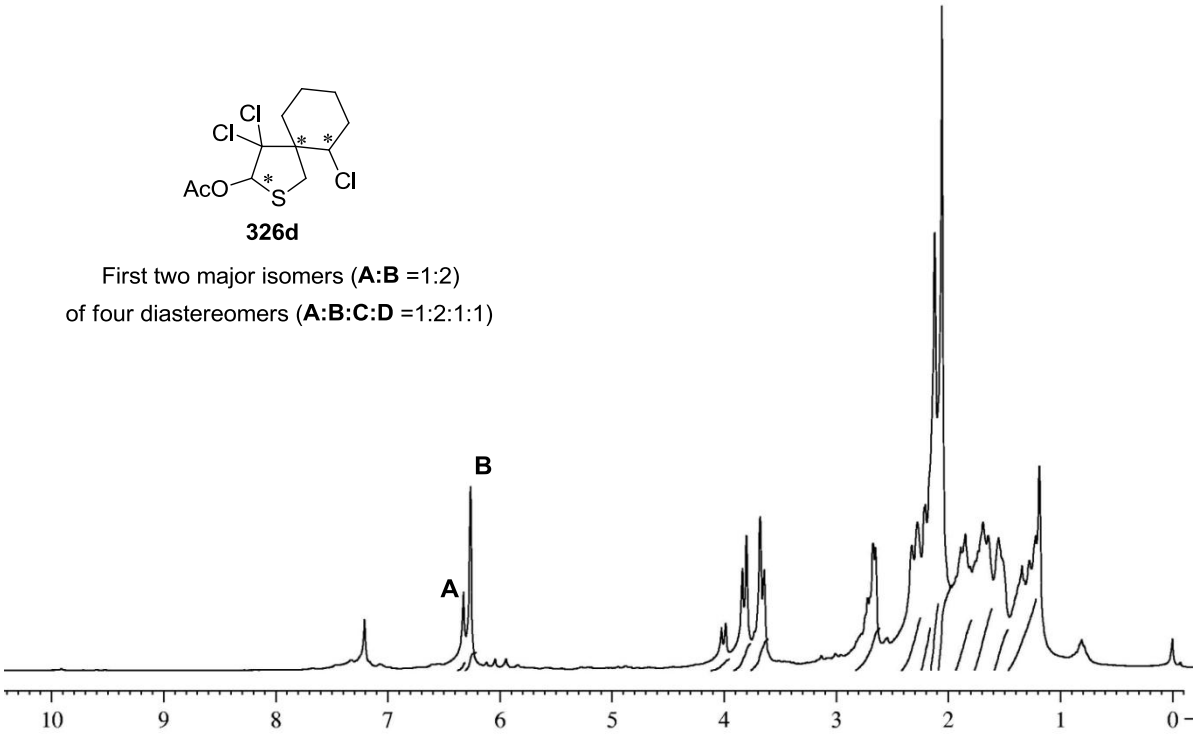


Fig. 156 ^{1}H NMR Spectrum of spiro(cyclohexyl)dihydrothiophene 326d (A&B)

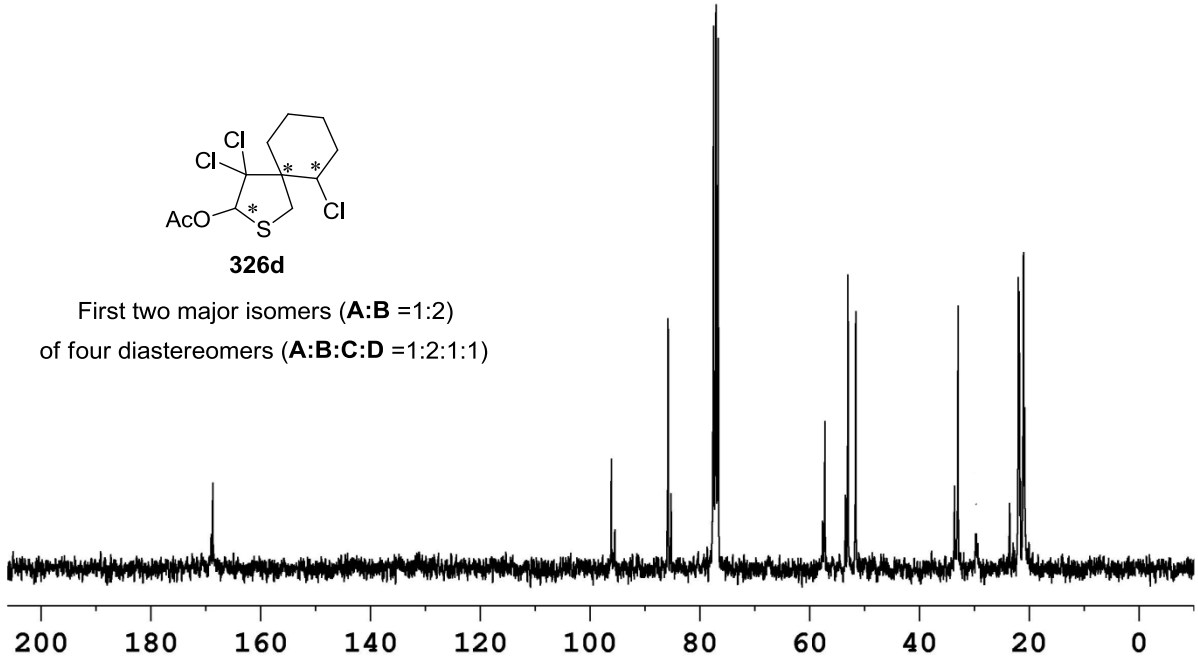


Fig. 157 ^{13}C{^{1}H} NMR Spectrum of spiro(cyclohexyl)dihydrothiophene 326d (A&B)

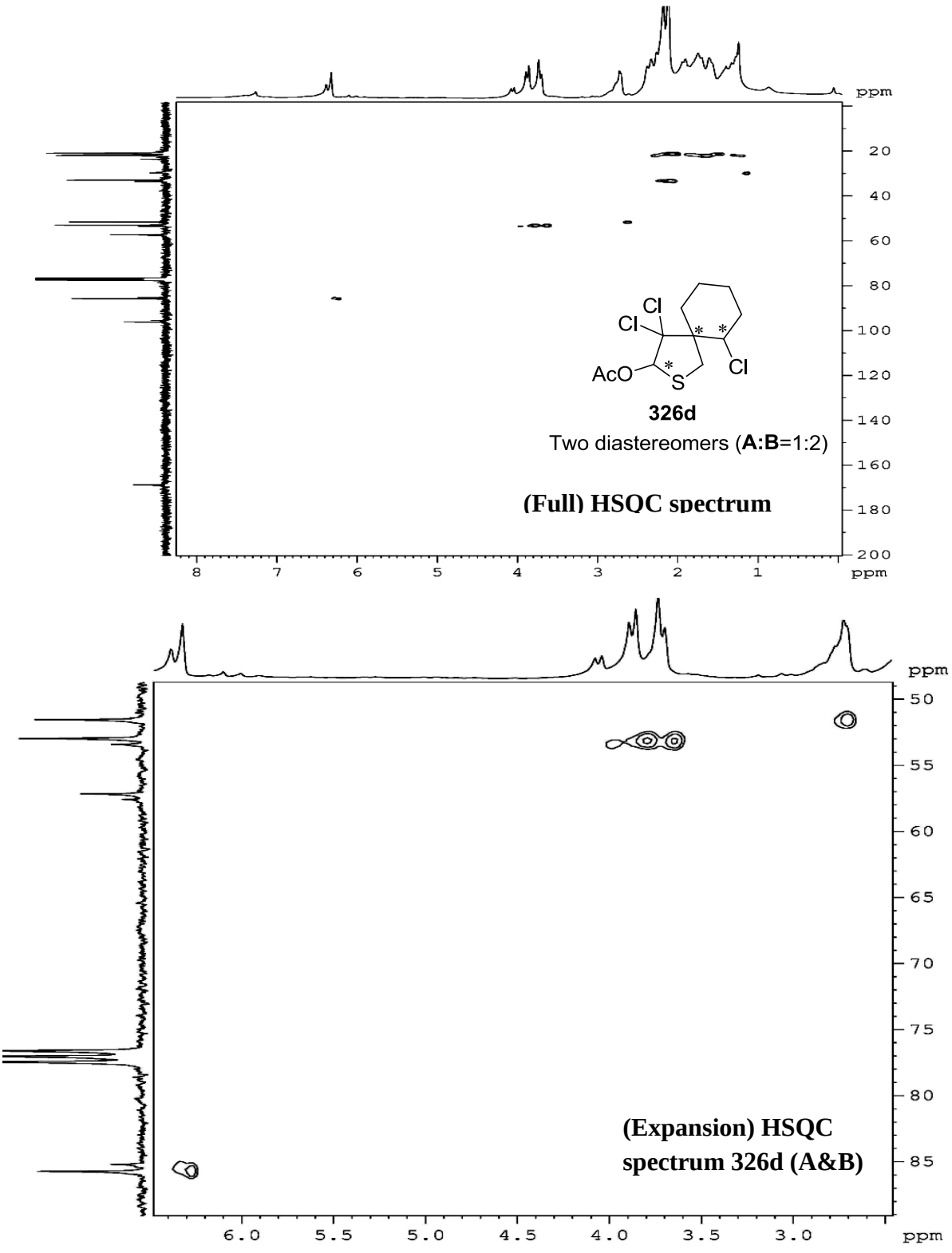


Fig. 158 HSQC Spectrum of spiro(cyclohexyl)dihydrothiophene 326d (A & B)

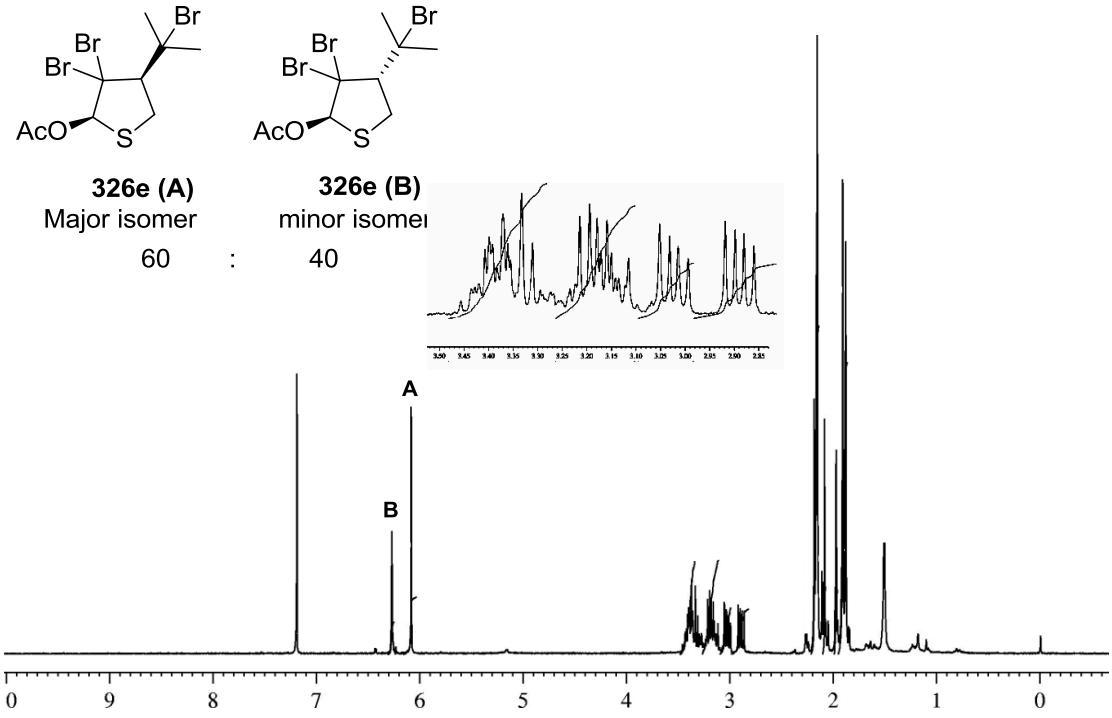


Fig. 159 ^{1}H NMR Spectrum of 3,3-dibromo-4-(2-bromopropan-2-yl)-tetrahydrothiophen-2-yl acetate 326e (A&B)

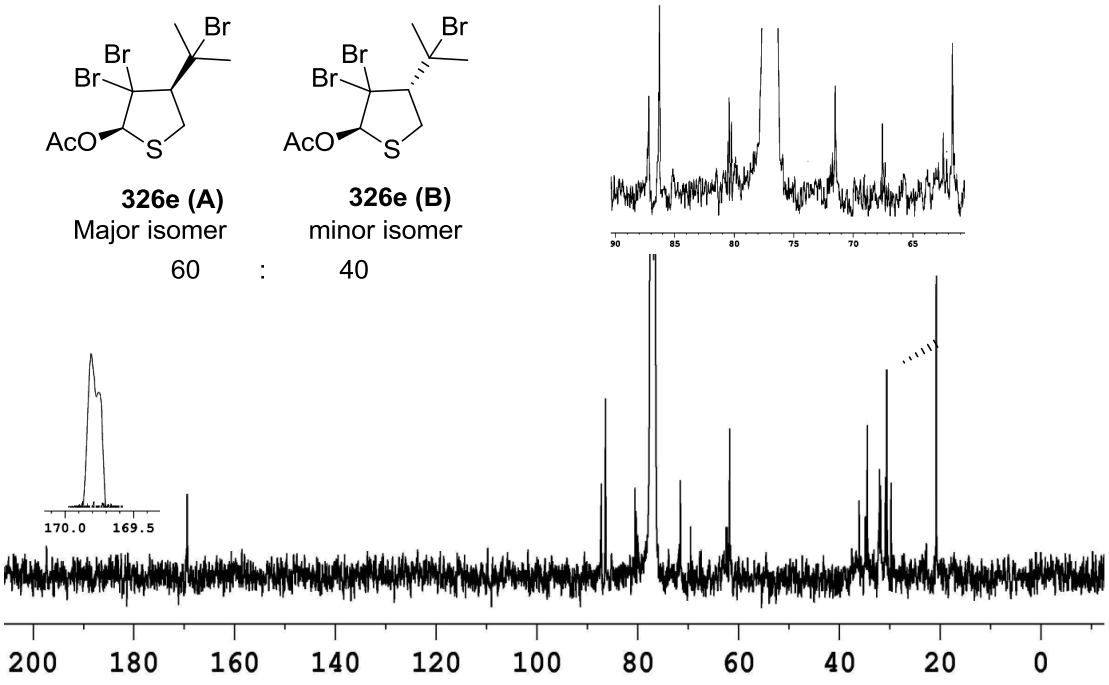


Fig. 160 ^{13}C{^{1}H} NMR Spectrum of 3,3-dibromo-4-(2-bromopropan-2-yl)-tetrahydrothiophen-2-yl acetate 326e (A&B)

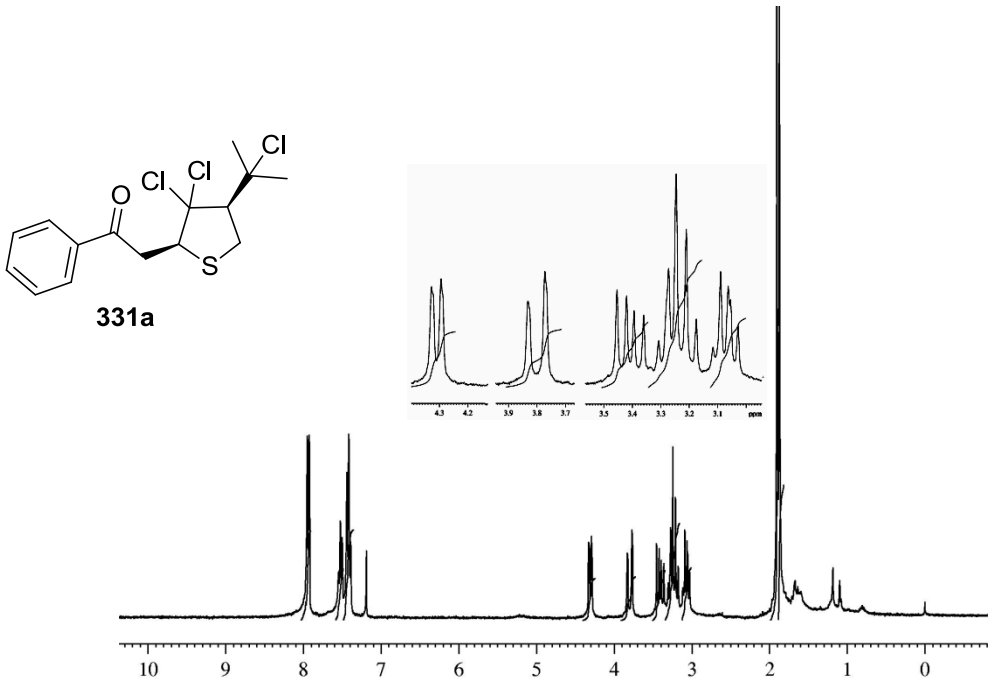


Fig. 161 ^{1}H NMR Spectrum of 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)-1-phenylethanone 331a

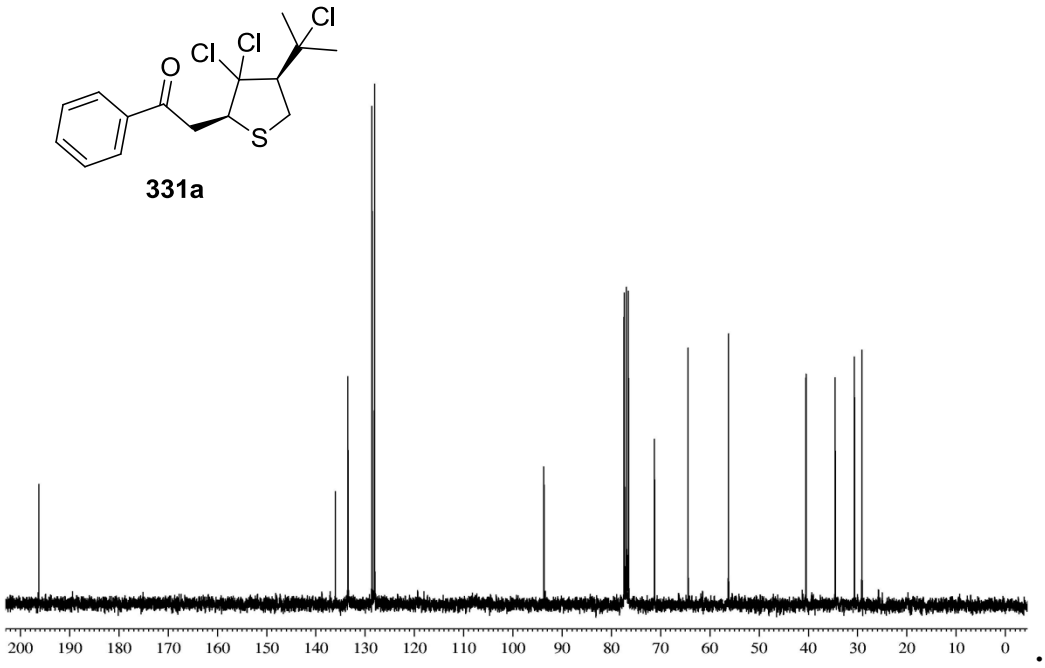
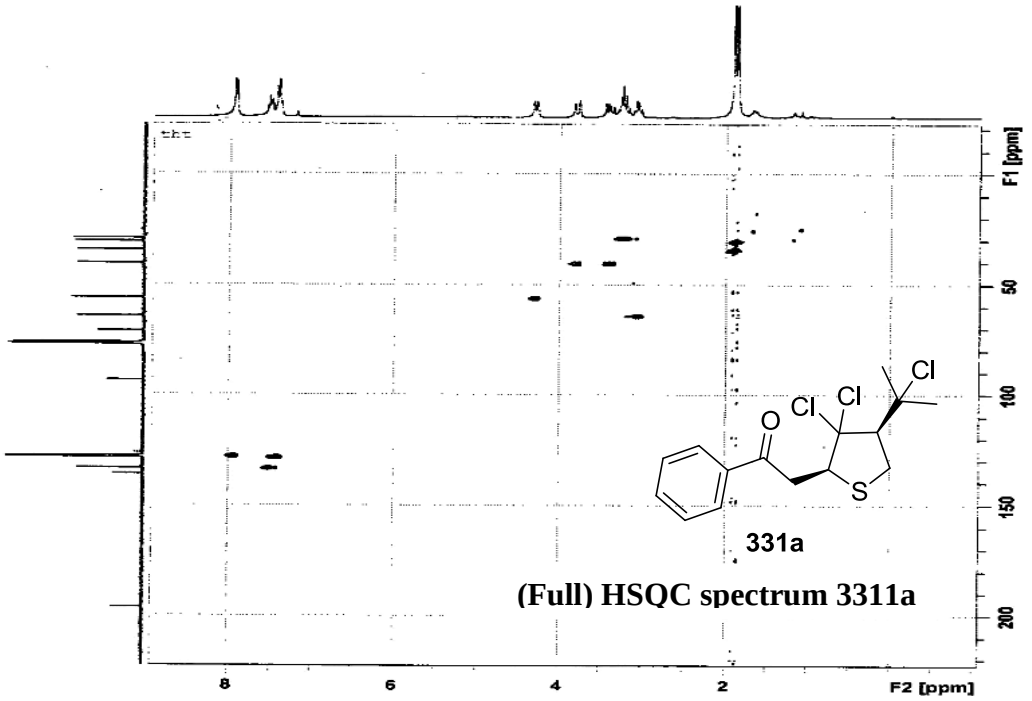


Fig. 162 ^{13}C{^{1}H} NMR Spectrum of 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)-1-phenylethanone331a



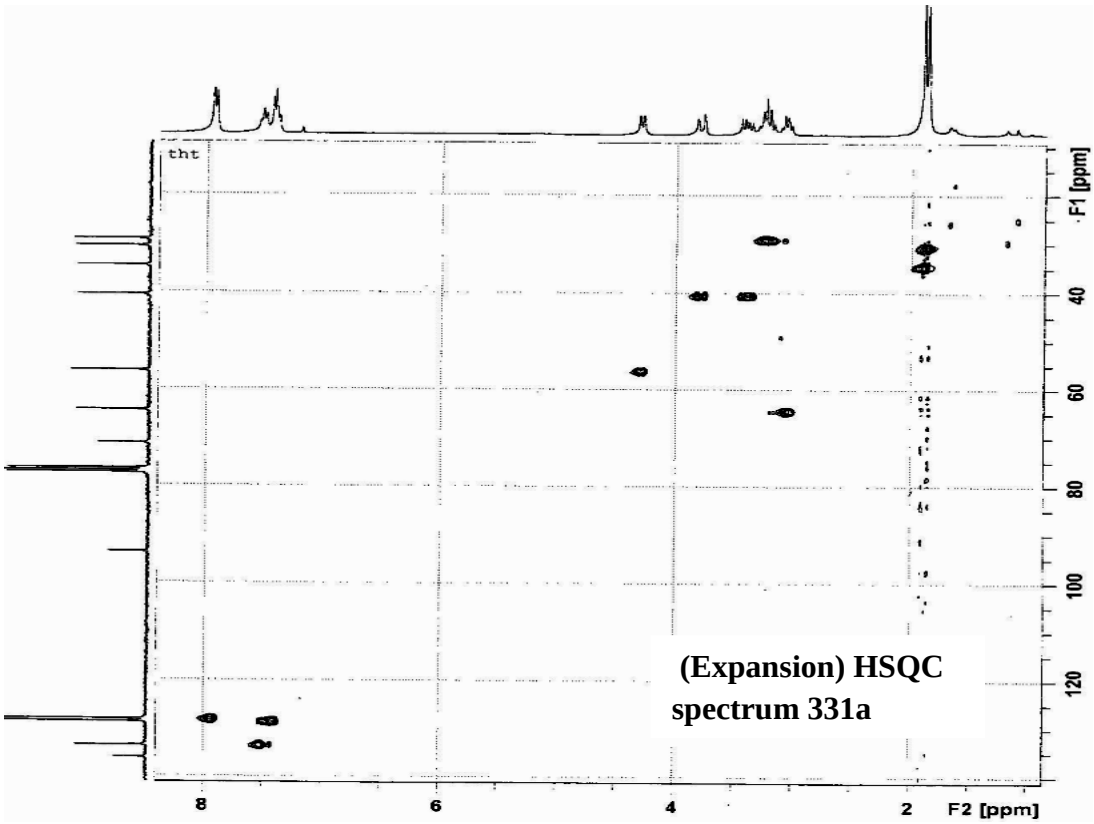
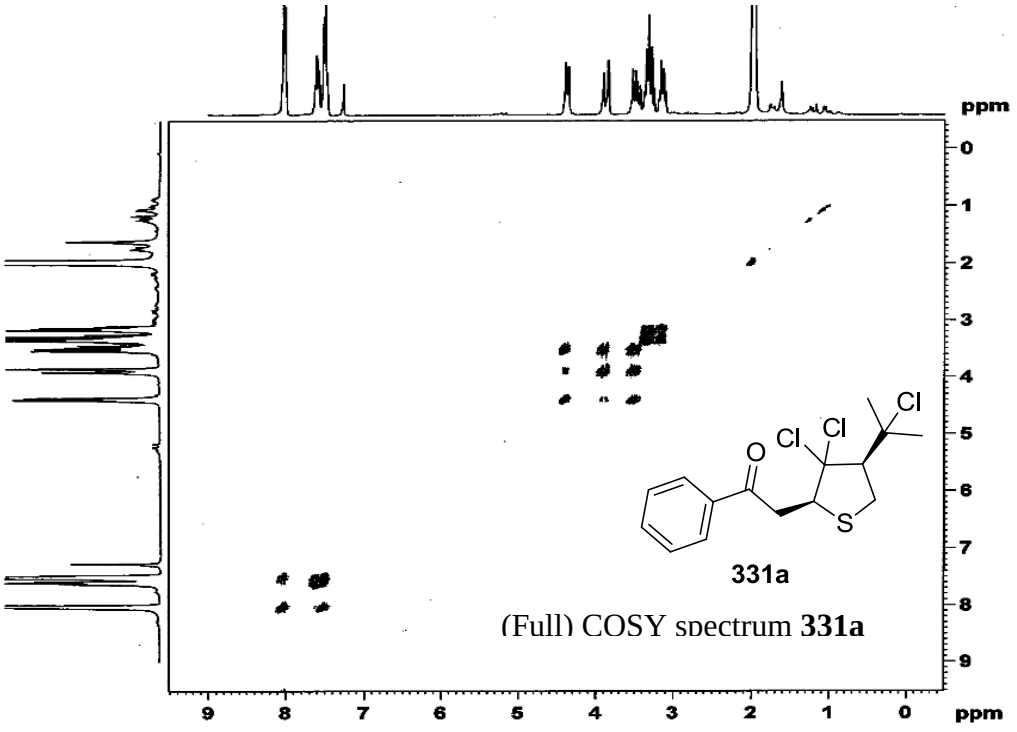


Fig. 163 HSQC Spectrum of 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)-1-phenylethanone 331a



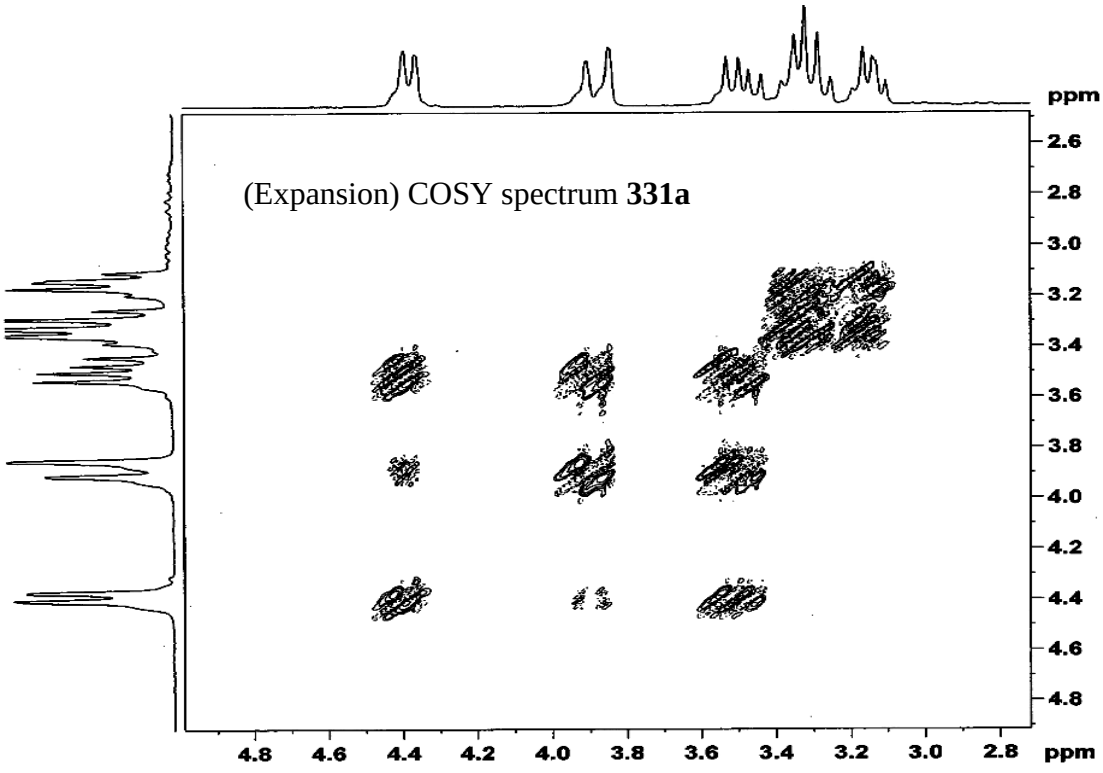


Fig. 164 ^{1}H-^{1}H COSY Spectrum of 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)-1-phenylethanone 331a

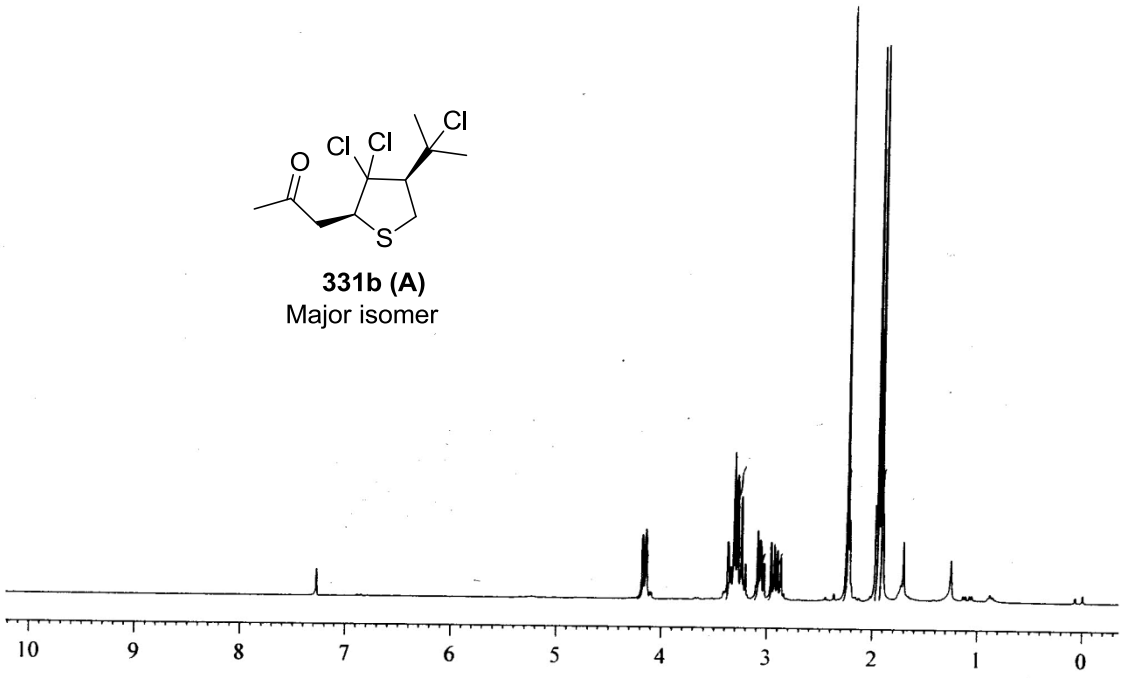


Fig. 165 ^{1}H NMR Spectrum of 1-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)propan-2-one 331b (A)(major diastereomer)

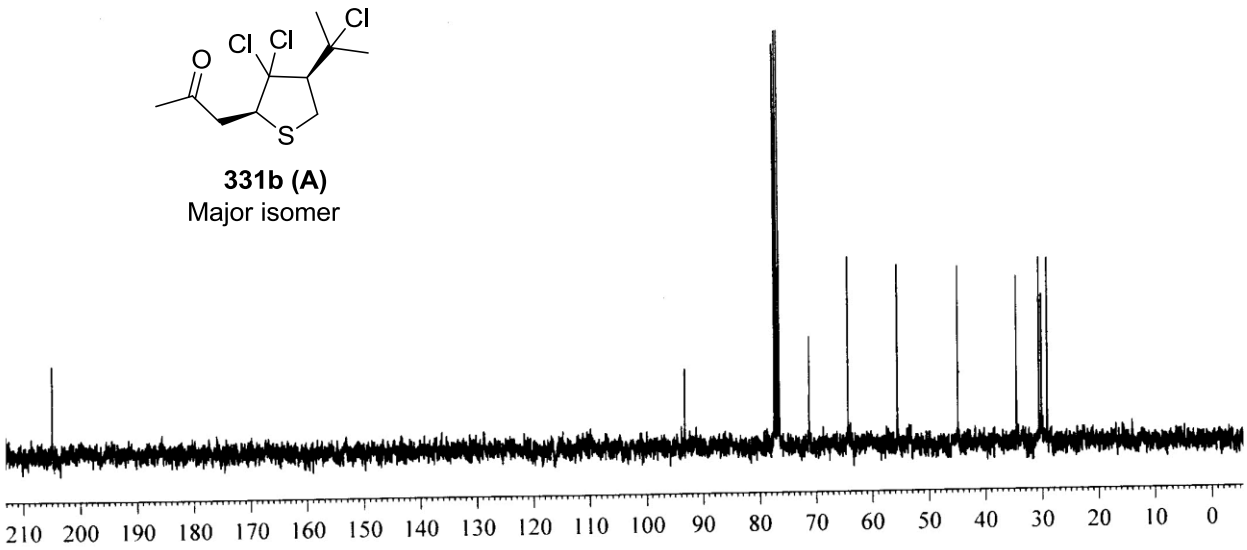


Fig. 166 ^{13}C{^{1}H} NMR Spectrum of 1-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)propan-2-one 331b (A)(major diastereomer)

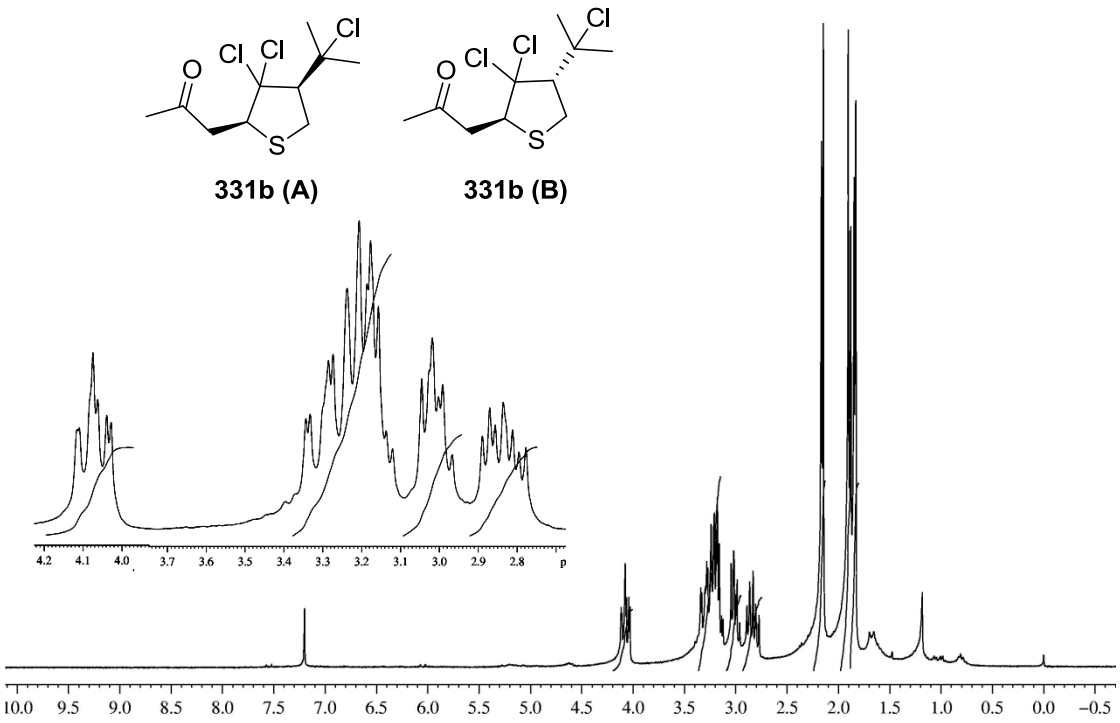


Fig. 167 ^{1}H NMR Spectrum of 331b (A & B) mixture obtained after partial separation of the major isomer 331b (A) by column chromatography.

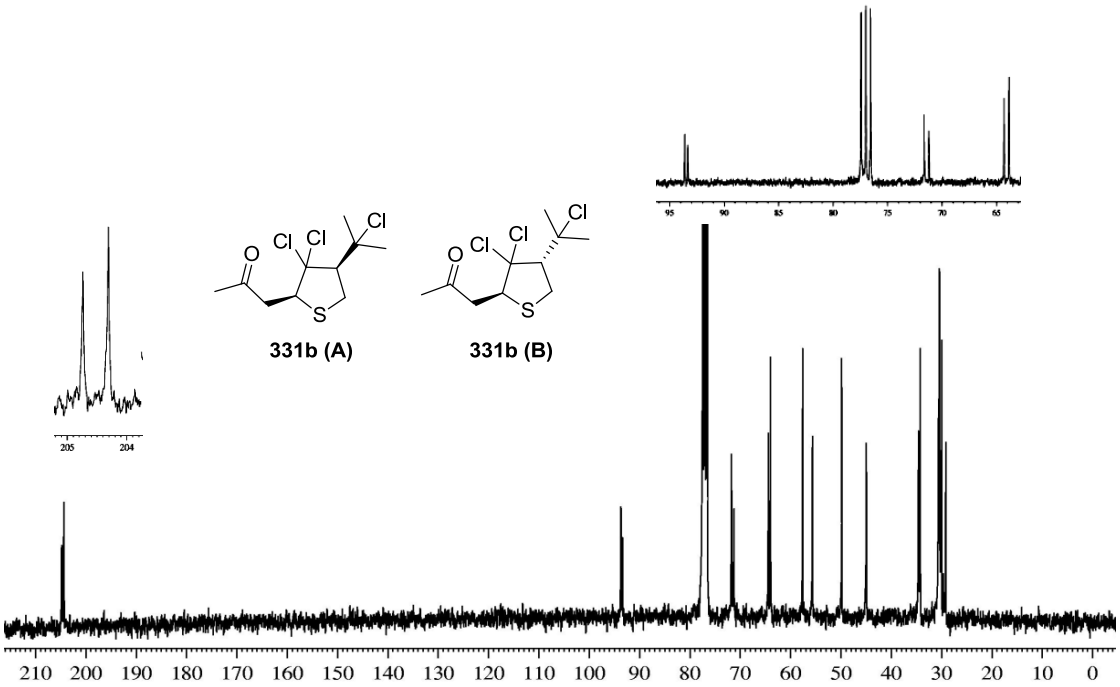


Fig. 168 ^{13}C{^{1}H} NMR Spectrum of 331b (A & B) mixture obtained after partial separation of the major isomer 331b (A) by column chromatography

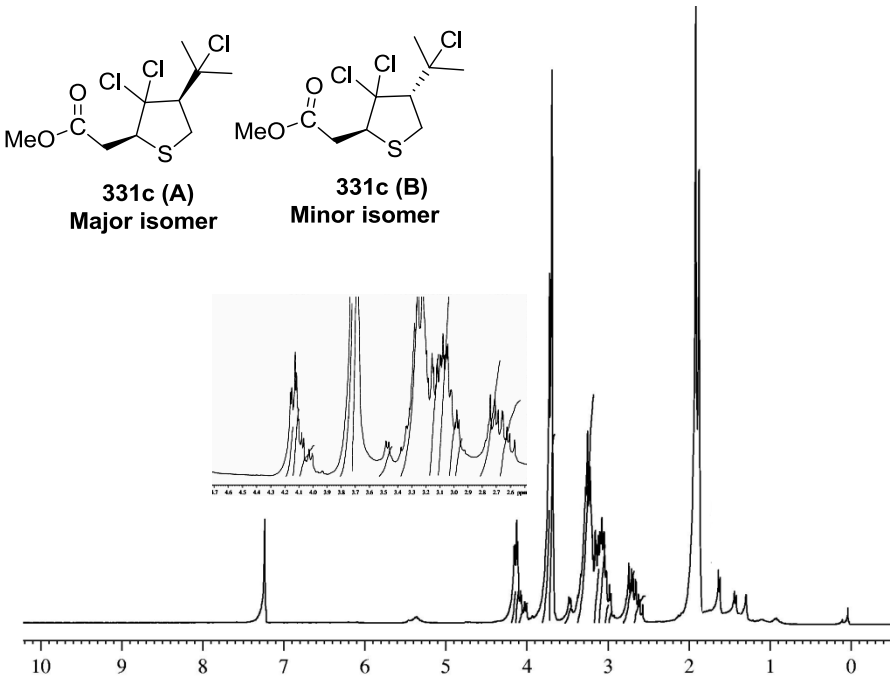


Fig. 169 ^{1}H NMR Spectrum of methyl 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetate 331c (A & B) (crude product)

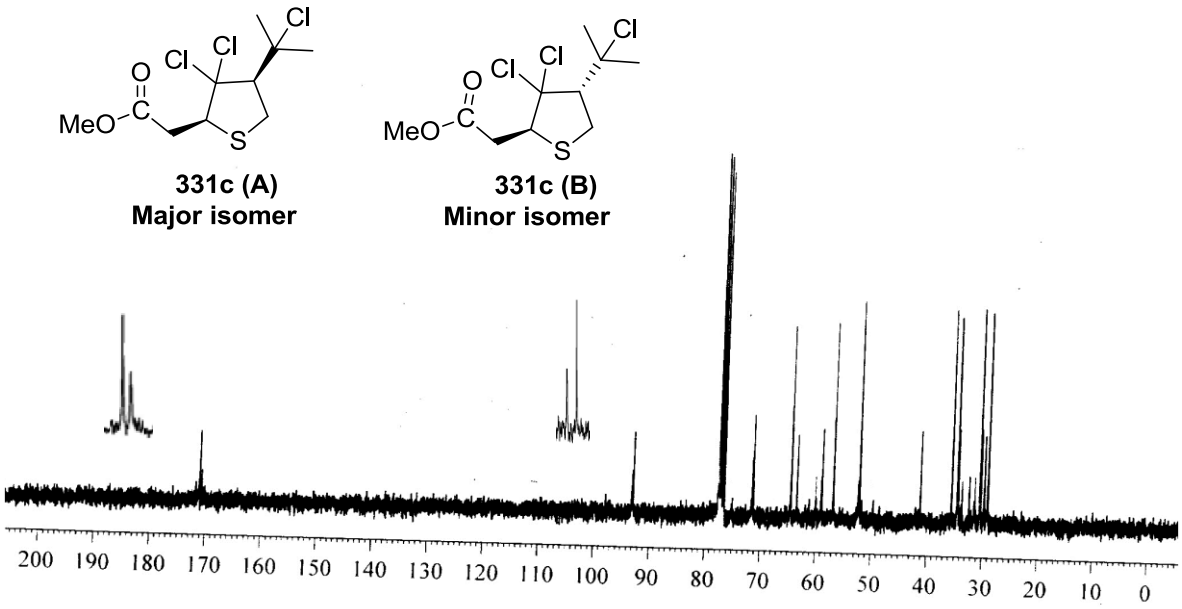


Fig. 170 ^{13}C{^{1}H} NMR Spectrum of methyl 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetate 331c (A & B) (crude product)

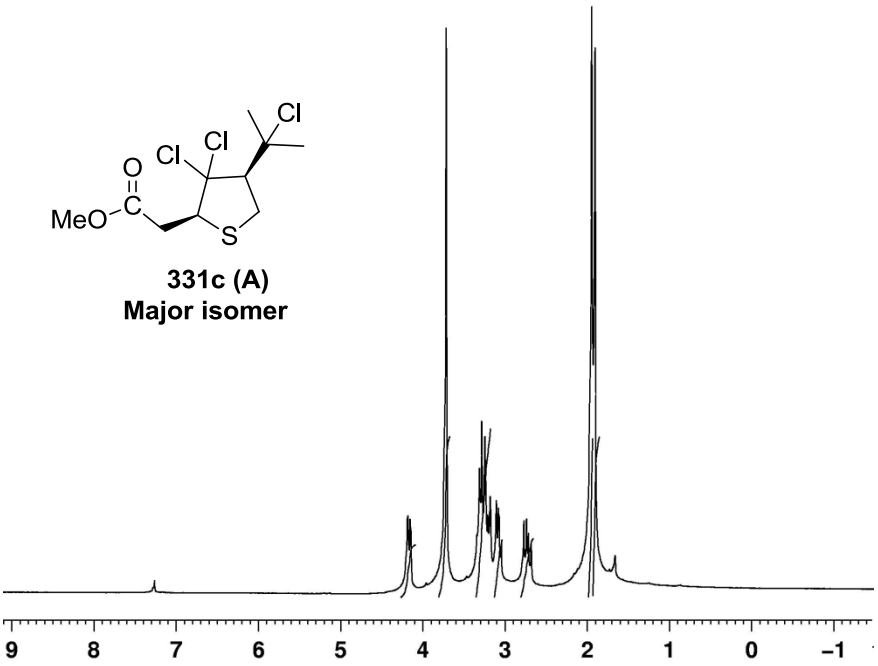


Fig. 171 ^{1}H NMR Spectrum of methyl 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetate 331c (A) (major diastereomer)

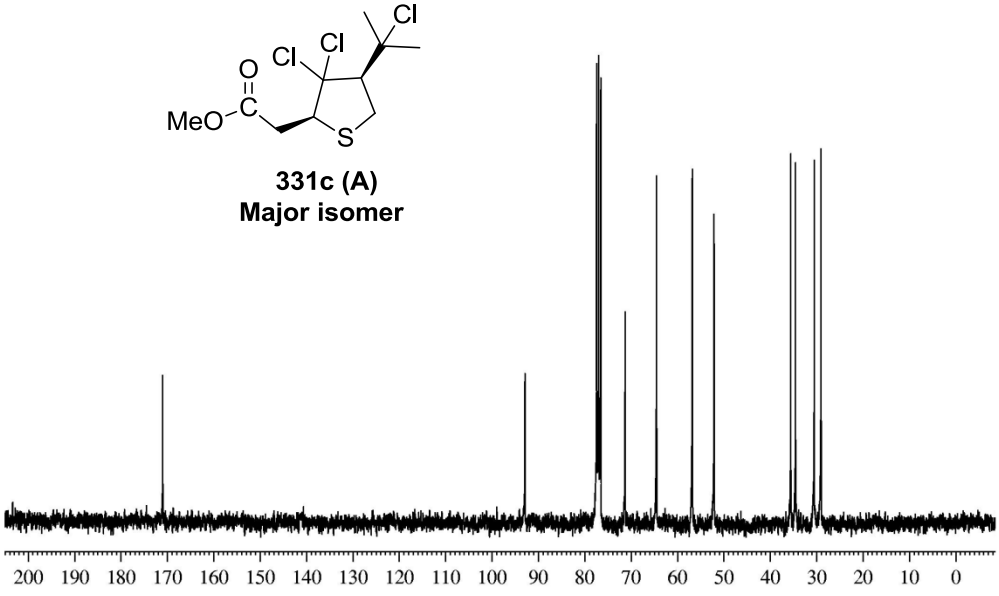


Fig. 172 ^{13}C NMR Spectrum of methyl 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetate 331c (A) (major diastereomer)

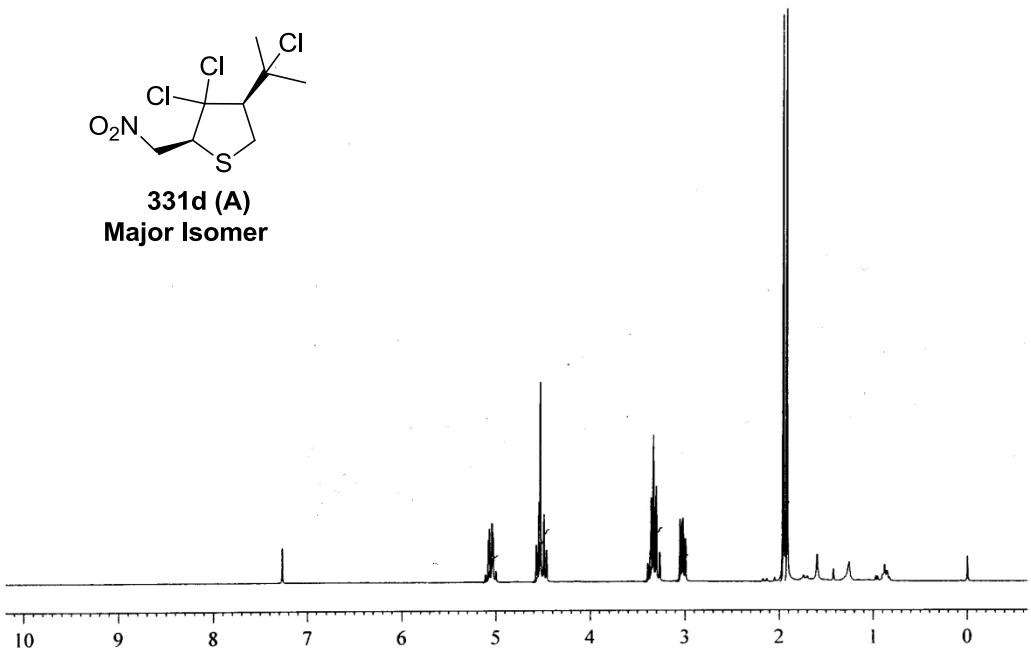


Fig. 173 ^{1}H NMR Spectrum of 3,3-dichloro-4-(2-chloropropan-2-yl)-2-(nitromethyl)-tetrahydrothiophene 331d (A) (major diastereomer)

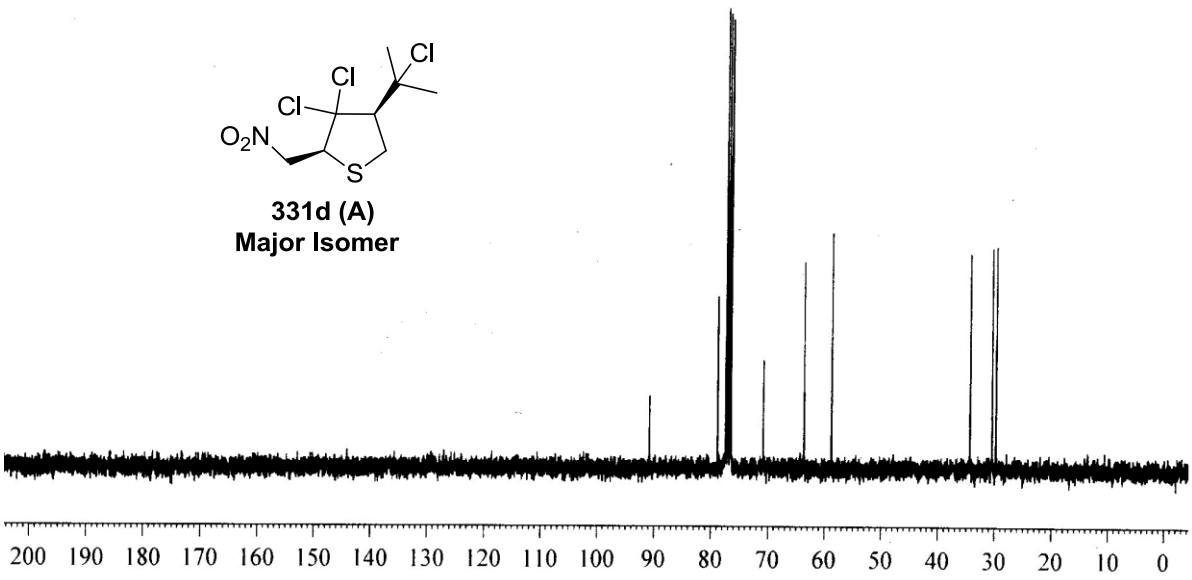


Fig. 174 ^{13}C{^{1}H} NMR Spectrum of 3,3-dichloro-4-(2-chloropropan-2-yl)-2-(nitromethyl)-tetrahydrothiophene 331d (A) (major diastereomer)

