SYNTHESIS AND REACTIONS OF SOME ORGANIC COMPOUNDS CONTAINING A TRICHLOROMETHYL GROUP

VINEET KUMAR SONI

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SYNTHESIS AND REACTIONS OF SOME ORGANIC COMPOUNDS CONTAINING A TRICHLOROMETHYL GROUP

BY

VINEET KUMAR SONI

Submitted

in fulfillment of the requirements of the degree of

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Dedicated

To

My Parents

Certificates

This is to certify that the thesis entitled “Synthesis and Reactions of Some Organic Compounds Containing a Trichloromethyl Group”, being submitted by Mr. Vineet Kumar Soni, 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. Vineet Kumar Soni 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
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ABSTRACT

Organic compounds containing a trichloromethyl group have come a long way to be recognized as a separate class of compounds. Trichloromethyl group is a constituent of some bioactive marine natural products and synthetic reagents. The synthetic importance of these compounds flows from some characteristic properties of the trichloromethyl group, such as electronegativity, nucleofugality, single electron redox reactivity, high hydrolytic stability and steric bulk. The thesis describes the present work on synthesis and reactions of some compounds containing a trichloromethyl group in chapters 2-5 following an introductory chapter on some relevant aspects of such compounds.

In chapter 2, a methodology to access α-functionalized trichloromethyl carbinols by a direct two step pathway starting from enolisable α-haloketones, α-haloesters and α-haloamides has been described. It involves substitution of the halo group (Br, I) by a nitrate group on reaction with $AgNO_3$ in MeCN at room temperature followed by tandem elimination of HNO_2 from the nitrate to a dicarbonyl compound and nucleophilic addition of $^-CCl_3$ to the newly formed aldo/keto group on treatment with sodium trichloroacetate in DMF at 5-25 °C. This method is quite general and gives the products generally in good yields. These functionalized trichloromethyl carbinols are important synthetic intermediates. Their importance in the synthesis of chloromethyl α-dicarbonyl compounds, trichloromethylated dihydrofurans and enolacetates of α-functionalize acid chlorides, a type of functionally dense trisubstituted alkenes, was demonstrated by applying known chemistry on a representative members. Similarly, through the Jocic-Reeve reaction, the synthesis of a tartronamic acid derivative was also demonstrated.

Chapter 3 presents CuCl/PMDETA (*N*,*N*′,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine)-catalyzed chlorine atom transfer radical cyclization (ATRC) of tetrasubstituted hydrazines having *N*-allyl-*N*′-trichloroacetyl substituents, in

DCE at reflux leading to the formation of chlorinated tetrahydropyridazin-3-ones exclusively by 6-*exo* cyclization or along with small amounts of chlorinated 1,2-diazepan-3-ones arising by 7-*endo* cyclization. The tetrasubstituted *N*-allyl-*N*′-trichloroacetylhydrazines were prepared from the Boc-protected aryl hydrazines by successive allylation and alkylation in a single reaction vessel followed by deprotection of the *N*-Boc group and trichloroacetylation at the NH group release. The proportions of these products depended on the nature of the alkene substituents. Thus, the tetrahydropyridazin-3-ones and 1,2-diazepan-3-ones were formed in 2:1 ratio in the case of terminally unsubstituted radical acceptor alkenes. Terminally mono or disubstituted alkene radical acceptors furnished tetrahydropyridazin-3-ones exclusively. Probably the less favourable 7-*endo* cyclization was suppressed further due to steric hindrance by the alkene substituent(s). The chlorinated products are synthetically and medicinally relevant molecules. This work demonstrates the synthesis of heterocycles having two ring forming hetero atoms by Cu(I)-catalyzed ATRC for the first time.

