

**COPPER(I)-CATALYZED CHLORINE ATOM TRANSFER
RADICAL CYCLIZATION IN THE SYNTHESIS OF 2,4-
DISUBSTITUTED-3-CHLOROFURANS AND
TETRAHYDROFURANO-FUSED BICYCLIC β -LACTAMS AND
SUGARS**

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**DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, DELHI
JULY, 2010**

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TETRAHYDROFURANO-FUSED BICYCLIC β -LACTAMS AND
SUGARS**

**BY
NEERAJ KUMAR**

**Submitted
in fulfillment of the requirements of the degree of
DOCTOR OF PHILOSOPHY
to the**



**DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, DELHI
JULY, 2010**

Dedicated to my parents

Certificates

This is to certified that the thesis entitled “Copper(I)-catalyzed chlorine atom transfer radical cyclization in the synthesis of 2,4-disubstitued-3-chlorofurans and tetrahydrofurano-fused bicyclic β -lactams and sugars”, being submitted by Mr. Neeraj Kumar, 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 our by him. Mr. Neeraj Kumar 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.

I.I.T Delhi
July, 2010

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ACKNOWLEDGEMENTS

I wish to express my deep sense of gratitude to my research supervisor **Dr. 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. K. Singh and the ex-Heads of the Department of Chemistry, Prof. H. M Chawla, Late Prof. U. K Nadir and Prof. B Jayaram for providing the essential facilities for carrying out my research. I am also thankful to Dr. N.G. Ramesh for his useful suggestions.

I would like to express many thanks to my laboratory colleagues, Dr. Arif Ali Khan, Mr. Virinder Singh, Mr. Manoj. T. P., Ashish, Ram Kumar, Vineet, Dharmendra and Nisha 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, Anjul, Atul, Suneel, Purnendhu Paari, Prosenjit Chattopadhyaya, Nabhakrishna, Senthil, Sathyanarayana, Rahul, Mukesh, Shaliesh, Shalabh, Vijay Kathri, Sarbjot Sokhi, Vipin, Praveen, Parminder, Nagaraja, Arun, Arunava, Vivek, Amit, Nem Singh, Jahangeer, Gyaneshwar, Rajesh, 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.

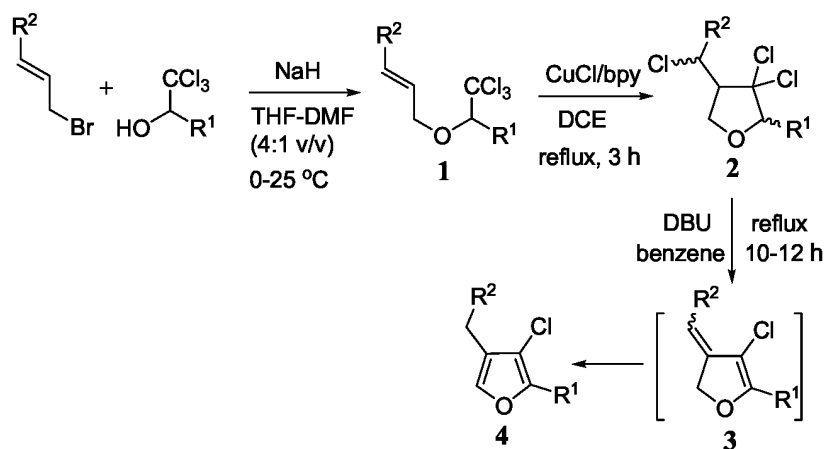
Lastly and most importantly, I take this opportunity to express my heartfelt affection, love and thanks to my parents and other family members.

Neeraj Kumar

ABSTRACT

The introductory chapter 1 of the thesis presents a brief account of transition metal-catalyzed halogen atom transfer radical cyclization (HATRC) of polyhalo compounds leading to the formation of various cyclic systems. It also describes the effect of ligands, *exo* vs. *endo* mode of cyclizations, use of reactive and less reactive polyhalo compounds in HATRC and application of HATRC in natural product synthesis, which are relevant to the new work presented in the succeeding chapters 2-4. The new work is primarily concerned with the application of CuCl-catalyzed HATRC in the presence of 2,2'-bipyridine (bpy), tetramethylethylenediamine (TMEDA) or pentamethyldiethylenetriamine (PMDETA) ligand to the synthesis of some new chlorine-containing compounds such as 2,4-disubstituted 3-chlorofurans, chlorinated bicyclic C-fused tetrahydrofuro[3,2-c]azetidin-2-ones and sugar-based chlorinated tetrahydrofuro[2,3-b]pyrans. It also describes application of 3-chlorofurans in the synthesis of highly substituted *m*-chlorophenolic biaryls by chlorine substituent promoted Diels-Alder reaction.