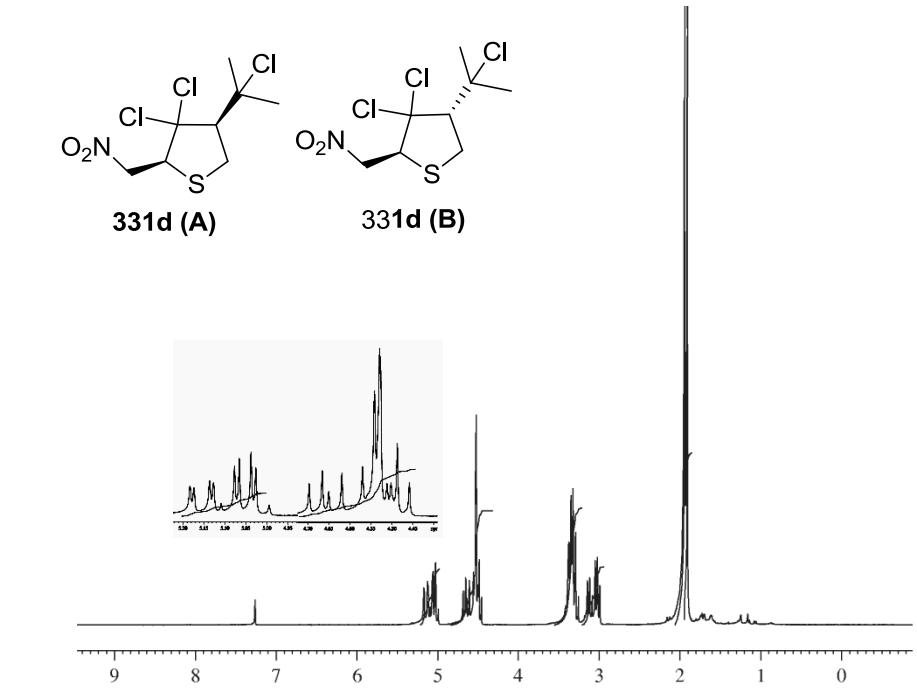


Fig. 175 ^{1}H NMR Spectrum of 331d (A & B) mixture obtained after partial separation of the major isomer 331d (A) by column chromatography

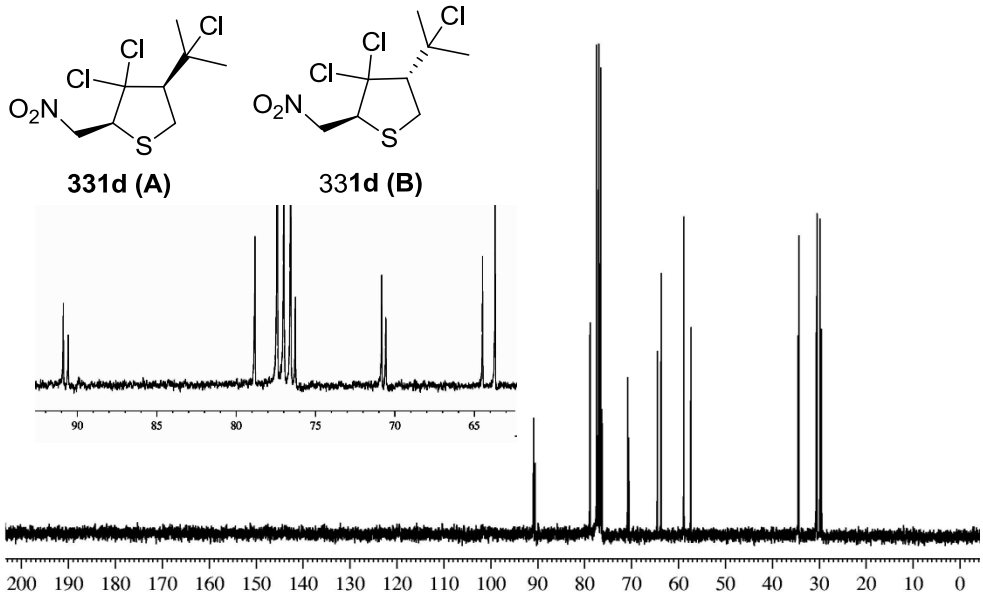


Fig. 176 ^{13}C{^{1}H} NMR Spectrum of 331d (A & B) mixture obtained after partial separation of the major isomer 331d (A) by column chromatography

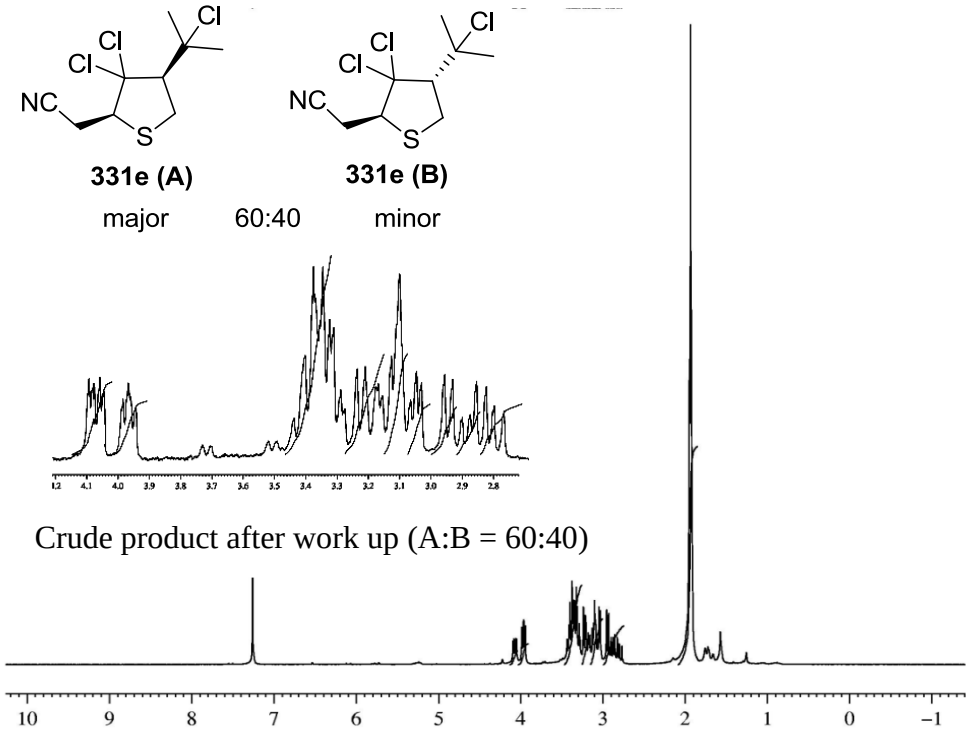


Fig. 177 ^{1}H NMR Spectrum of 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetonitrile 331e (A & B) after purification by column chromatography

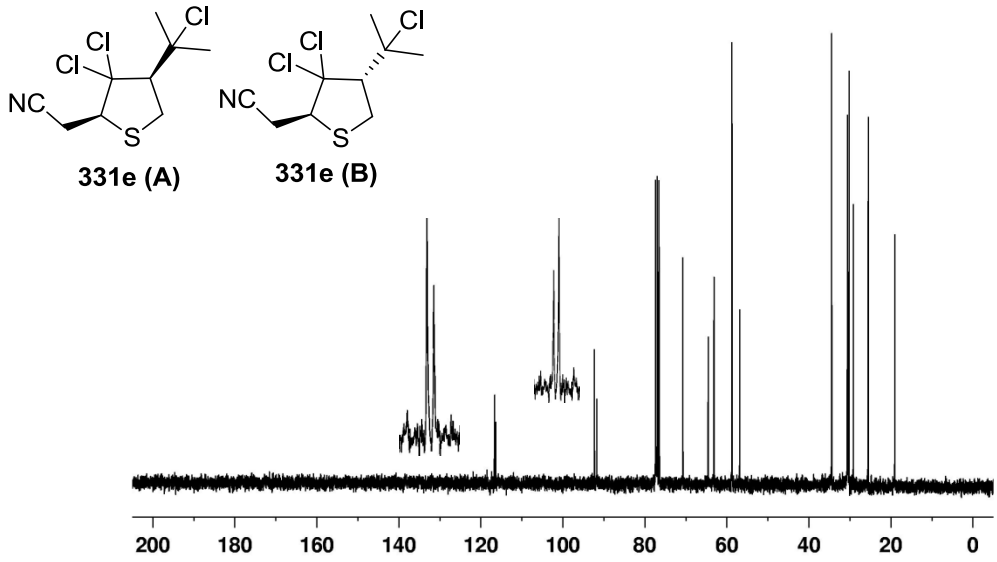


Fig. 178 ^{13}C NMR Spectrum of 2-(3,3-dichloro-4-(2-chloropropan-2-yl)-tetrahydrothiophen-2-yl)acetonitrile 331e (A & B) after purification by column chromatography.

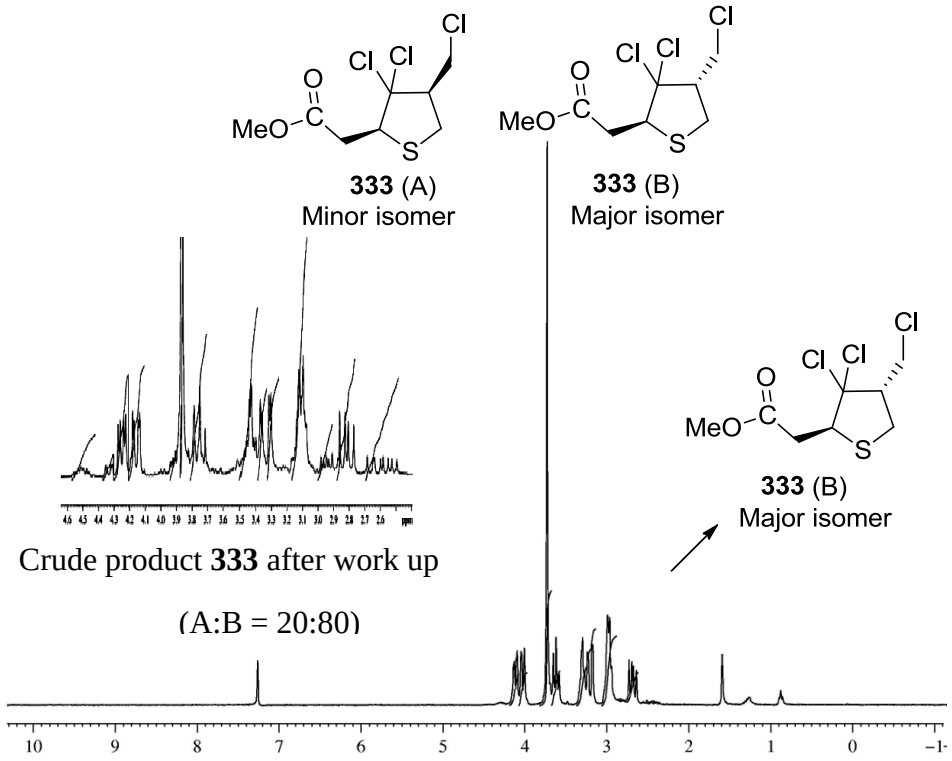


Fig. 179 ^{1}H NMR Spectrum of methyl 2-(3,3-dichloro-4-(chloromethyl)-tetrahydrothiophen-2-yl)acetate 333(B) (major diastereomer)

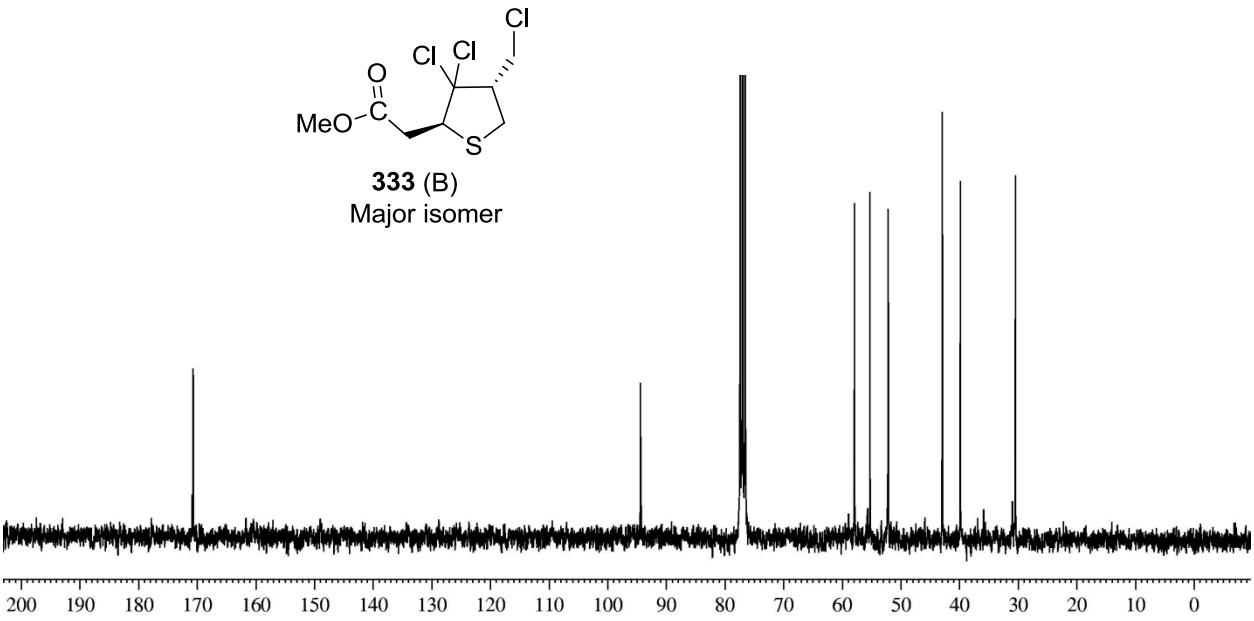


Fig. 180 ^{13}C{^{1}H} NMR Spectrum of methyl 2-(3,3-dichloro-4-(chloromethyl)-tetrahydrothiophen-2-yl)acetate 333(B) (major diastereomer)

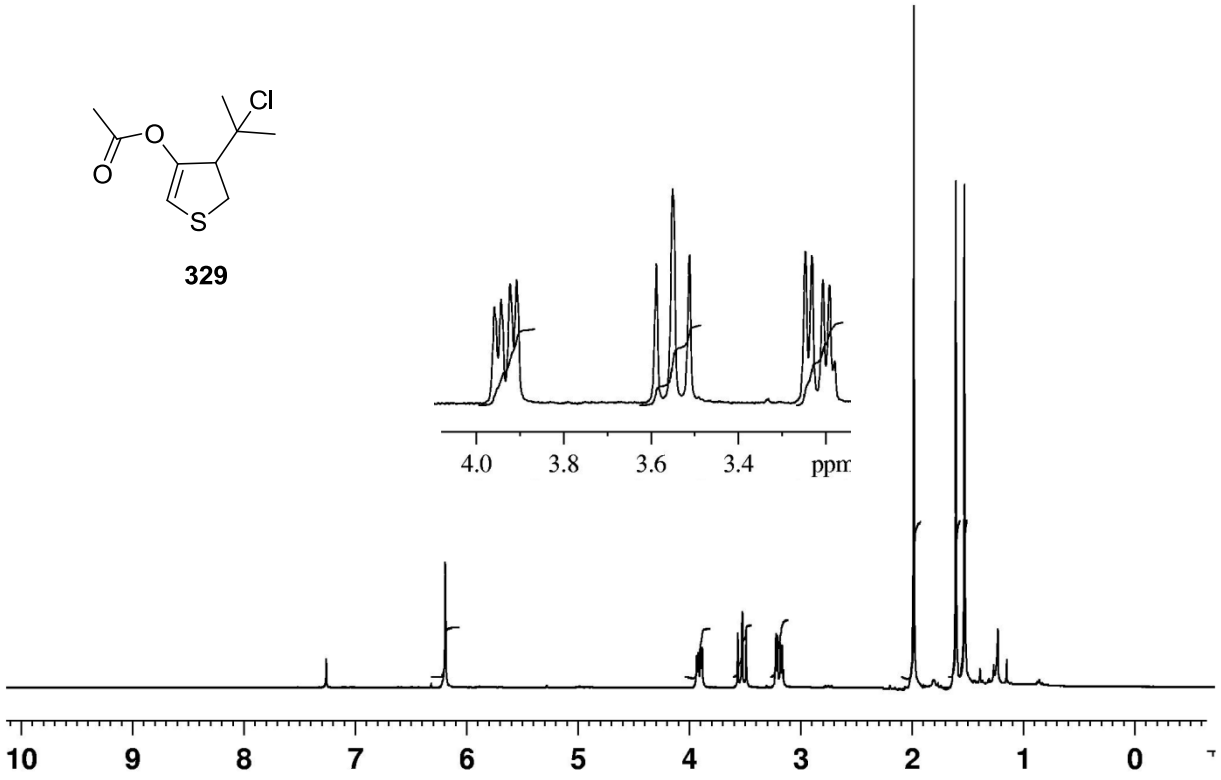


Fig. 181 ^{1}H NMR Spectrum of 4-(2-chloropropan-2-yl)-4,5-dihydrothiophen-3-yl acetate 329

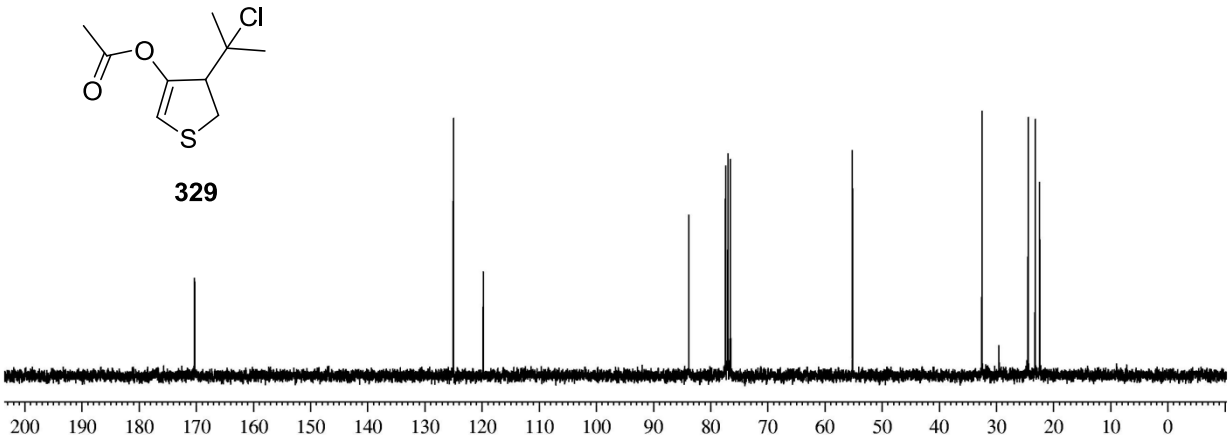


Fig. 182 ^{13}C{^{1}H} NMR Spectrum of 4-(2-chloropropan-2-yl)-4,5-dihydrothiophen-3-yl acetate 329

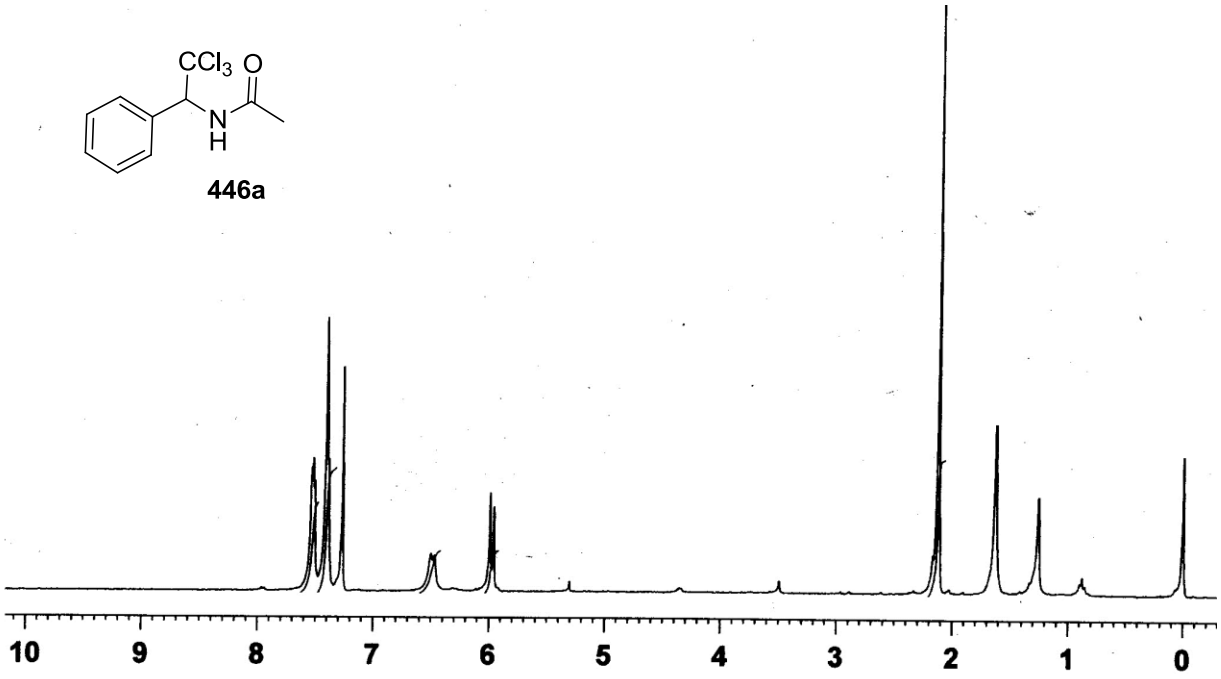


Fig. 183 ^{1}H NMR spectrum of *N*-(2,2,2-trichloro-1-phenylethyl)acetamide 446a

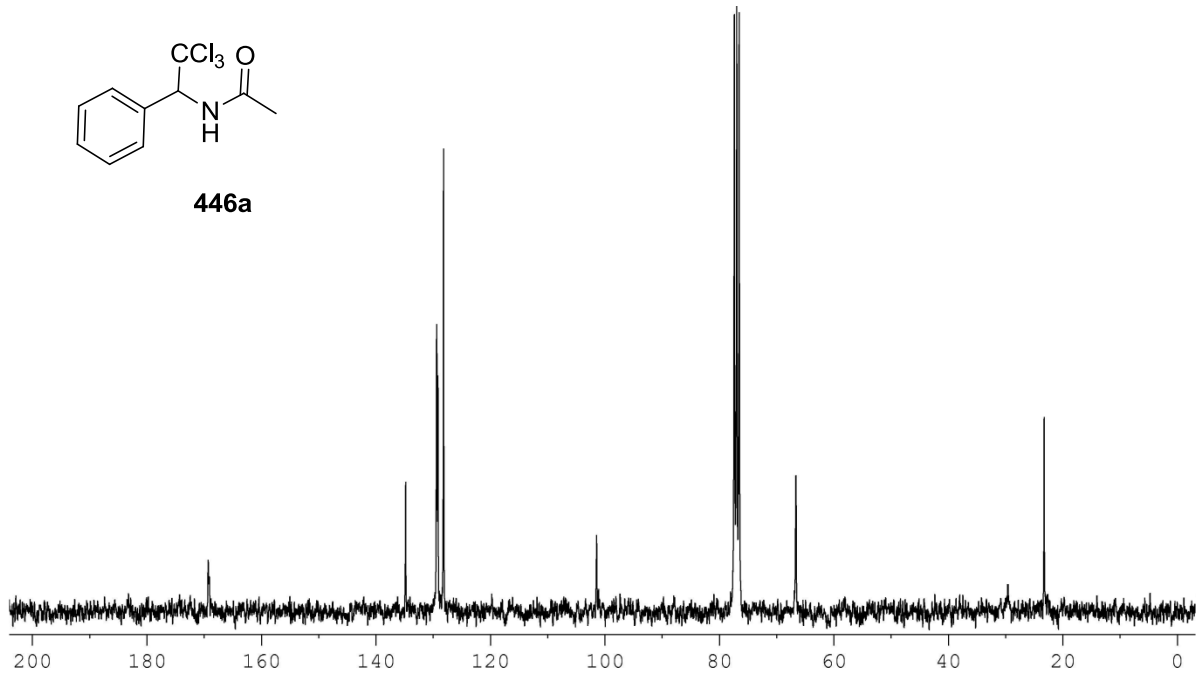


Fig. 184 ^{13}C{^{1}H} NMR spectrum of *N*-(2,2,2-trichloro-1-phenylethyl)acetamide 446a

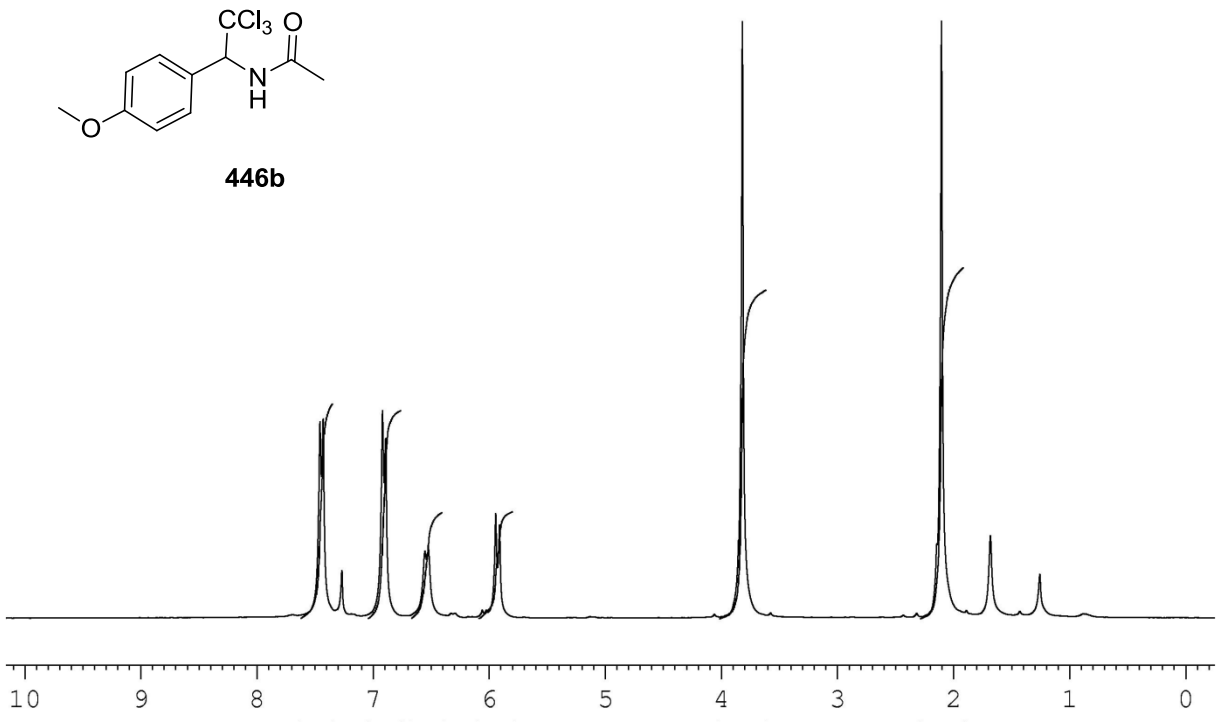


Fig. 185 ^{1}H NMR spectrum of *N*-(2,2,2-trichloro-1-(4-methoxyphenyl)ethyl)acetamide 446b

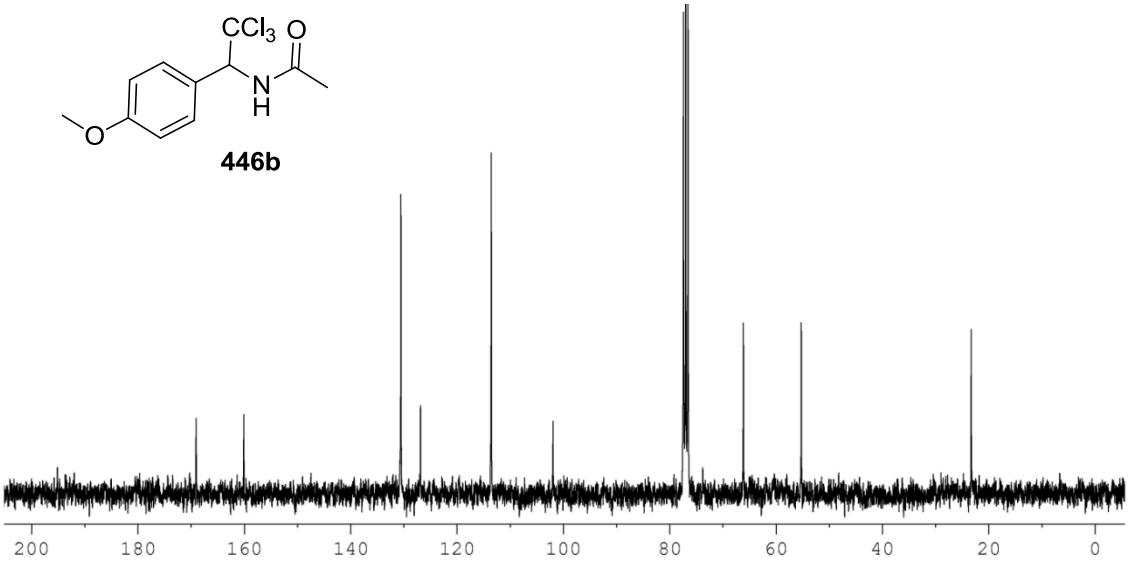


Fig. 186 ^{13}C{^{1}H} NMR spectrum of *N*-(2,2,2-trichloro-1-(4-methoxyphenyl)ethyl)acetamide 446b

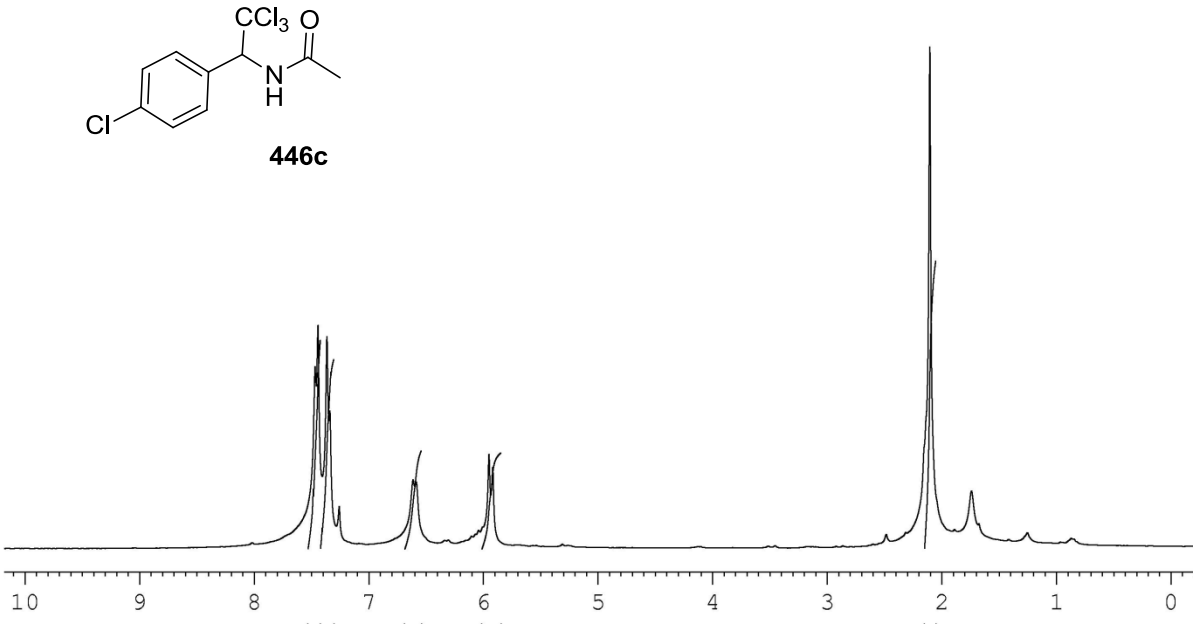


Fig. 187 ^{1}H NMR spectrum of *N*-(2,2,2-trichloro-1-(4-chlorophenyl)ethyl)acetamide 446c

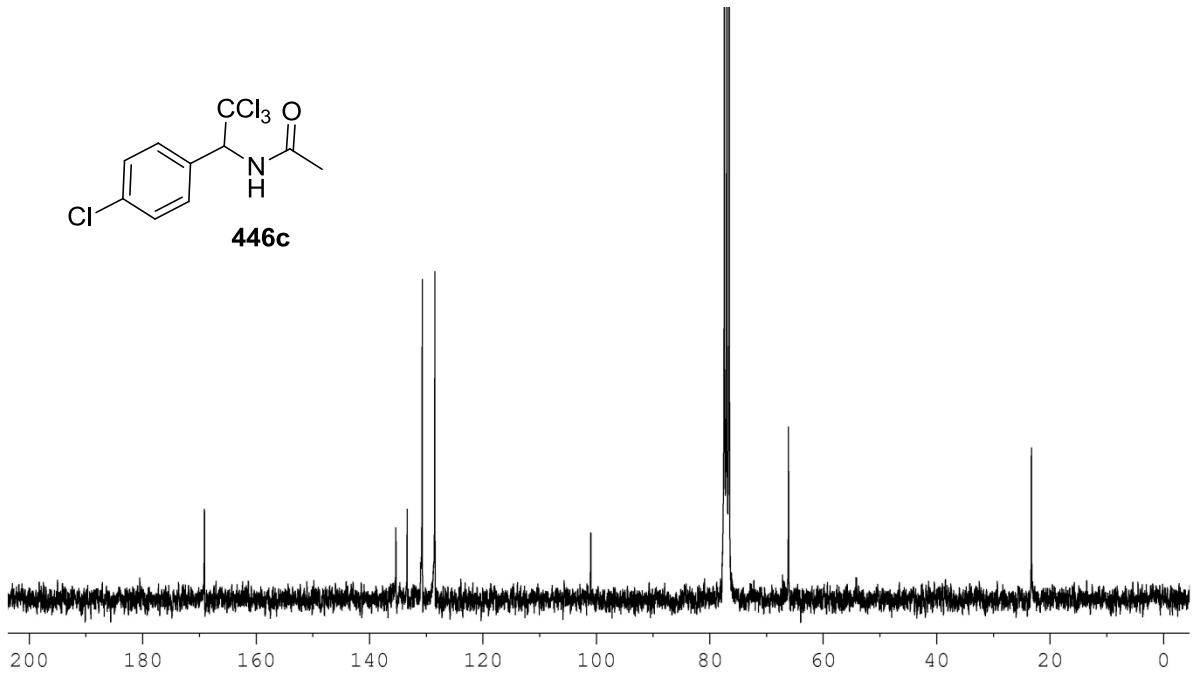


Fig. 188 ^{13}C{^{1}H} NMR spectrum of *N*-(2,2,2-trichloro-1-(4-chlorophenyl)ethyl)acetamide 446c

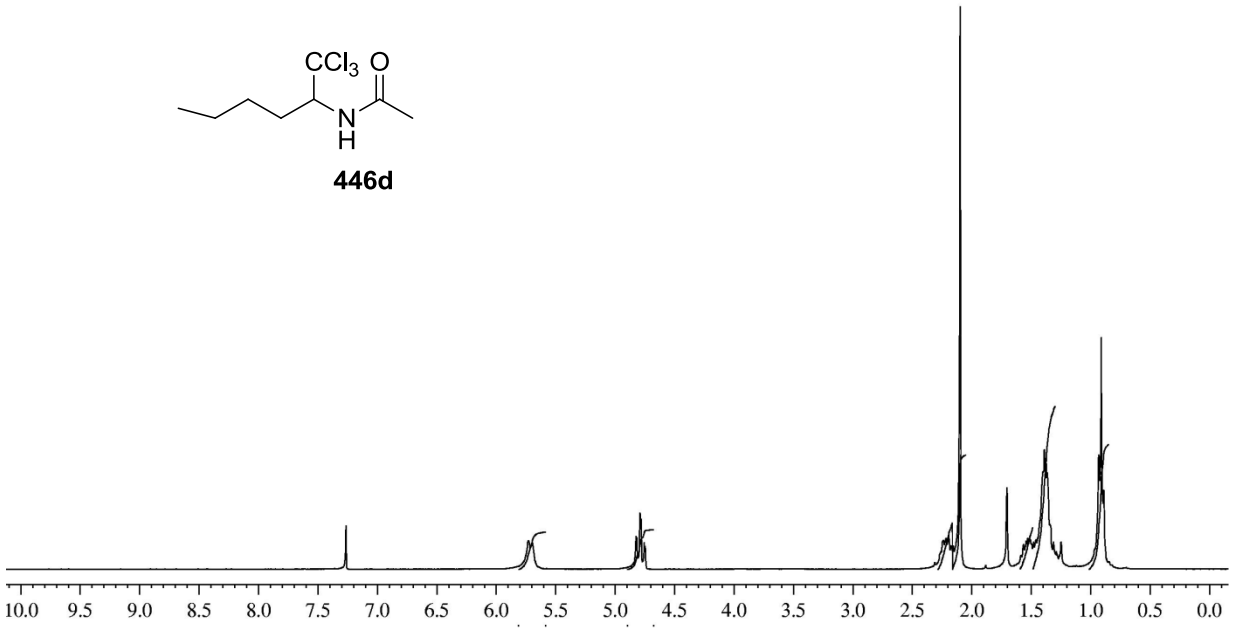


Fig. 189 ^{1}H NMR spectrum of *N*-(1,1,1-trichlorohexan-2-yl)acetamide 446d

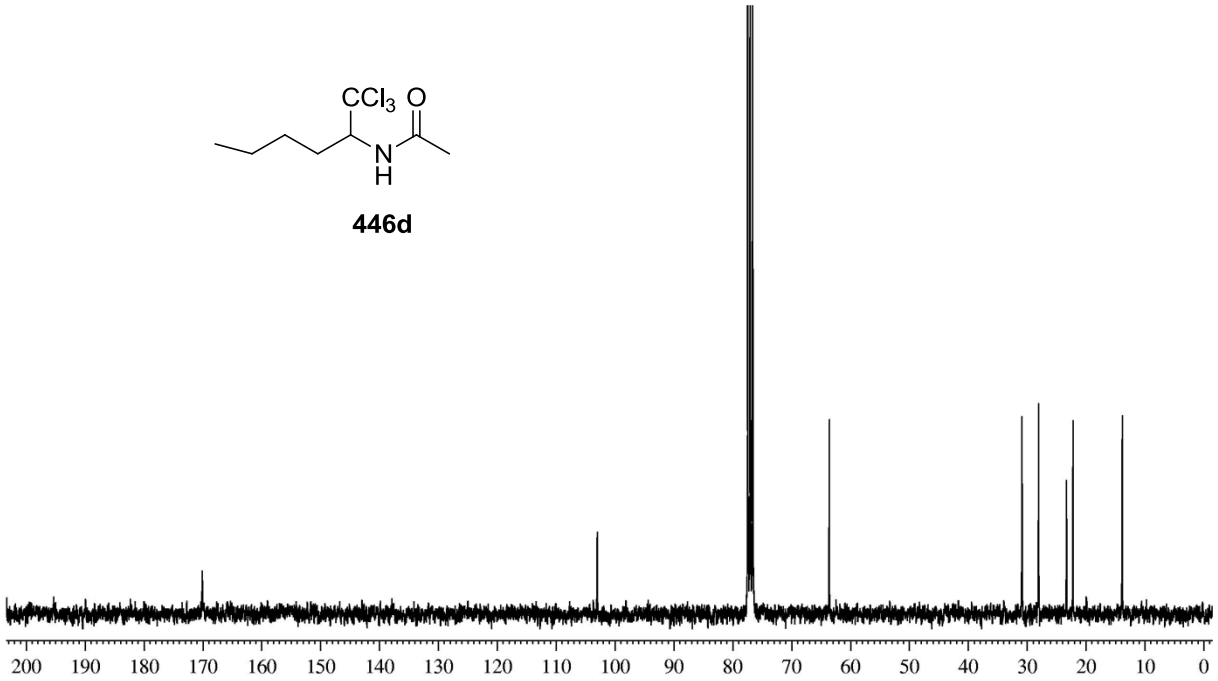


Fig. 190 ^{13}C{^{1}H} NMR spectrum of *N*-(1,1,1-trichlorohexan-2-yl)acetamide 446d

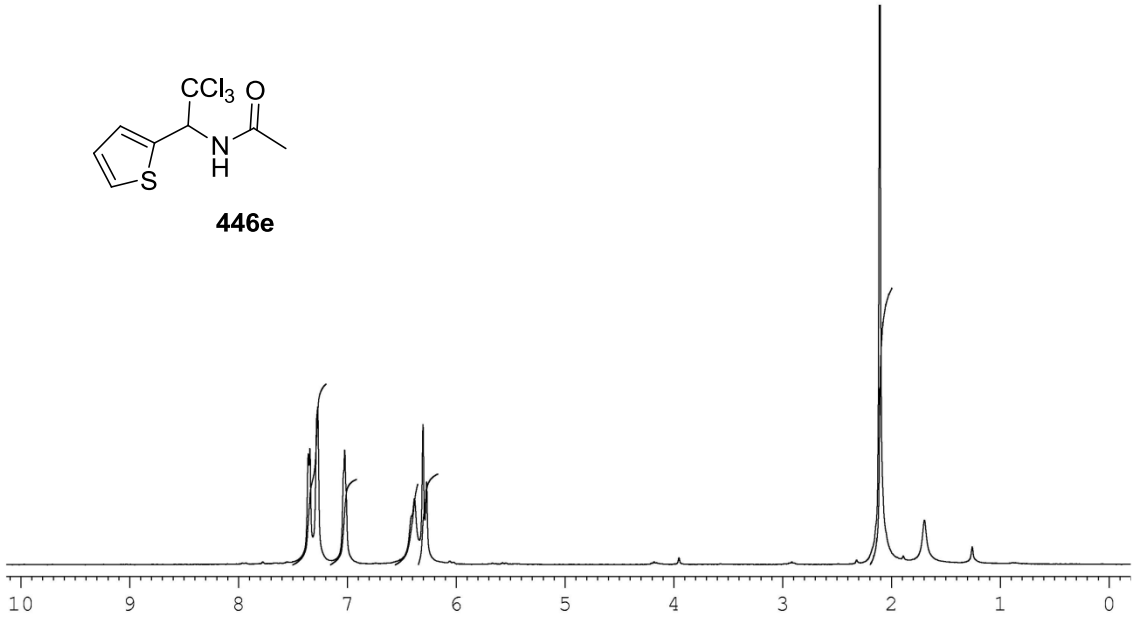


Fig. 191 ^{1}H NMR spectrum of *N*-(2,2,2-trichloro-1-(thiophen-2-yl)ethyl)acetamide 446e

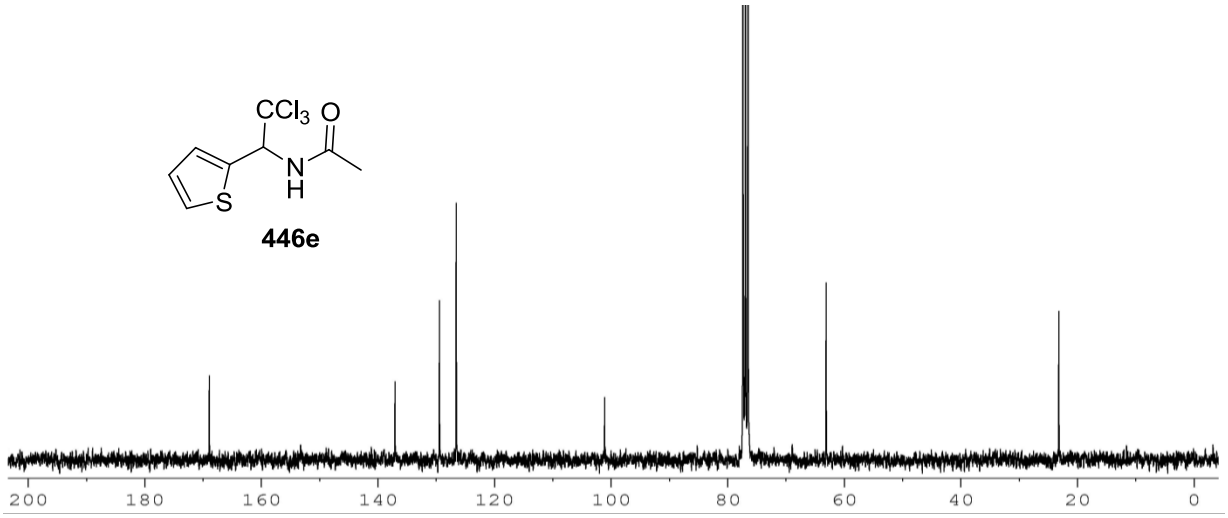


Fig. 192 ^{13}C{^{1}H} NMR spectrum of *N*-(2,2,2-trichloro-1-(thiophen-2-yl)ethyl)acetamide 446e

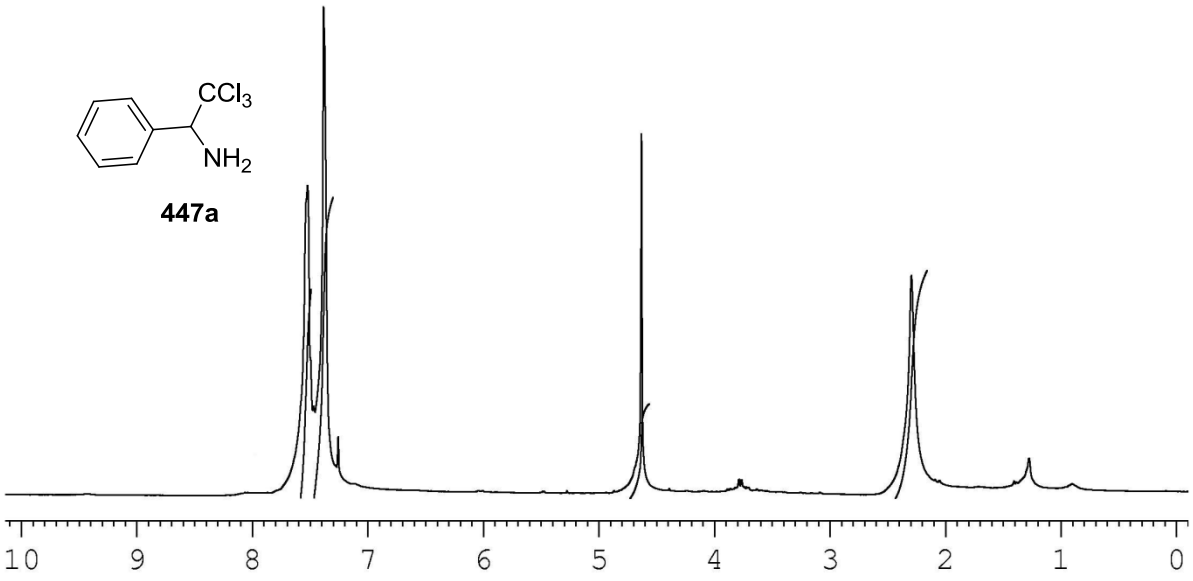


Fig. 193 ^{1}H NMR spectrum of 2,2,2-trichloro-1-phenylethanamine 447a

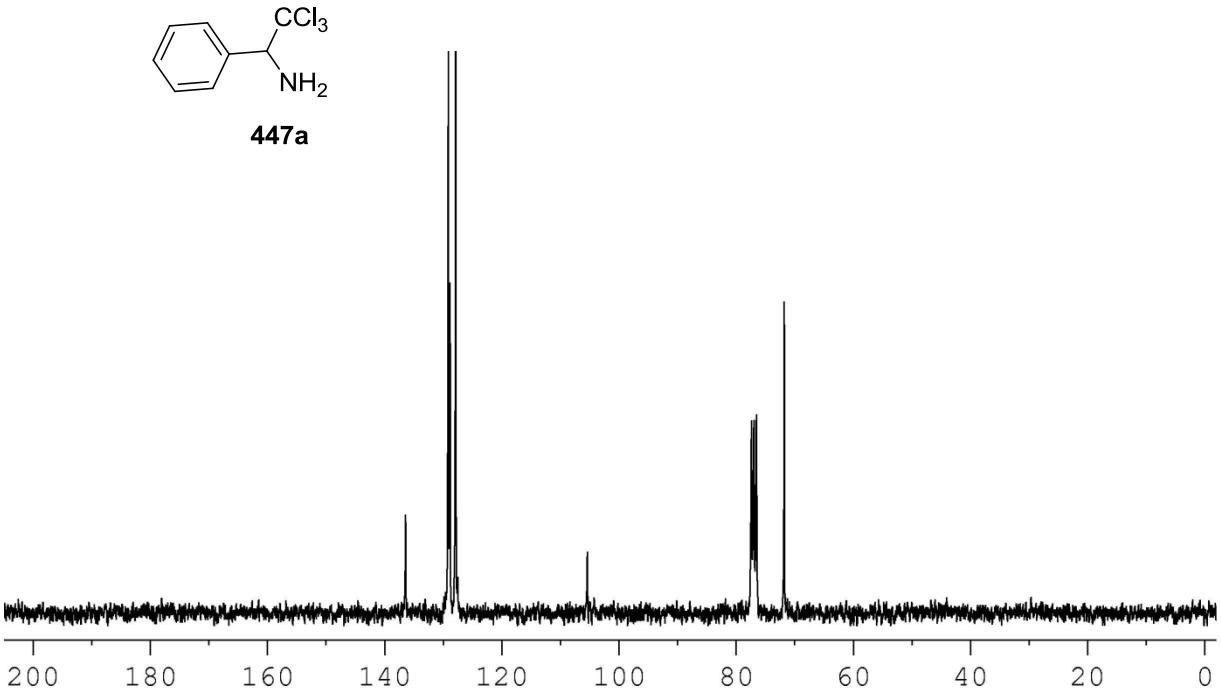


Fig. 194 ^{13}C{^{1}H} NMR spectrum of 2,2,2-trichloro-1-phenylethanamine 447a

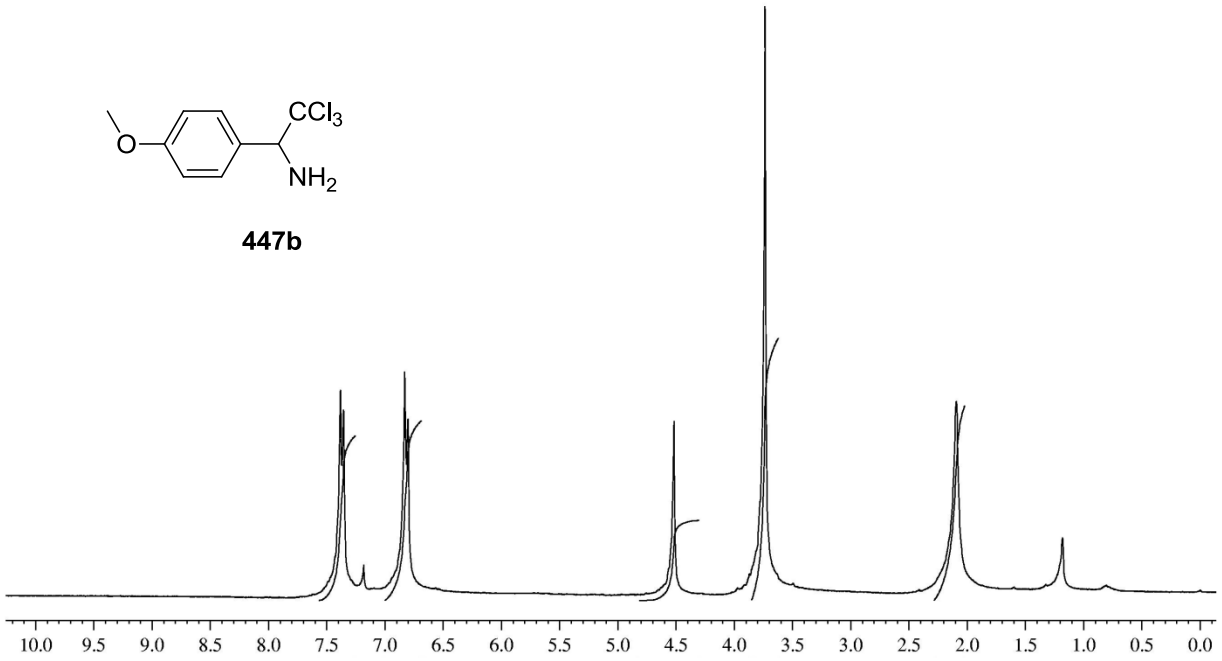


Fig. 195 ^{1}H NMR spectrum of 2,2,2-trichloro-1-(4-methoxyphenyl)ethanamine 447b