Benzoxazolone is a privileged scaffold in medicinal chemistry. It is present in many clinical pharmaceuticals and drug candidates. Chapter 4 describes a single pot synthesis of 3-alkylbenzoxaozlones from *N*-alkyl-*N*-arylhydroxylamines through *O*-trichloroacetylation, trichloroacetoxy *ortho*-shift and cyclization sequence, all taking place in the same reaction vessel. The reported synthesis of benzoxazolones generally relied on cyclocarbonylation of *o*-aminophenols by phosgene, urea or other carbonyl group donors or carbon monoxide itself. The present synthesis uses more easily accessible and air-stable nitroarenes to start with. Nitroarenes were converted to the *N*-alkyl-*N*-arylhydroxylamines in two steps by known methods. Treatment of benzene ring unsubstituted or *p*-substituted *N*-alkyl-*N*-arylhydroxylamines with trichloroacetyl chloride and triethylamine at room temperature (23-25 ˚C) in diethyl ether or DCM (Method A) provided 3-alkylbenzoxazolones in 61-90% isolated yields. In the cases of the hydroxylamines having an active *N*-benzylic hydrogen atom, a competing base-promoted β-elimination of Cl_3CCO_2H in the *O*-trichloroacetylated hydrazines also occurred to produce variable amounts of benzylideneanilines. The problem was circumvented by performing the reaction in two stages in the same reaction vessel. First, the trichloroacetylation was performed in the absence of Et_3N at room temperature (23−25 °C) for a few hours and then treated with Et_3N (Method B). The reaction occurred smoothly to provide the products without β-elimination to imines.

In the case of *m*-substituted *N*-arylhydroxylamines, the trichloroacetoxy group showed a tendency to migrate to the less hindered *ortho* position away from the *m*-substituent selectively, leading to the formation of a mixture of regioisomeric 5- and 7-substituted benzoxazolones or 5-substituted benzoxazolones exclusively, depending on the nature of the *m*-substituent. *o*-Substituted *N*-arylhydroxylamines afforded the normal 4-substituted benzoxazolones as the major products by acyloxy shift to the unoccupied *ortho* position. Other minor products, the nature of which depended on the nature of the *o*-substituent were also formed. The polysubstituted 3-alkylbenzoxazolones have also been prepared from the corresponding *N*-benzyl-*N*-arylhydroxylamines by Method B.

A mechanism involving the cyclohexadienone imine has been proposed for the formation of all the products.

Benzoylation of alcohols is a fundamental reaction in organic synthesis. Benzoylation of phenolic alcohols and amino alcohols with conventional benzoylating reagents, which is generally performed in the presence of excess inorganic or organic base, occurs at the more nucleophilic phenolate oxygen or at the amine nitrogen selectively. However, the inverse selectivity, that is, selective benzoylation of the alcoholic group in the presence of a phenolic or amino group is difficult to realize.

Chapter 5 deals with that this type of inverse selectivity wherein trichloromethyl phenyl ketone is used as the benzoylating reagent. Selective benzoylation is demonstrated by both competition experiments and by taking bifunctional molecules having two different groups. Primary and secondary alcoholic groups are selectively benzoylated over phenolic or aromatic amino group on treatment with trichloromethyl phenyl ketone in the presence of 2-10 mol% of PMDETA as a catalyst at room temperature (20-25 ˚C) under mild and green conditions.

Competition experiments with 1:1 mixtures of a benzyl alcohol and the corresponding phenol with 1 equiv of trichloromethyl phenyl ketone in the presence of 5 mol% of PMDETA catalyst for 4-6 h showed that benzylic alcohols were exclusively benzoylated generally in excellent yields and the phenols were recovered unchanged. The competition experiment with a 1:1 mixture of a secondary alcohol cyclohexanol and phenol required a higher amount of the catalyst (10 mol%) to provide cyclohexyl benzoate selectively in 88% isolated yield and the recovered phenol (89%). Similarly, aralkyl benzoates were obtained exclusively in excellent yields by benzoylation of several phenolic alcohols with 1 equivalent of trichloromethyl phenyl ketone in the presence of 2 mol% of catalyst in acetonitrile (1 mL).

The reaction of a 1:1 mixture of benzyl alcohol and aniline with 1 equiv of trichloromethyl phenyl ketone in the presence of 2 mol% of PMDETA resulted in the formation of benzylbenzoate in 92% isolated yield along with the recovered aniline (72%). However, a small amount (14%) of benzanilide was also isolated as a result benzoylation of aniline. A small amount of dibenzoylated products (13-14%) along with the mono-*O*-benzoylated products (76-78%) were also formed in the benzoylation of hydroxymethyl anilines, where 1.2 equiv of the reagent was required to complete the reaction. Though the benzoylation of phenolic alcohols was almost chemospecific, the selectivity in the benzoylation of amino alcohols was less than excellent but still it may be considered appreciable in view of the difficulty level of the task and in the absence of a greener and better known method.

Additionally, the reaction of a 1:1 mixture of benzyl amine and aniline with 1 equiv of trichloromethyl phenyl ketone in the presence of 2 mol% of PMDETA resulted in the formation of *N*-benzylbenzamide as the only benzoylated product in 95% isolated yield along with the recovered aniline (89%), showing that selective benzoylation of alkylamino group over the arylamino group could also be realized.