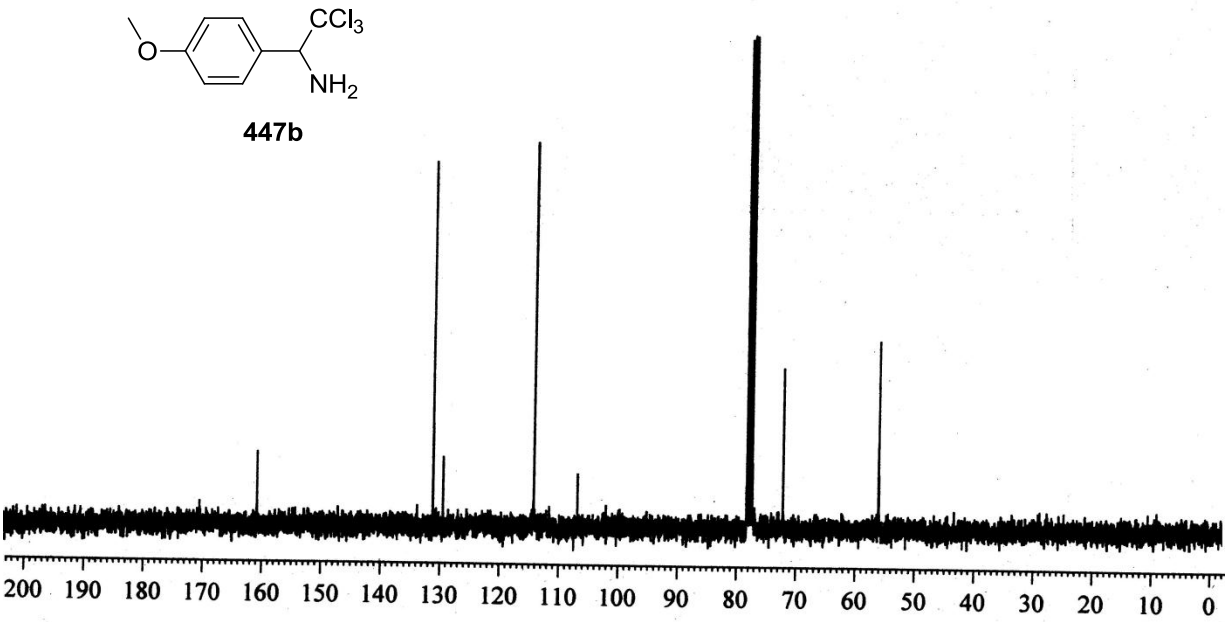


Fig. 196 ^{13}C{^{1}H} NMR spectrum of 2,2,2-trichloro-1-(4-methoxyphenyl)ethanamine 447b

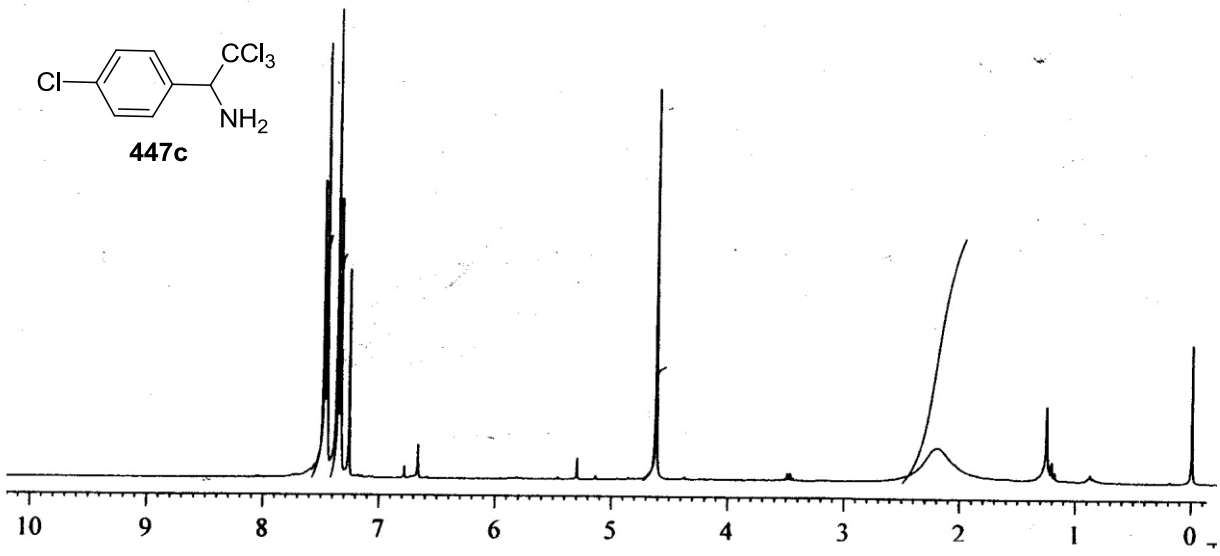


Fig. 197 ^{1}H NMR spectrum of 2,2,2-trichloro-1-(4-chlorophenyl)ethanamine 447c

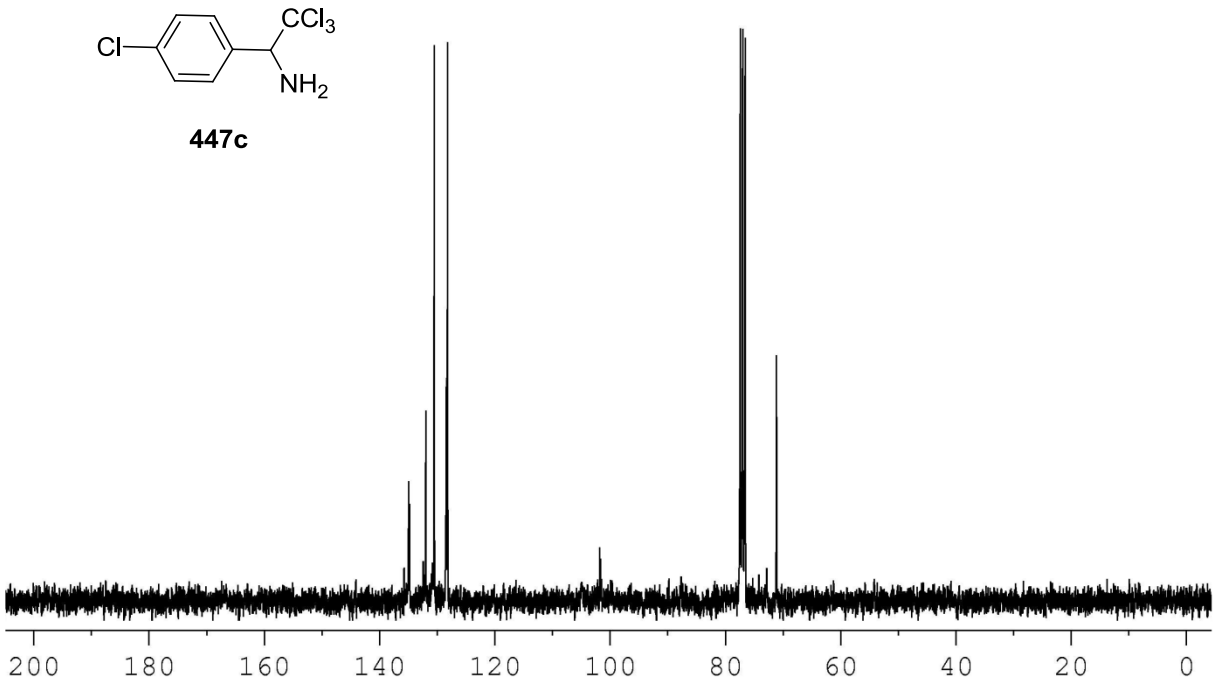


Fig. 198 ^{13}C{^{1}H} NMR spectrum of 2,2,2-trichloro-1-(4-chlorophenyl)ethanamine 447c

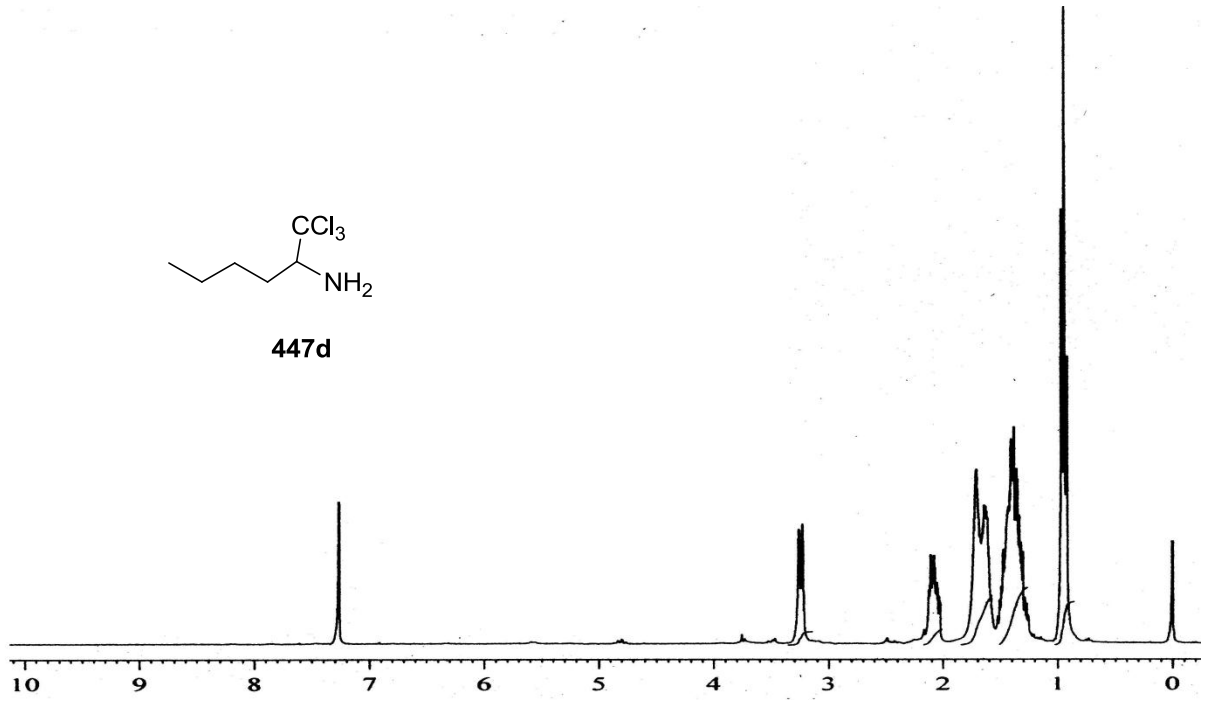


Fig. 199 ^{1}H NMR spectrum of 1,1,1-trichlorohexan-2-amine 447d

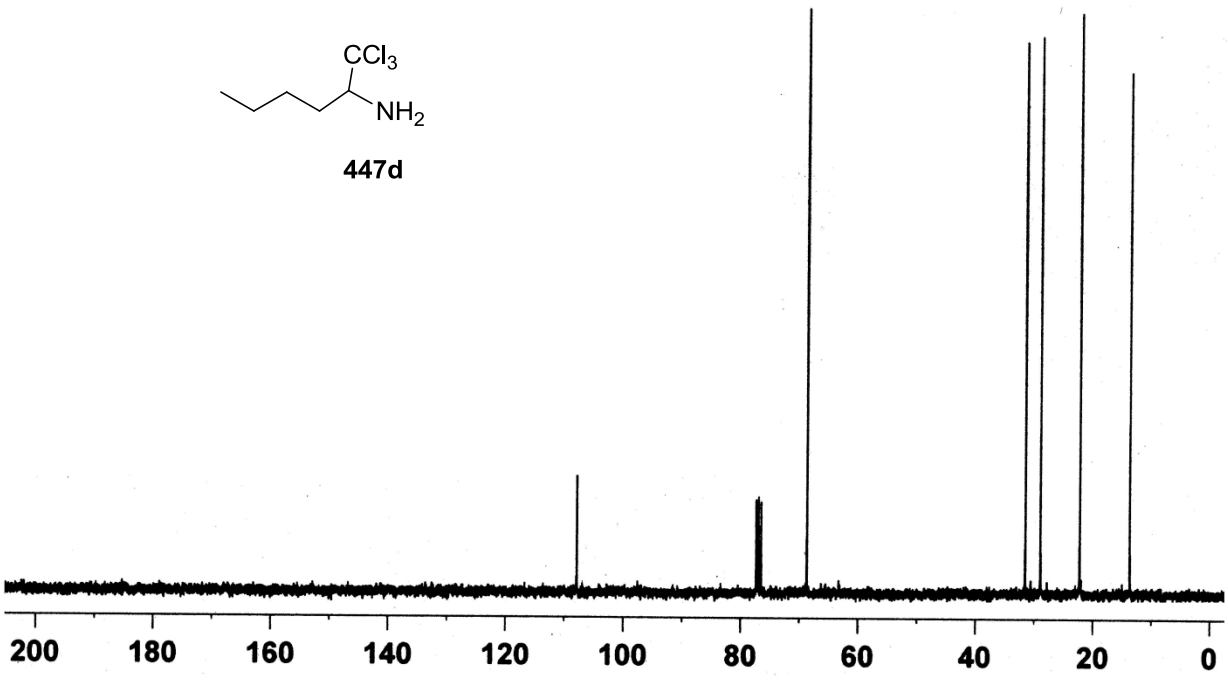


Fig. 200 ^{13}C{^{1}H} NMR spectrum of 1,1,1-trichlorohexan-2-amine 447d

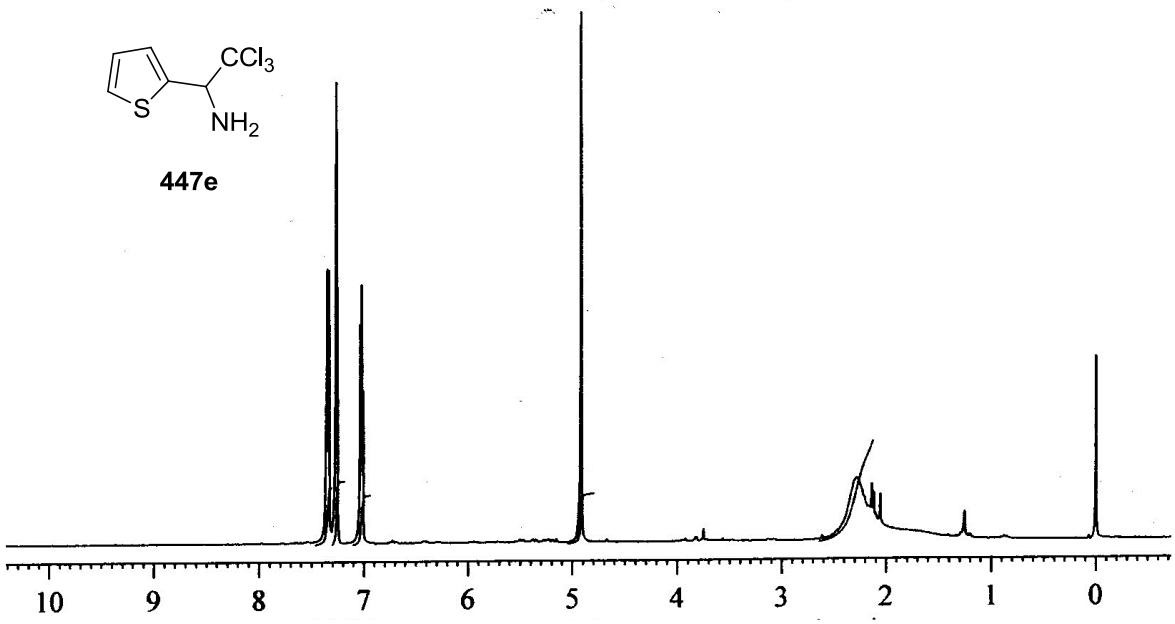


Fig. 201 ^{1}H NMR spectrum of 2,2,2-trichloro-1-(thiophen-2-yl)ethanamine 447e

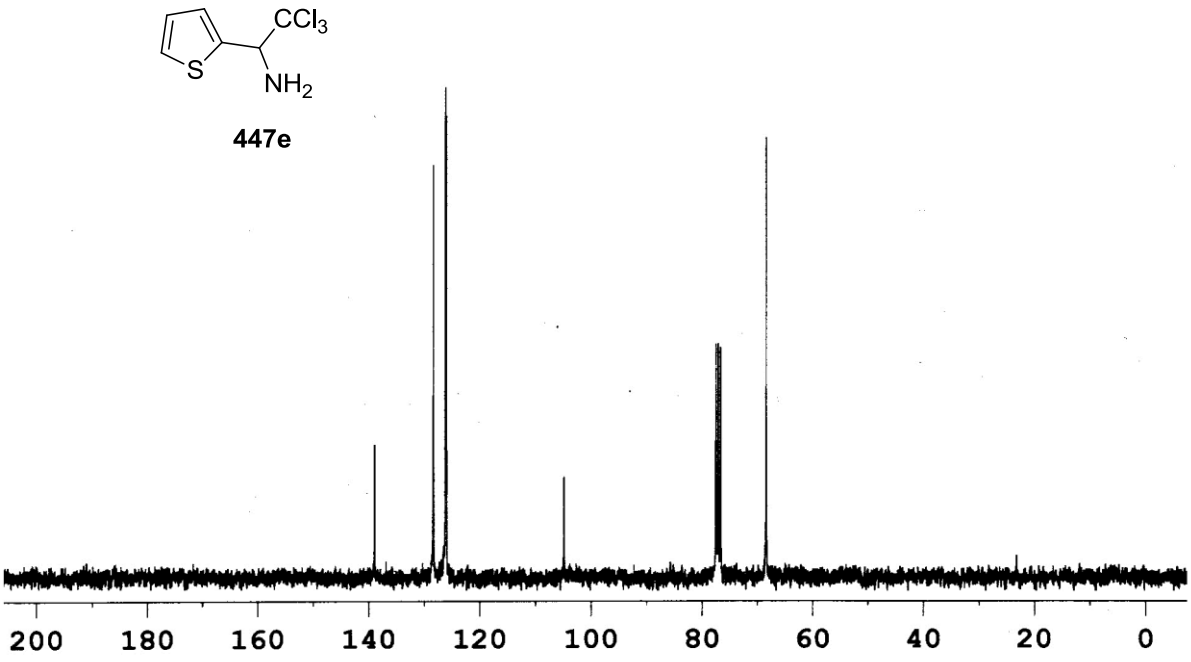


Fig. 202 ^{13}C{^{1}H} NMR spectrum of 2,2,2-trichloro-1-(thiophen-2-yl)ethanamine 447e

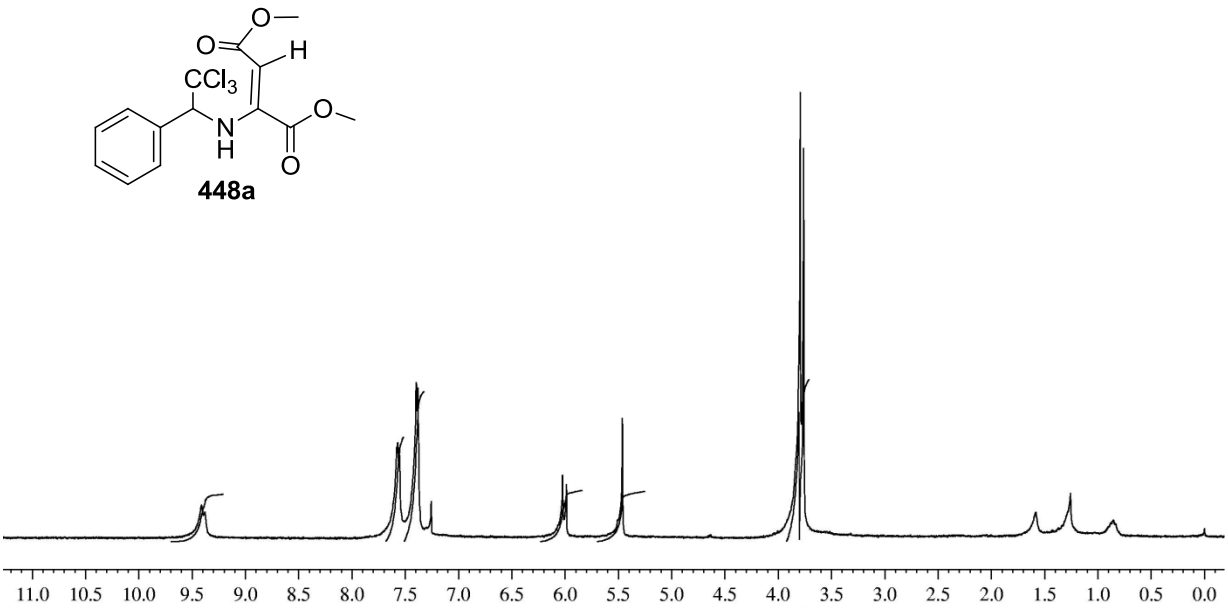


Fig. 203 ^{1}H NMR spectrum of dimethyl 2-(2,2,2-trichloro-1-phenylethylamino)fumarate 448a

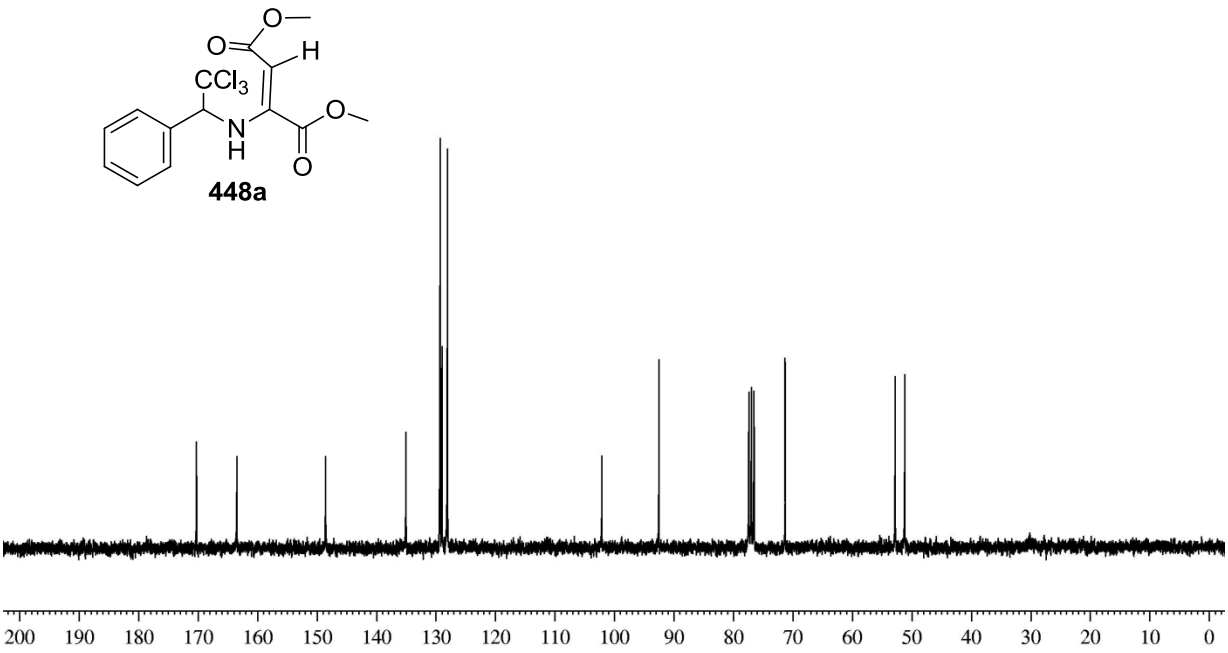


Fig. 204 ^{13}C{^{1}H} NMR spectrum of dimethyl 2-(2,2,2-trichloro-1-phenylethylamino) fumarate 448a

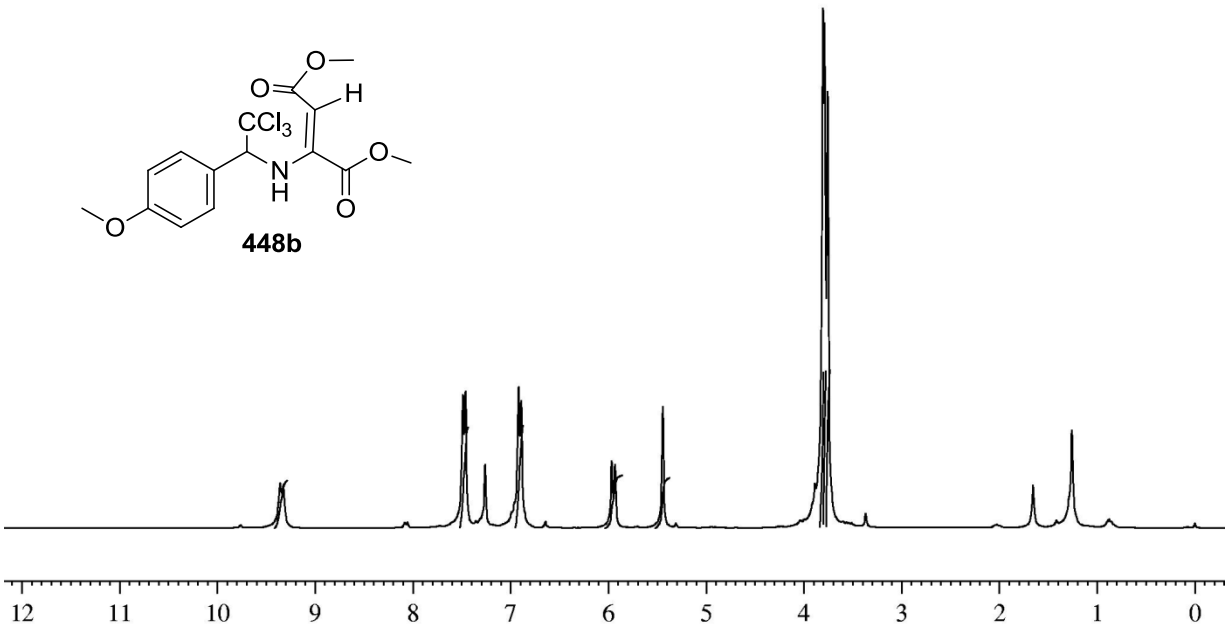


Fig. 205 ^{1}H NMR spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethylamino)fumarate 448b

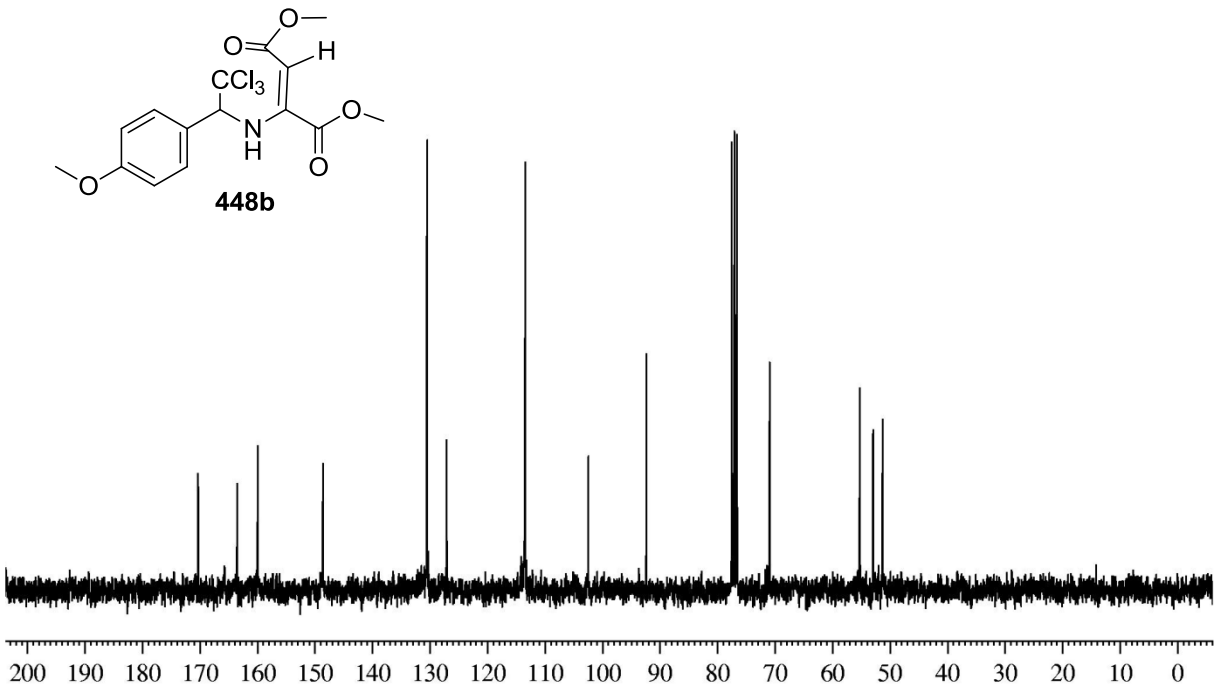


Fig. 206 ^{13}C{^{1}H} NMR spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethylamino)fumarate 448b

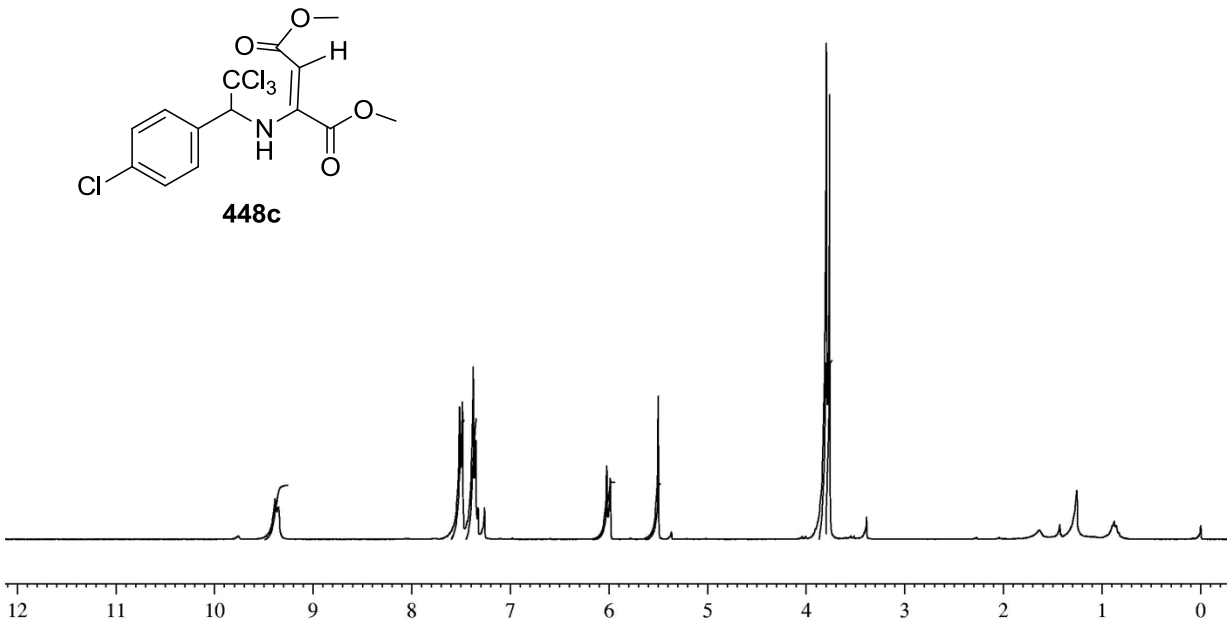


Fig. 207 ^{1}H NMR spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)fumarate 448c

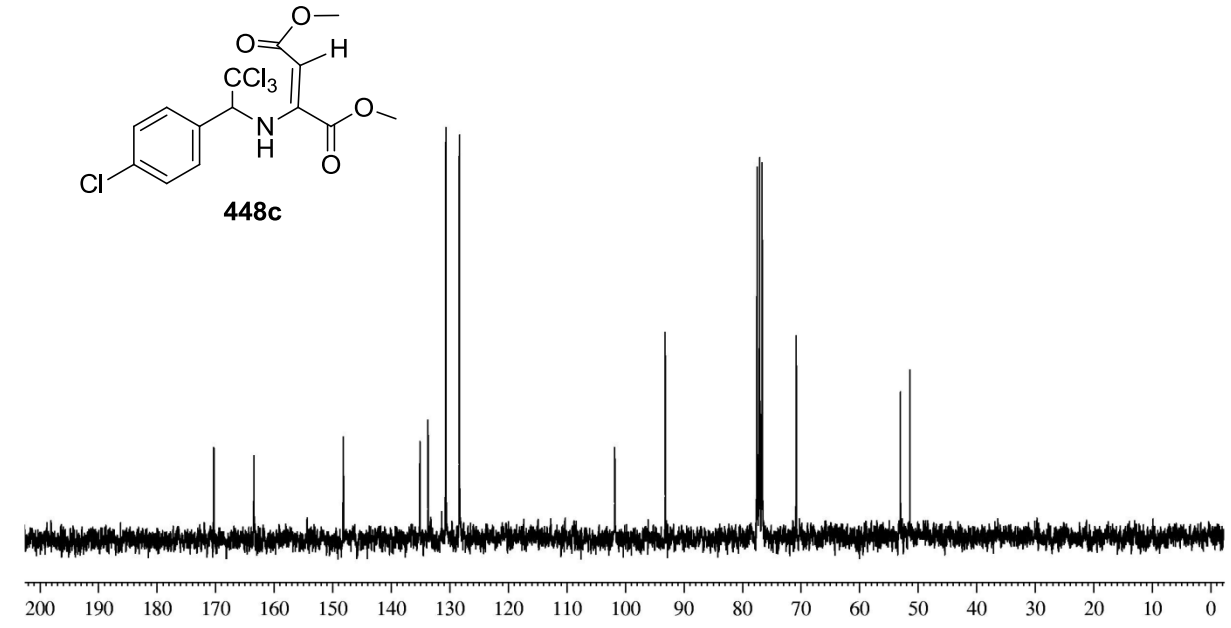


Fig. 208 ^{13}C{^{1}H} NMR spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)fumarate 448c

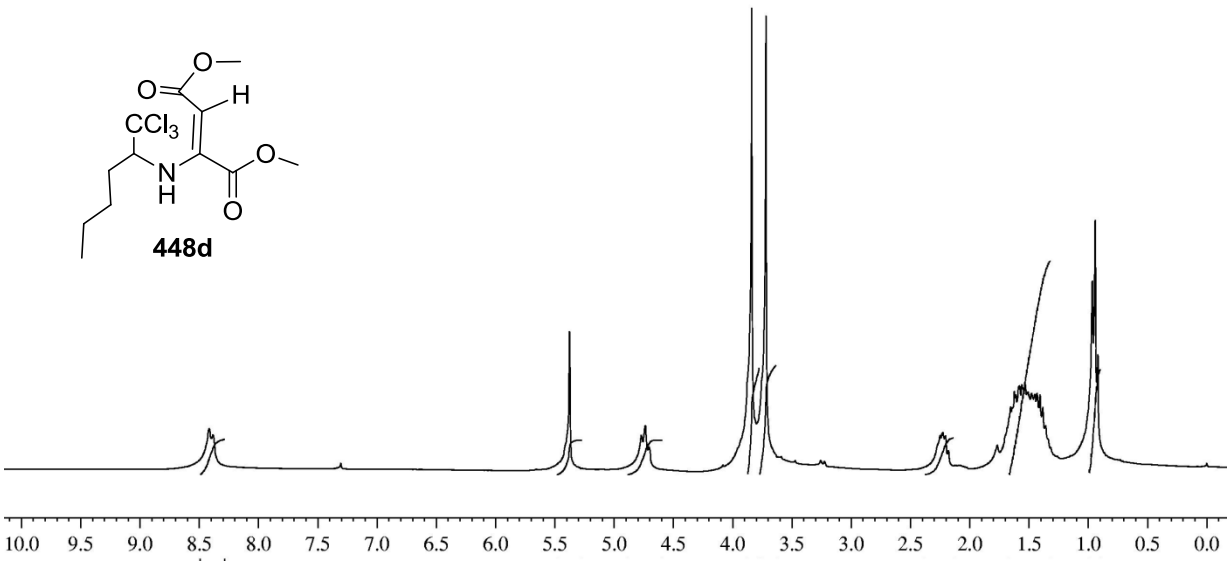


Fig. 209 ^{1}H NMR spectrum of dimethyl 2-(1,1,1-trichlorohexan-2-ylamino) fumarate 448d

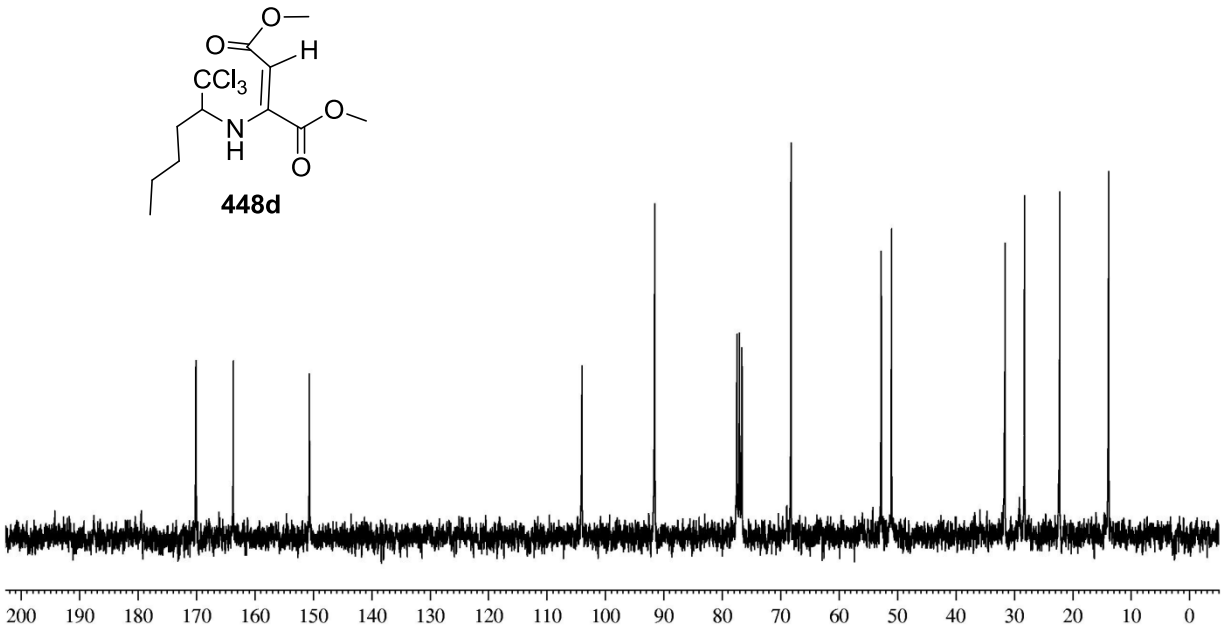


Fig. 210 ^{13}C{^{1}H} NMR spectrum of dimethyl 2-(1,1,1-trichlorohexan-2-ylamino) fumarate 448d

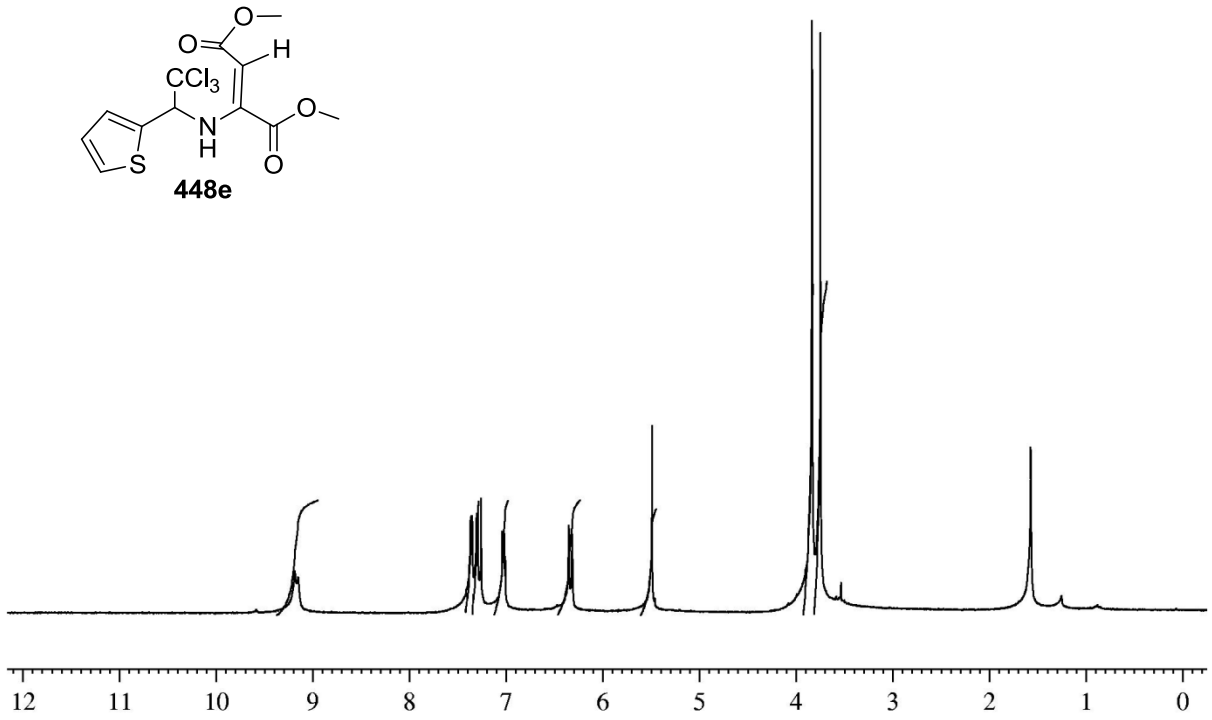


Fig. 211 ^{1}H NMR spectrum of dimethyl 2-(2,2,2-trichloro-1-(thiophen-2-yl)ethylamino) fumarate 448e

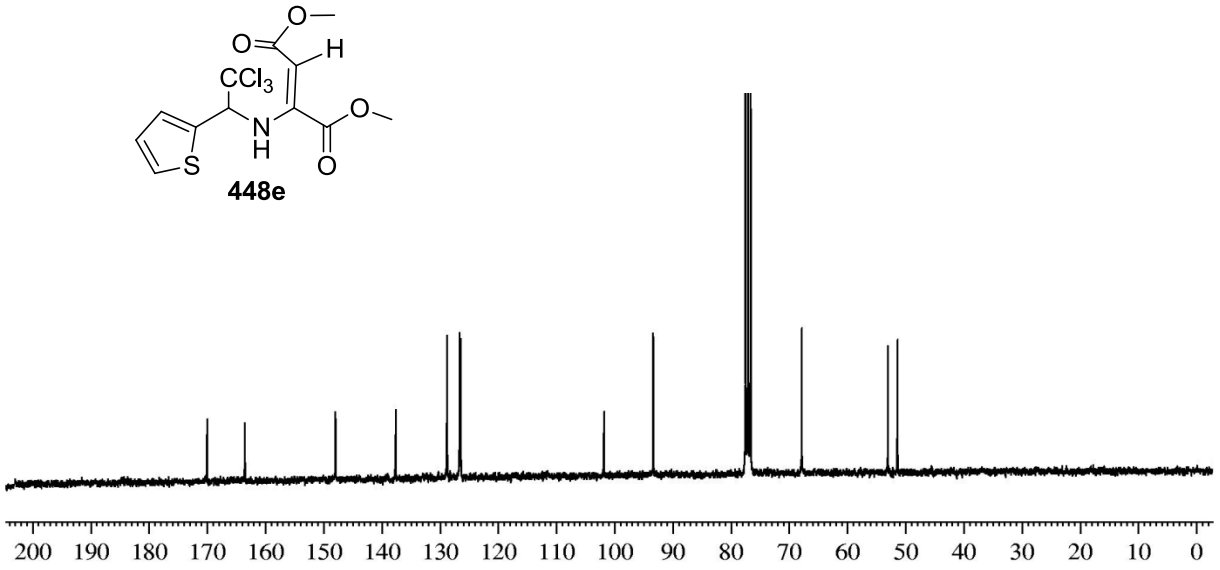


Fig. 212 ^{13}C{^{1}H} NMR spectrum of dimethyl 2-(2,2,2-trichloro-1-(thiophen-2-yl)ethylamino)fumarate 448e

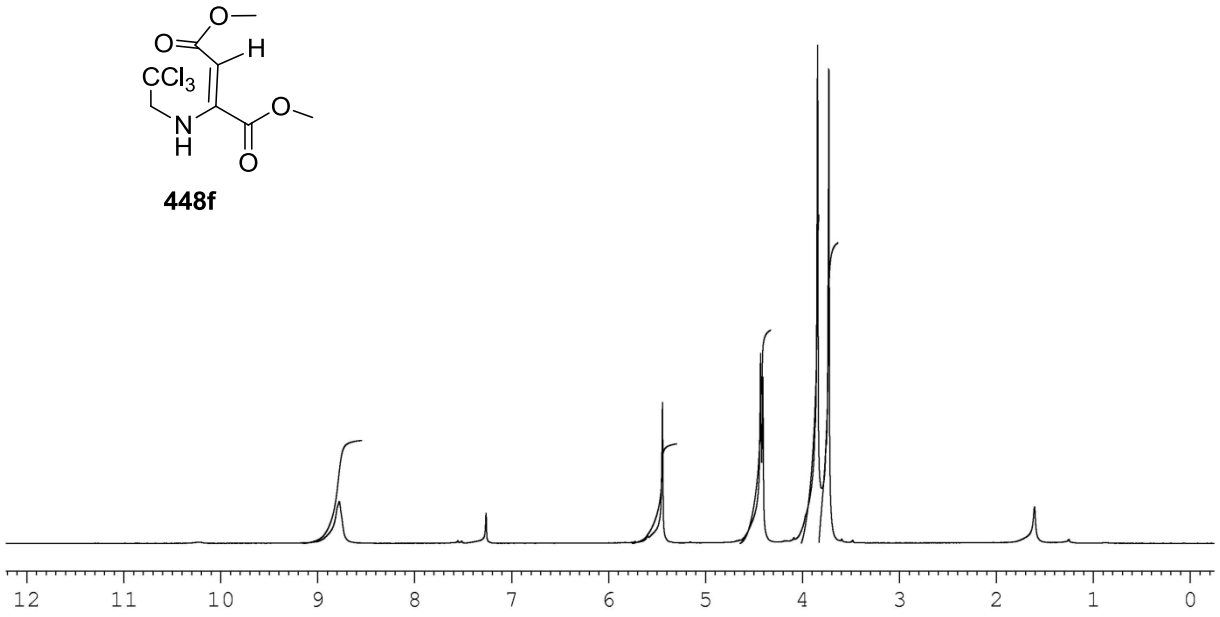


Fig. 213 ^{1}H NMR spectrum of dimethyl 2-(2,2,2-trichloroethylamino)fumarate 448f

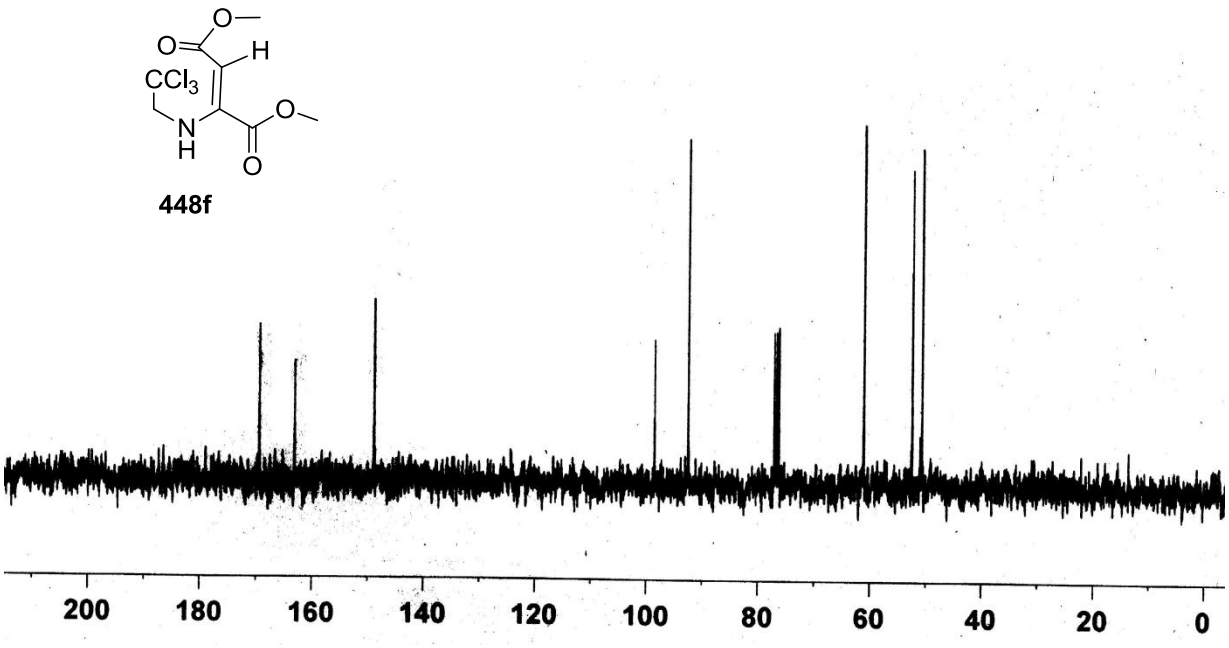


Fig. 214 ^{13}C{^{1}H} NMR spectrum of dimethyl 2-(2,2,2-trichloroethylamino)fumarate 448f

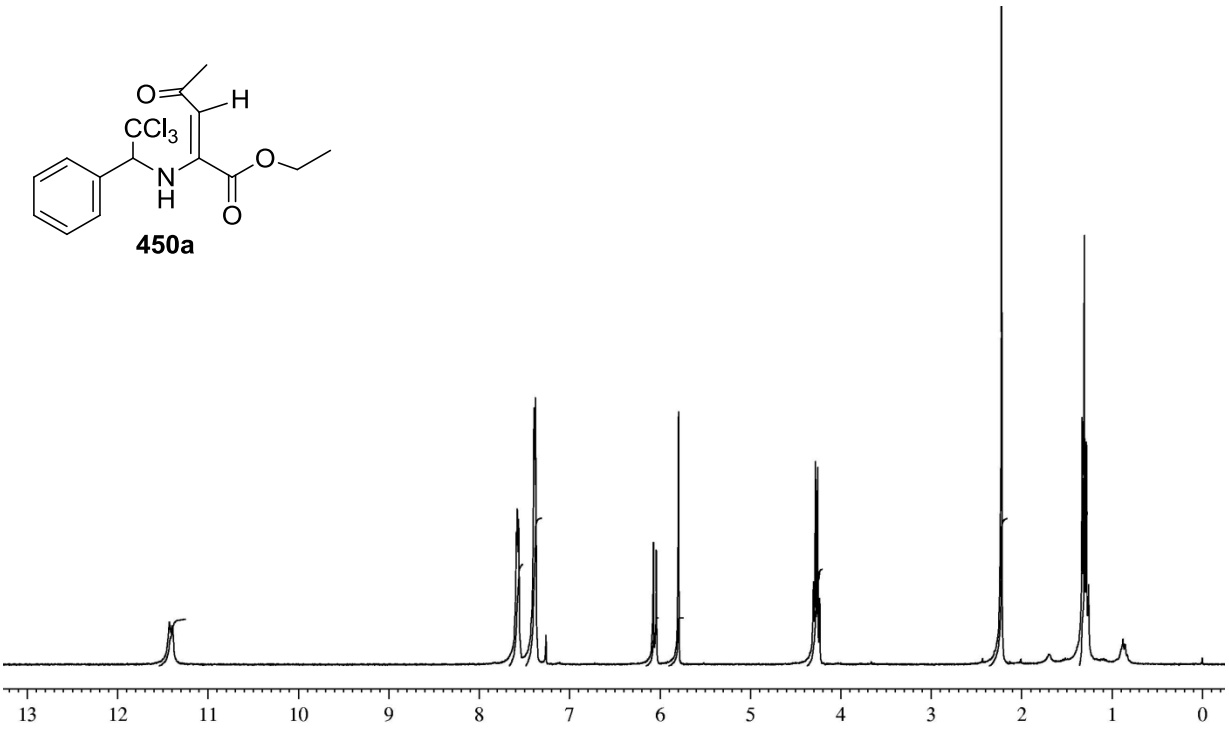


Fig. 215 ^{1}H NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloro-1-phenylethylamino)pent-2-enoate 450a

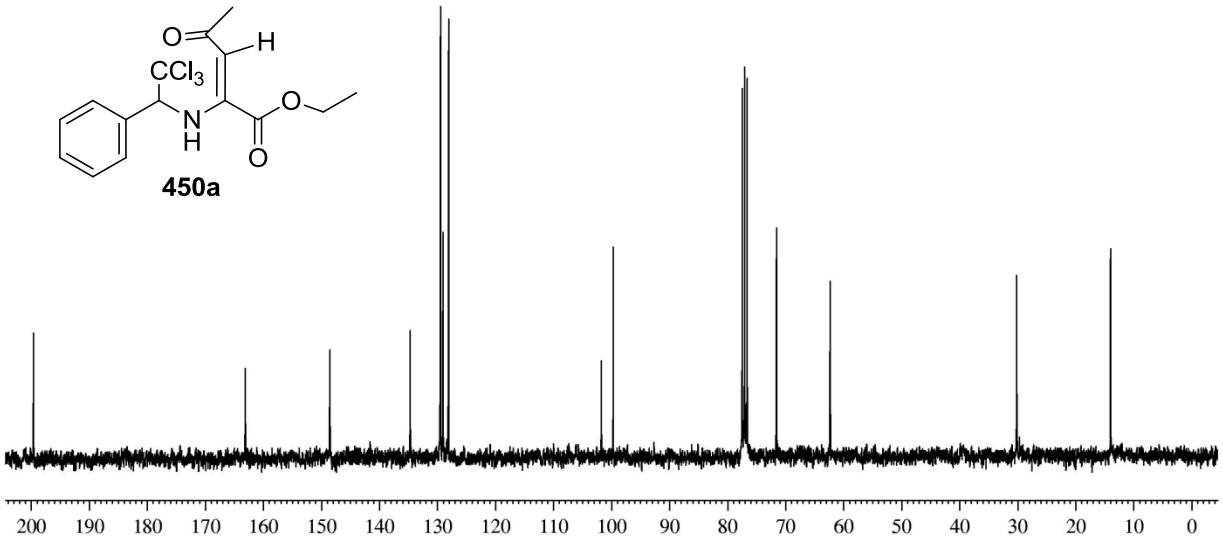


Fig. 216 ^{13}C{^{1}H} NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloro-1-phenylethylamino)pent-2-enoate 450a

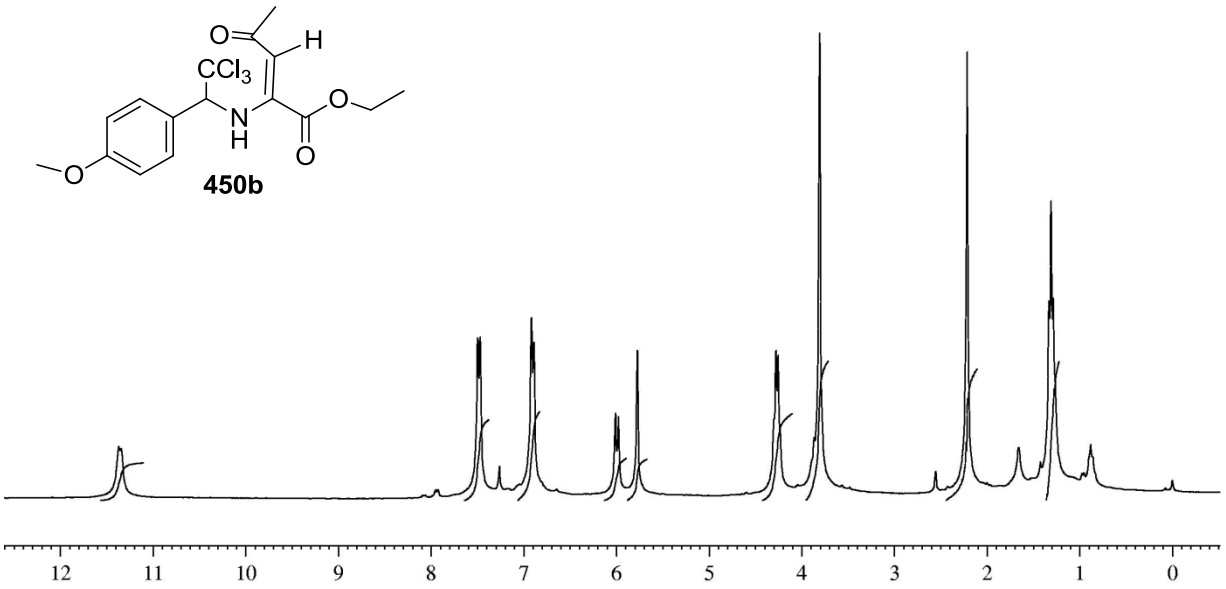


Fig. 217 ^{1}H NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethylamino)pent-2-enoate 450b

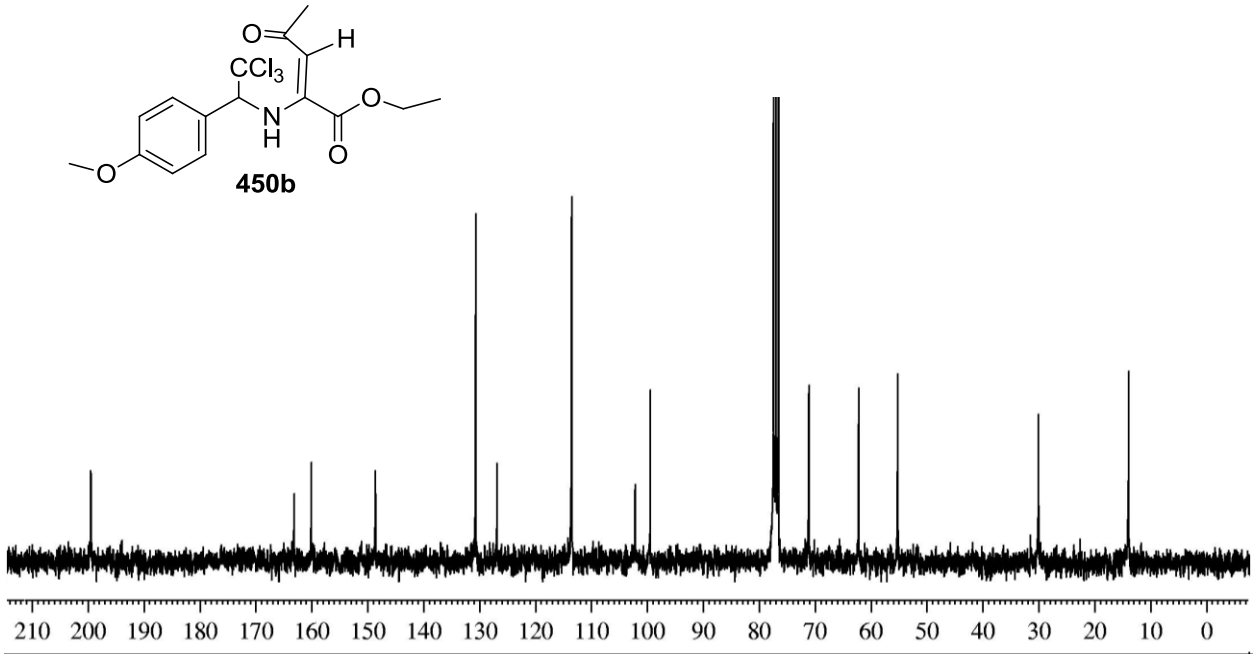


Fig. 218 ^{13}C{^{1}H} NMR spectrum of (*Z*) ethyl 4-oxo-2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethylamino)pent-2-enoate 450b

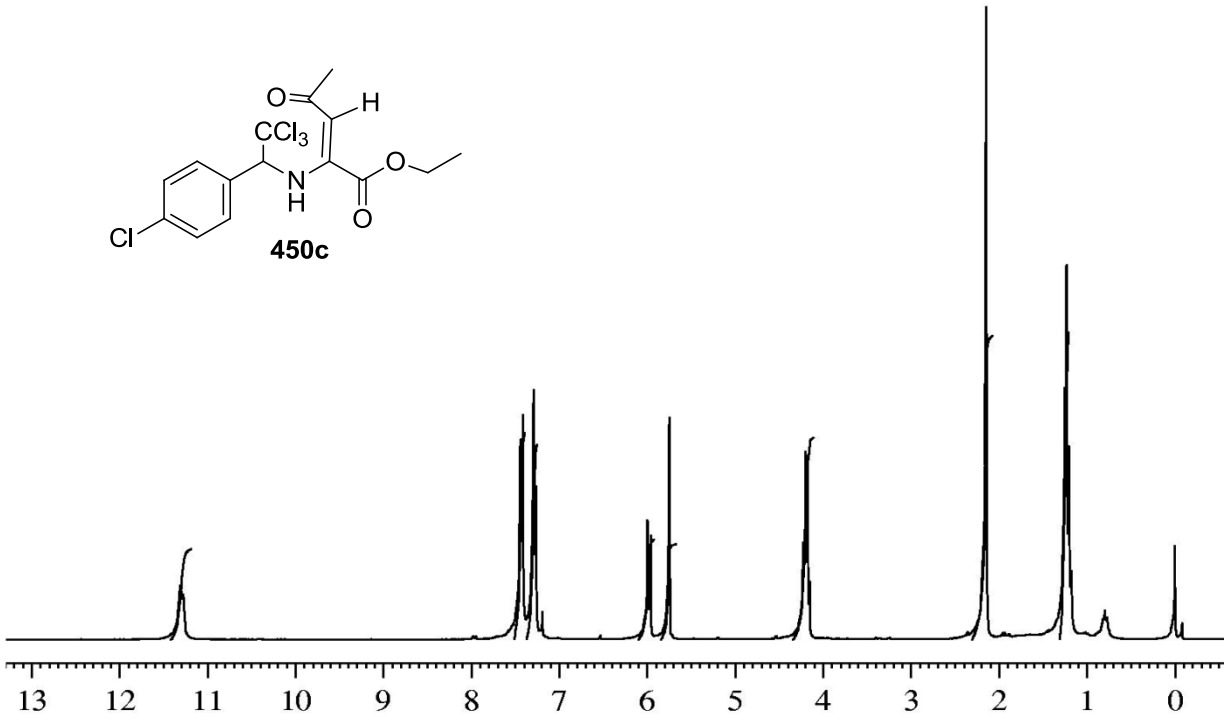


Fig. 219 ^{1}H NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)pent-2-enoate 450c

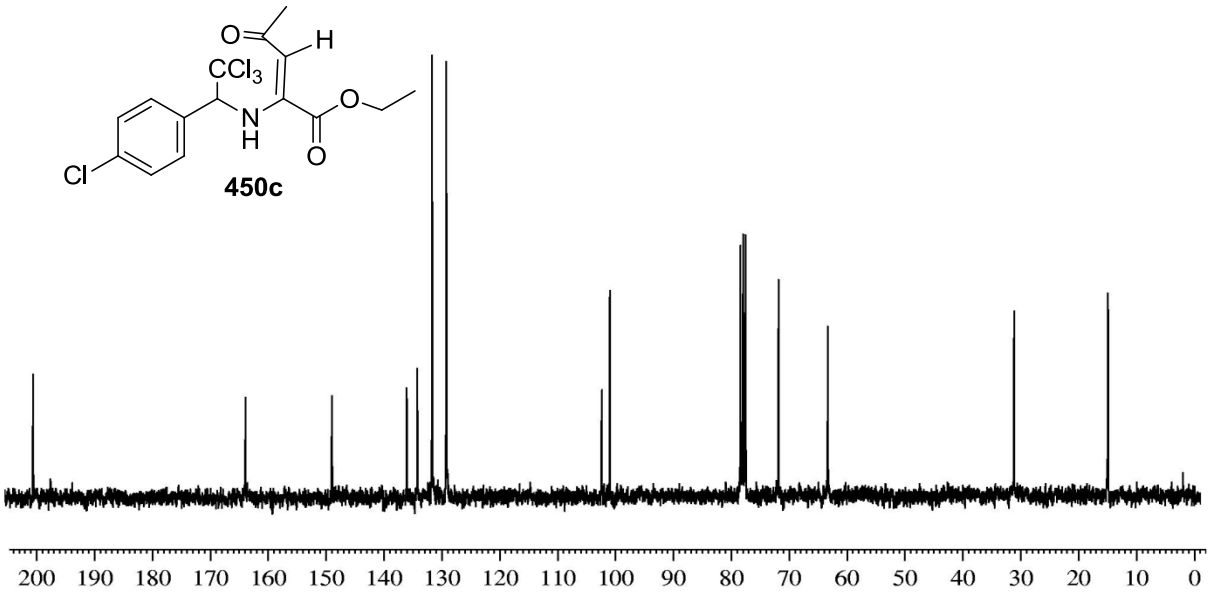


Fig. 220 ^{13}C{^{1}H} NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)pent-2-enoate 450c

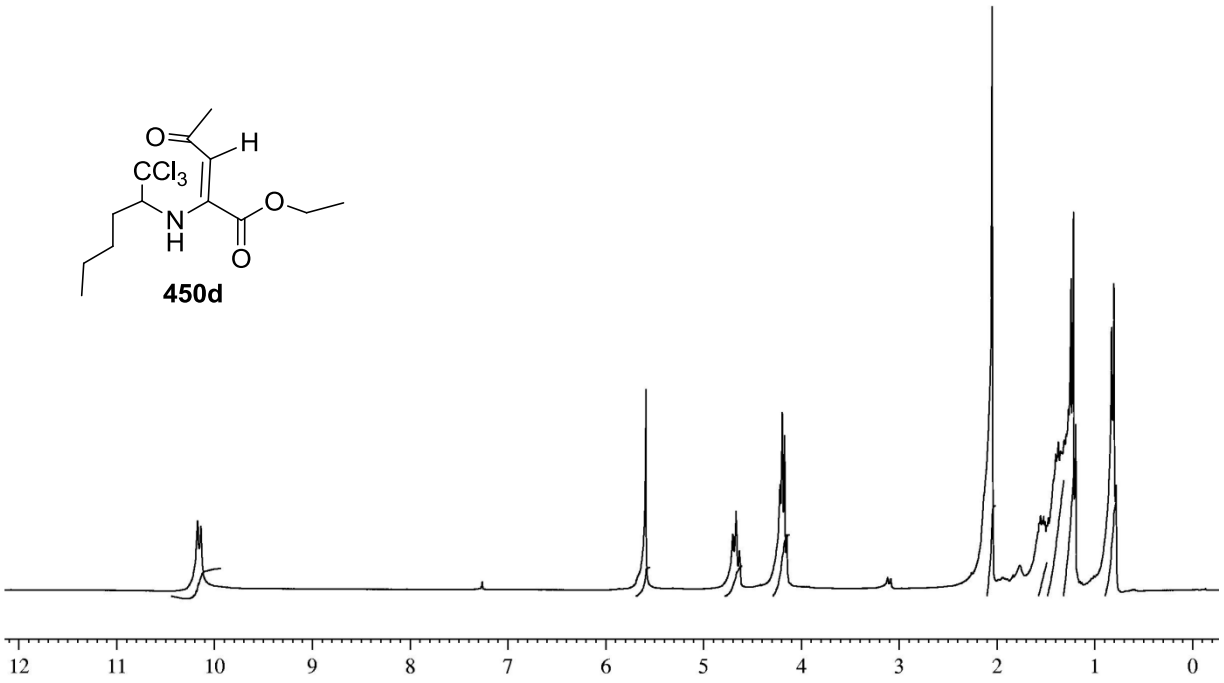


Fig. 221 ^{1}H NMR spectrum of (*Z*)-ethyl 4-oxo-2-(1,1,1-trichlorohexan-2-ylamino)pent-2-enoate 450d

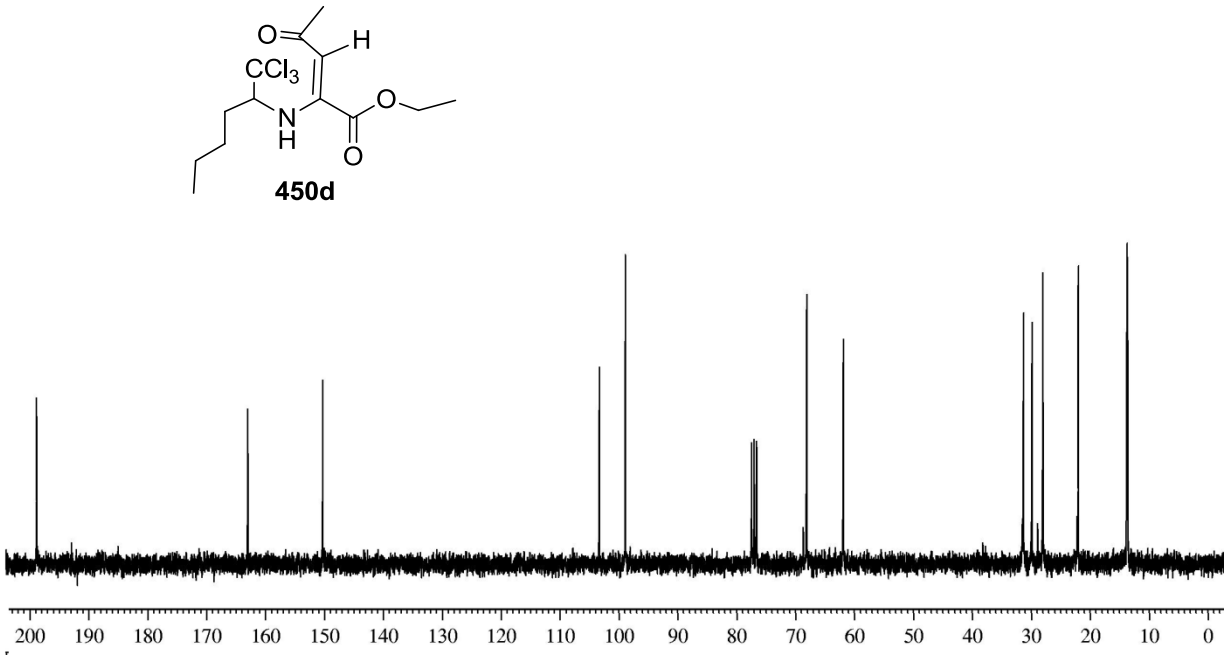


Fig. 222 ^{13}C{^{1}H} NMR spectrum of (*Z*)-ethyl 4-oxo-2-(1,1,1-trichlorohexan-2-ylamino)pent-2-enoate 450d

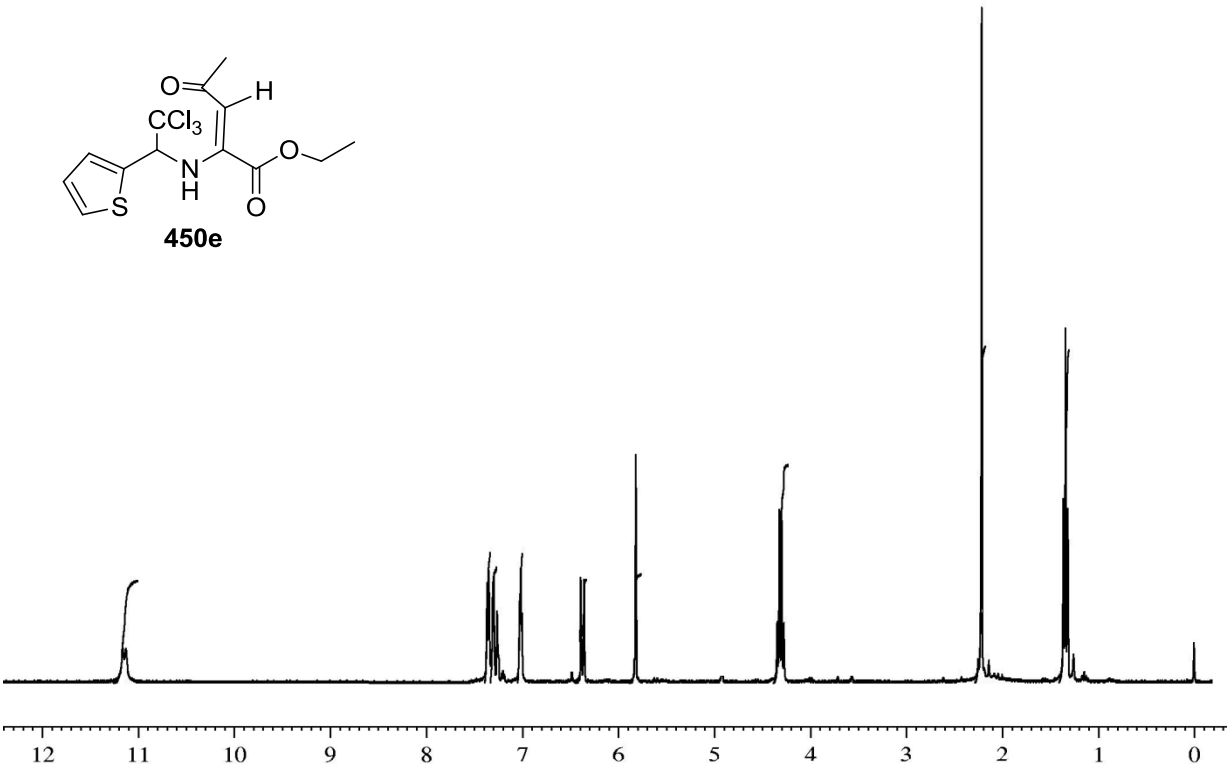


Fig. 223 ^{1}H NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloro-1-(thiophen-2-yl)ethylamino)pent-2-enoate 450e

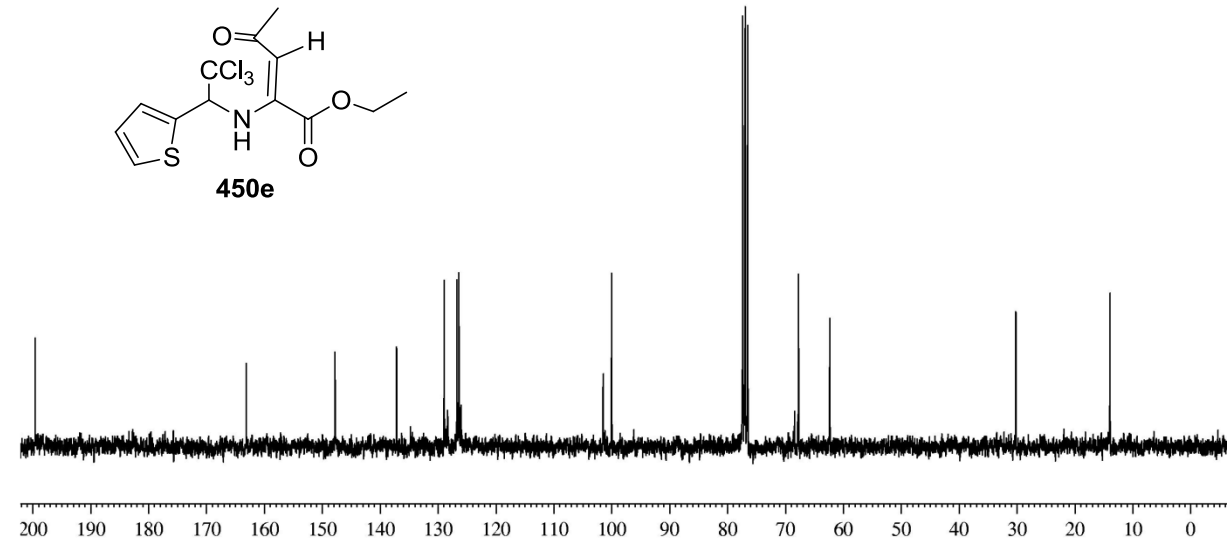


Fig. 224 ^{13}C{^{1}H} NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloro-1-(thiophen-2-yl)ethylamino)pent-2-enoate 450e

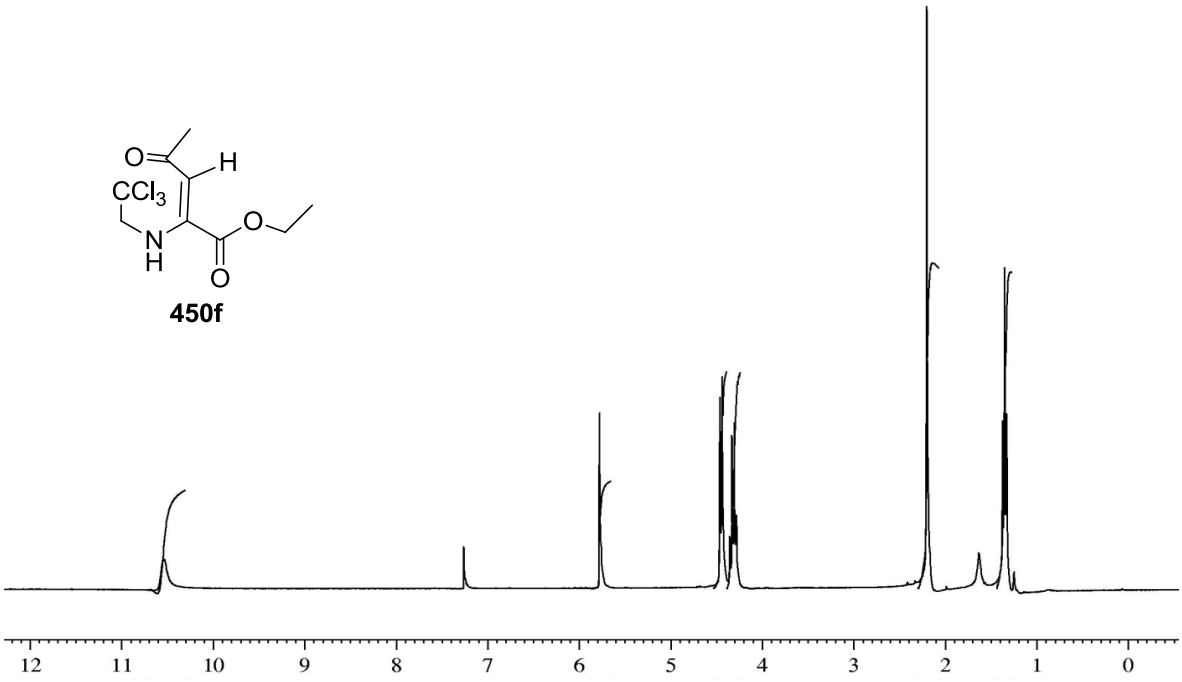


Fig. 225 ^{1}H NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloroethylamino)pent-2-enoate 450f

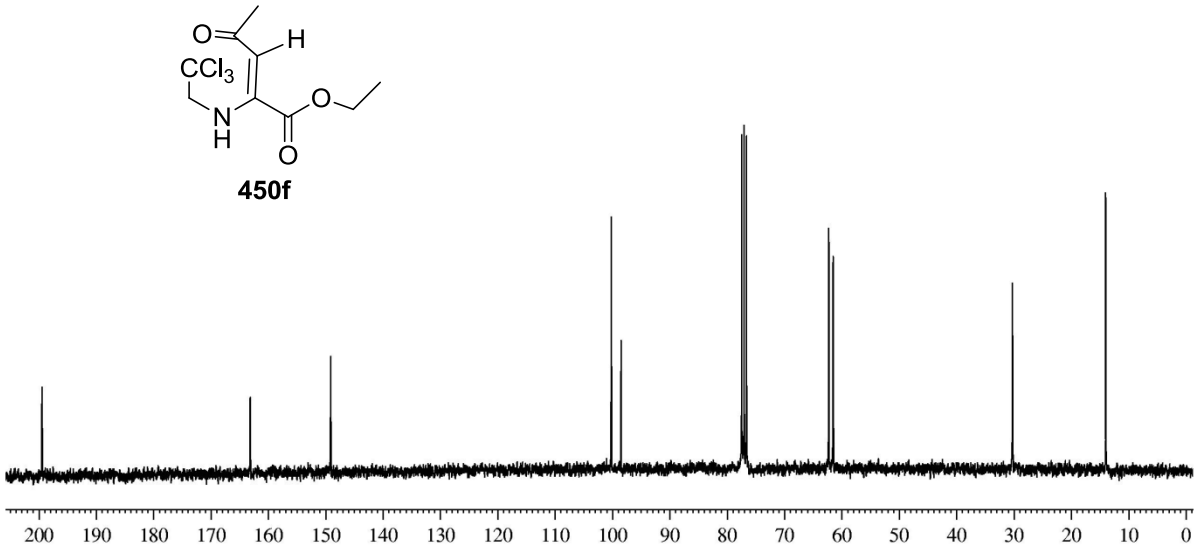


Fig. 226 ^{13}C{^{1}H} NMR spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloroethylamino)pent-2-enoate 450f

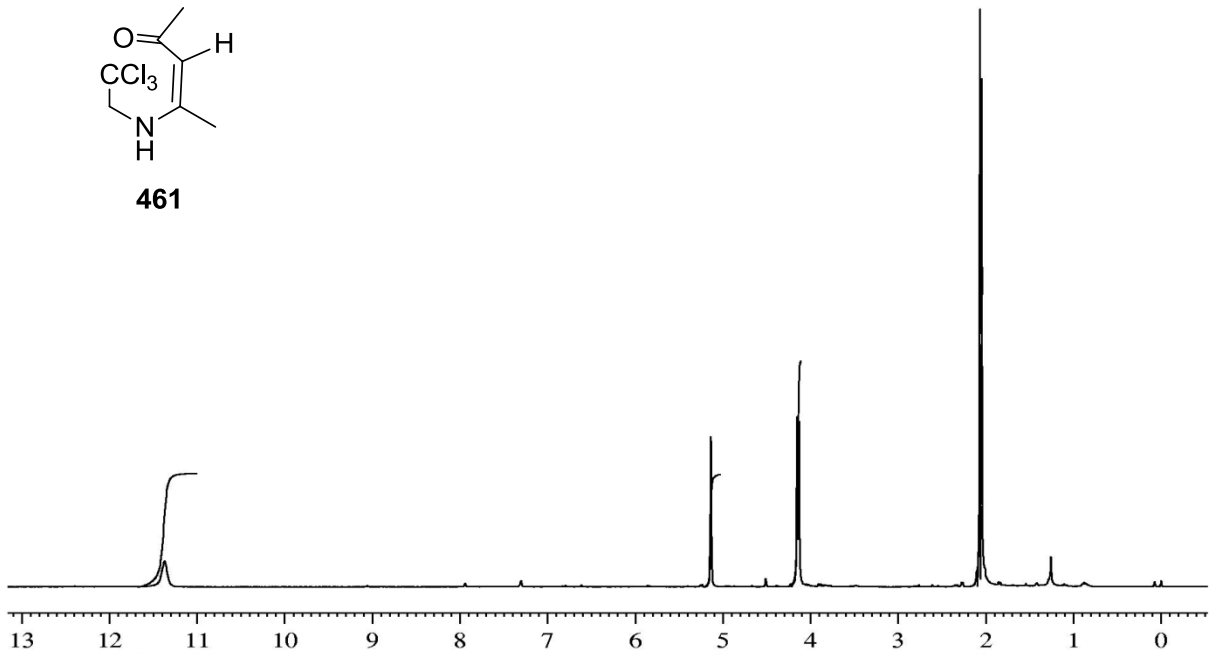


Fig. 227 ^{1}H NMR spectrum of (*Z*)-4-(2,2,2-trichloroethylamino)pent-3-en-2-one 461

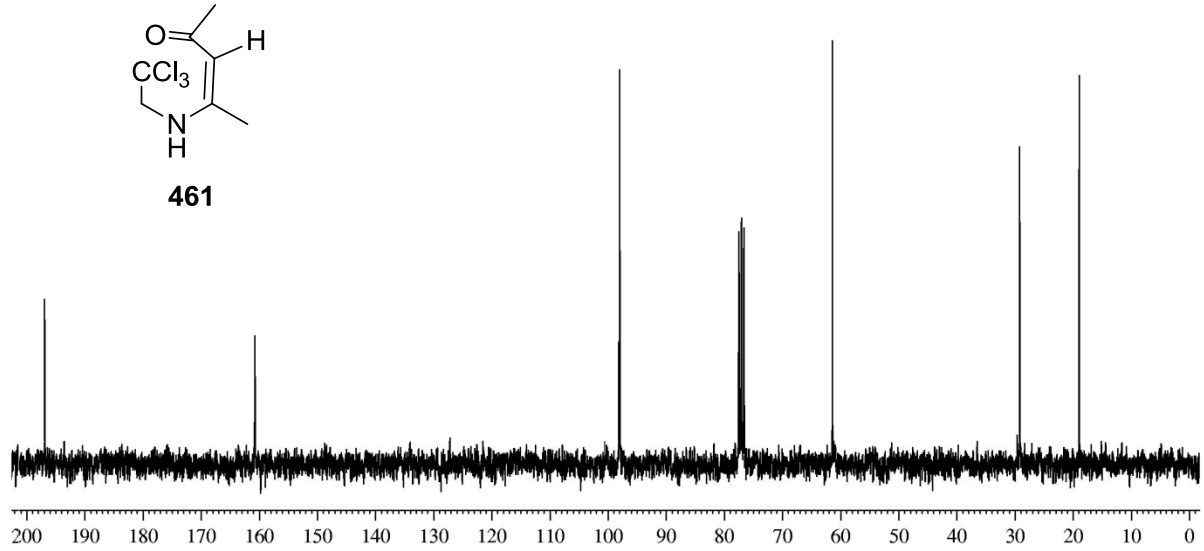


Fig. 228 ^{13}C{^{1}H} NMR spectrum of (*Z*)- 4-(2,2,2-trichloroethylamino)pent-3-en-2-one 461

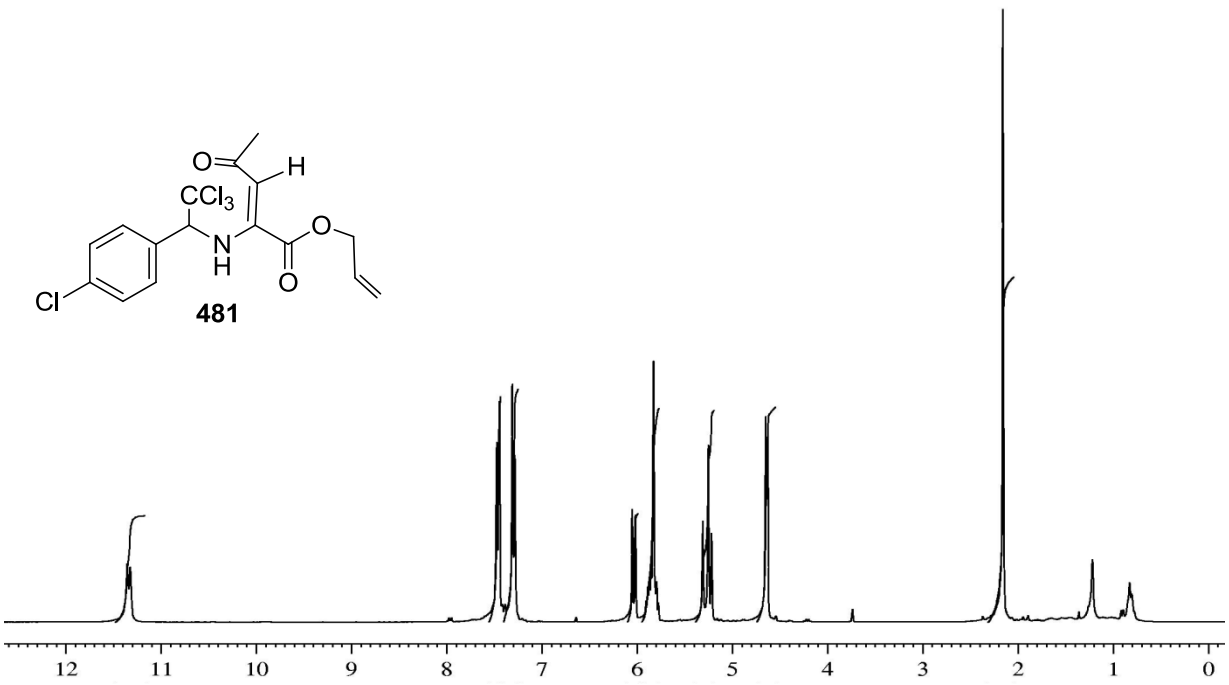


Fig. 229 ^{1}H NMR spectrum of (*Z*)-allyl 4-oxo-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)pent-2-enoate 481

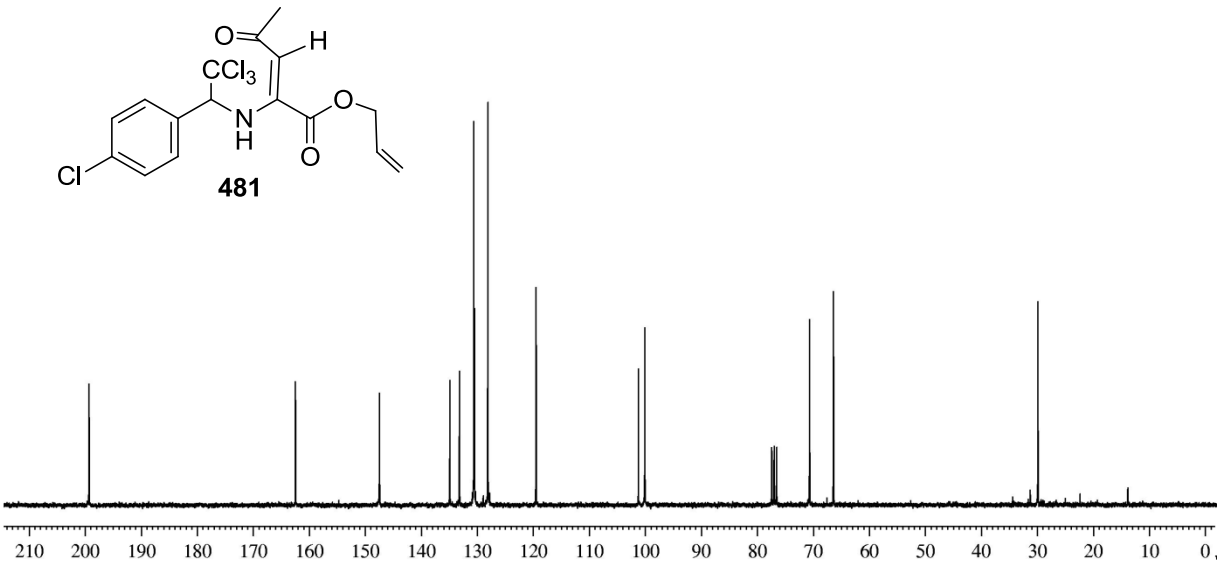


Fig. 230 ^{13}C{^{1}H} NMR spectrum of (*Z*)-allyl 4-oxo-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethylamino)pent-2-enoate 481

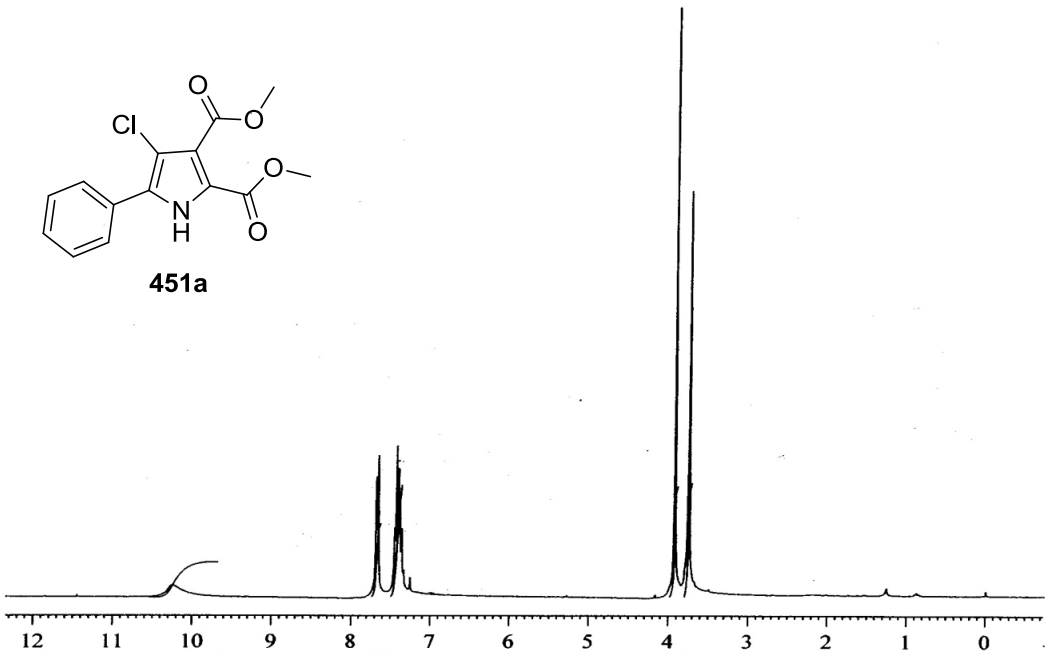


Fig. 231 ^{1}H NMR spectrum of dimethyl 4-chloro-5-phenyl-1H-pyrrole-2,3-dicarboxylate 451a

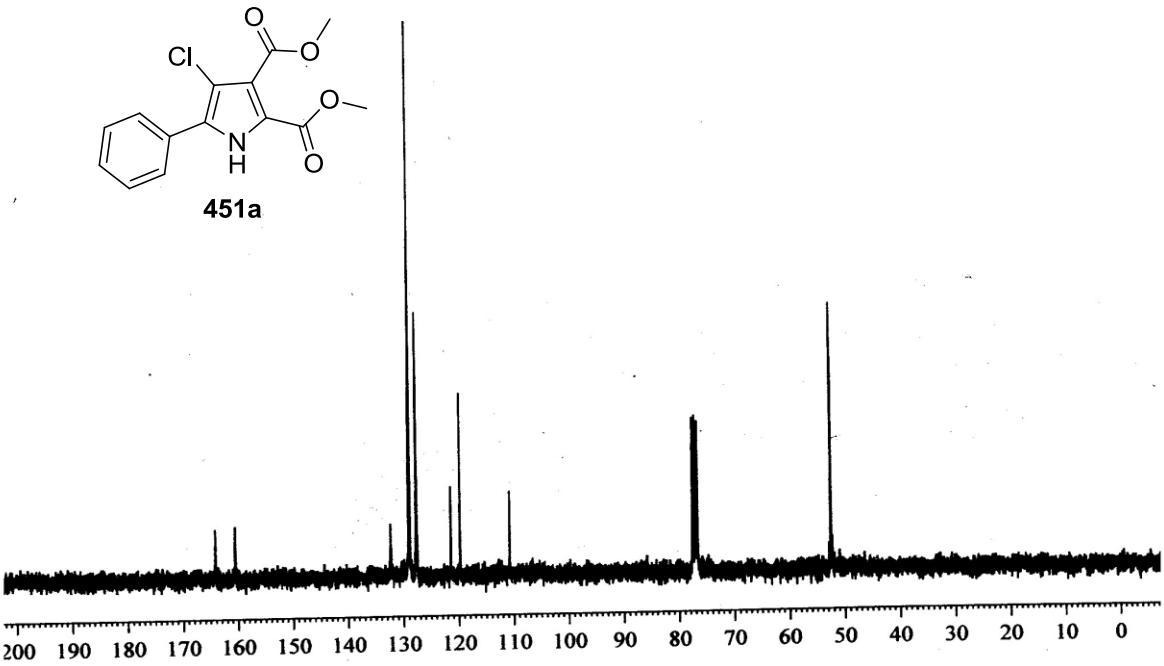


Fig. 232 ^{13}C{^{1}H} NMR spectrum of dimethyl 4-chloro-5-phenyl-1H-pyrrole-2,3-dicarboxylate 451a

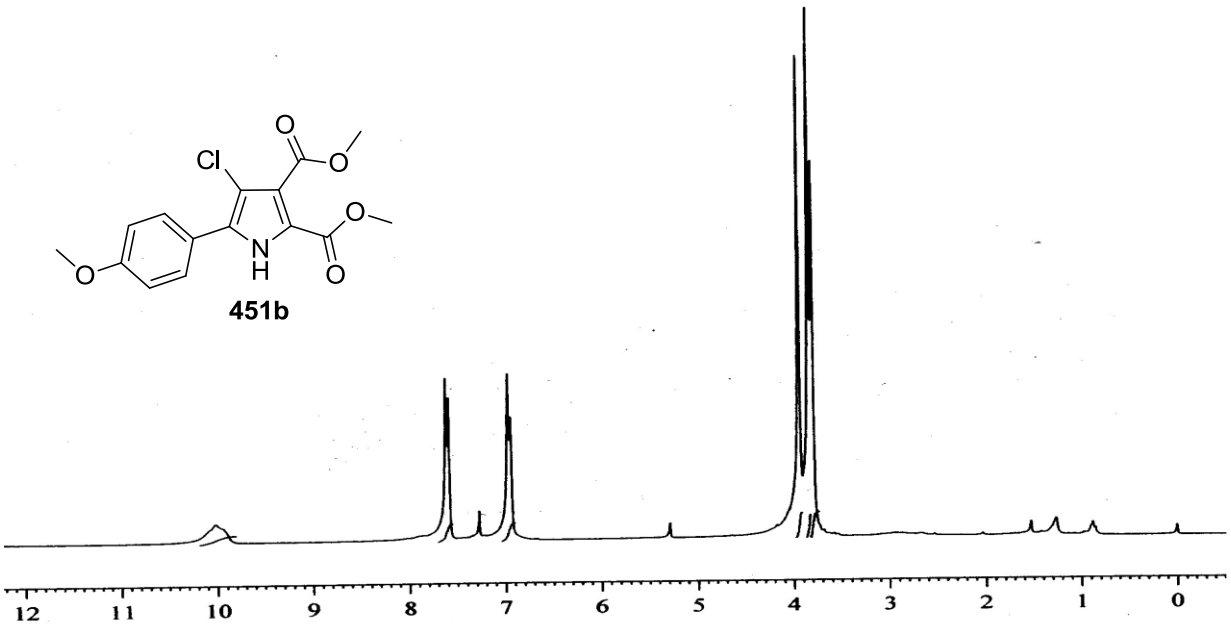


Fig. 233 ^{1}H NMR spectrum of dimethyl 4-chloro-5-(4-methoxyphenyl)-1H-pyrrole-2,3-dicarboxylate 451b

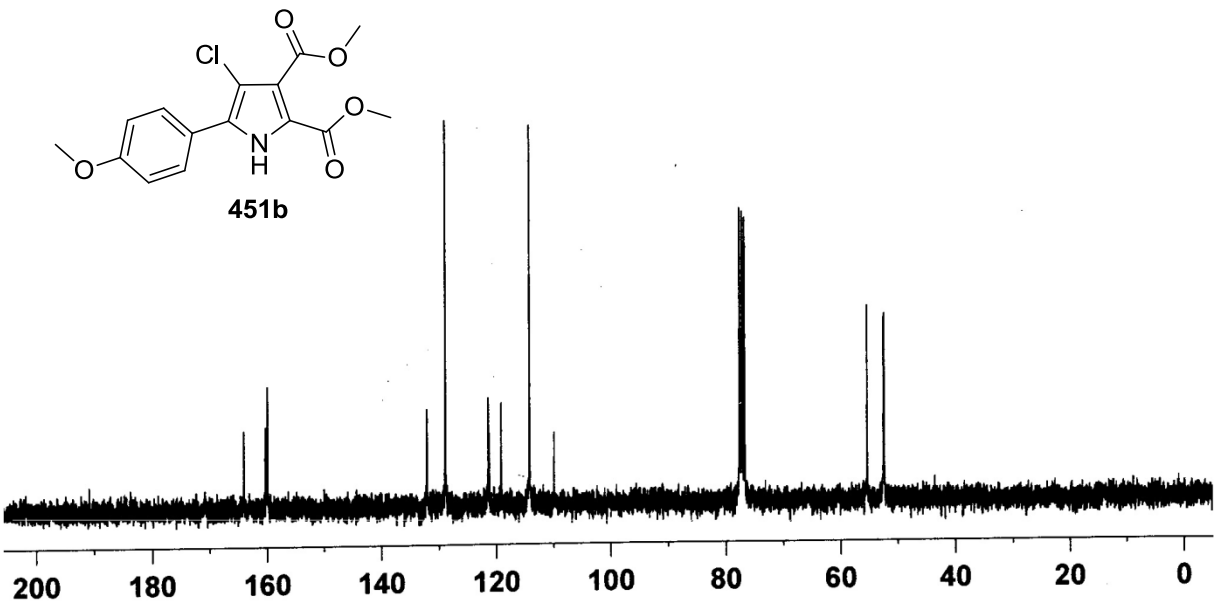


Fig. 234 ^{13}C{^{1}H} NMR spectrum of dimethyl 4-chloro-5-(4-methoxyphenyl)-1H-pyrrole-2,3-dicarboxylate 451b

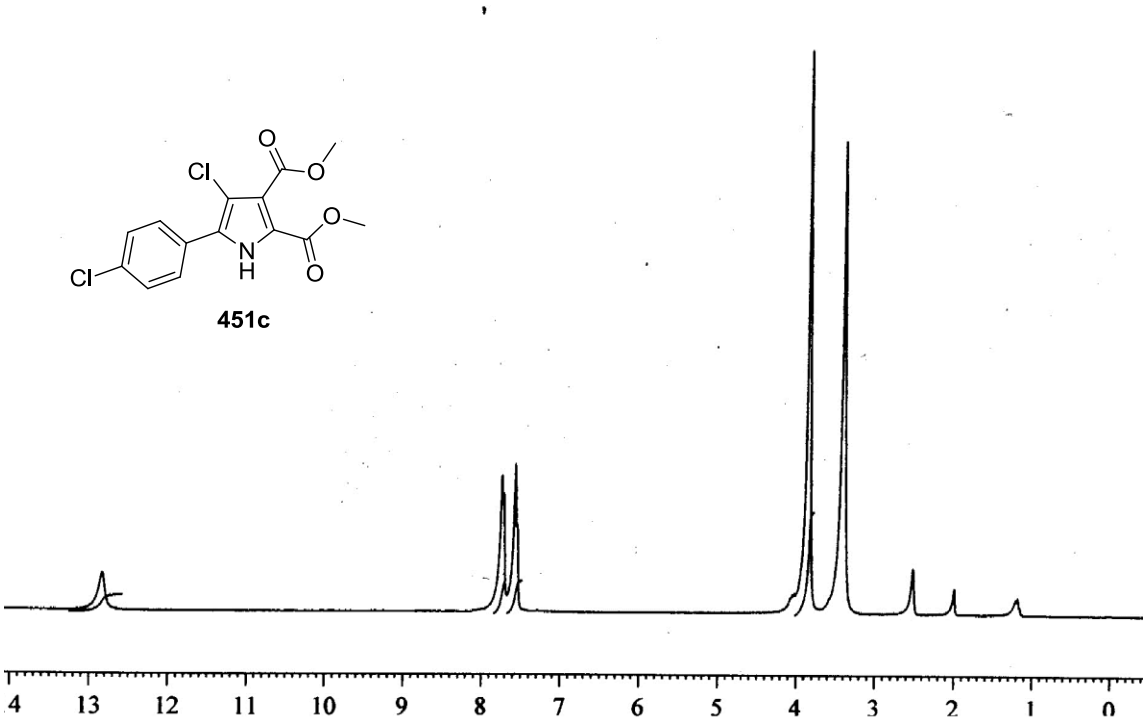


Fig. 235 ^{1}H NMR spectrum of dimethyl 4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2,3-dicarboxylate (in DMSO) 451c