Liquid mixtures or compounds could be benzoylated in the absence of a solvent. However, solid alcohols required a small amount of a solvent (acetonitrile) in order to facilitate mixing of the reactants. Under these conditions, the functional groups like carbon-carbon double and triple bonds, epoxide, TBDMS ether and aryl acetate ester were not disturbed.

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LIST OF ABBREVIATIONS

%	percent
°C	degree centigrade
w	weak
δ	chemical shift
4-ABOA	4-acetylbenzoxazolone
Ac	acetyl
ACE	angiotensin converting enzyme
ADAM	alkenyldiarylmethanes
AIBN	2, 2′-azobisisobutyronitrile
aq.	aqueous
Ar	aryl
atm	atmosphere
ATPH	aluminum tris(2,6-diphenylphenoxide)
ATRC	Atom Transfer Radical Cyclization
Bn	benzyl
BOA	benzoxazolone
bpy	2,2′-bipyridine
br	broad singlet (spectral)
Bu	*n*-butyl
BuLi	*n*-butyllithium
cat.	catalytic
Cbz	carboxybenzyl
CCR1	chemokine receptor 1
CDI	1-carbonyldiimidazole

CGRP	calcitonin gene related peptide
COMT	catechol-*O*-methyl transferase
conc.	concentrated
COX	Cyclooxygenase
d	doublet
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet- doublet
ddd	doublet-doublet-doublet
DDT	dichlorodiphenyltrichloroethane
DEPT	Distortionless Enhancement by Polarization Transfer
DIABOA	2,4-dihydroxy-5-acetyl-1,4-benzoxazin-3(4*H*)-one
DIAD	diisopropyl azodicarboxylate
DIBOA	2,4-dihydroxy-1,4-benzoxazin-3(4*H*)-one
dil	dilute
DIMBOA	dihydroxy-7-methoxy-1,4-benzoxazin-3(4*H*)-one
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess−Martin periodinane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dt	doublet-triplet

e.g	for example
equiv	equivalent(s)
Et	ethyl
FAAH	Fatty acid amide hydrolase
g	gram
h	hour
Hz	Hertz
IR	Infra-Red
J	coupling constant
Lit.	Literature
LPS	lipopolysaccharide
m	medium in IR; multiplet in NMR
m/z	mass/charge
M^+	molecular ion
MBOA	6-methoxybezoxazolone
Me	methyl
Me_6-tren	*N*,*N*,*N'*,*N'*,*N''*,*N''*-hexamethyltriethylenetetraamine
MIF	migration inhibitory factor
min	minutes
mmol	milli mol
mol	mole
mp	melting point
NEP	neutral endopeptidase
NHC	*N*-heterocyclic carbene
NMDA	*N*-methyl-D-aspartate

NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NNRTIs	non-nucleoside reverse transcriptase inhibitors
NPMIs	*N*-alkyl-2-pyridylmethanimines
n-Pr	*n*-propyl
NPSP	*N*-(phenylseleno)phthalimide
ORL1	opioid receptor-like1
p-ClPIFA	*p*-chlorophenyliodine(III) bis(trifluoroacetate
PDE-1	phosphodiesterase 1
Ph	phenyl
PMDETA	*N,N',N',N'',N''*-Pentamethyldiethylenetriamine
PPA	polyphosphoric acid
PPARα/γ	peroxisome proliferator-activated α/γ reaceptors
ppm	parts per million
q	quartet
s	strong in IR; singlet in NMR
t	triplet
TASF	tris-(diethylamino)sulfonium difluoromethylsilicate
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDMS	*tert*-butyldimethylsilyl
TBDMS	tert-butyldimethylsilyl
td	triplet-doublet
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMSCl	trimethylsilyl chloride
TPA	tris(2-pyridylmethyl)amine
TPP	triphenylphosphine
[mmim]I	1-methyl-3-methylimidazolium iodide

NOTES

1. All melting points reported in the thesis are uncorrected and were taken on an electrical melting point apparatus.
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 compounds was done by column chromatography on 60-120 mesh silica gel 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 $CDCl_3$ using a Bruker 300 MHz FT spectrometer with tetramethylsilane as internal standard.
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 micrOTOF-Q II, ESI-TOF/MS mass spectrometer at IIT, Delhi.

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