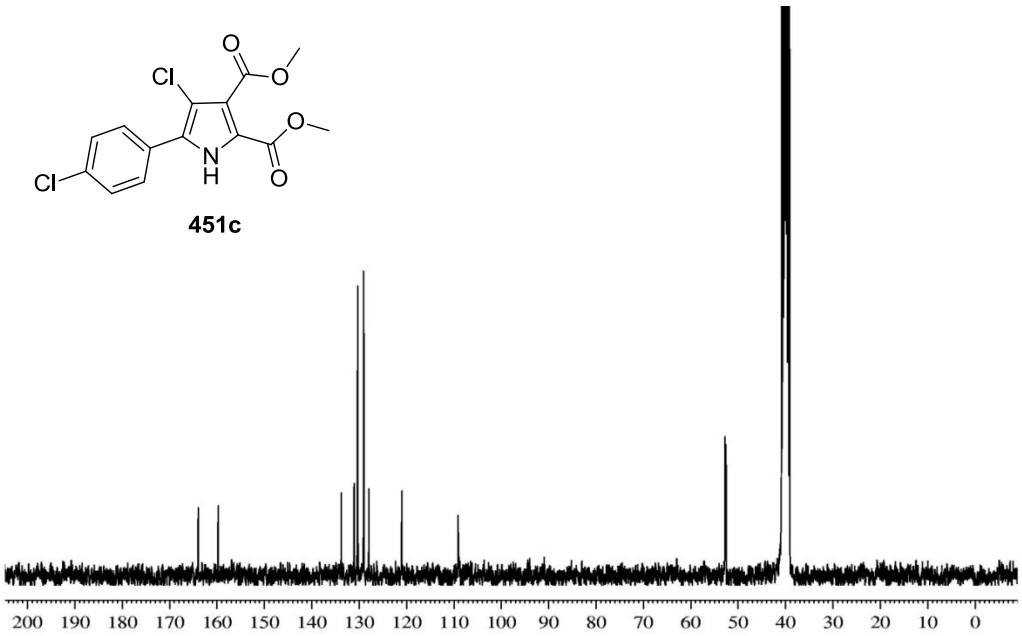


Fig. 236 ^{13}C{^{1}H} NMR spectrum of dimethyl 4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2,3-dicarboxylate (in DMSO) 451c

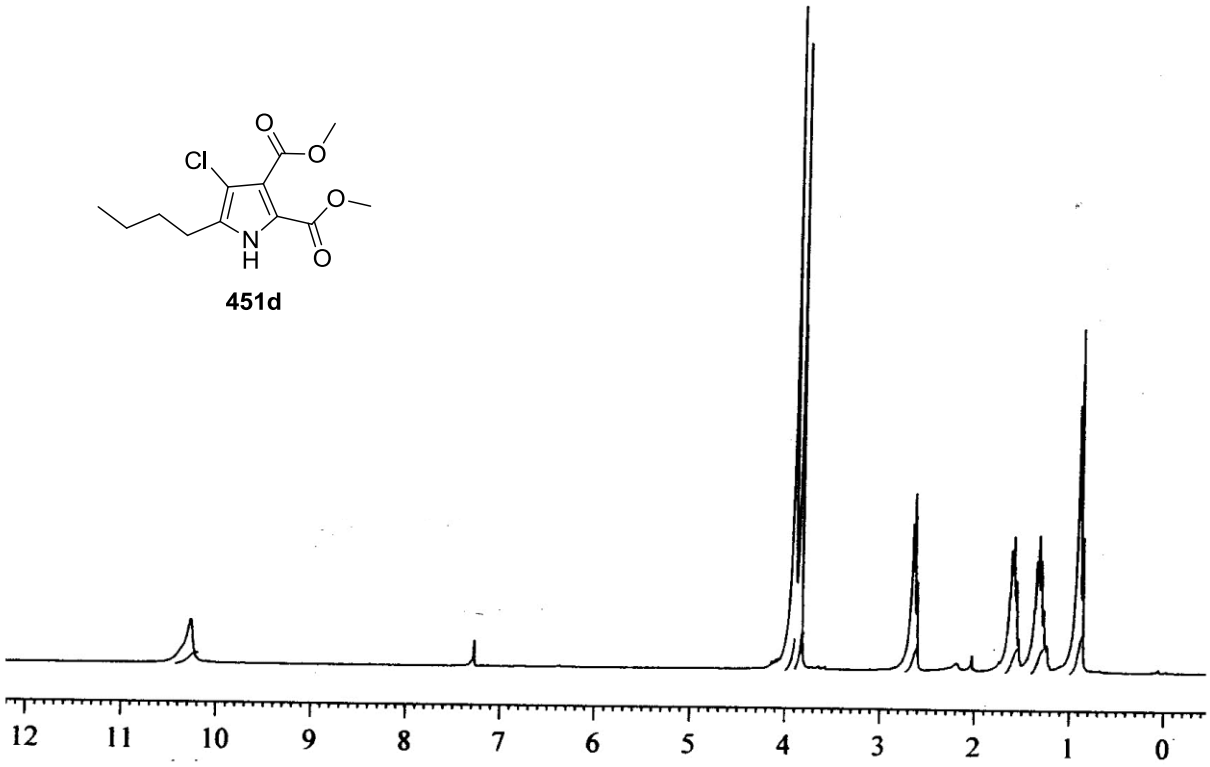


Fig. 237 ^{1}H NMR spectrum of dimethyl 5-butyl-4-chloro-1H-pyrrole-2,3-dicarboxylate 451d

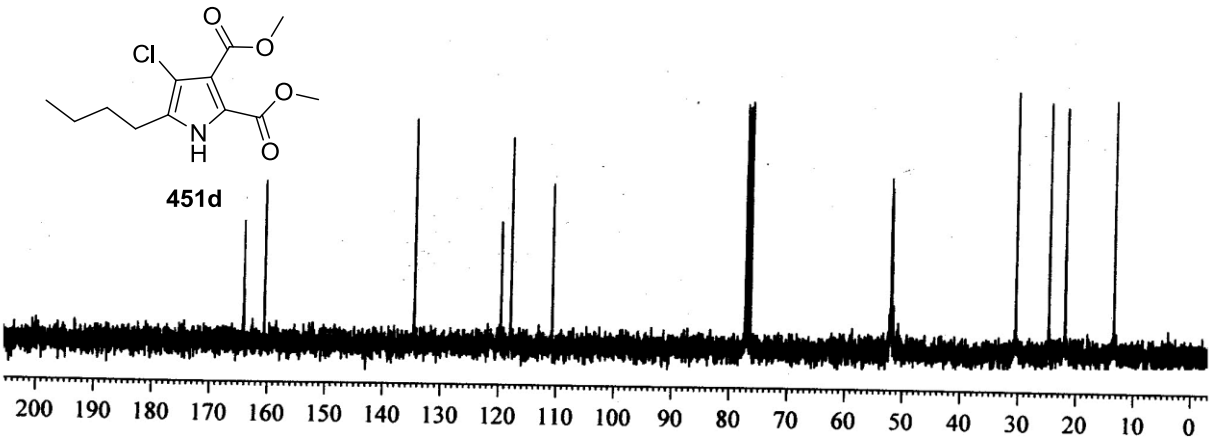


Fig. 238 ^{13}C{^{1}H} NMR spectrum of dimethyl 5-butyl-4-chloro-1H-pyrrole-2,3-dicarboxylate 451d

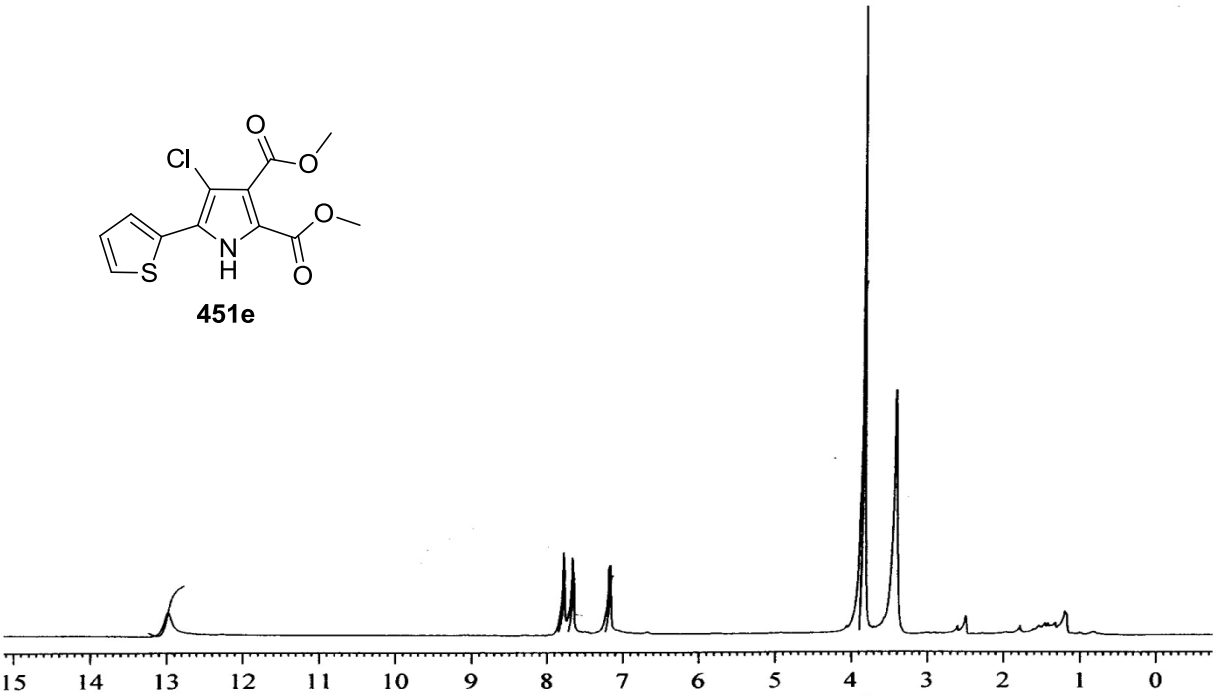


Fig. 239 ^{1}H NMR spectrum of dimethyl 4-chloro-5-(thiophen-2-yl)-1H-pyrrole-2,3-dicarboxylate 451e

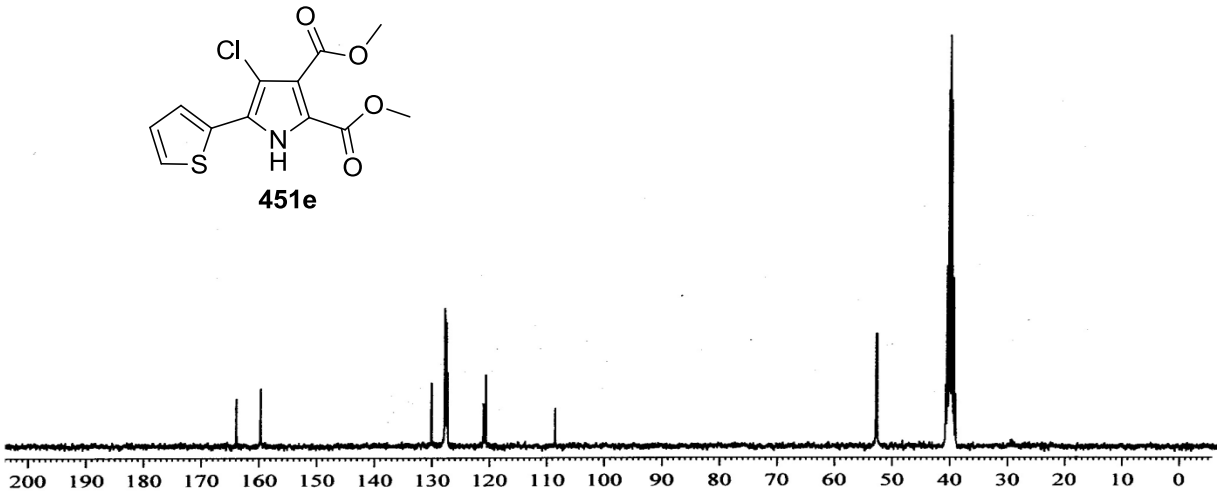


Fig. 240 ^{13}C{^{1}H} NMR spectrum of dimethyl 4-chloro-5-(thiophen-2-yl)-1H-pyrrole-2,3-dicarboxylate 451e

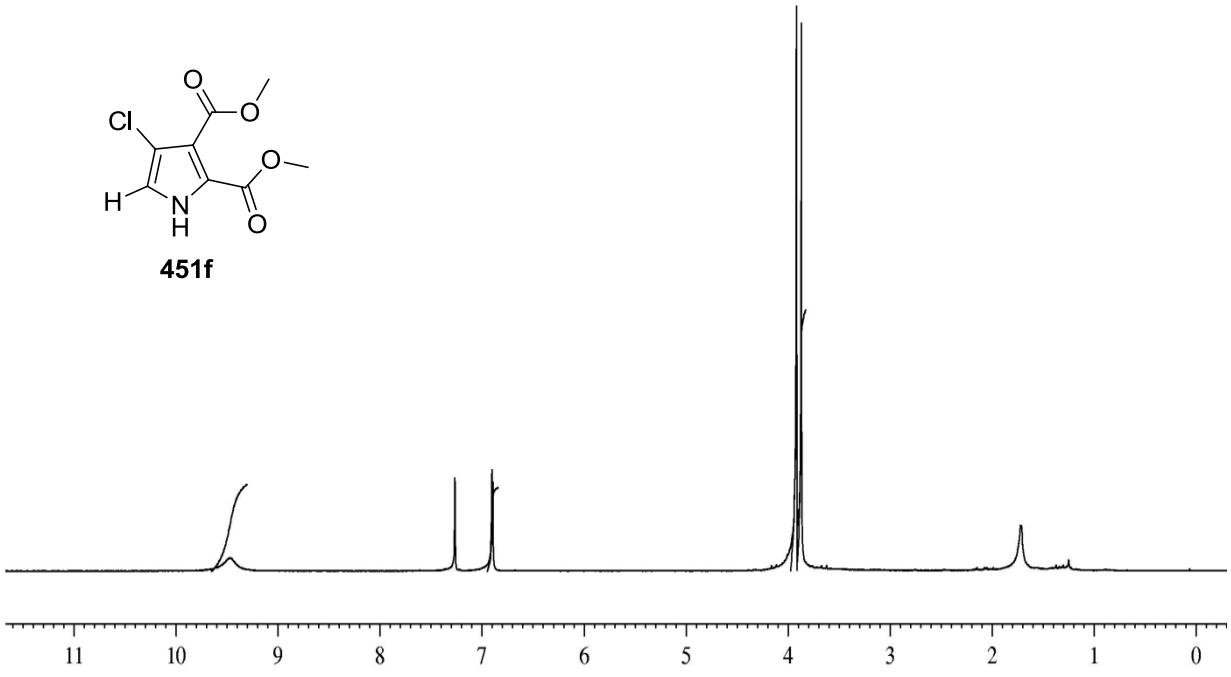


Fig. 241 ^{1}H NMR spectrum of dimethyl 4-chloro-1H-pyrrole-2,3-dicarboxylate 451f

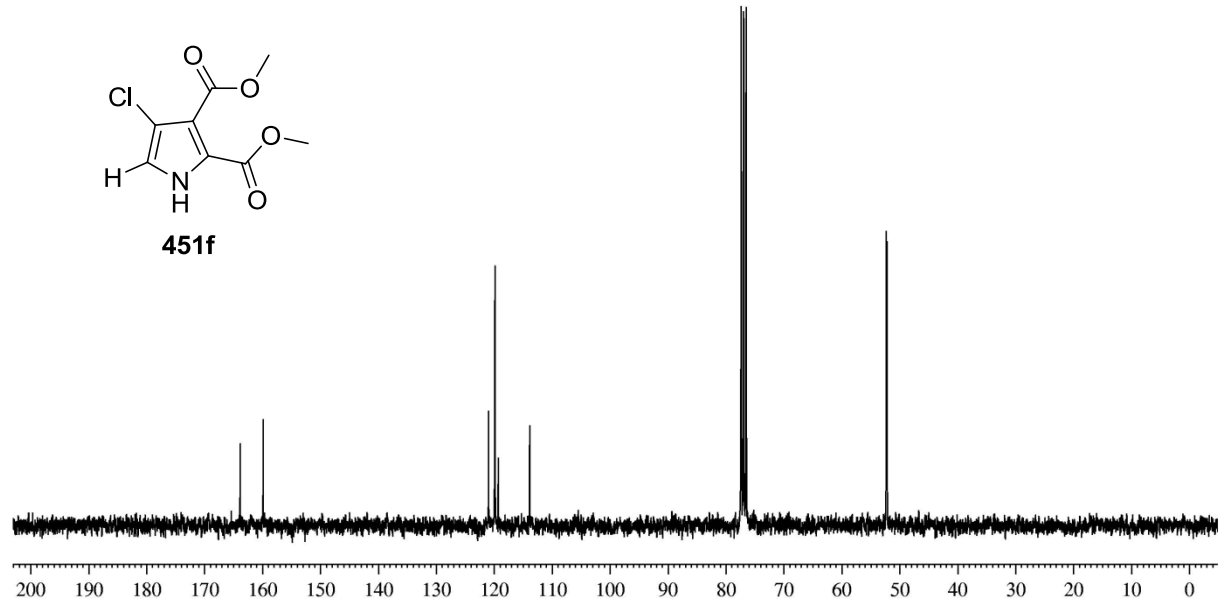


Fig. 242 ^{13}C{^{1}H} NMR spectrum of dimethyl 4-chloro-1H-pyrrole-2,3-dicarboxylate 451f

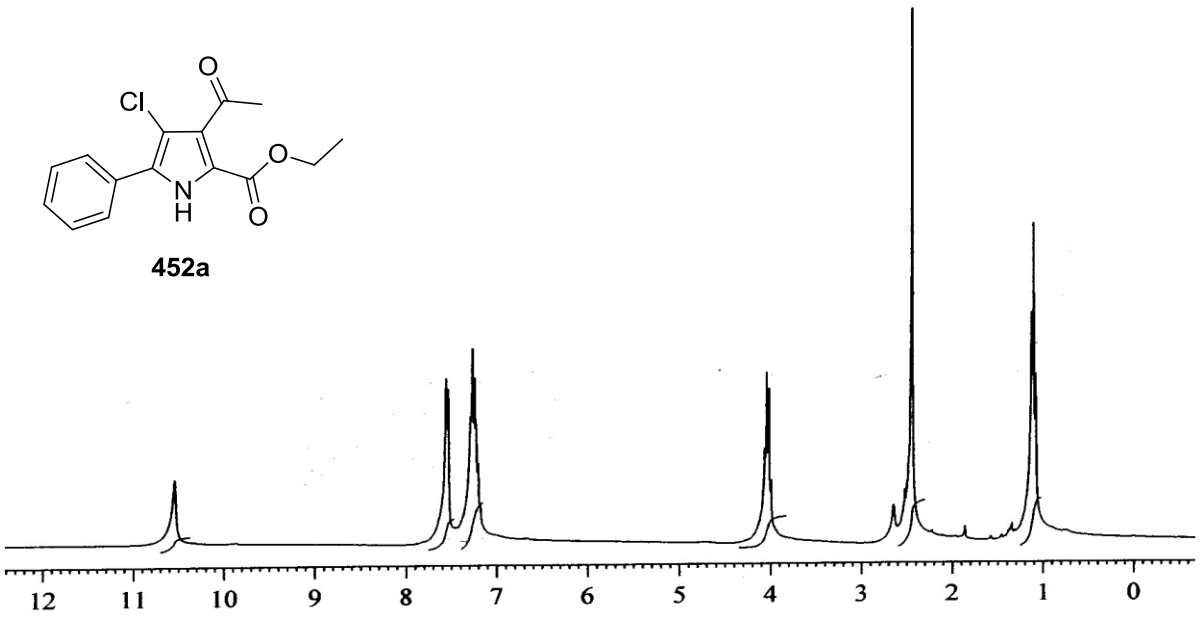


Fig. 243 ^{1}H NMR spectrum of ethyl 3-acetyl-4-chloro-5-phenyl-1H-pyrrole-2-carboxylate 452a

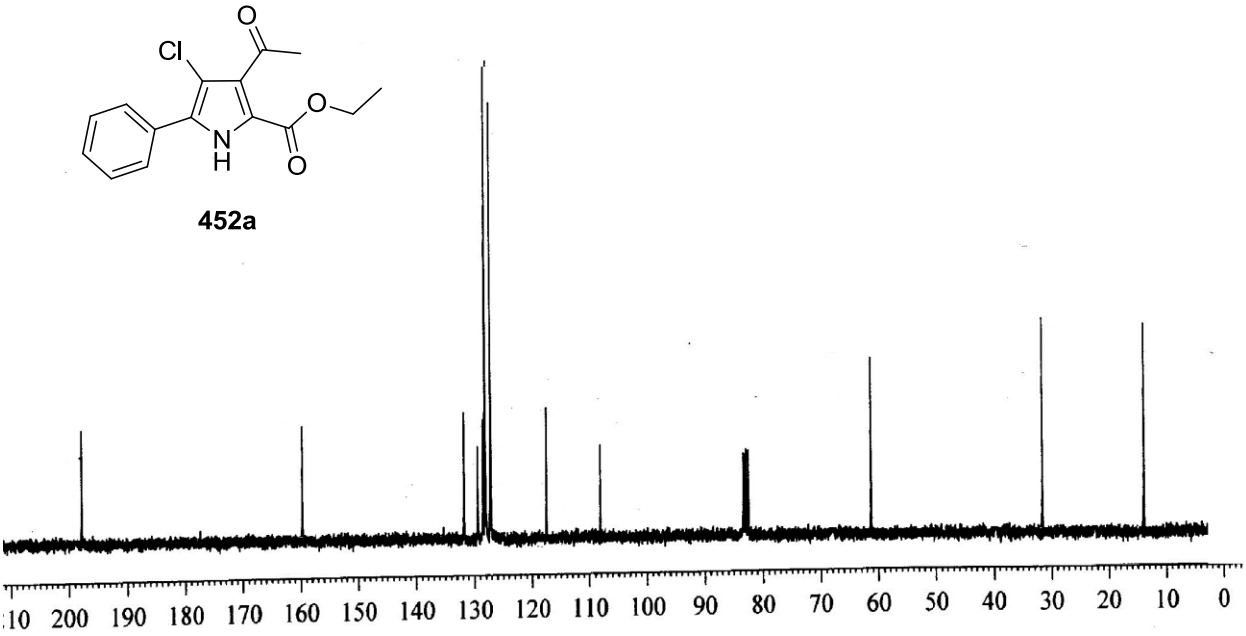


Fig. 244 ^{13}C{^{1}H} NMR spectrum of ethyl 3-acetyl-4-chloro-5-phenyl-1H-pyrrole-2-carboxylate 452a

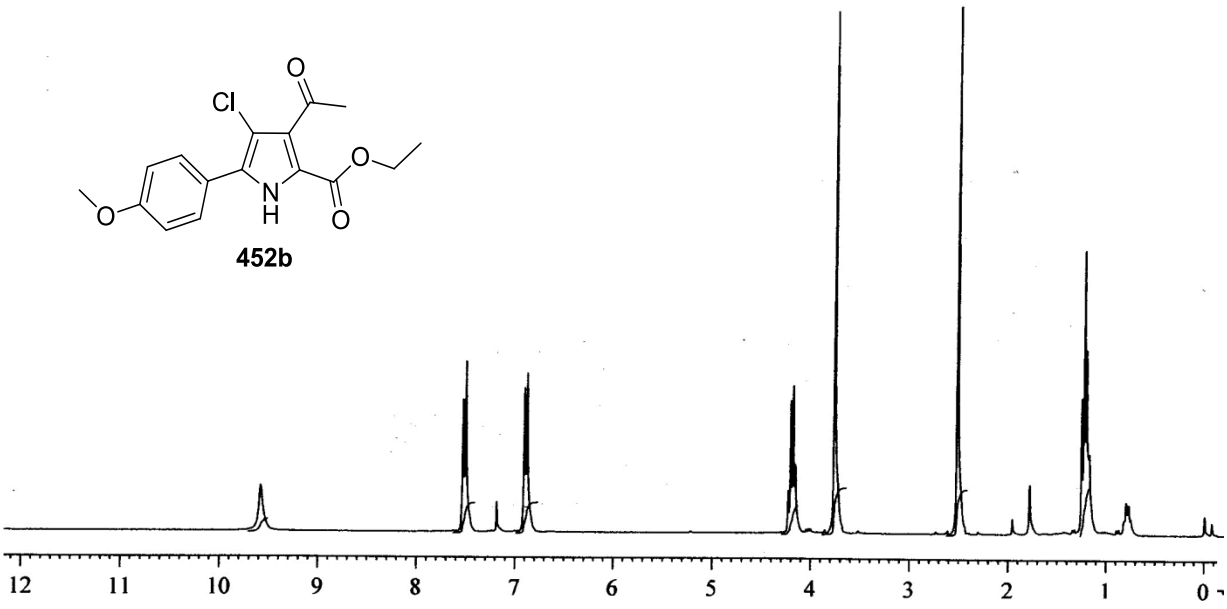


Fig. 245 ^{1}H NMR spectrum of ethyl 3-acetyl-4-chloro-5-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate 452b

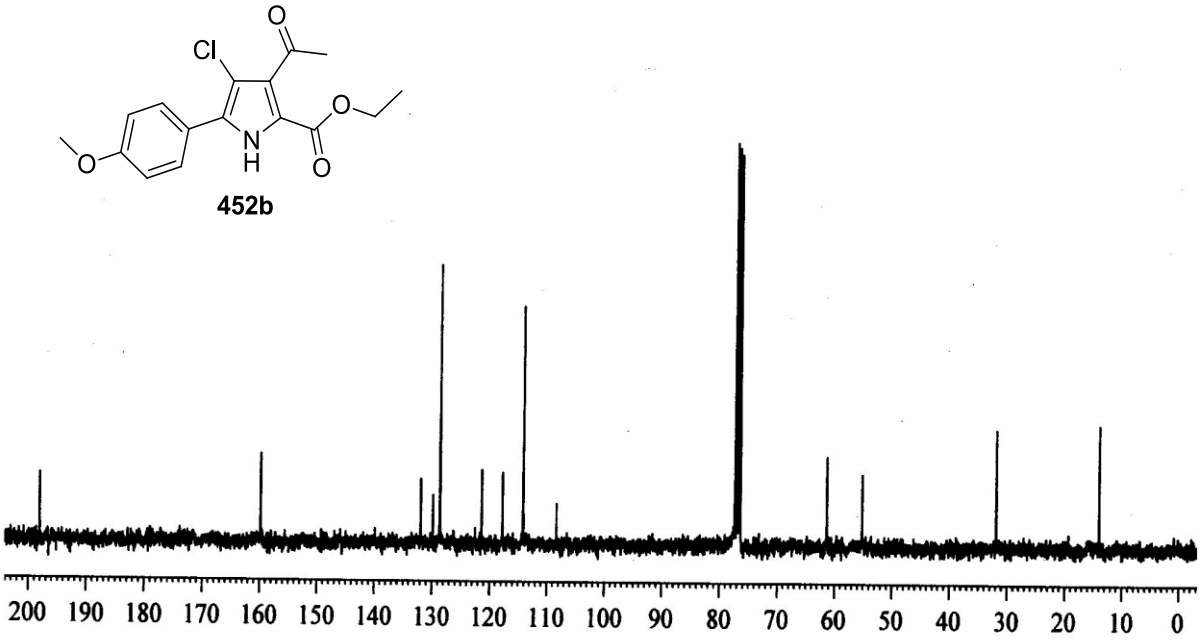


Fig. 246 ^{13}C{^{1}H} NMR spectrum of ethyl 3-acetyl-4-chloro-5-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate 452b

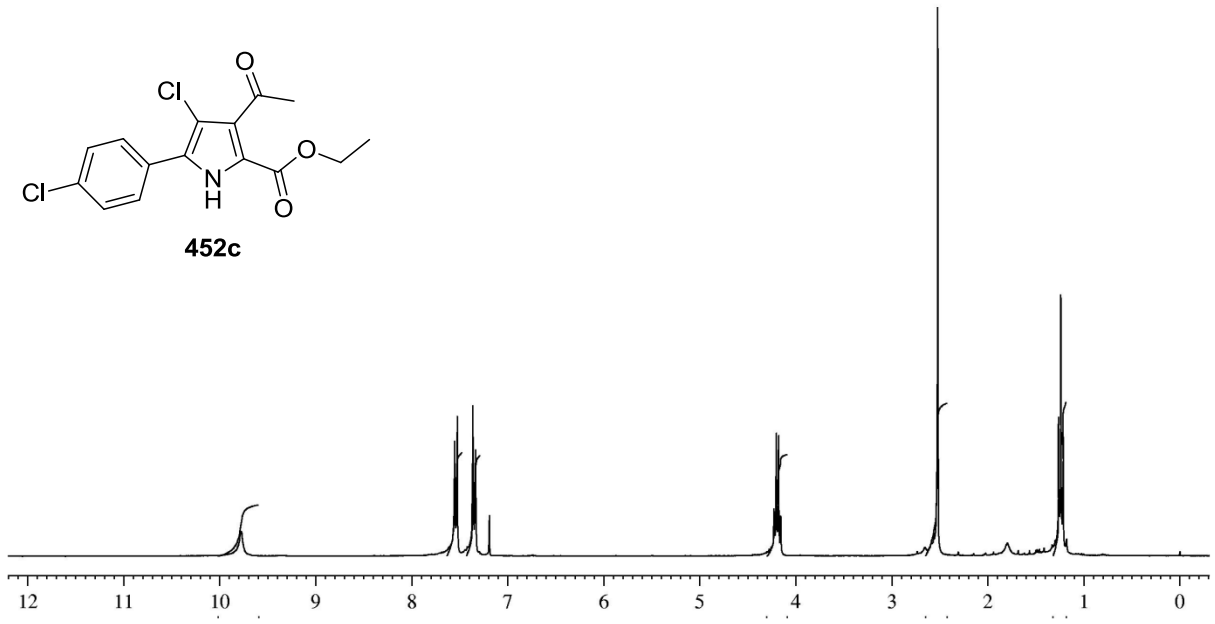


Fig. 247 ^{1}H NMR spectrum of ethyl 3-acetyl-4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2-carboxylate 452c

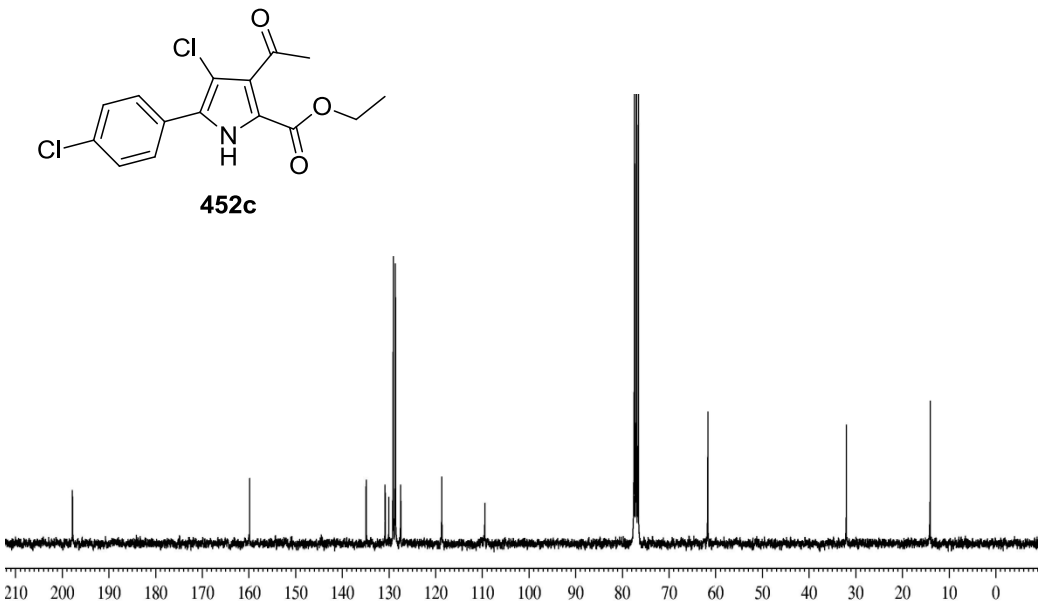


Fig. 248 ^{13}C{^{1}H} NMR spectrum of ethyl 3-acetyl-4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2-carboxylate 452c

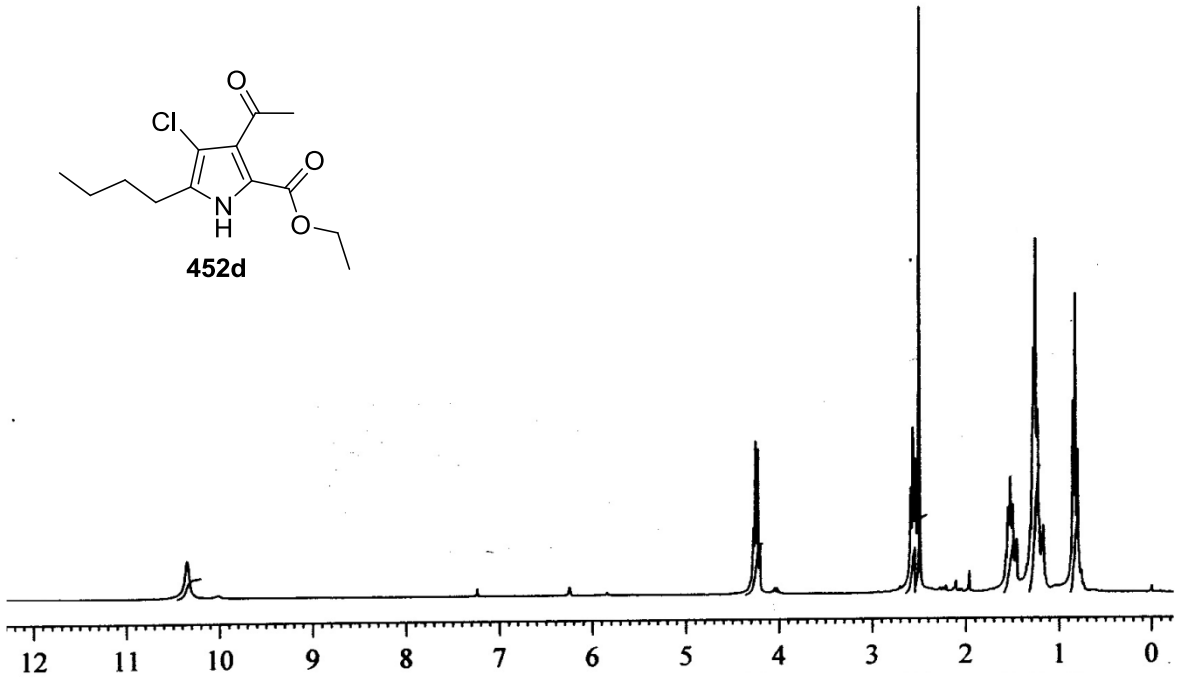


Fig. 249 ^{1}H NMR spectrum of ethyl 3-acetyl-5-butyl-4-chloro-1H-pyrrole-2-carboxylate 452d

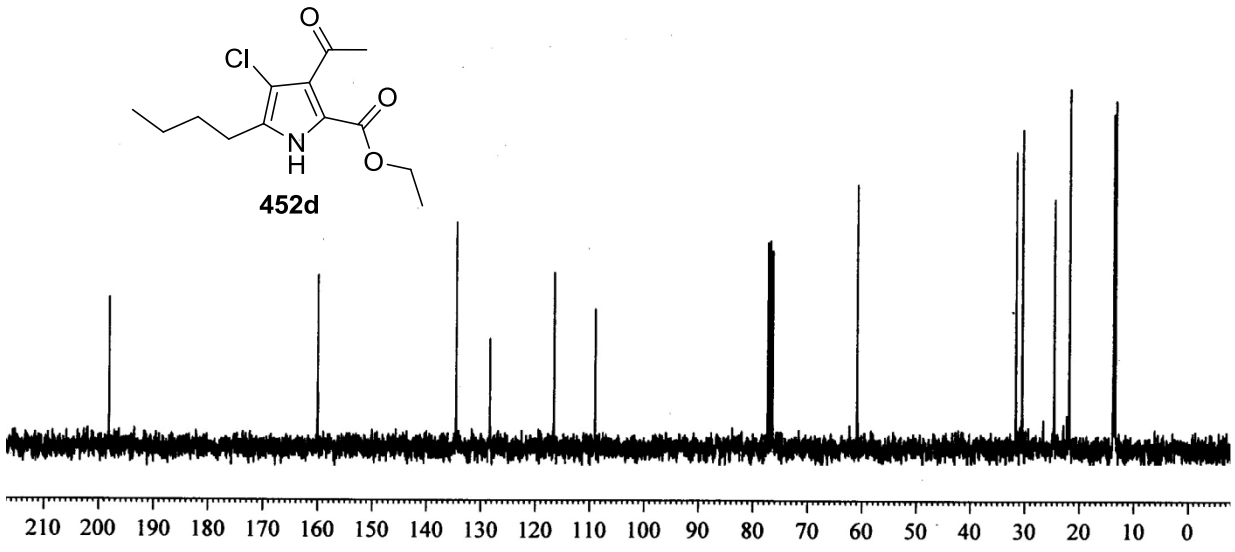


Fig. 250 ^{13}C{^{1}H} NMR spectrum of ethyl 3-acetyl-5-butyl-4-chloro-1H-pyrrole-2-carboxylate 452d

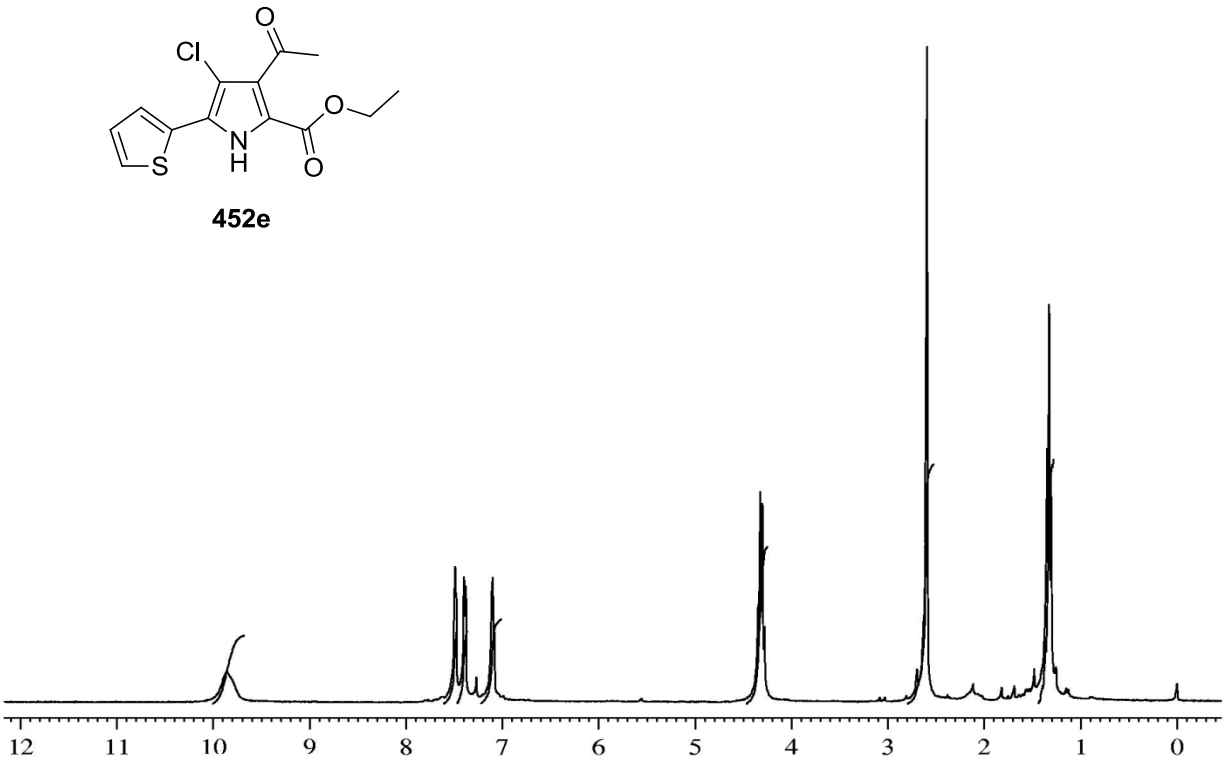


Fig. 251 ^{1}H NMR spectrum of ethyl 3-acetyl-4-chloro-5-(thiophen-2-yl)-1H-pyrrole-2-carboxylate 452e

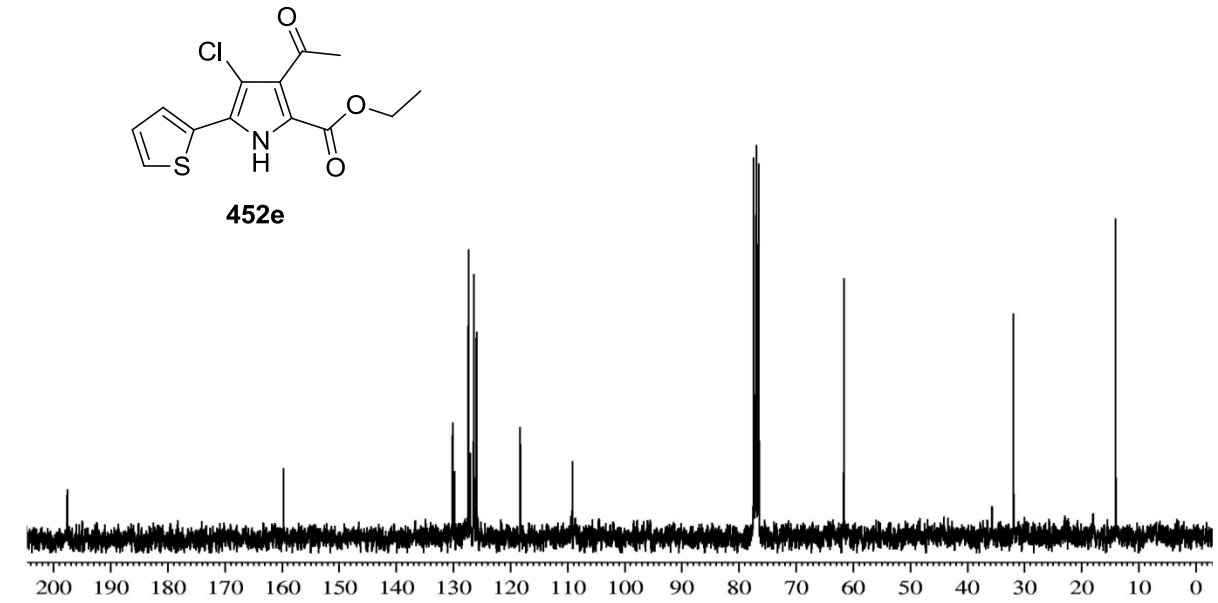


Fig. 252 ^{13}C{^{1}H} NMR spectrum of ethyl 3-acetyl-4-chloro-5-(thiophen-2-yl)-1H-pyrrole-2-carboxylate 452e

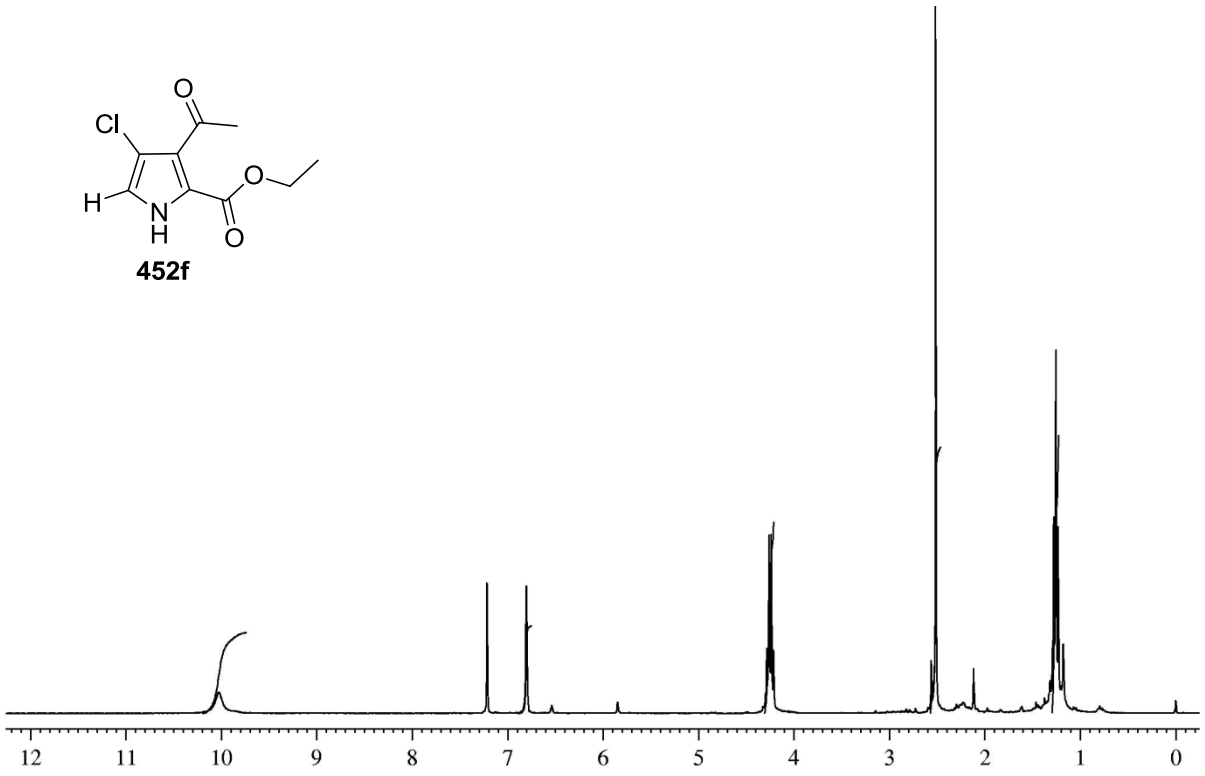


Fig. 253 ^{1}H NMR spectrum of ethyl 3-acetyl-4-chloro-1H-pyrrole-2-carboxylate 452f

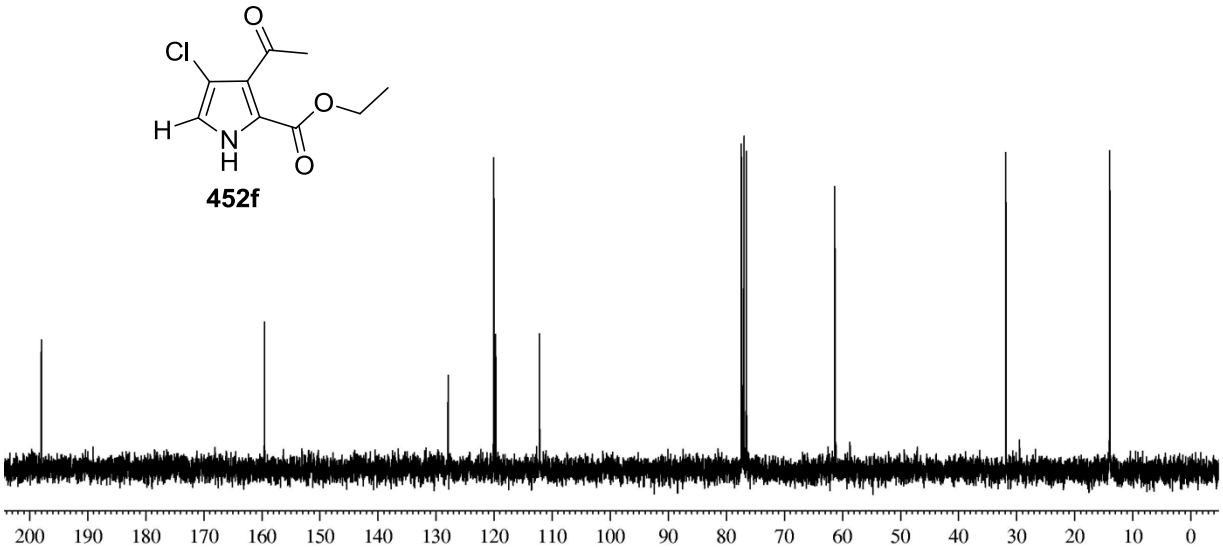


Fig. 254 ^{13}C{^{1}H} NMR spectrum of ethyl 3-acetyl-4-chloro-1H-pyrrole-2-carboxylate 452f

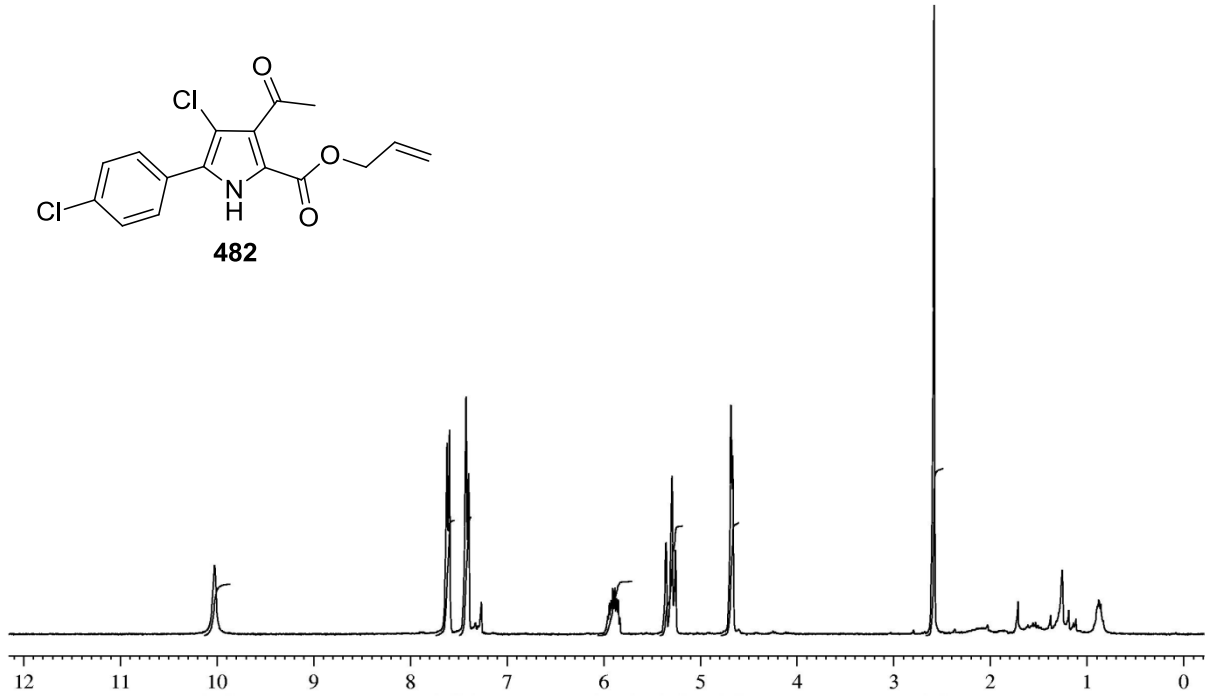


Fig. 255 ^{1}H NMR spectrum of allyl 3-acetyl-4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2-carboxylate 482

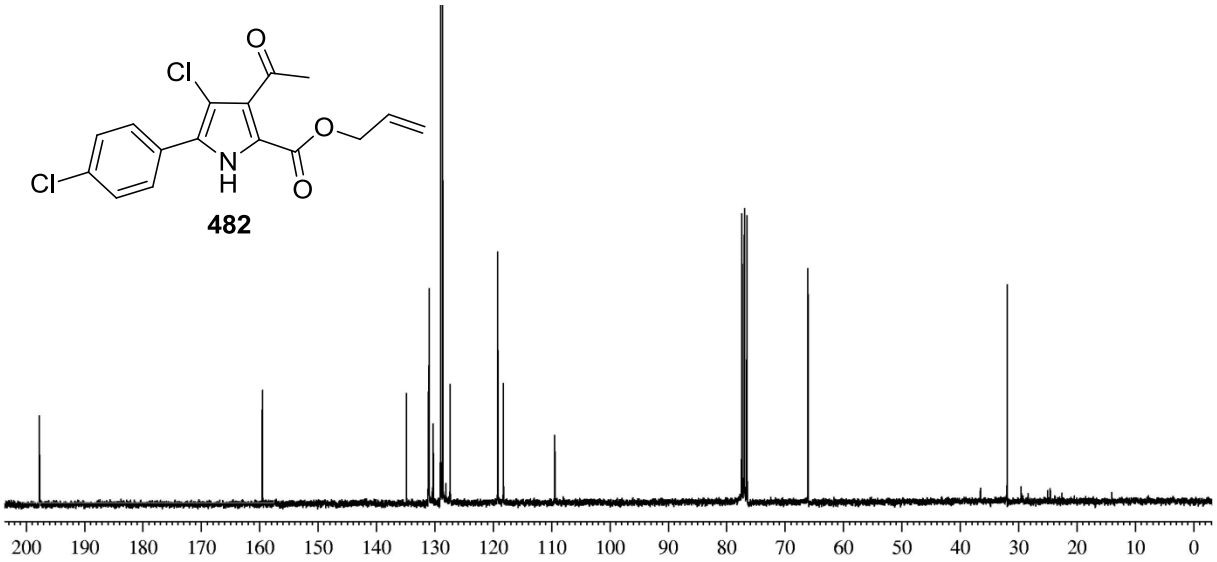


Fig. 256 ^{13}C{^{1}H} NMR spectrum of allyl 3-acetyl-4-chloro-5-(4-chlorophenyl)-1H-pyrrole-2-carboxylate 482

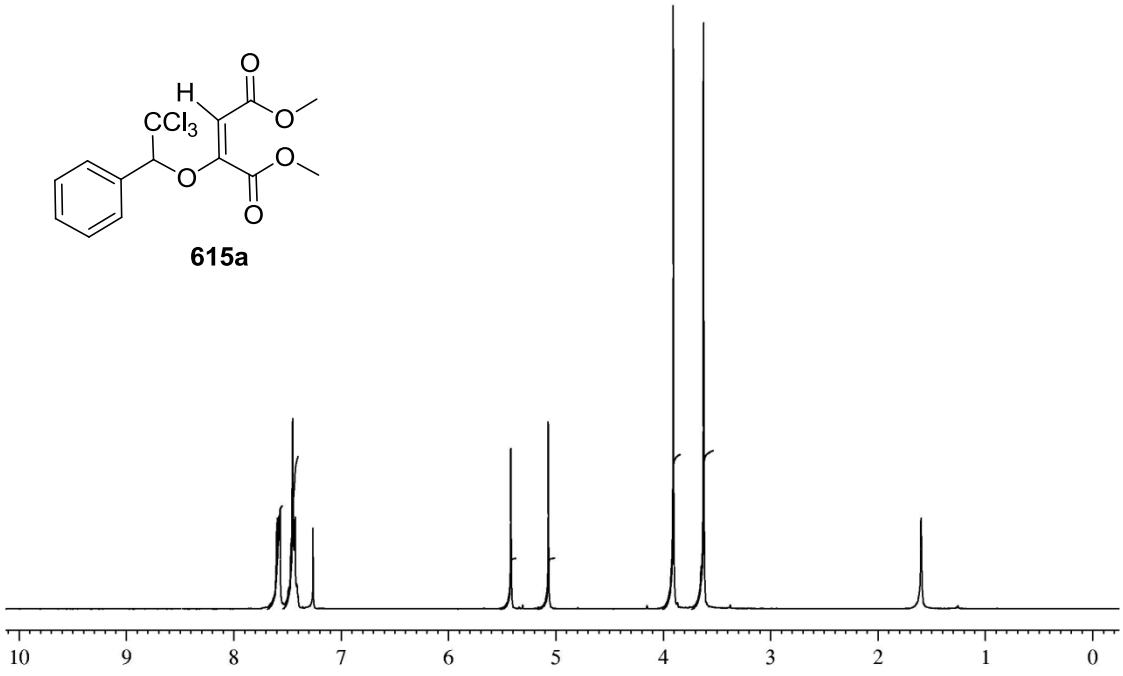


Fig. 257 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-phenylethoxy)maleate 615a

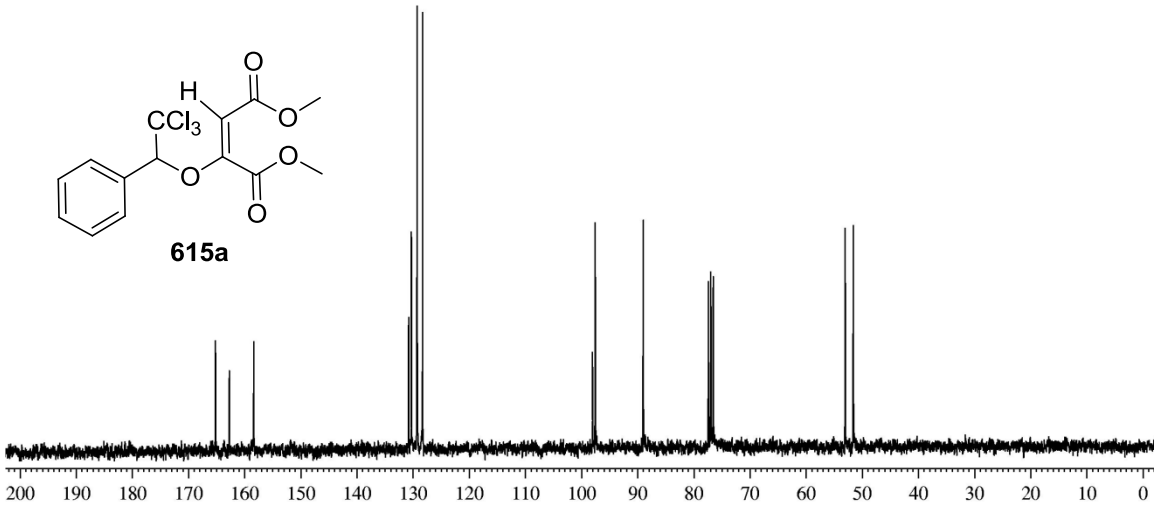


Fig. 258 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-phenylethoxy)maleate 615a

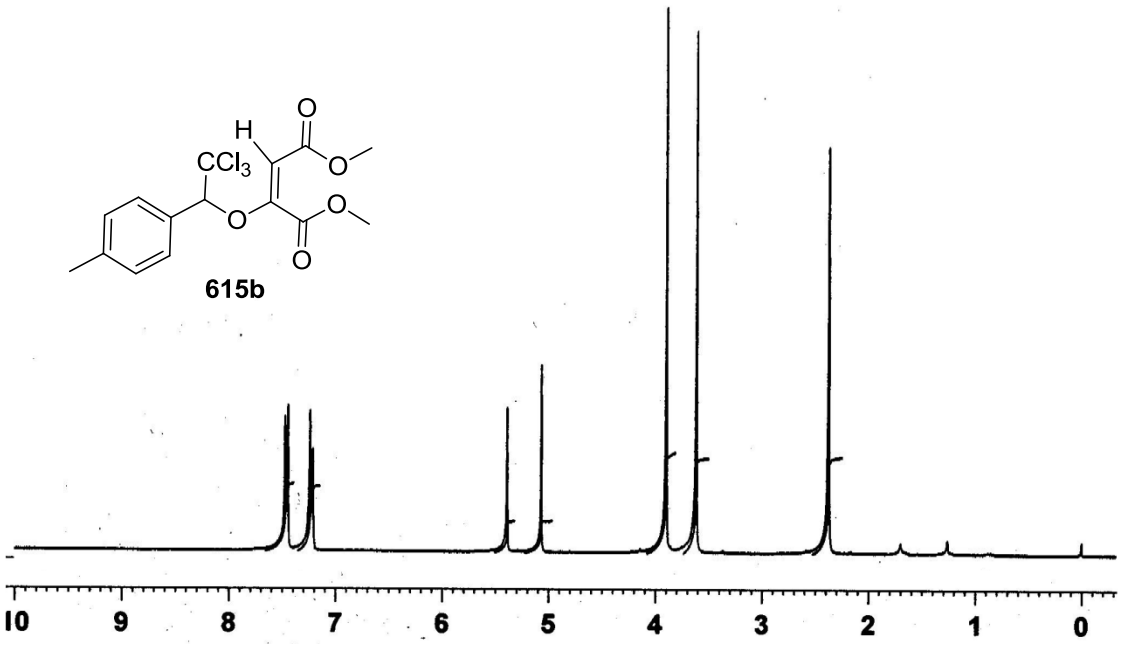


Fig. 259 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-p-tolylethoxy)maleate 615b

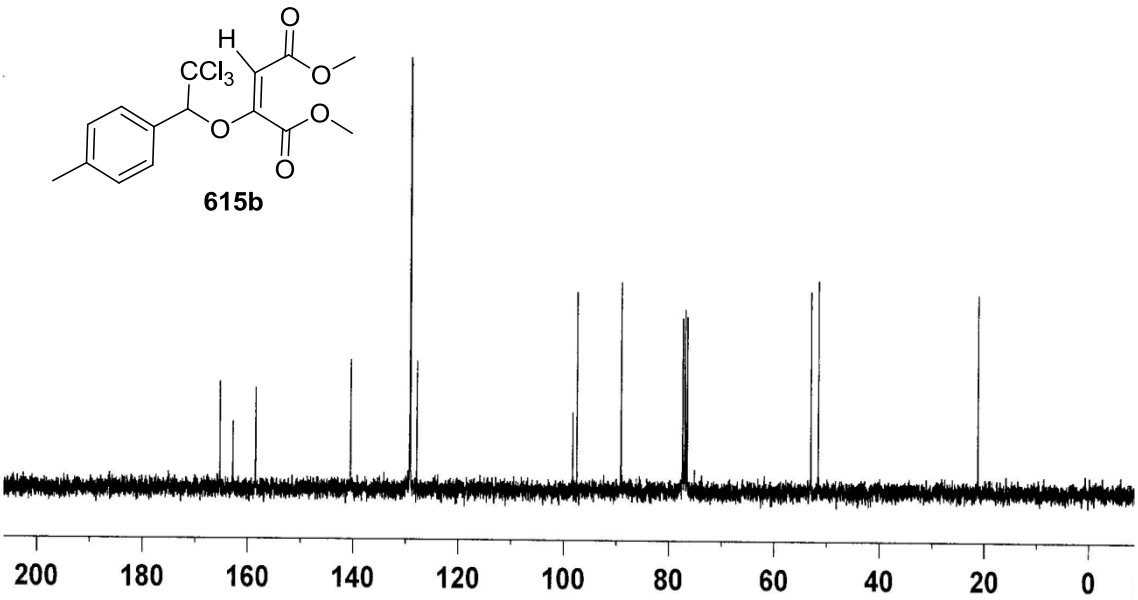


Fig. 260 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-p-tolylethoxy)maleate 615b

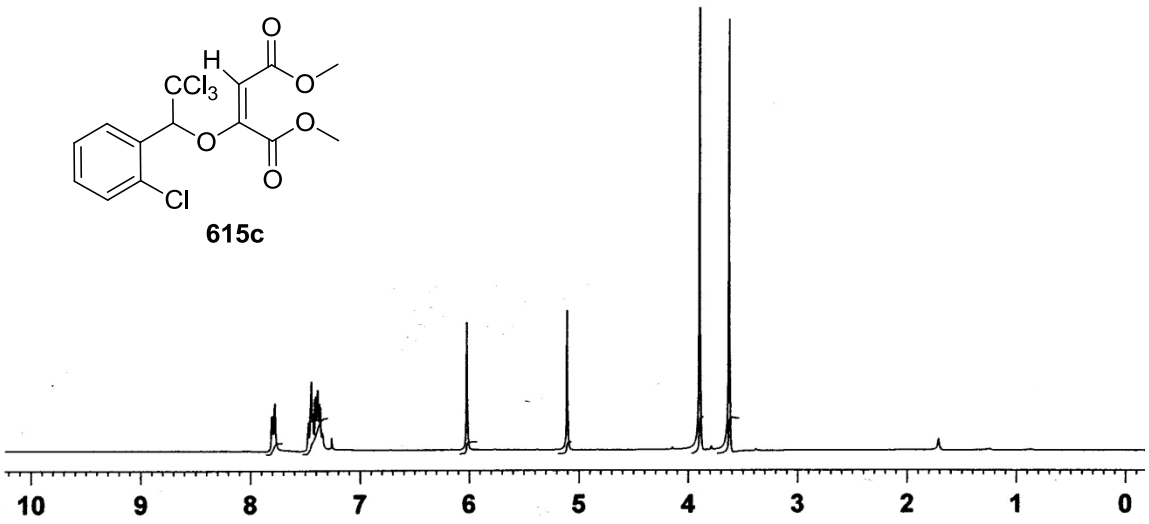


Fig. 261 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(2-chlorophenyl)ethoxy) maleate 615c

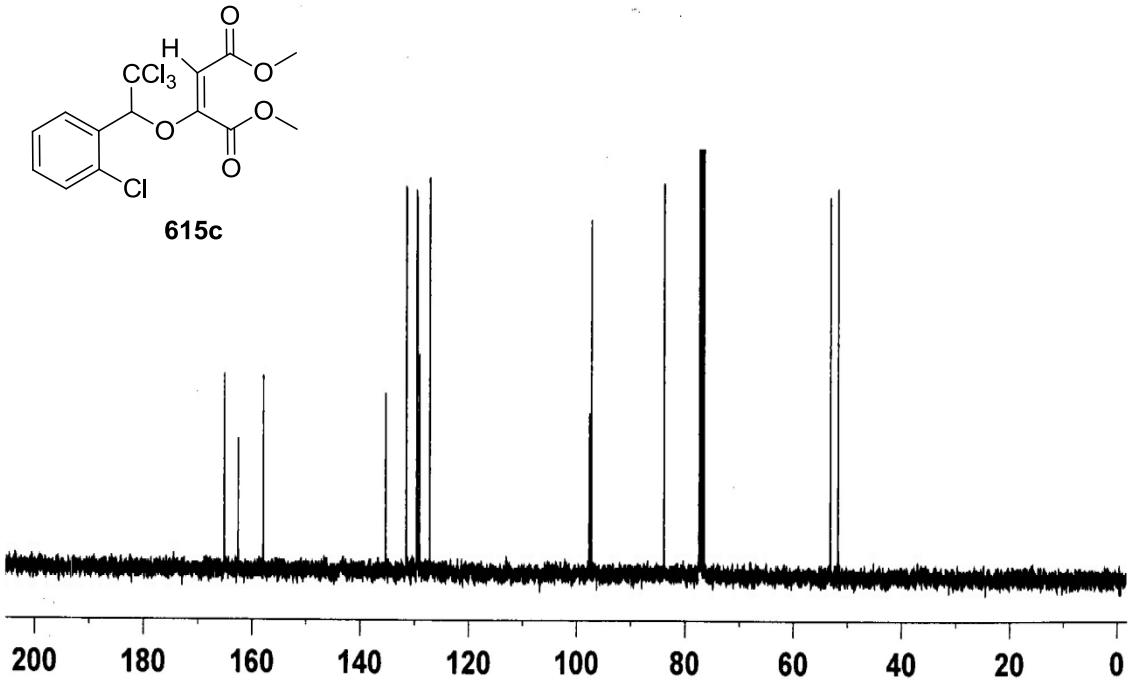


Fig. 262 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(2-chlorophenyl) ethoxy) maleate 615c

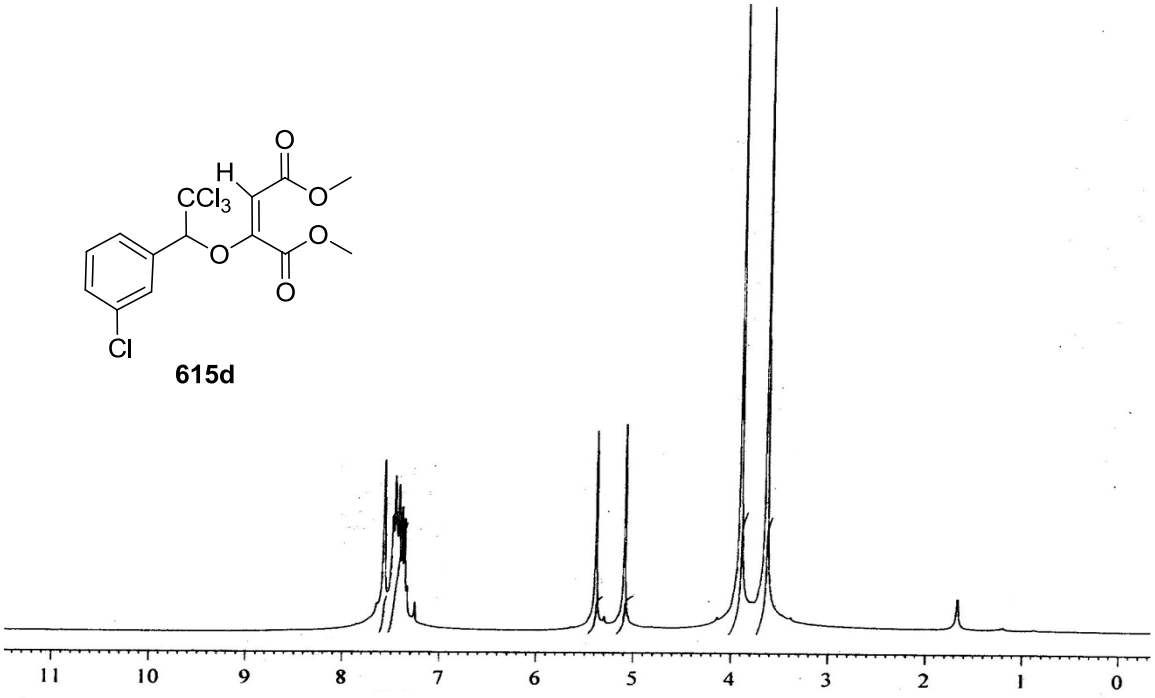


Fig. 263 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(3-chlorophenyl)ethoxy) maleate 615d

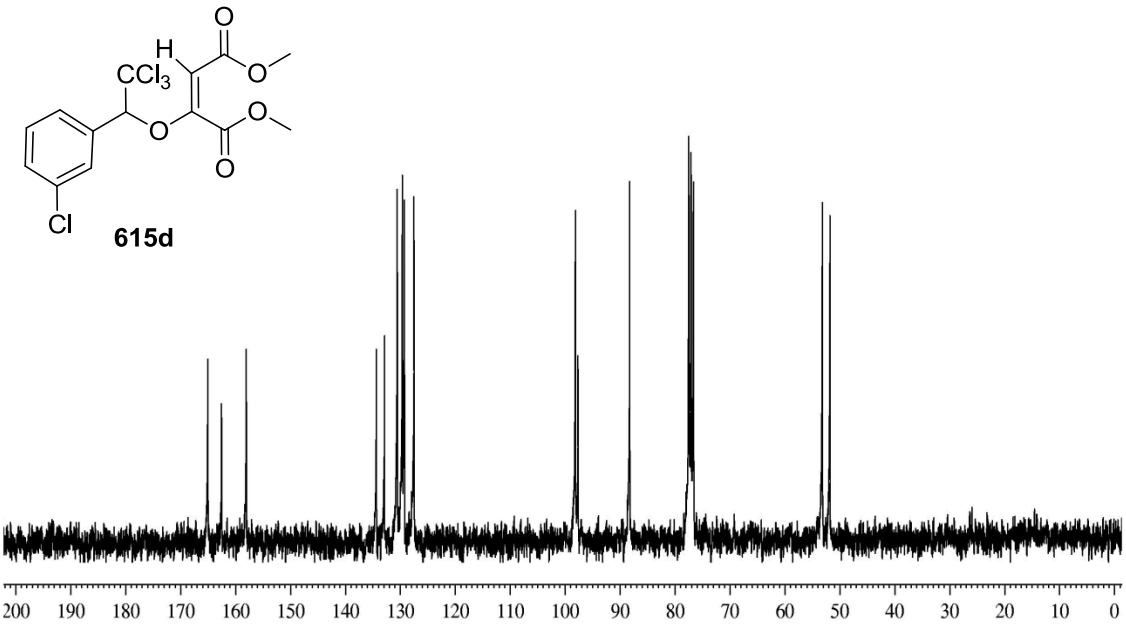


Fig. 264 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(3-chlorophenyl) ethoxy) maleate 615d

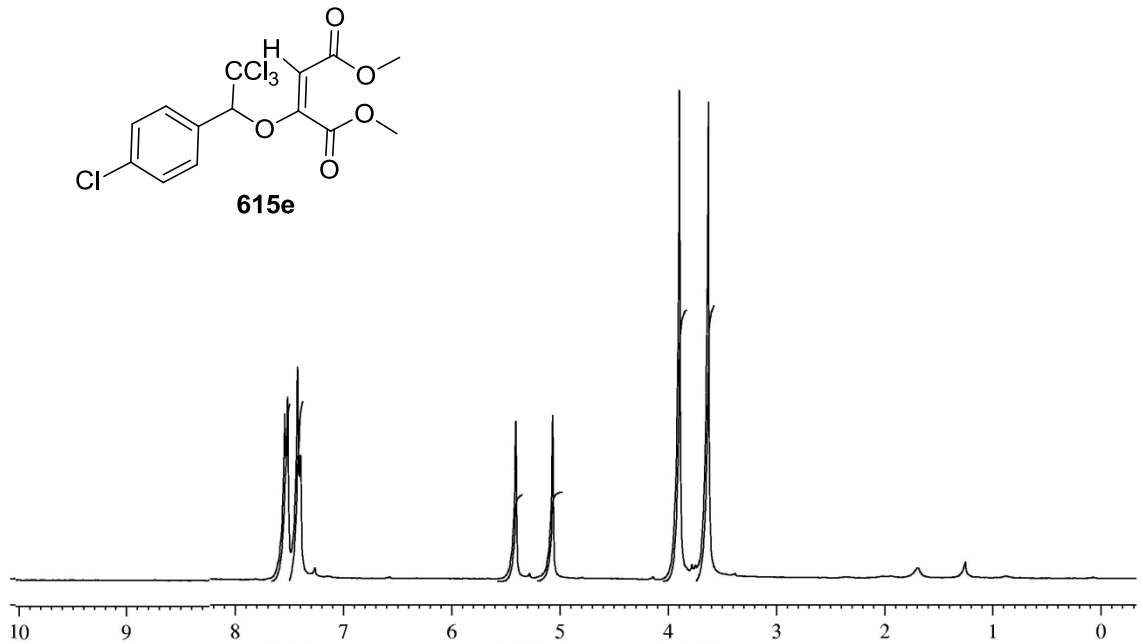


Fig. 265 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-chlorophenyl)ethoxy) maleate 615e

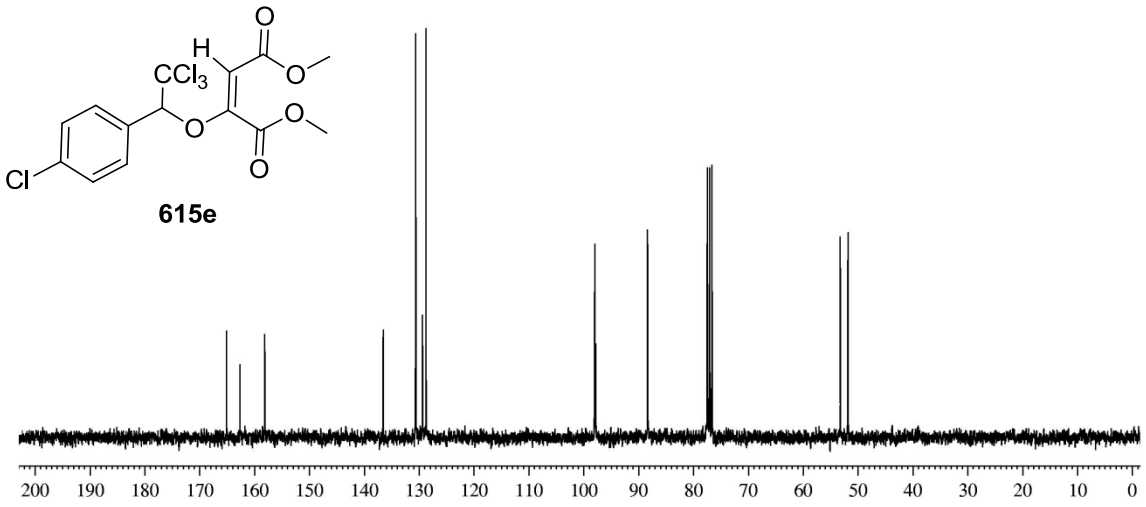


Fig. 266 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-chlorophenyl) ethoxy) maleate 615e

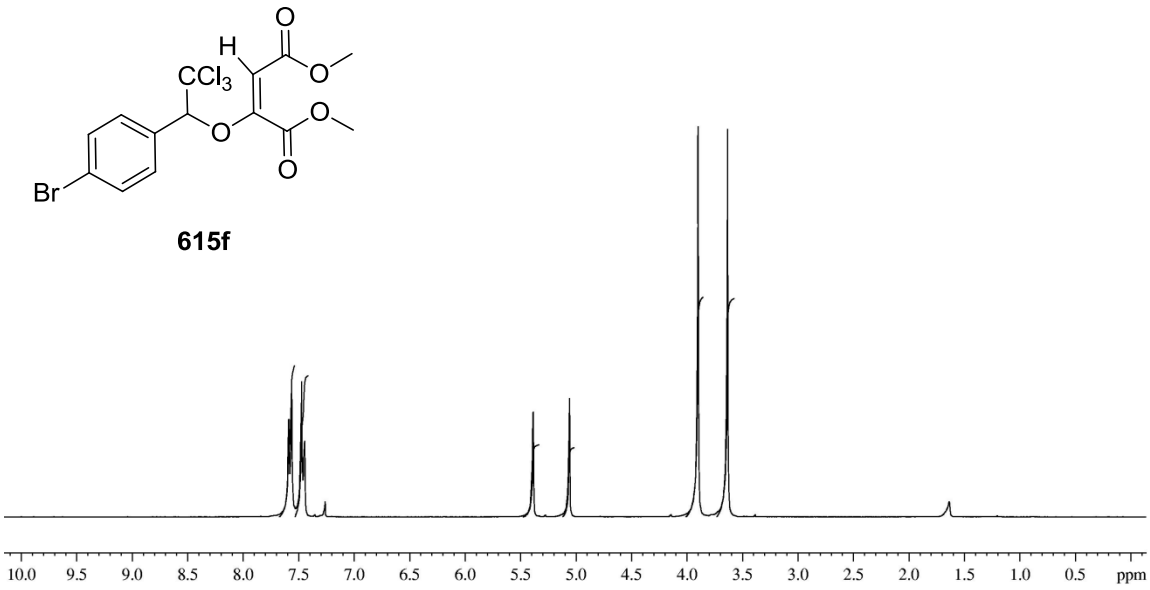


Fig. 267 ^{1}H NMR Spectrum of dimethyl 2-(1-(4-bromophenyl)-2,2,2-trichloroethoxy) maleate 615f

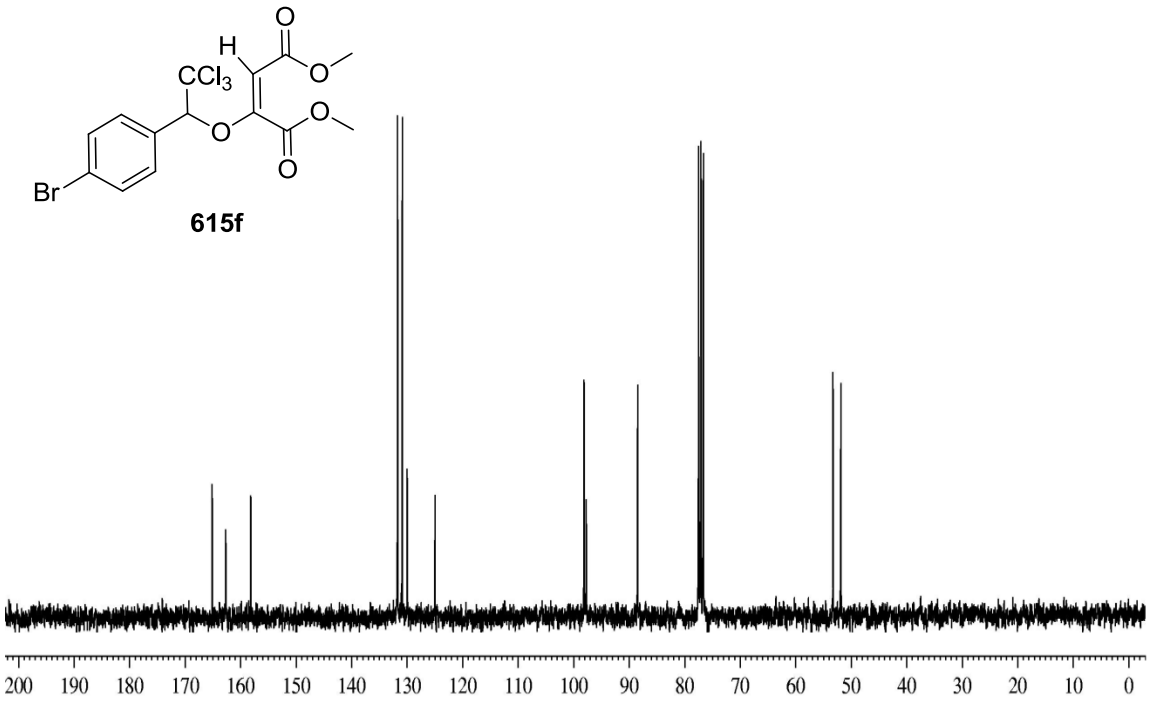


Fig. 268 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(1-(4-bromophenyl)-2,2,2-trichloro ethoxy)maleate 615f

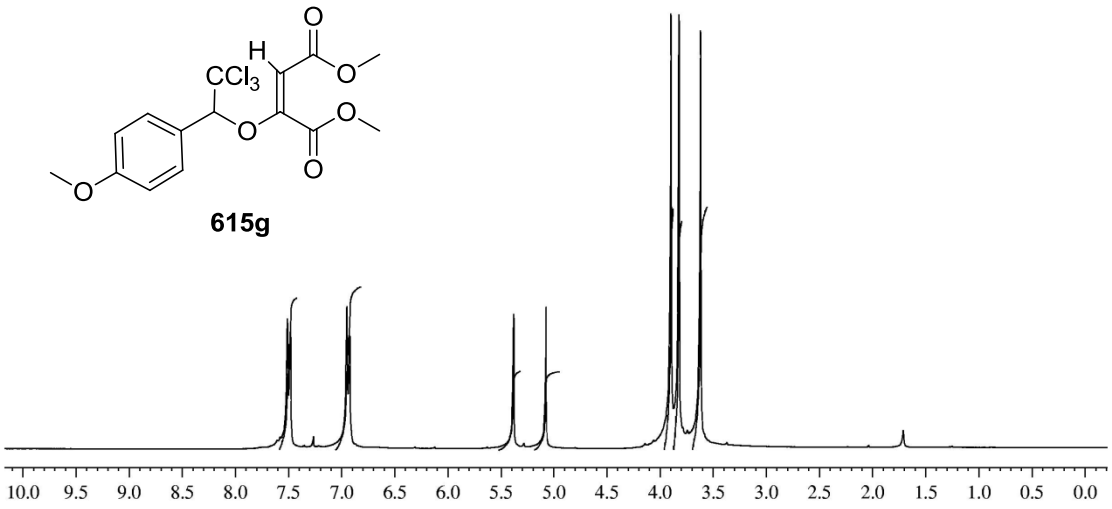


Fig. 269 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethoxy)maleate 615g

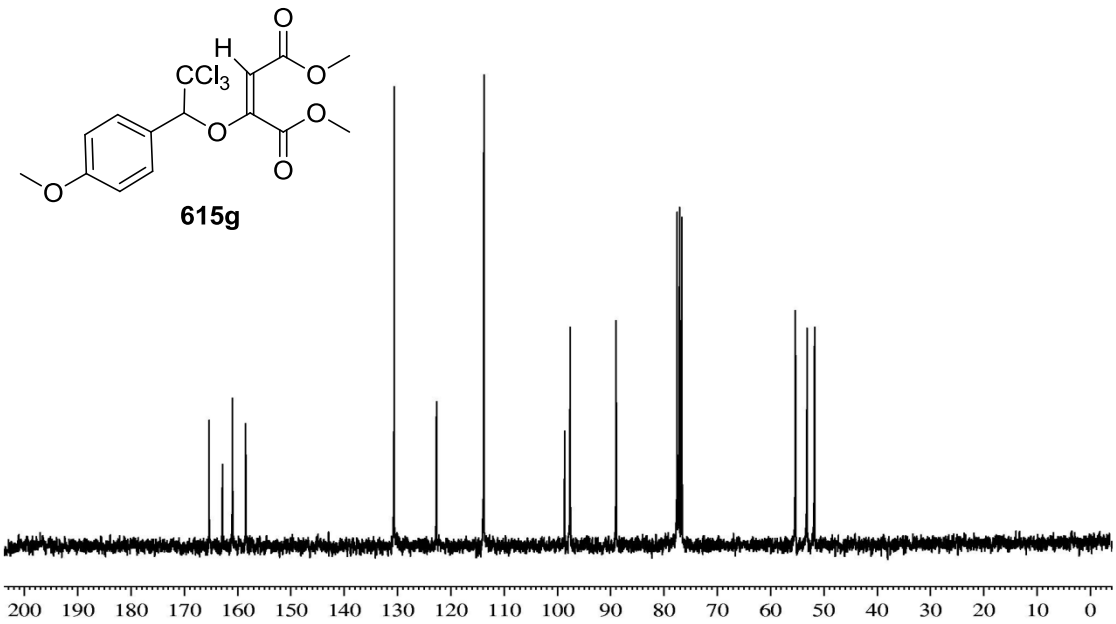


Fig. 270 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-methoxyphenyl)ethoxy)maleate 615g

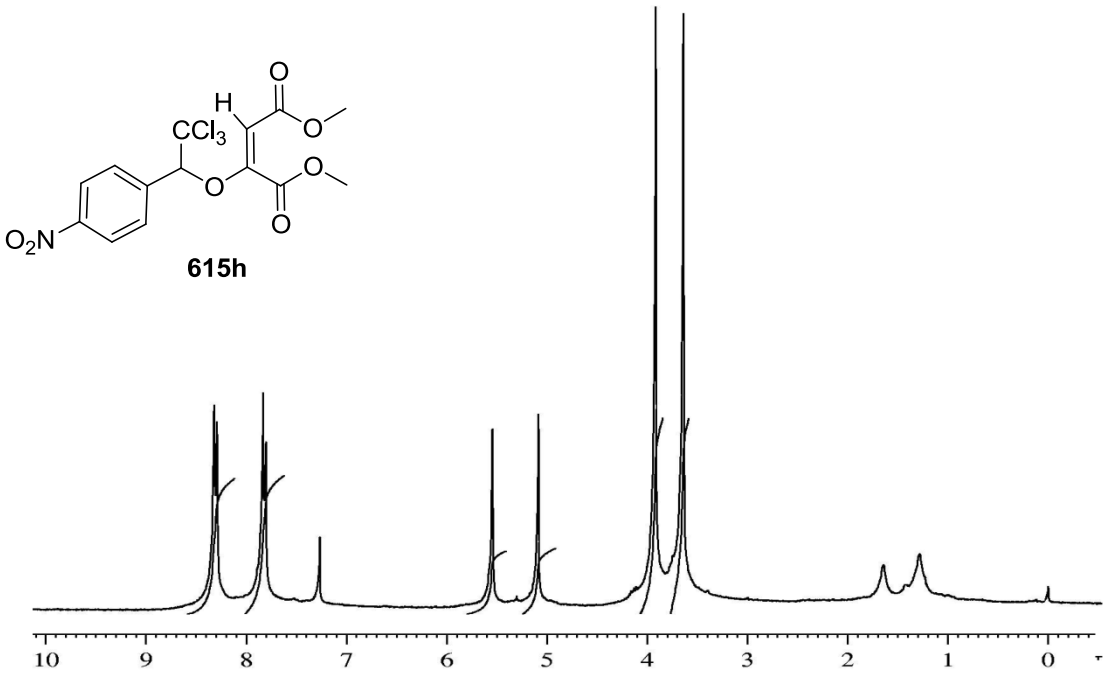


Fig. 271 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-nitrophenyl)ethoxy) maleate 615h

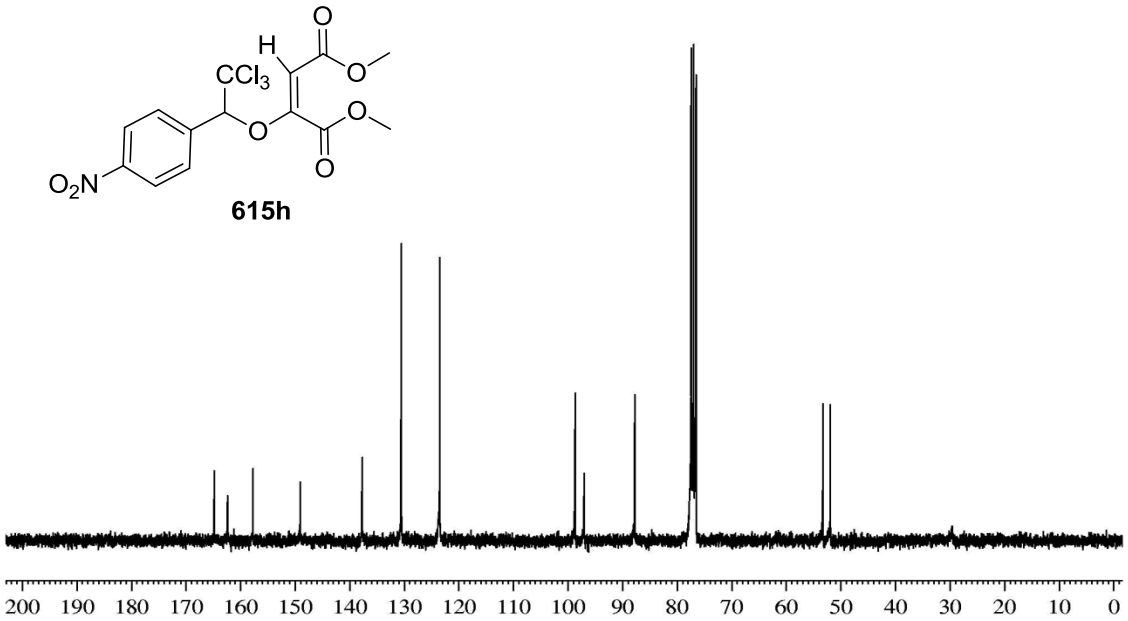


Fig. 272 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(4-nitrophenyl)ethoxy)maleate 615h

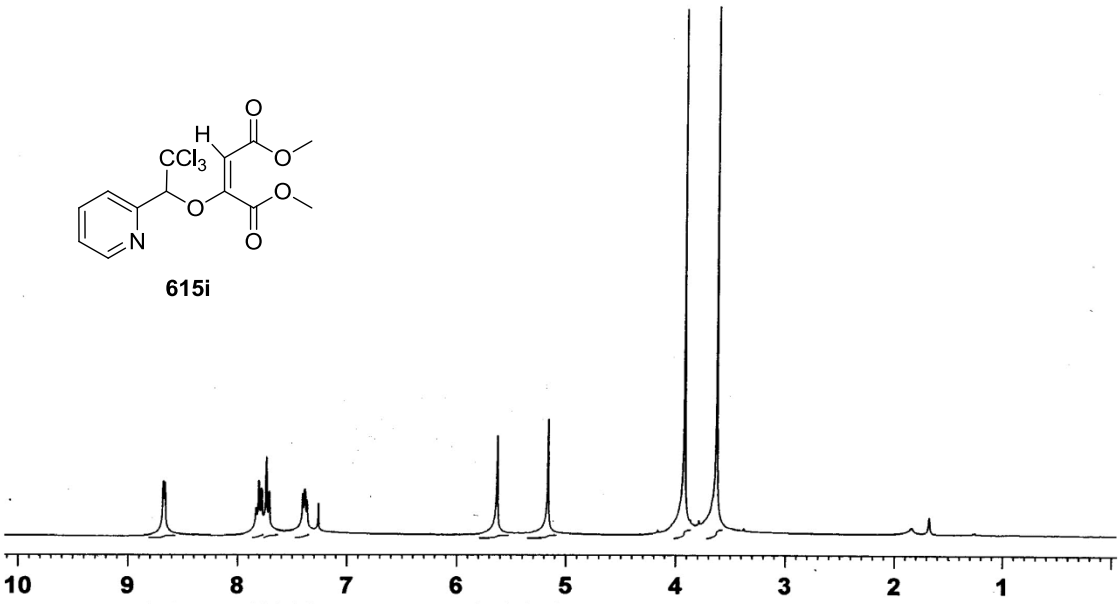


Fig. 273 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(pyridin-2-yl)ethoxy)maleate 615i

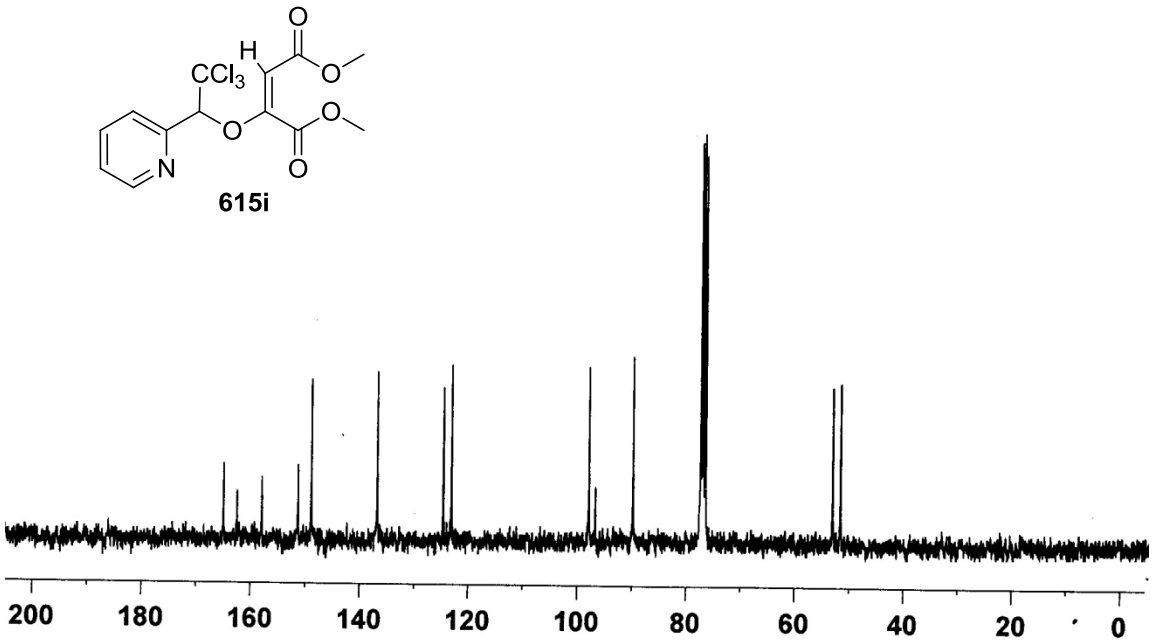


Fig. 274 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloro-1-(pyridin-2-yl)ethoxy)maleate 615i

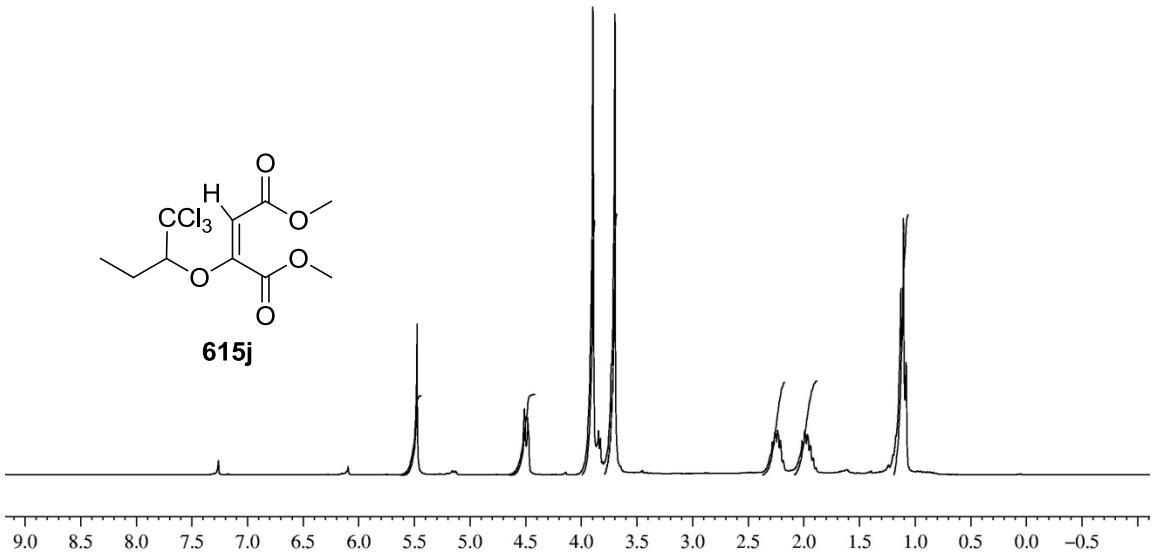


Fig. 275 ^{1}H NMR Spectrum of dimethyl 2-(1,1,1-trichlorobutan-2-yloxy)maleate 615j

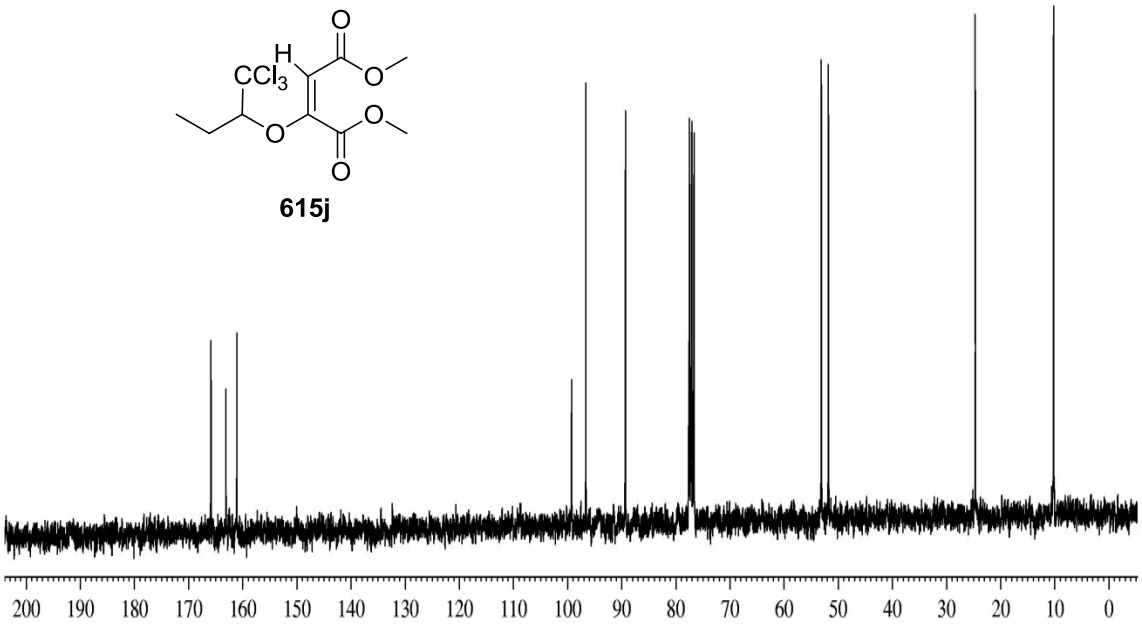


Fig. 276 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(1,1,1-trichlorobutan-2-yloxy)maleate 615j

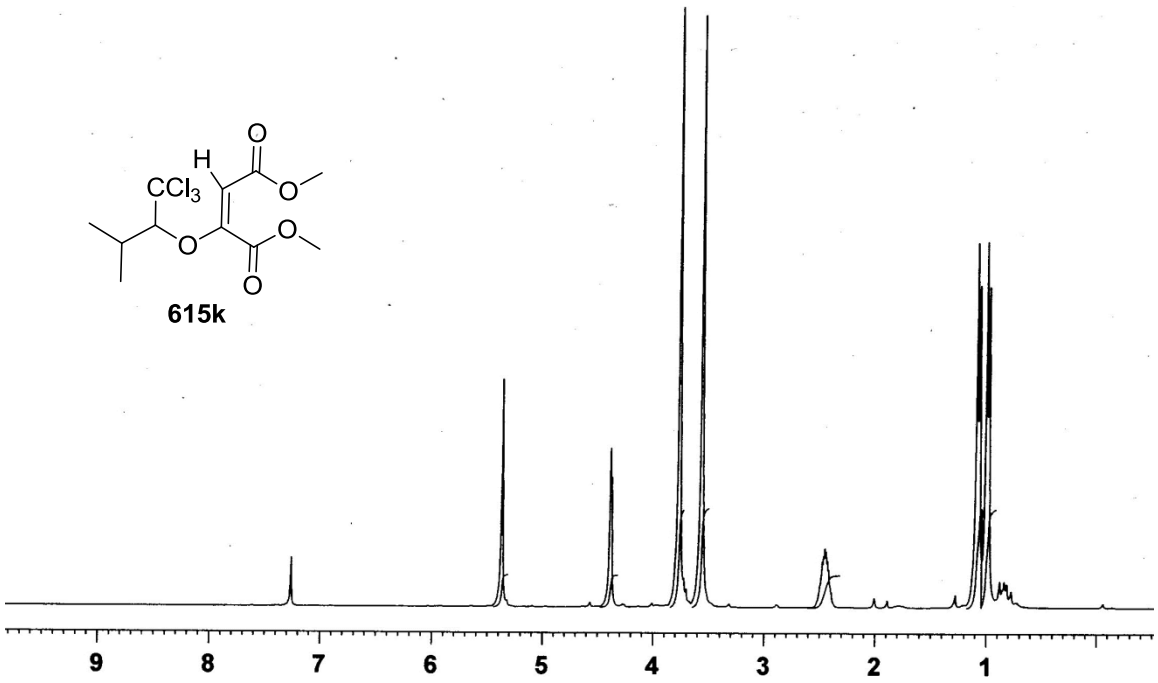


Fig. 277 ^{1}H NMR Spectrum of dimethyl 2-(1,1,1-trichloro-3-methylbutan-2-yloxy) maleate 615k

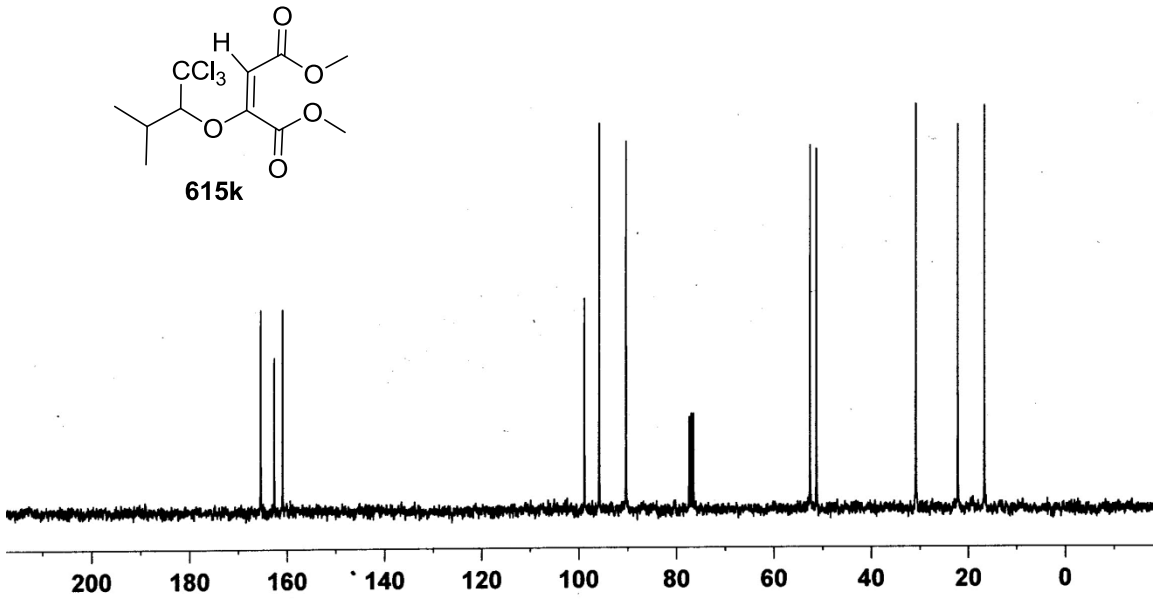


Fig. 278 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(1,1,1-trichloro-3-methylbutan-2-yloxy)maleate 615k

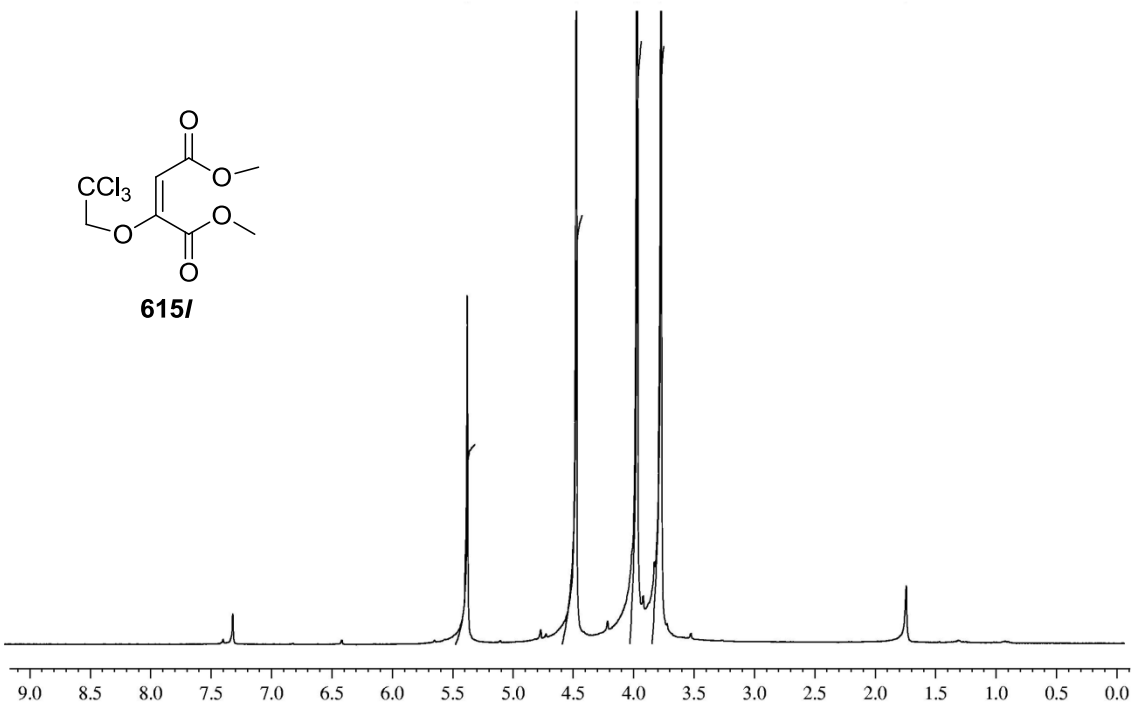


Fig. 279 ^{1}H NMR Spectrum of dimethyl 2-(2,2,2-trichloroethoxy)maleate 615*l*

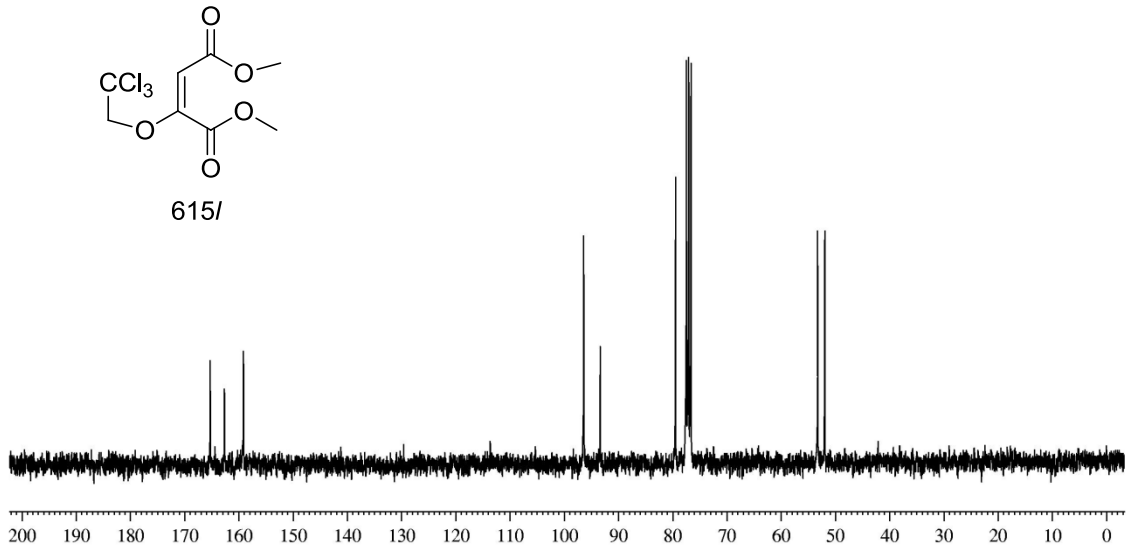


Fig. 280 ^{13}C{^{1}H} NMR Spectrum of dimethyl 2-(2,2,2-trichloroethoxy)maleate 615*l*

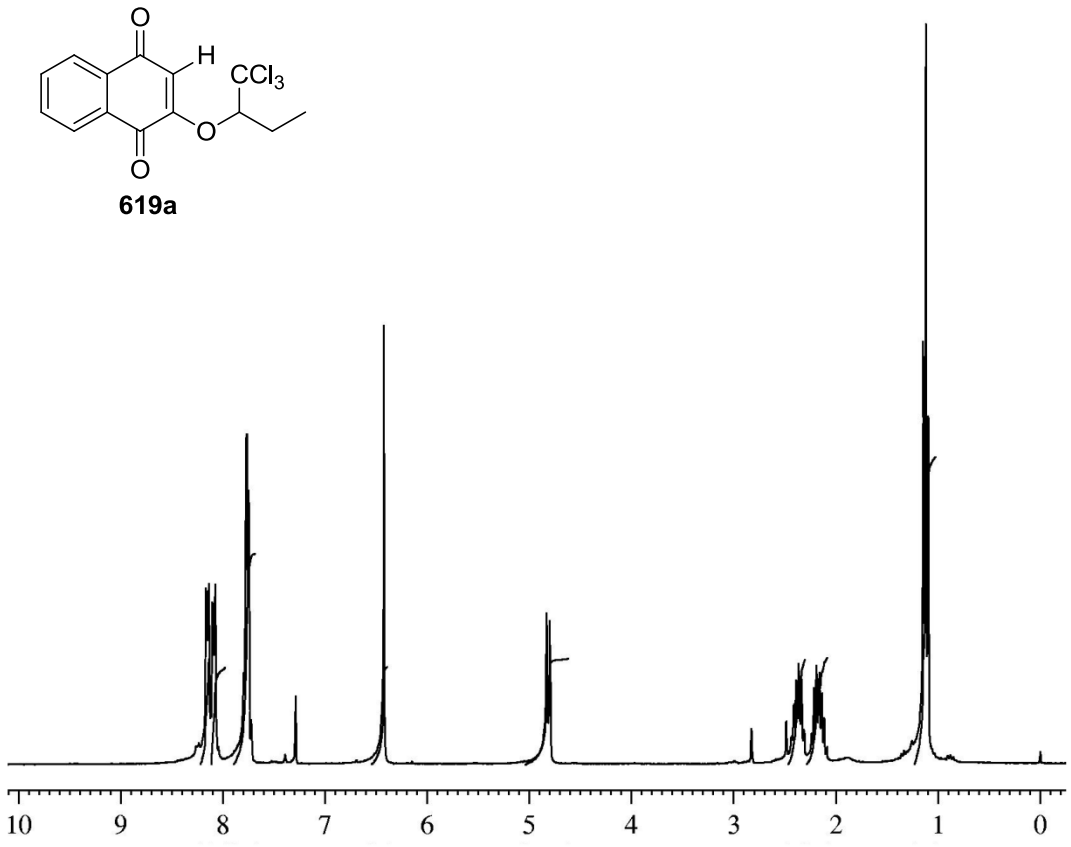


Fig. 281 ^{1}H NMR Spectrum of 2-(1,1,1-trichlorobutan-2-yloxy)naphthalene-1,4-dione 619a

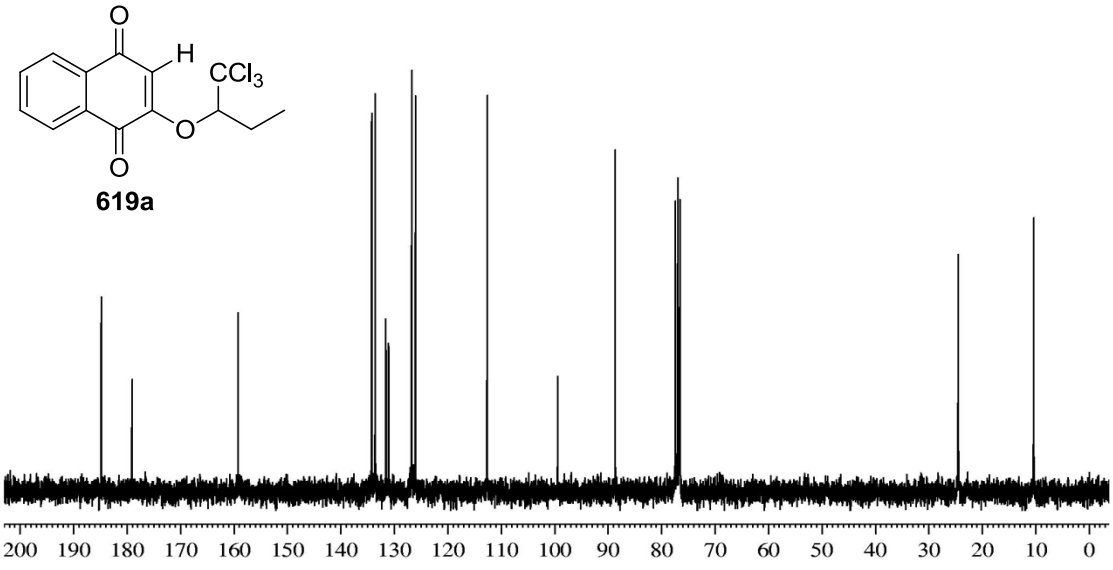


Fig. 282 ^{13}C{^{1}H} NMR Spectrum of 2-(1,1,1-trichlorobutan-2-yloxy)naphthalene-1,4-dione 619a

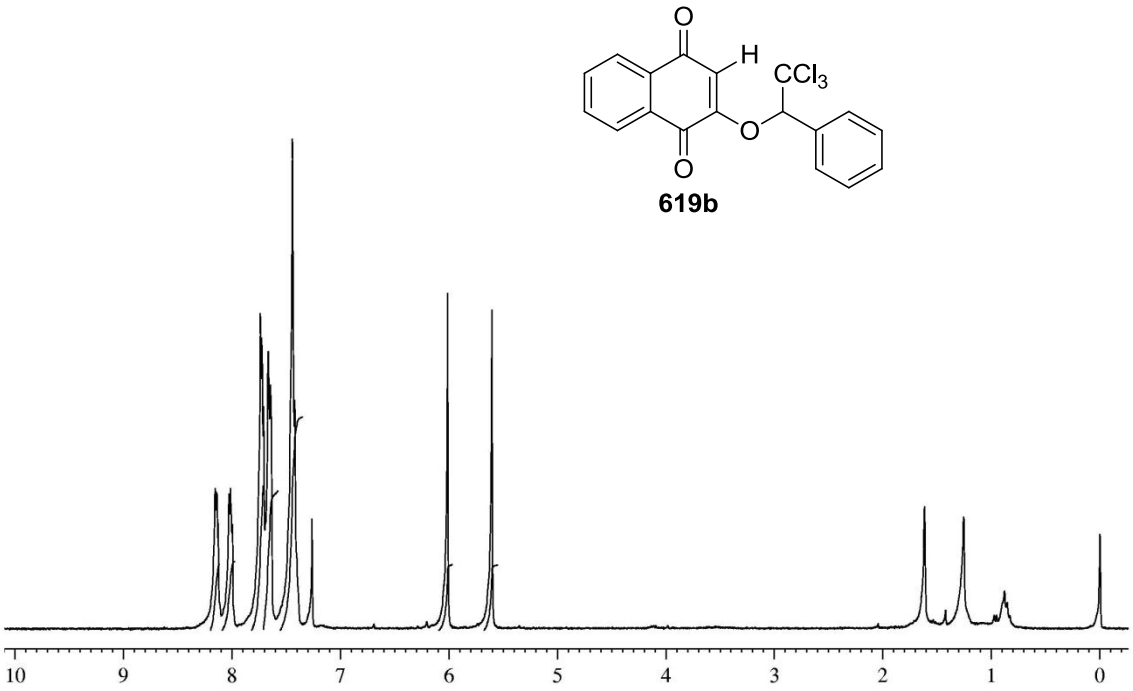


Fig. 283 ^{1}H NMR Spectrum of 2-(2,2,2-trichloro-1-phenylethoxy)naphthalene-1,4-dione 619b

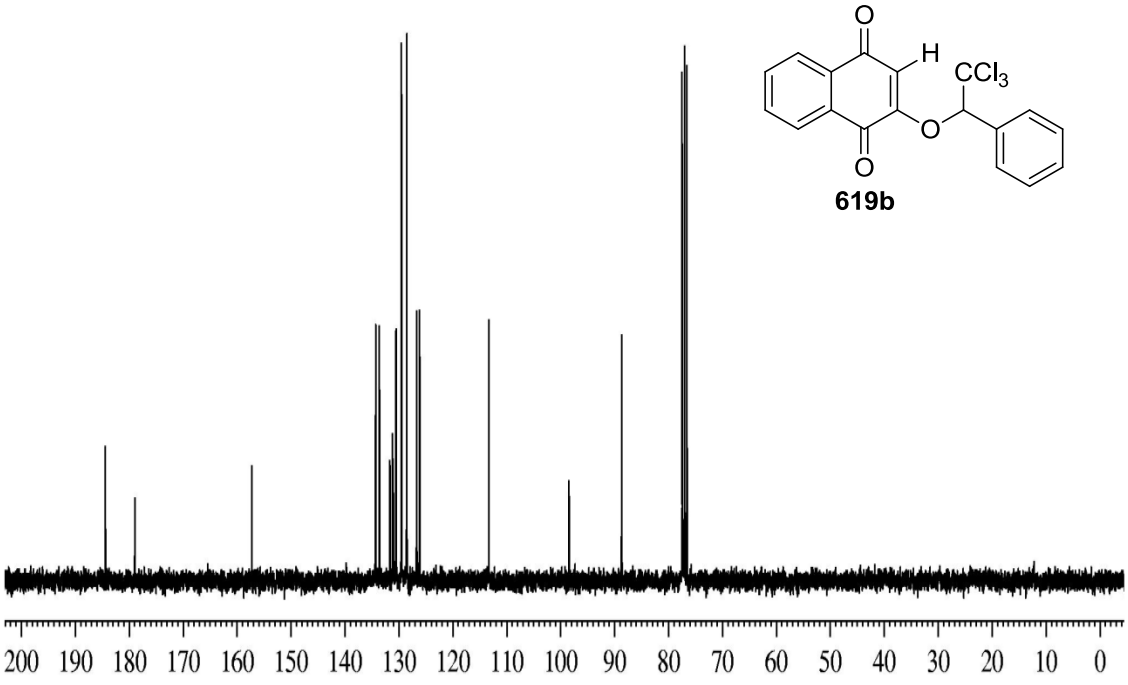


Fig. 284 ^{13}C{^{1}H} NMR Spectrum of 2-(2,2,2-trichloro-1-phenylethoxy)naphthalene-1,4-dione 619b

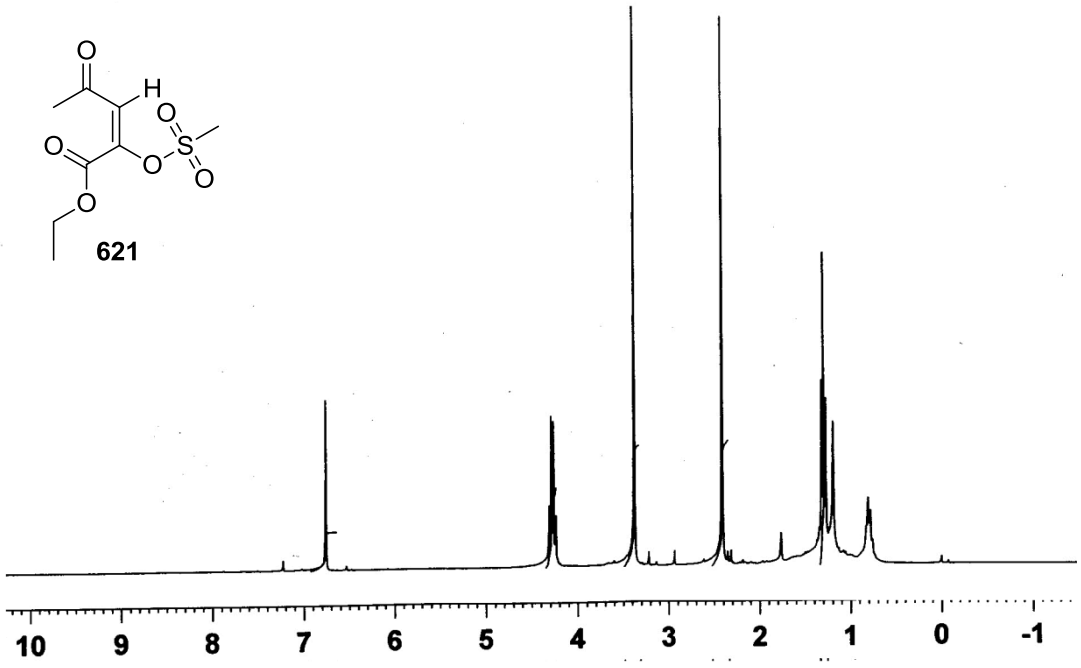


Fig. 285 ^{1}H NMR Spectrum of (*E*)-ethyl 2-(methylsulfonyloxy)-4-oxopent-2-enoate 621

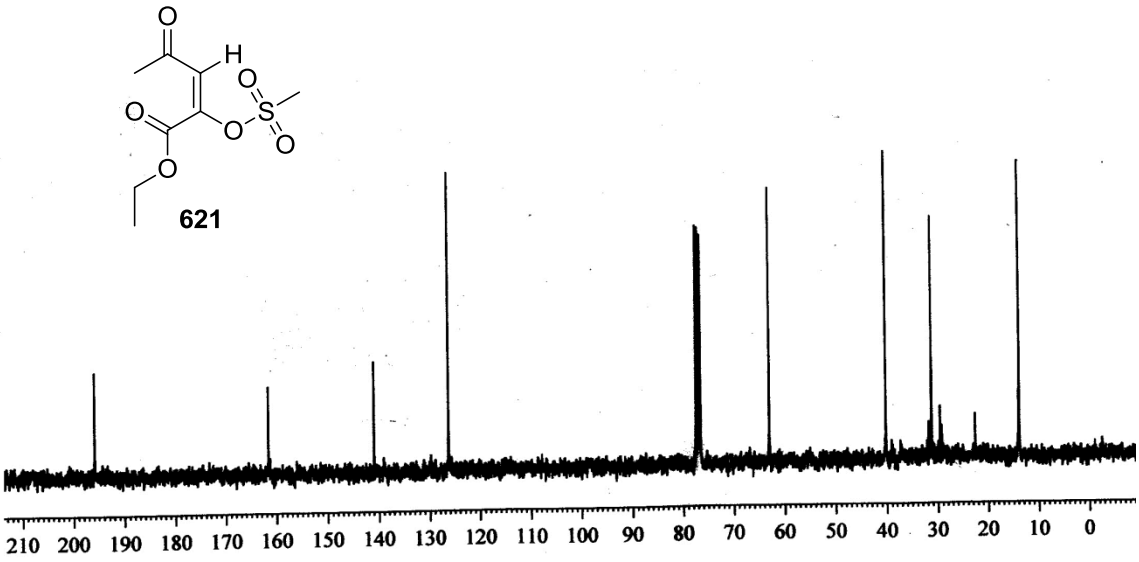


Fig. 286 ^{13}C{^{1}H} NMR Spectrum of (*E*)-ethyl 2-(methylsulfonyloxy)-4-oxopent-2-enoate 621

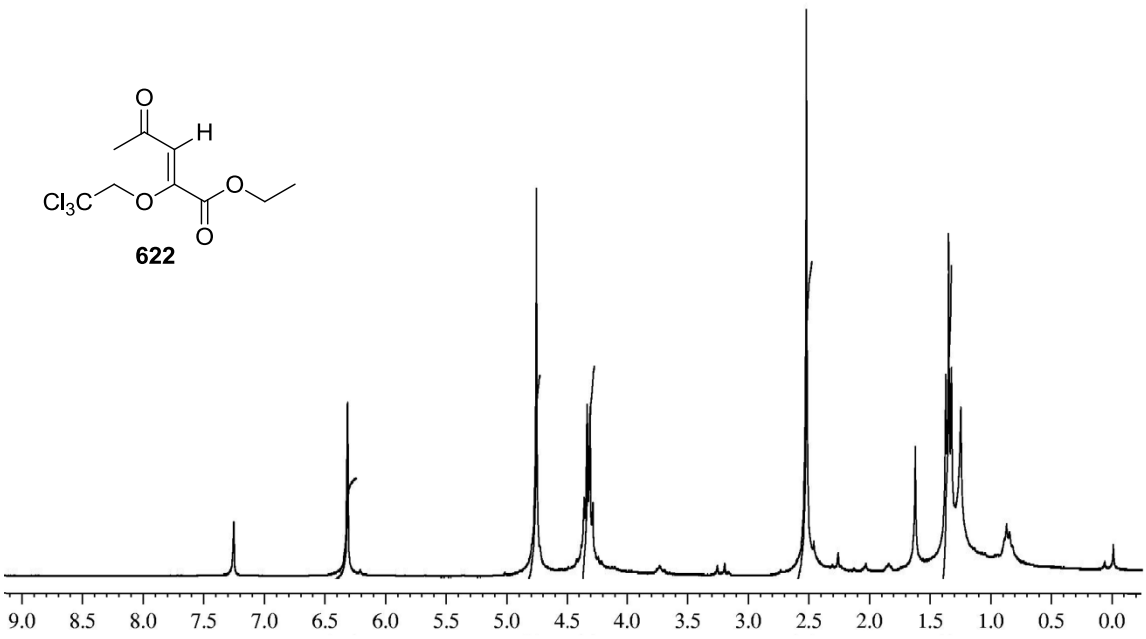


Fig. 287 ^{1}H NMR Spectrum of *(Z)*-ethy l 4-oxo-2-(2,2,2-trichloroethoxy)pent-2-enoate 622

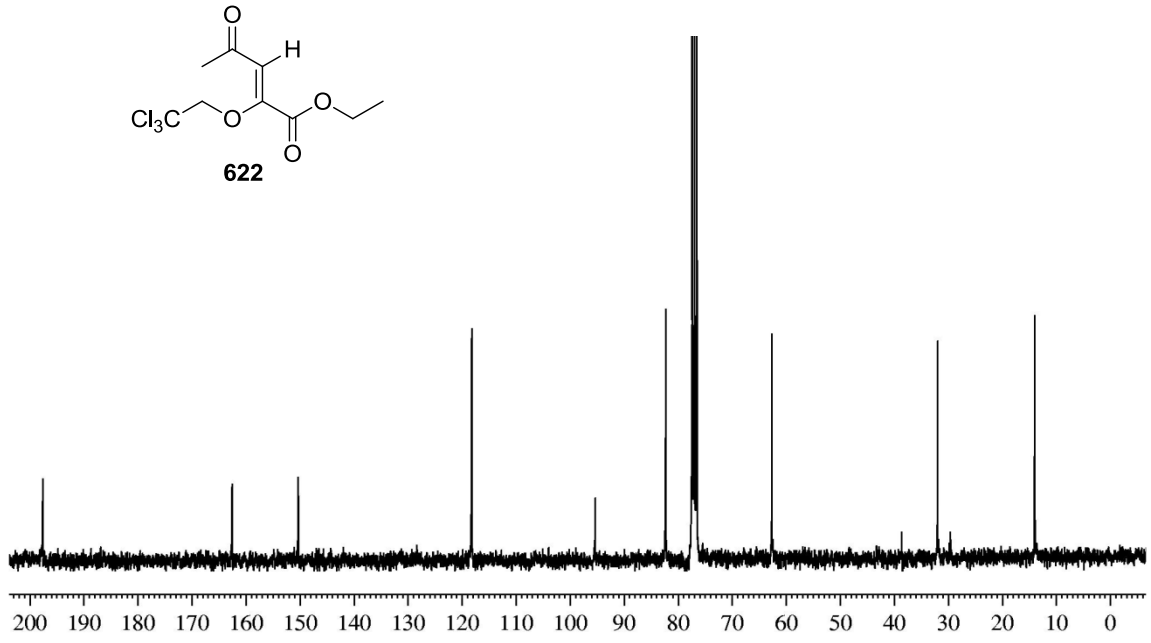


Fig. 288 ^{13}C{^{1}H} NMR Spectrum of (*Z*)-ethyl 4-oxo-2-(2,2,2-trichloroethoxy)pent-2-enoate 622

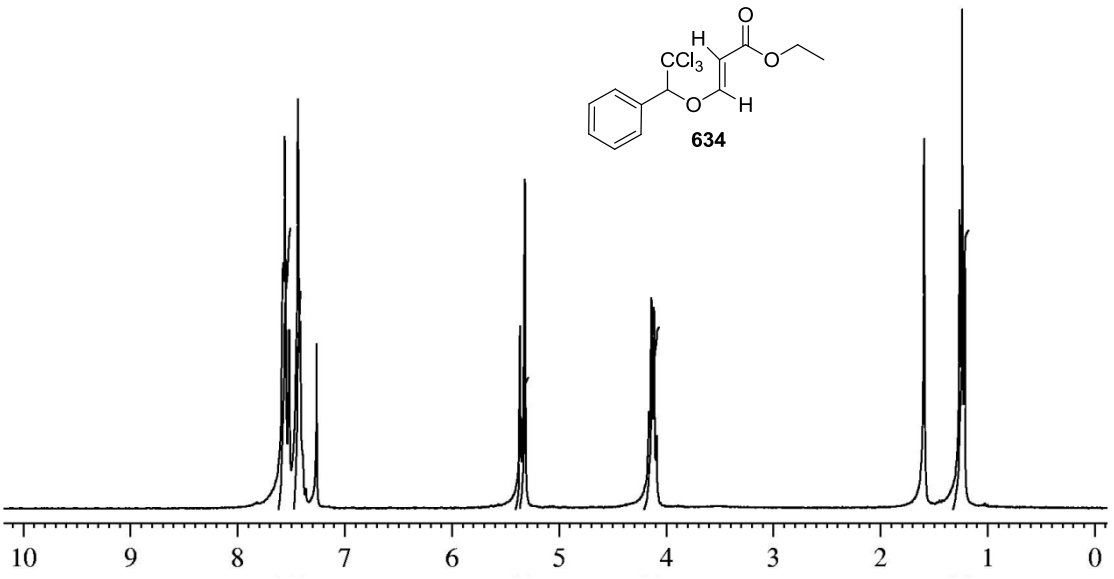


Fig. 289 ^{1}H NMR Spectrum of (*E*)-ethyl 3-(2,2,2-trichloro-1-phenylethoxy)acrylate 634

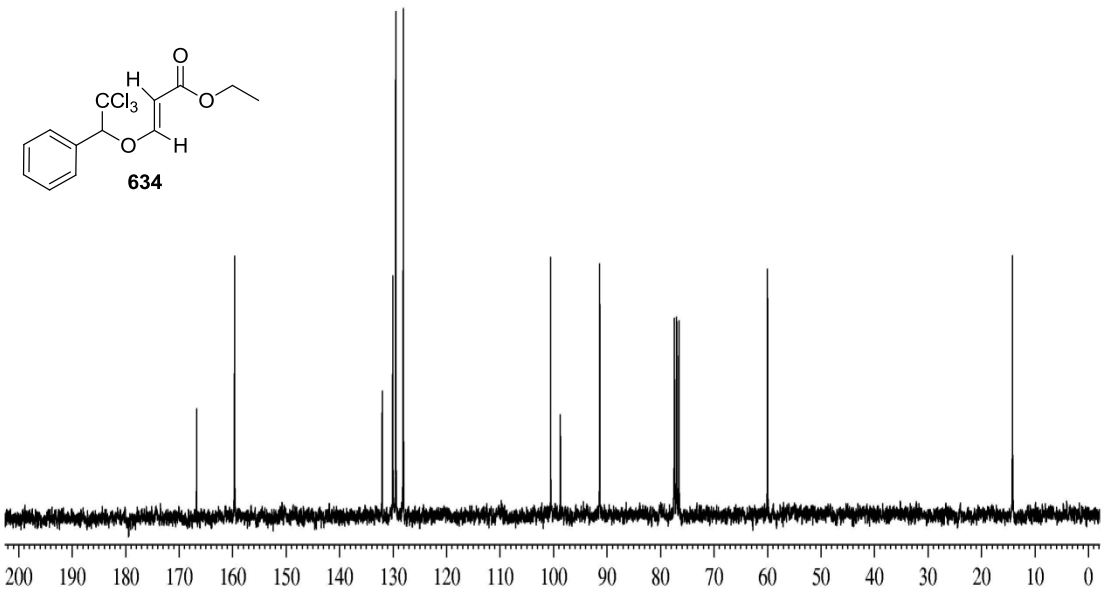


Fig. 290 ^{13}C{^{1}H} NMR Spectrum of (*E*)-ethyl 3-(2,2,2-trichloro-1-phenylethoxy)acrylate 634

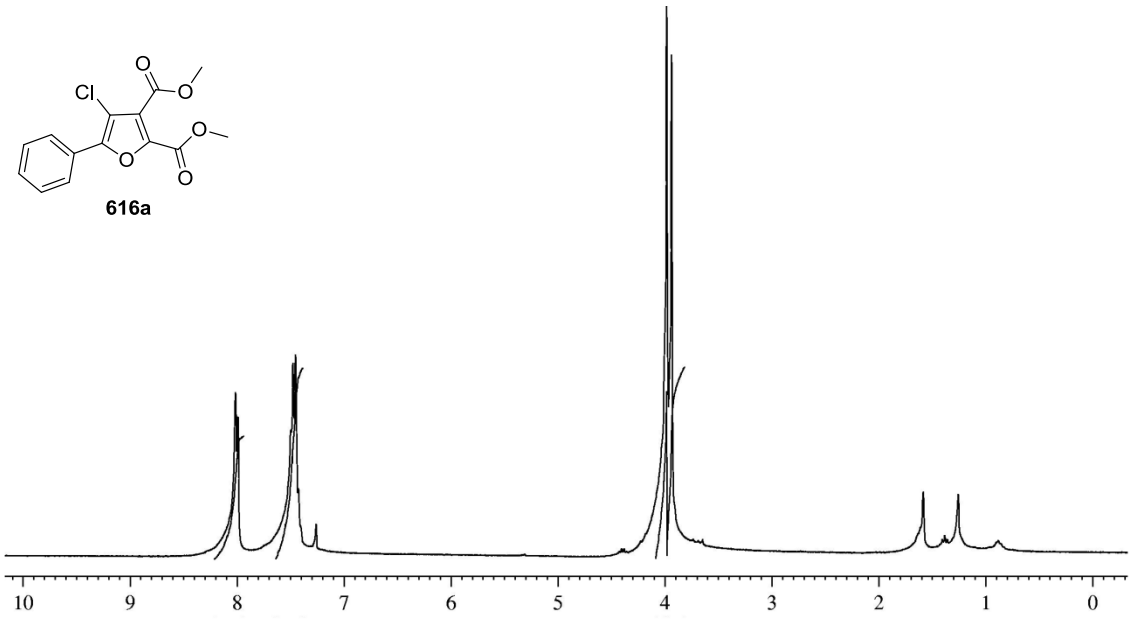


Fig. 291 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-phenylfuran-2,3-dicarboxylate 616a

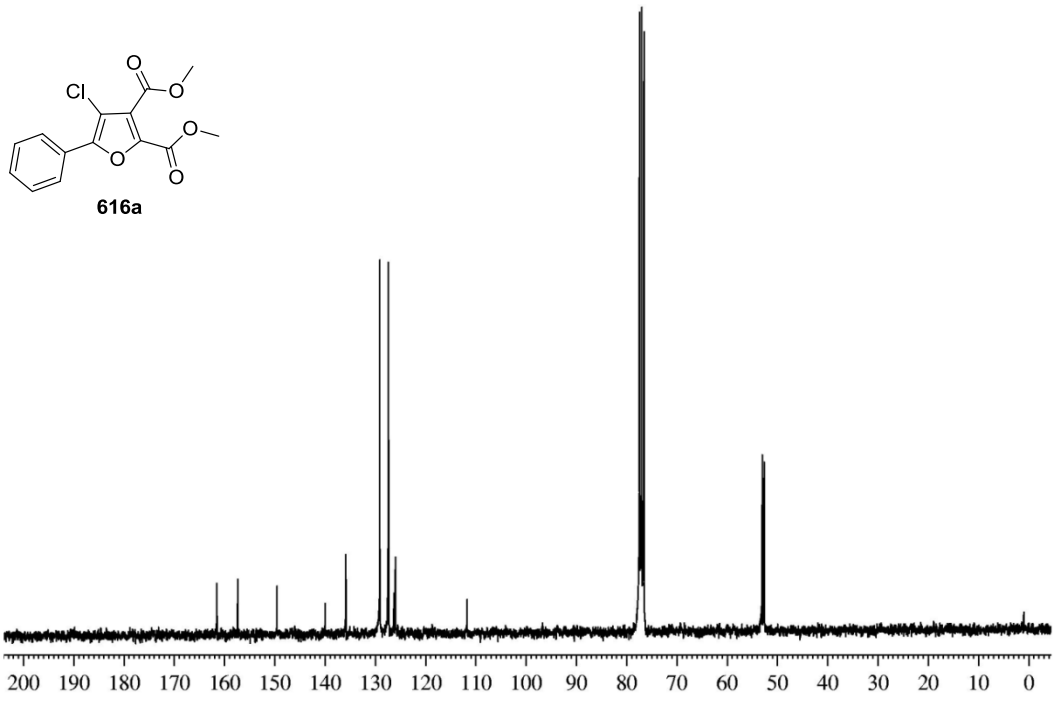


Fig. 292 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-phenylfuran-2,3-dicarboxylate 616a

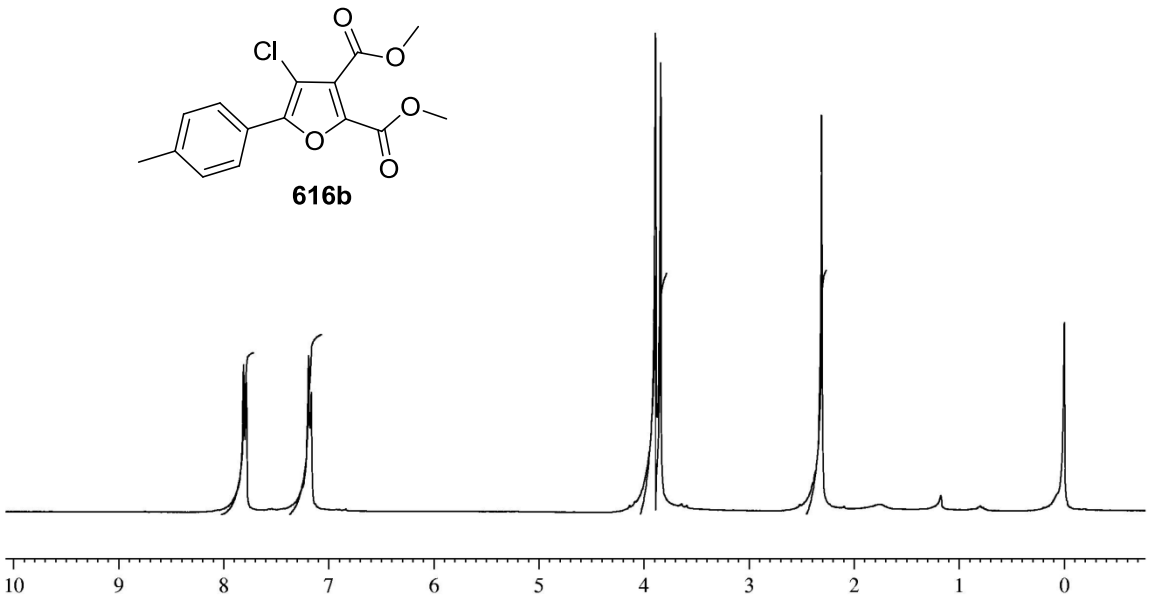


Fig. 293 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-p-tolylfuran-2,3-dicarboxylate 616b

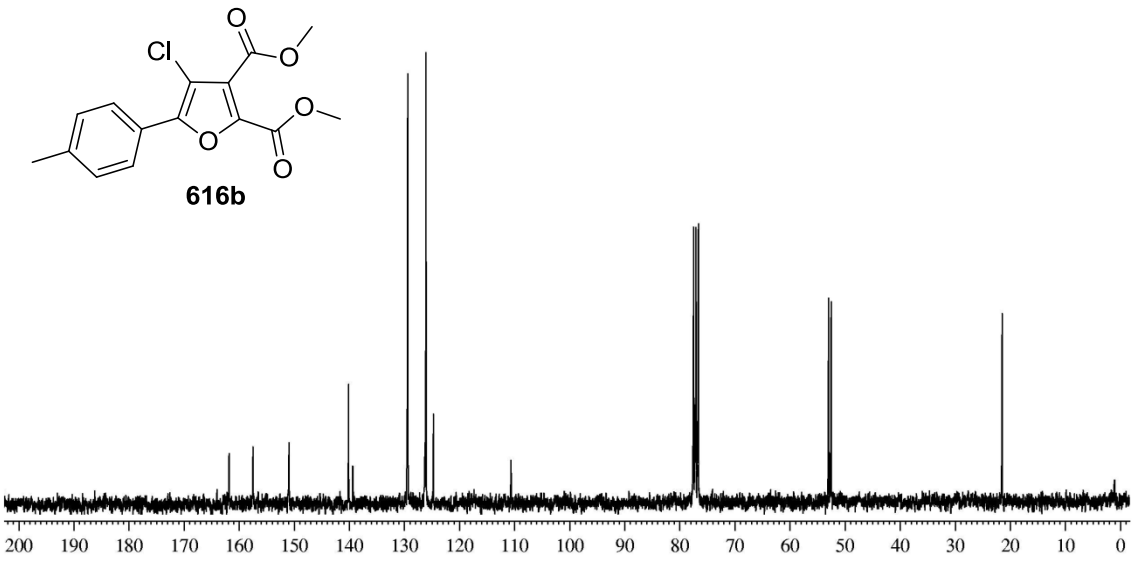


Fig. 294 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-p-tolylfuran-2,3-dicarboxylate 616b

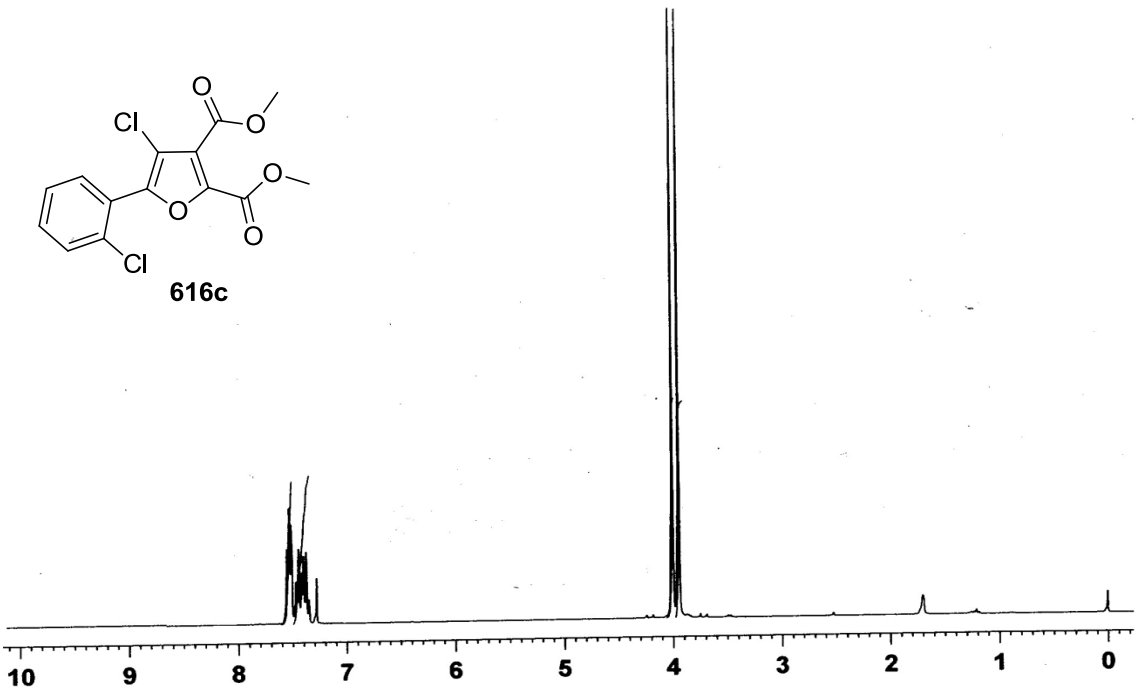


Fig. 295 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-(2-chlorophenyl)furan-2,3-dicarboxylate 616c

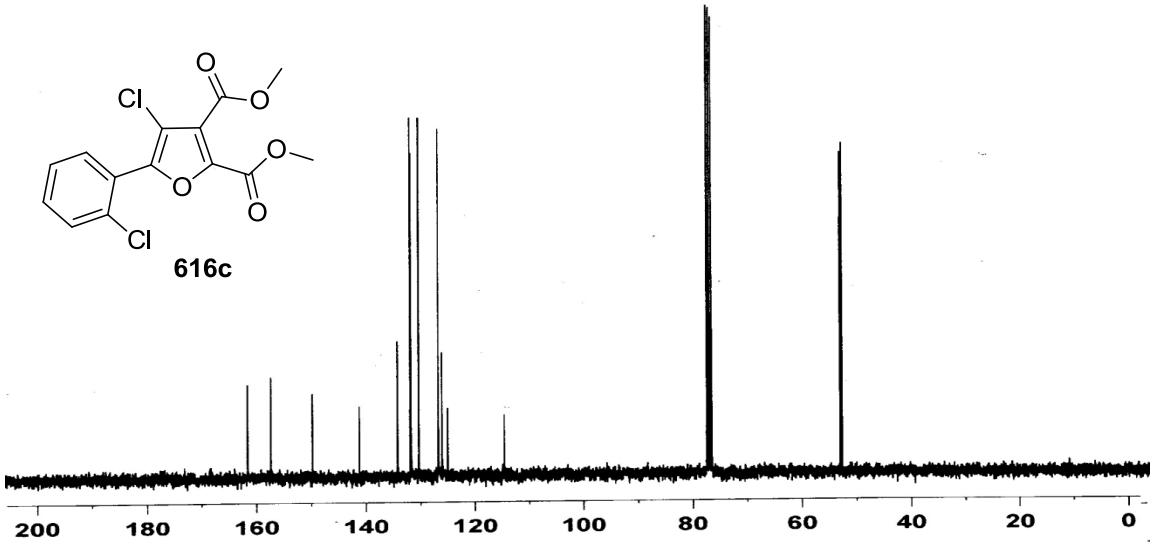


Fig. 296 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-(2-chlorophenyl)furan-2,3-dicarboxylate 616c

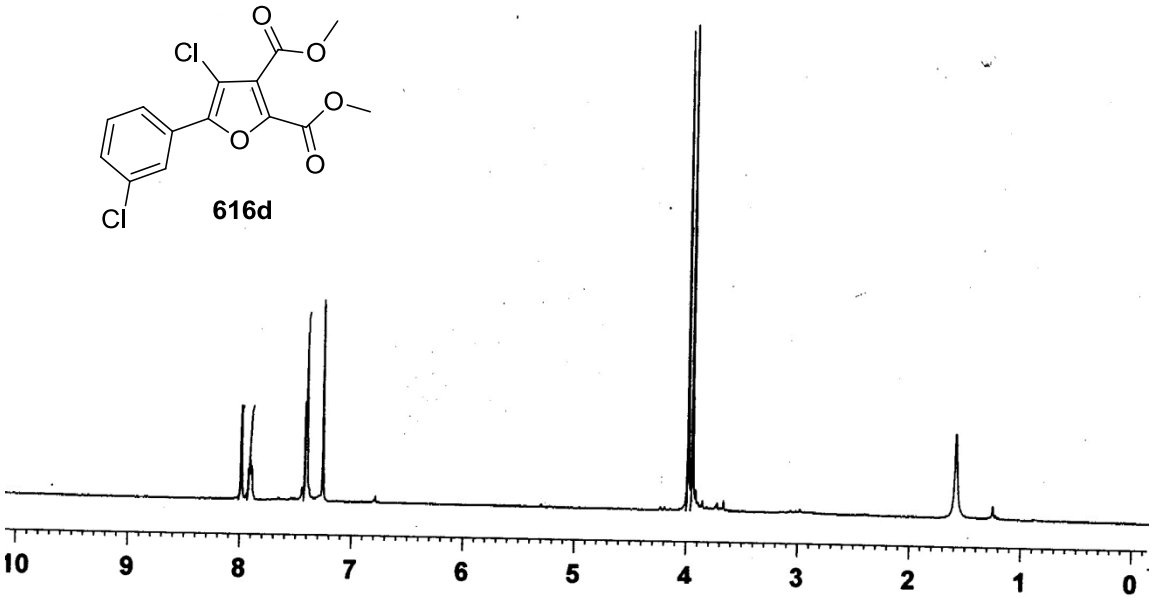


Fig. 297 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-(3-chlorophenyl)furan-2,3-dicarboxylate 616d

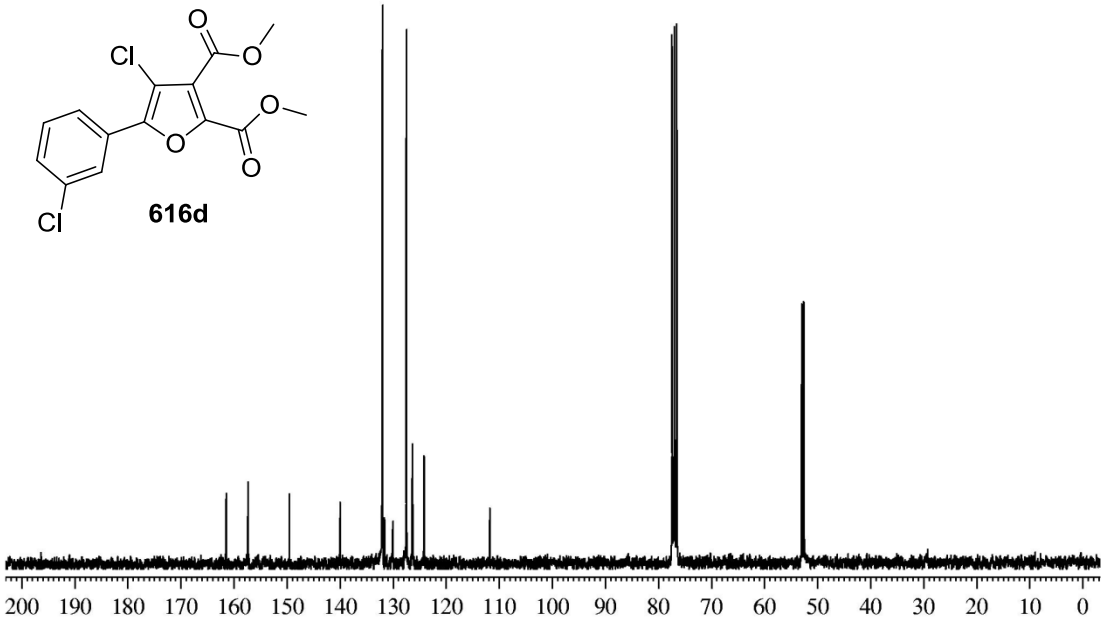


Fig. 298 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-(3-chlorophenyl)furan-2,3-dicarboxylate 616d

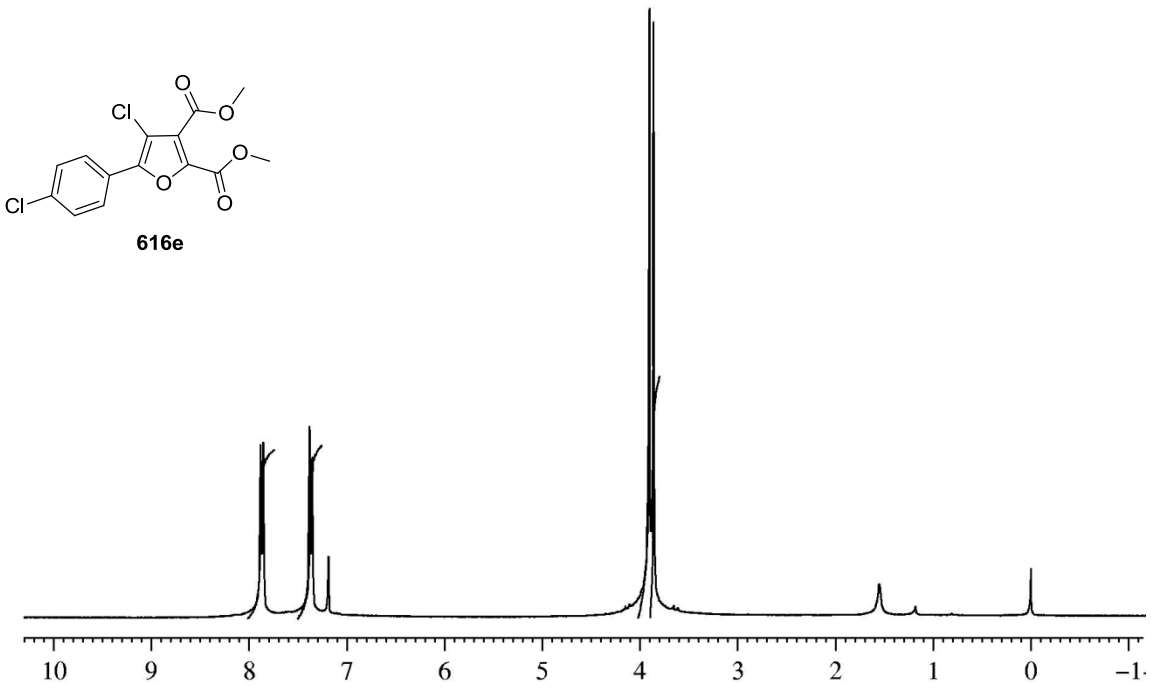


Fig. 299 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-(4-chlorophenyl)furan-2,3-dicarboxylate 616e

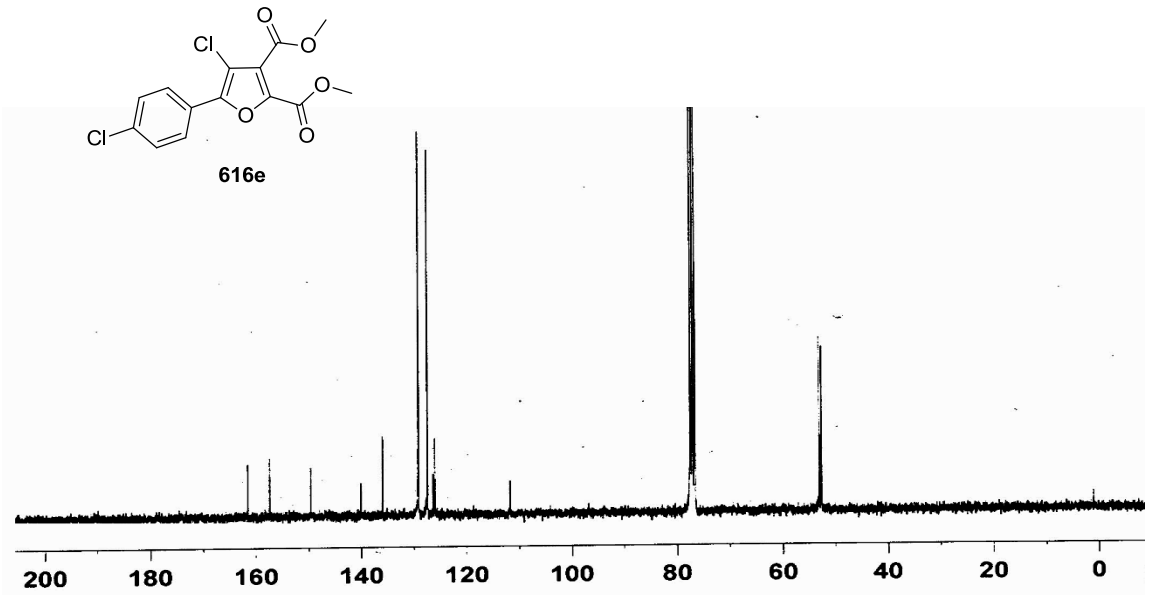


Fig. 300 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-(4-chlorophenyl)furan-2,3-dicarboxylate 616e

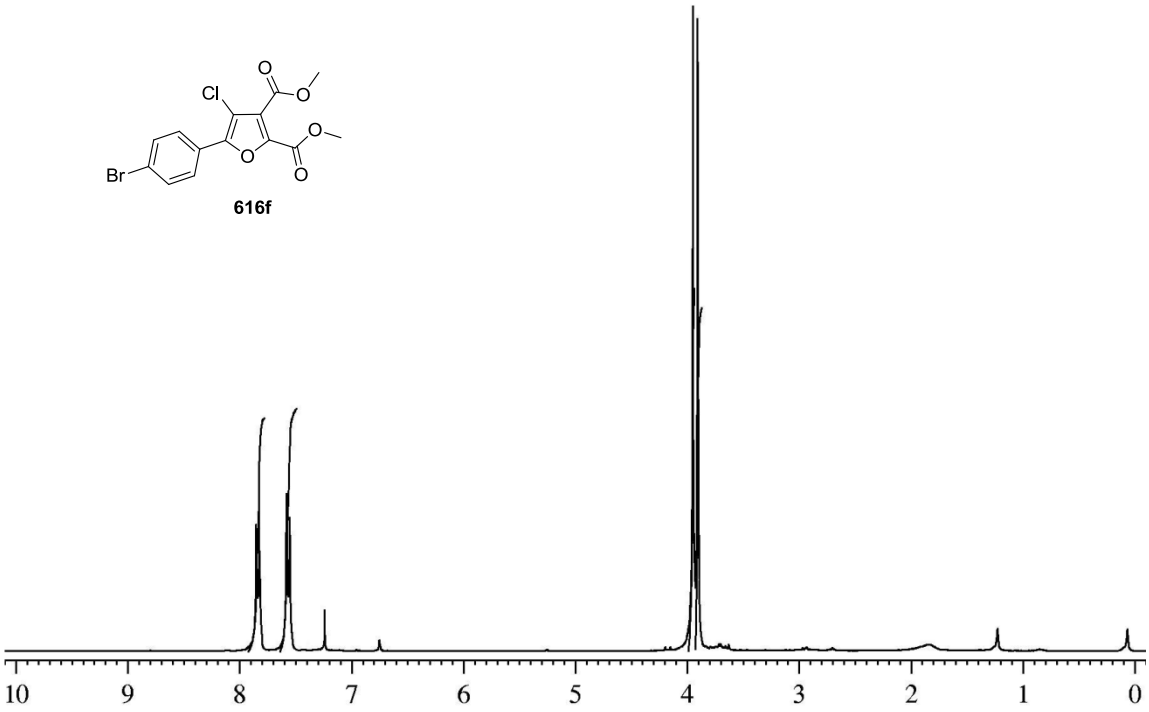


Fig. 301 ^{1}H NMR Spectrum of dimethyl 5-(4-bromophenyl)-4-chlorofuran-2,3-dicarboxylate 616f

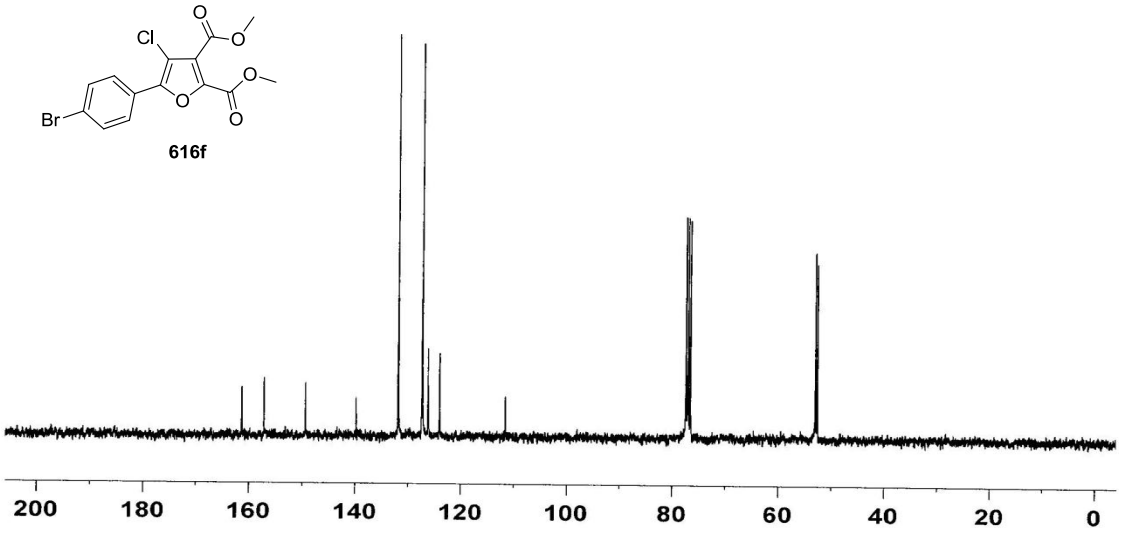


Fig. 302 ^{13}C{^{1}H} NMR Spectrum of dimethyl 5-(4-bromophenyl)-4-chlorofuran-2,3-dicarboxylate 616f

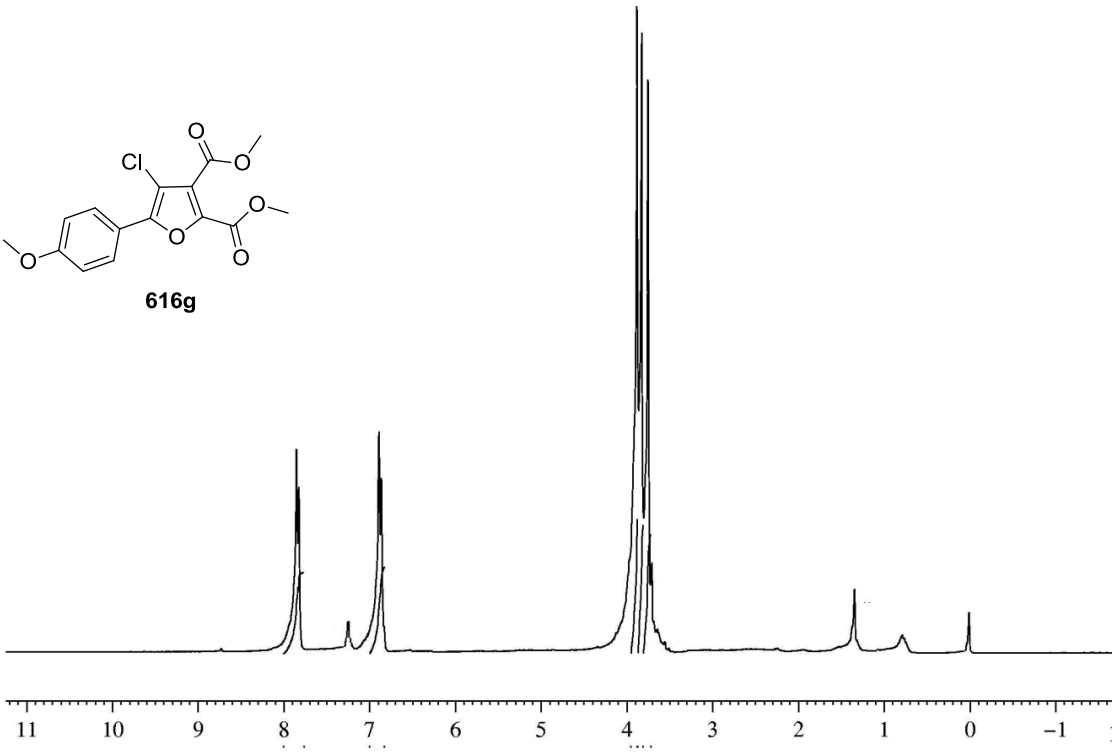


Fig. 303 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-(4-methoxyphenyl)furan-2,3-dicarboxylate 616g

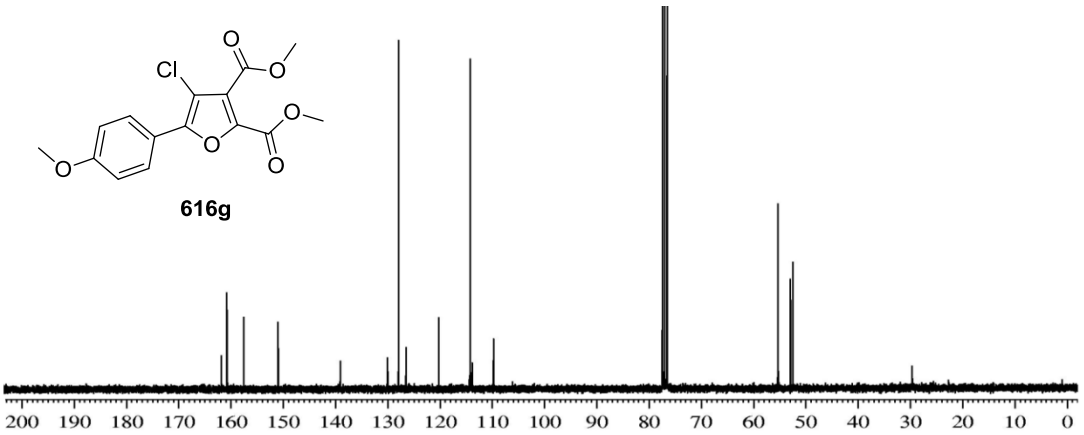


Fig. 304 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-(4-methoxyphenyl)furan-2,3-dicarboxylate 616g

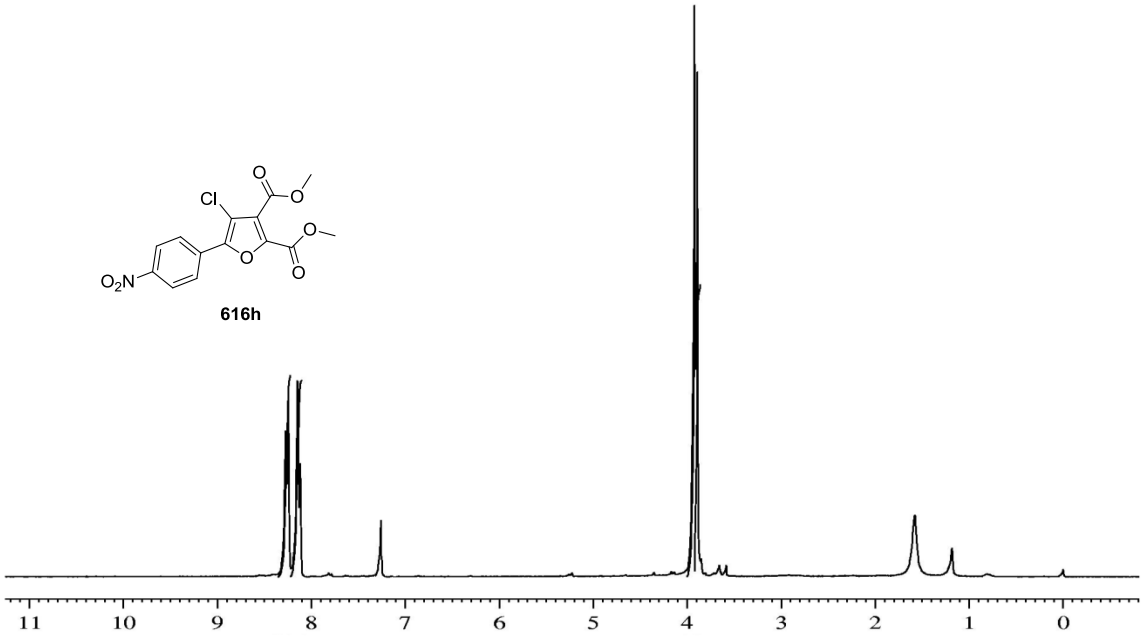


Fig. 305 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-(4-nitrophenyl)furan-2,3-dicarboxylate 616h

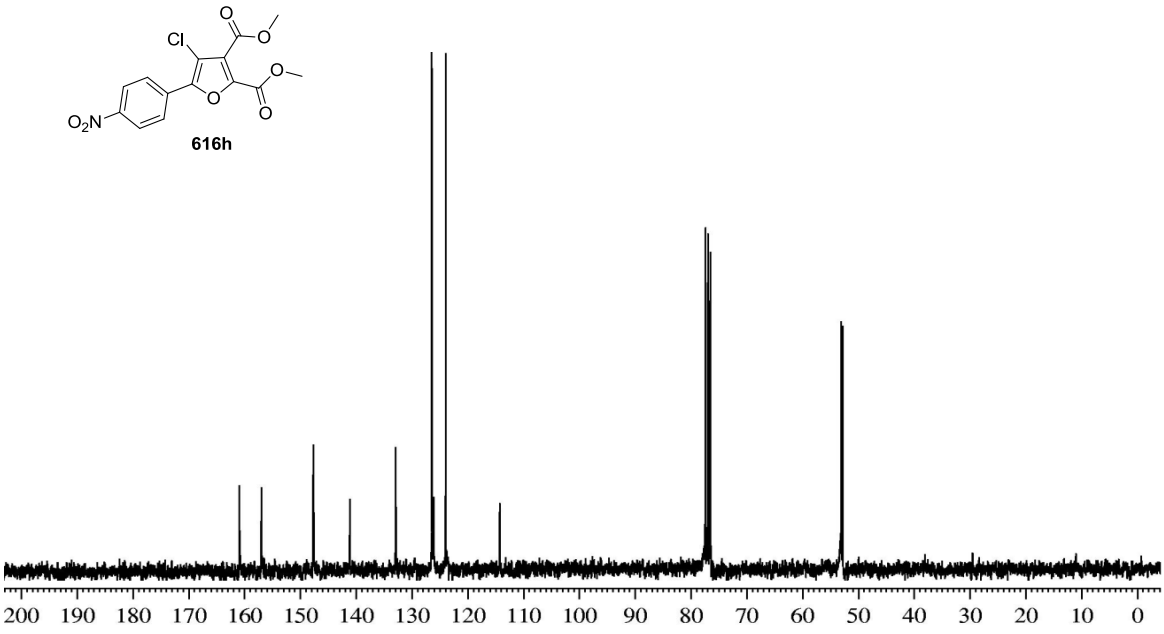


Fig. 306 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-(4-nitrophenyl)furan-2,3-dicarboxylate 616h

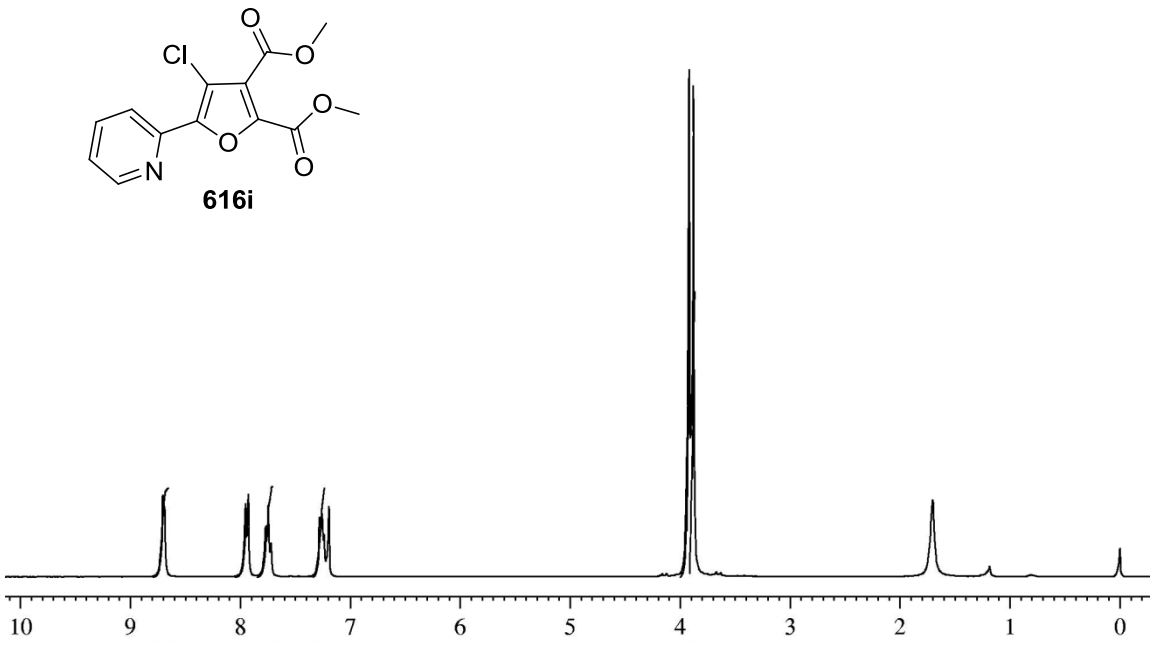


Fig. 307 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-(pyridin-2-yl)furan-2,3-dicarboxylate 616i

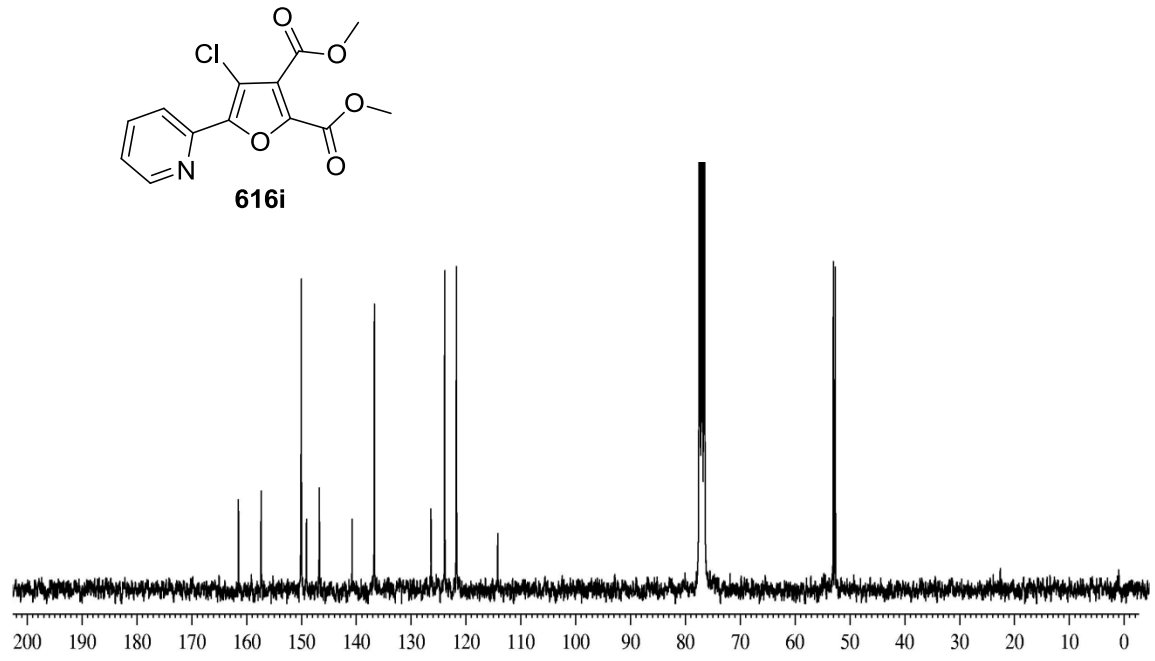


Fig. 308 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-(pyridin-2-yl)furan-2,3-dicarboxylate 616i

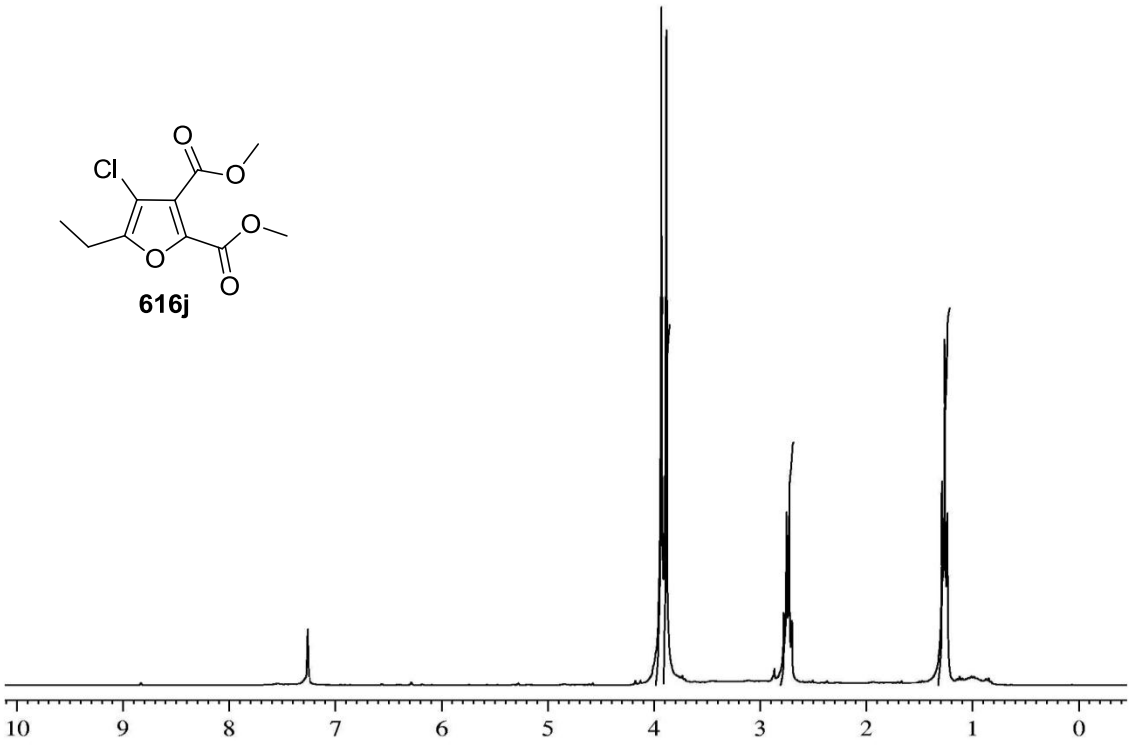


Fig. 309 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-ethylfuran-2,3-dicarboxylate 616j

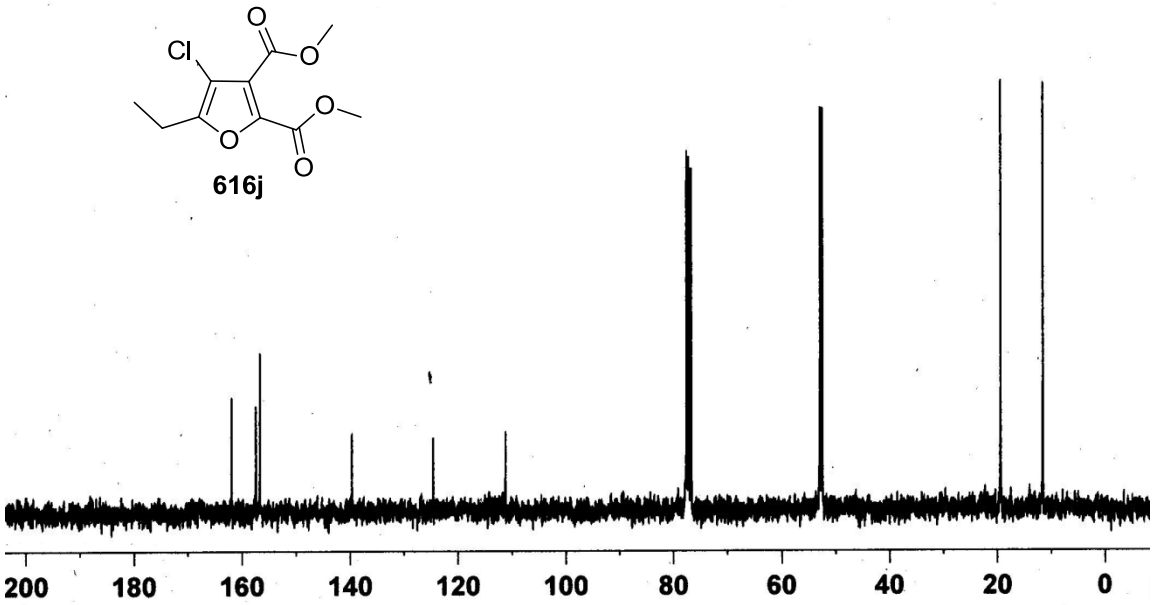


Fig. 310 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-ethylfuran-2,3-dicarboxylate 616j

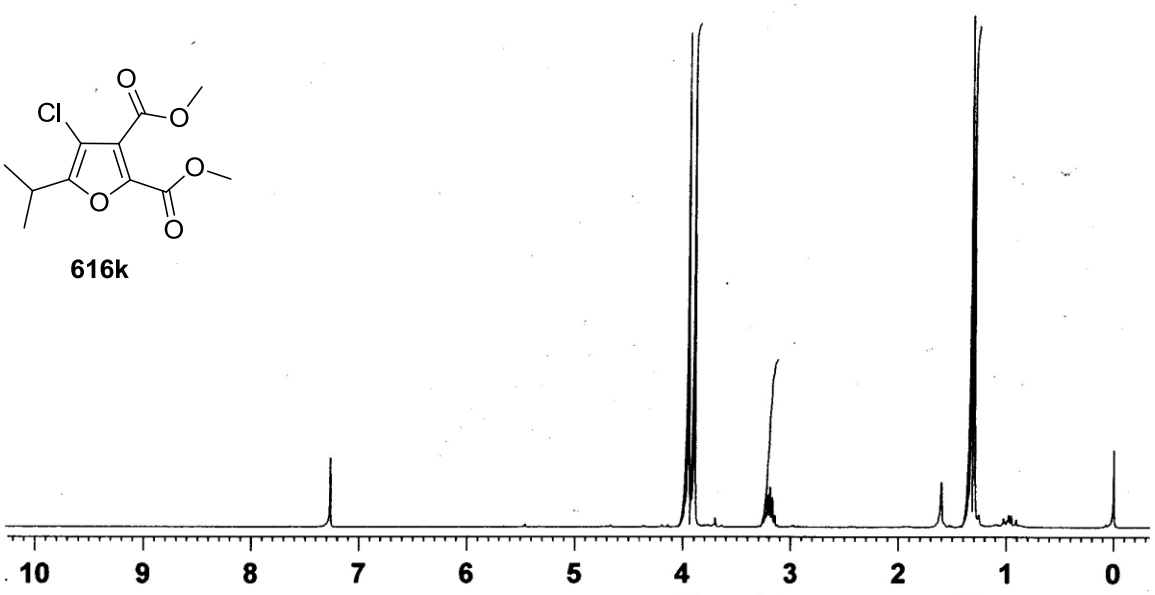


Fig. 311 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-isopropylfuran-2,3-dicarboxylate 616k

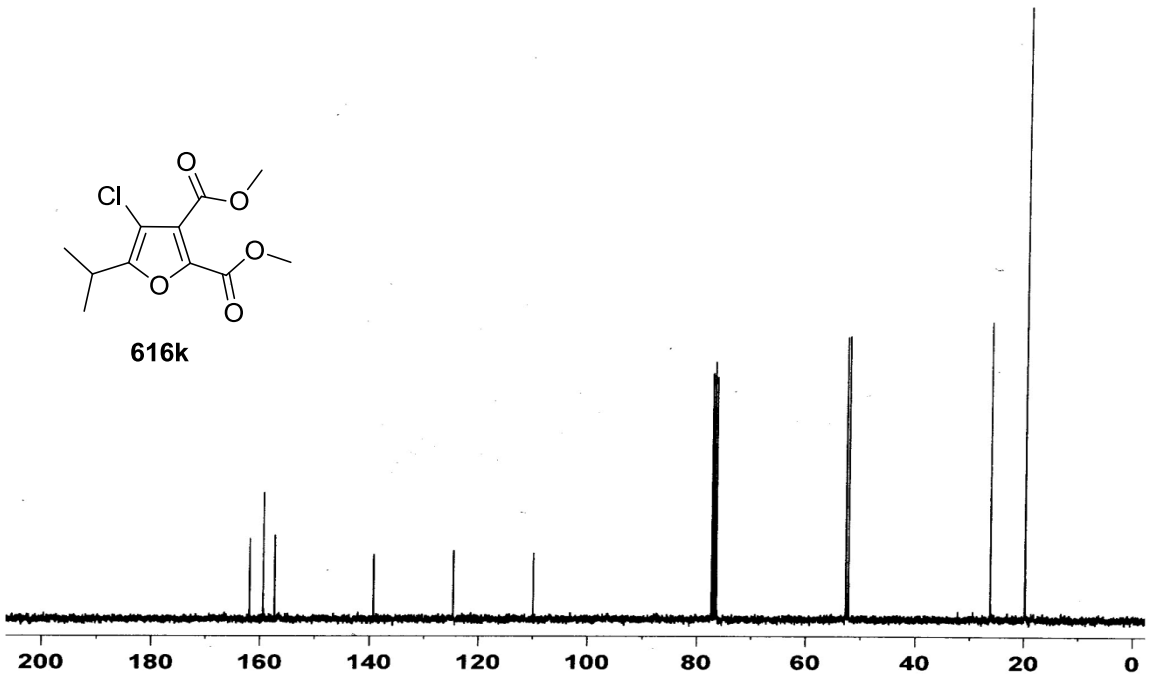


Fig. 312 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-isopropylfuran-2,3-dicarboxylate 616k

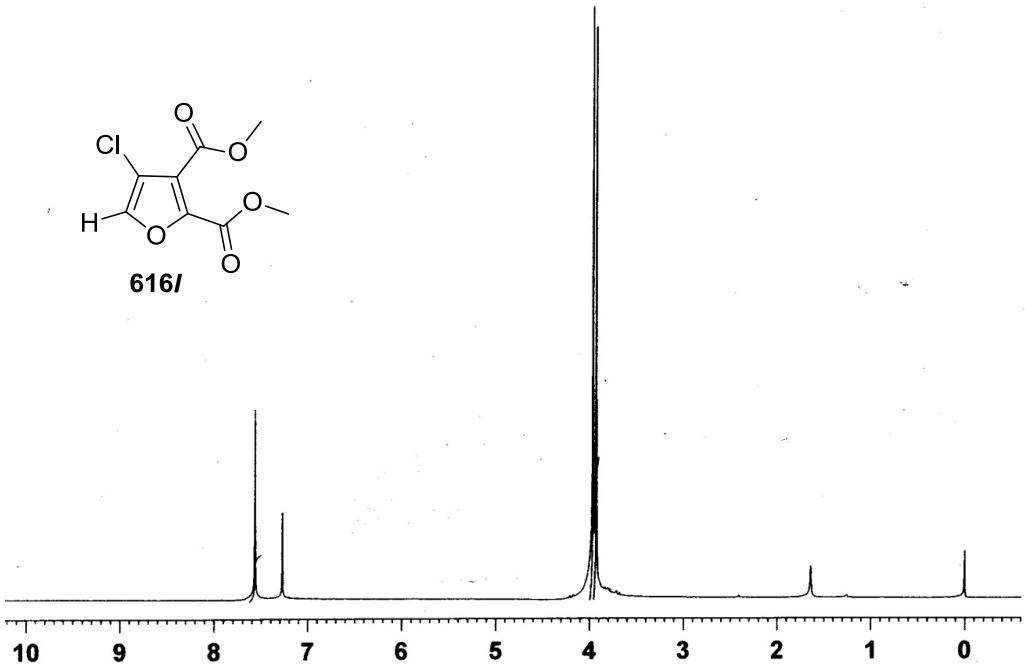


Fig. 313 ^{1}H NMR Spectrum of dimethyl 4-chlorofuran-2,3-dicarboxylate 616*l*

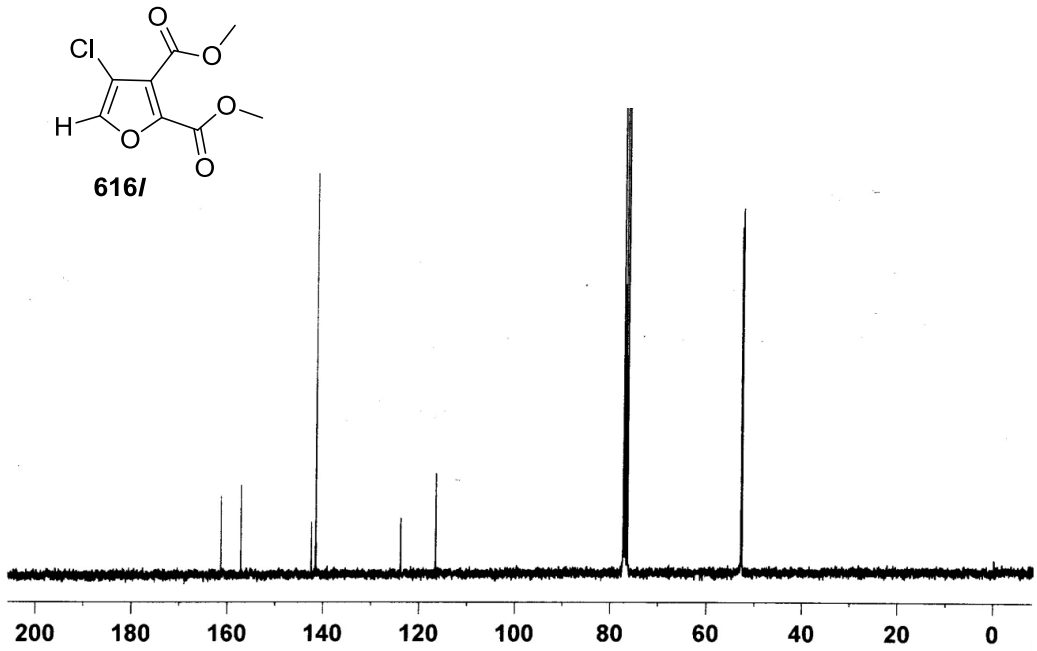


Fig. 314 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chlorofuran-2,3-dicarboxylate 616*l*

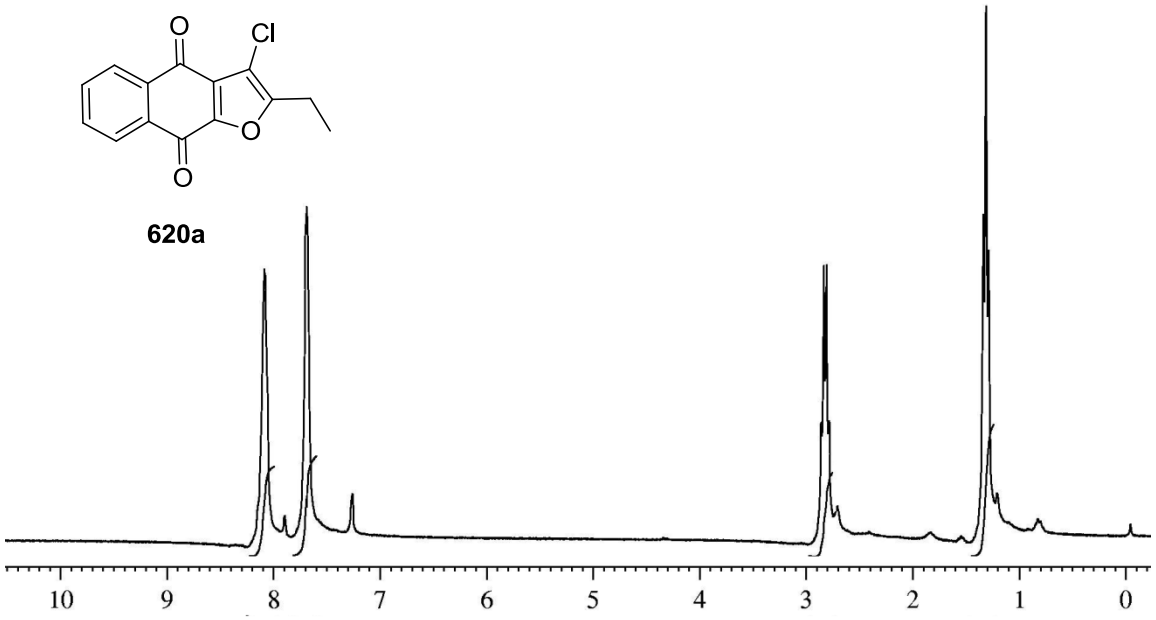


Fig. 315 ^{1}H NMR Spectrum of 3-chloro-2-ethylnaphtho[2,3-b]furan-4,9-dione 620a

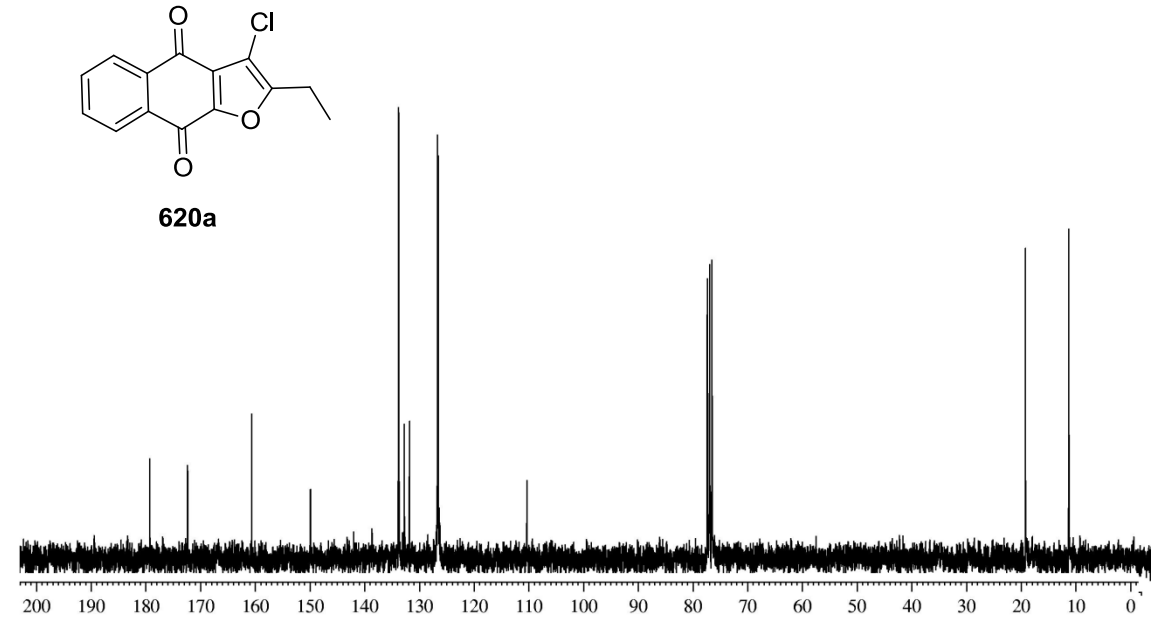


Fig. 316 ^{13}C{^{1}H} NMR Spectrum of 3-chloro-2-ethylnaphtho[2,3-b]furan-4,9-dione 620a

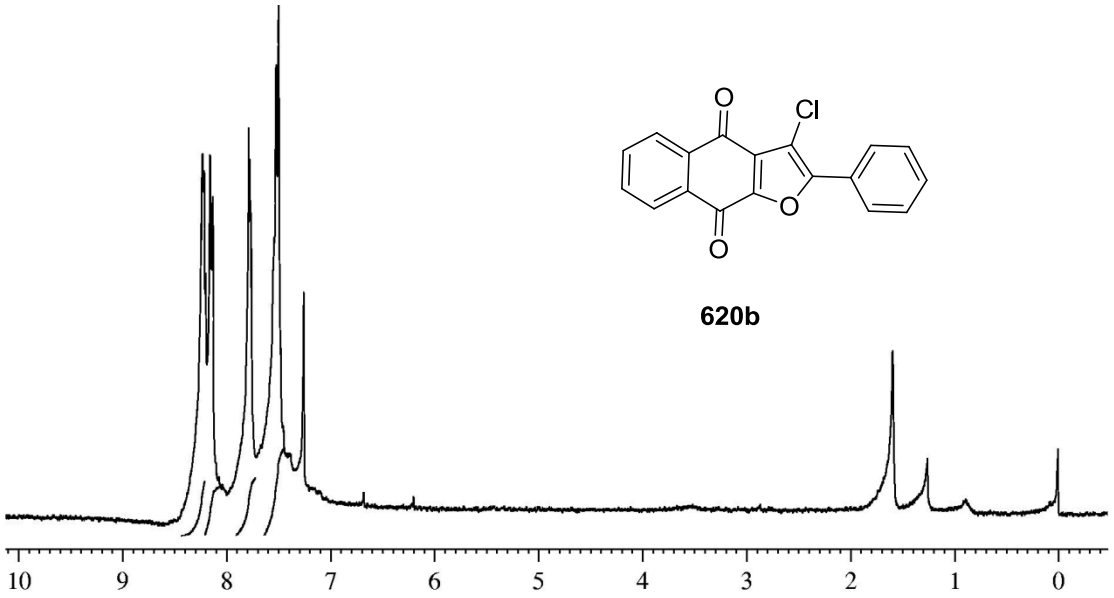


Fig. 317 ^{1}H NMR Spectrum of 3-chloro-2-phenylnaphtho[2,3-b]furan-4,9-dione 620b

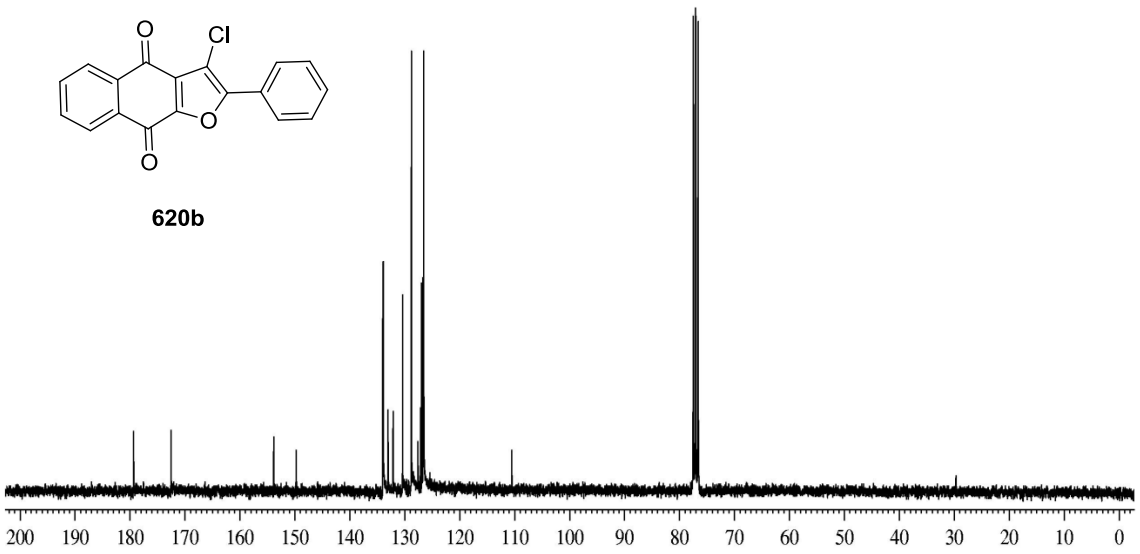


Fig. 318 ^{13}C{^{1}H} NMR Spectrum of 3-chloro-2-phenylnaphtho[2,3-b]furan-4,9-dione 620b

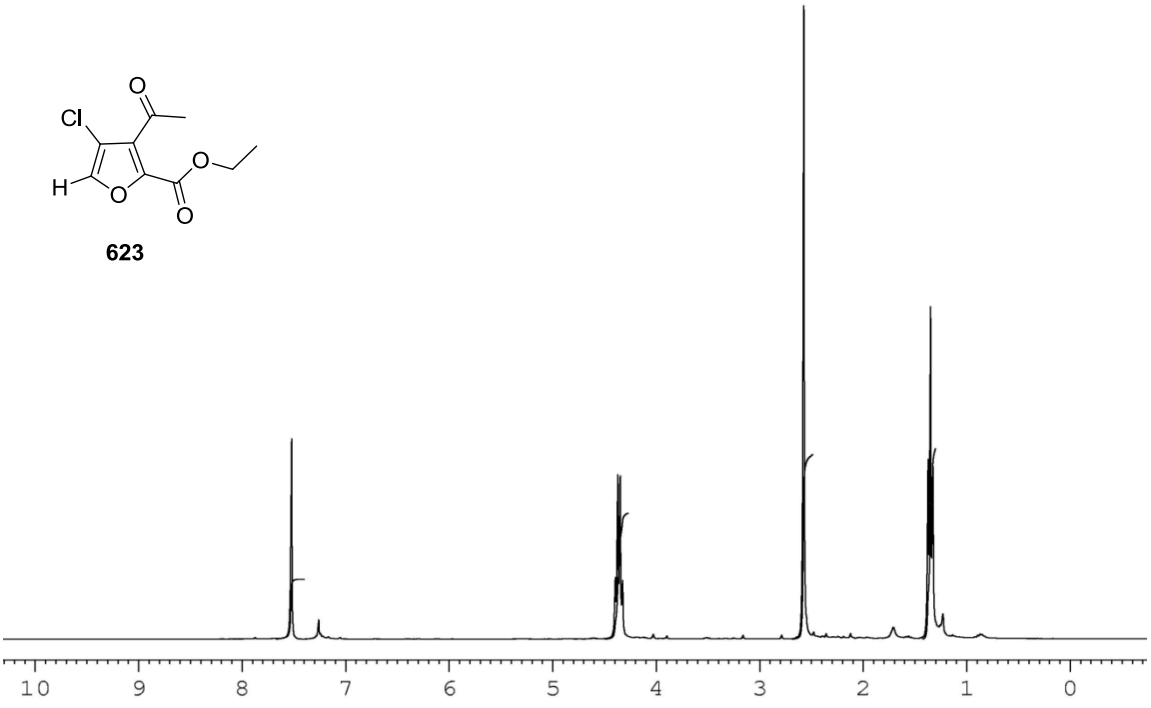


Fig. 319 ^{1}H NMR Spectrum of ethyl 3-acetyl-4-chlorofuran-2-carboxylate 623

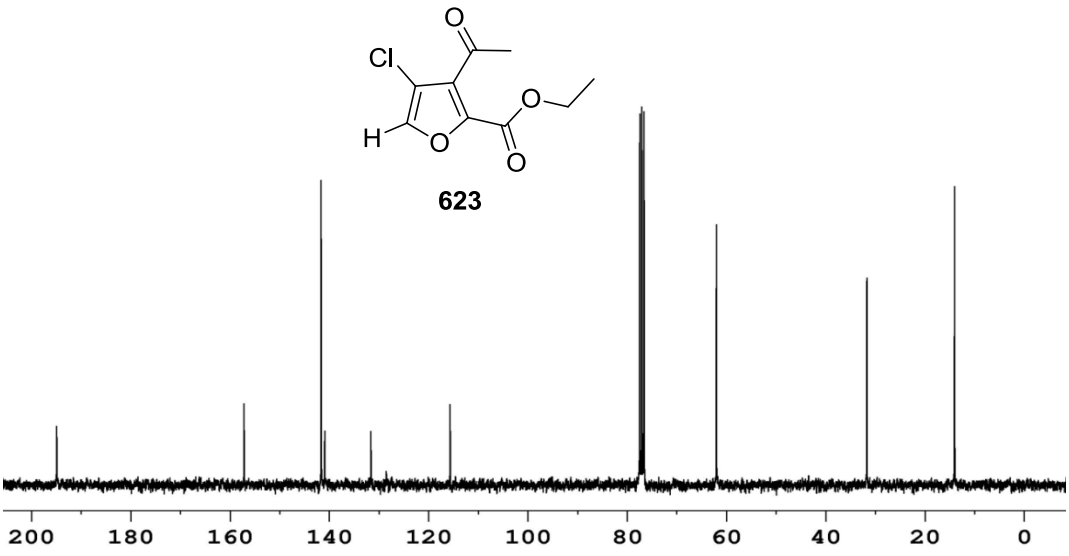


Fig. 320 ^{13}C{^{1}H} NMR Spectrum of ethyl 3-acetyl-4-chlorofuran-2-carboxylate 623

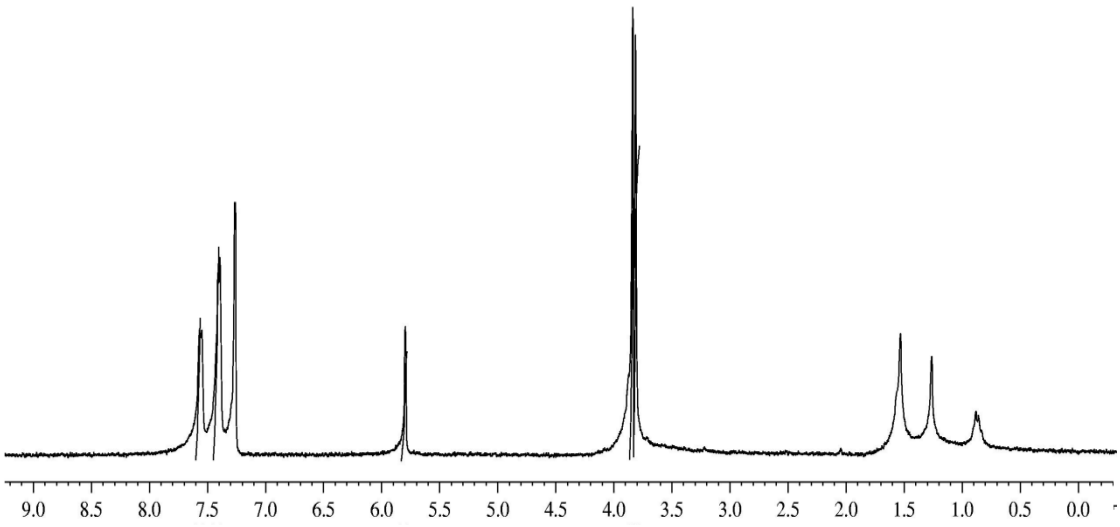


Fig. 321 ^{1}H NMR Spectrum of dimethyl 4-chloro-5-phenyldihydrofuran-2,3-dicarboxylate 633

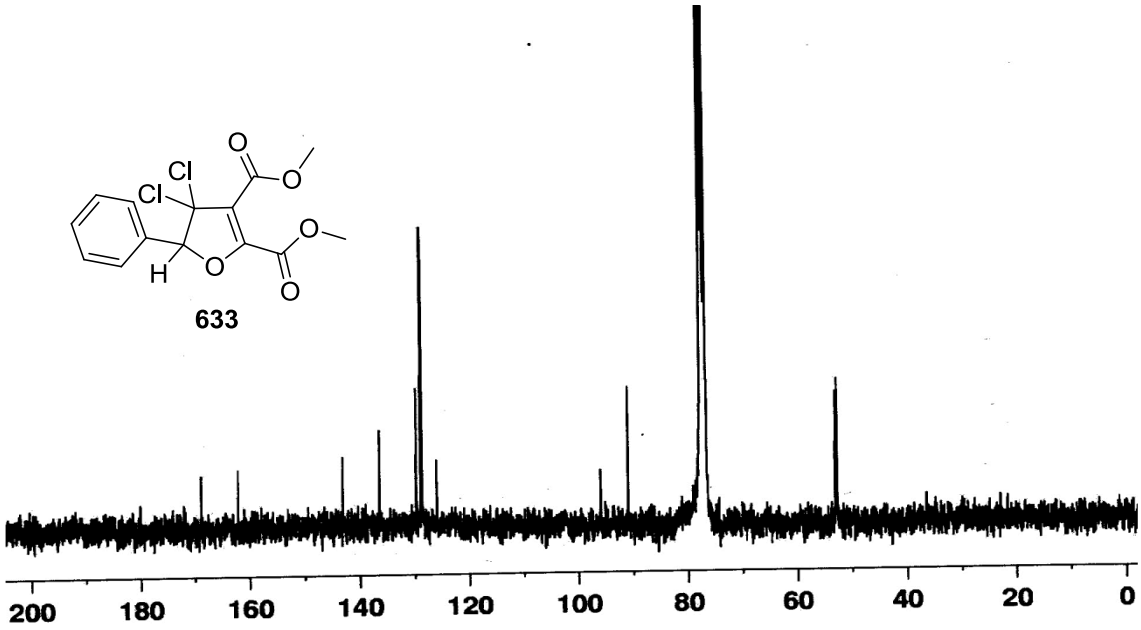


Fig. 322 ^{13}C{^{1}H} NMR Spectrum of dimethyl 4-chloro-5-phenyldihydrofuran-2,3-dicarboxylate 633

Bio-data of the Author

Name	:	Dharmendra Kumar Gupta
Fathers Name	:	Mr. Maheswari Gupta
Mothers Name	:	Smt. Kishori Devi
Date of Birth	:	1st January 1979
Nationality	:	Indian
Marital Status	:	Unmarried
Educational Qualifications	:	M.Sc. (Chemistry)
	:	B.Sc. (Chemistry)

Publication:

1. "Organocatalytic selective benzoylation of alcohols with trichloromethyl phenyl ketone: inverse selectivity in benzoylation of alcohols containing phenol or aromatic amine functionality" Ram N. Ram, Vineet Kumar Soni, Dharmendra Kumar Gupta *Tetrahedron* **2012**, *68*, 9068-9075.