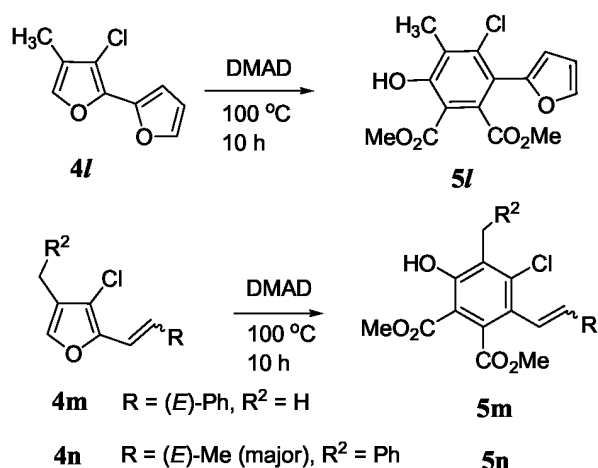
2,4-Disubstituted 3-chlorofurans were synthesized from readily available 2,2,2-trichloroethyl allyl ethers. The method involves CuCl/bpy-catalyzed regioselective HATRC of 2,2,2-trichloroethyl allyl ethers **1** (Scheme 1) as the key step. The allyl ethers were easily prepared by allylation of 2,2,2-trichloroethanols with allyl bromide in THF-DMF mixture (4:1 v/v) in the presence of NaH. The regioselectivity of the reaction was excellent in that only five membered ring was formed by 5-*exo-trig* radical cyclization to afford the tetrahydrofurnas **2** exclusively. Tandem double dehydrochlorination and isomerization of the tetrahydrfurans **2** with DBU in refluxing benzene furnished the desired 2,4-disubstituted 3-chlorofurans **4** in 42-77% overall yields.



Scheme 1

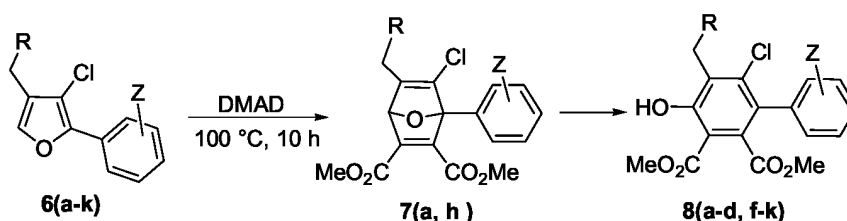
R ¹	R ²	R ¹	R ²	R ¹	R ²
a: <i>n</i> -Pr	H	g: 2-ClC ₆ H ₄	H	m: <i>E</i> -PhCH=CH	H
b: Ph	H	h: 4-ClC ₆ H ₄	H	n: MeCH=CH	Ph
c: 2-MeOC ₆ H ₄	H	i: 3-BrC ₆ H ₄	H	o: 3-MeC ₆ H ₄	Ph
d: 4-MeOC ₆ H ₄	H	j: 4-O ₂ NC ₆ H ₄	H	p: 3-MeC ₆ H ₄	<i>i</i> -Pr
e: 3,4-(MeO) ₂ C ₆ H ₃	H	k: 2-pyridyl	H		
f: 4-Me ₂ NC ₆ H ₄	H	l: 2-furyl	H		

The Diels-Alder reaction of the chlorofurans **4(l-n)** with dimethyl acetylenedicarboxylate (DMAD) was investigated. The results showed that the chlorofurano diene moiety participated exclusively in the Diels-Alder reaction in the presence of a non-chlorinated furano diene as in **4l** or in the presence of chlorinated exocyclic diene moieties as in **4m** and **4n** (Scheme 2). The structure of **5l** was confirmed by single crystal X-ray diffraction spectroscopy. These experiments provided experimental support by intramolecular competition to the theoretical predictions that a halogen substituent on the furan ring would facilitate its Diels-Alder reaction more than when it is present at an acyclic or a cyclic carbo-diene.



Scheme 2

The halogen effect in furan Diels-Alder reaction was exploited in the synthesis of a series of highly substituted *m*-chlorophenolic biaryls by Diels-Alder reaction with DMAD (**Scheme 3**).

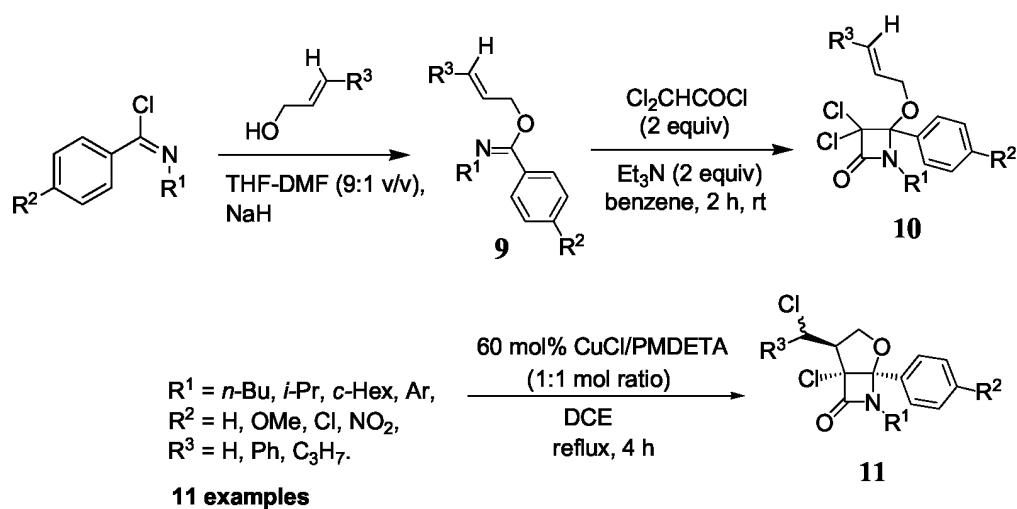


R, Z = a: H, H; **b:** H, 2-OMe; **c:** H, 4-OMe; **d:** H, 3,4-(OMe)₂; **e:** H, 4-N(Me)₂; **f:** H, 2-Cl;
g: H, 4-Cl; **h:** H, 3-Br; **i:** H, 4-NO₂; **j:** Ph, 3-Me; **k:** i-Pr, 3-Me

Scheme 3

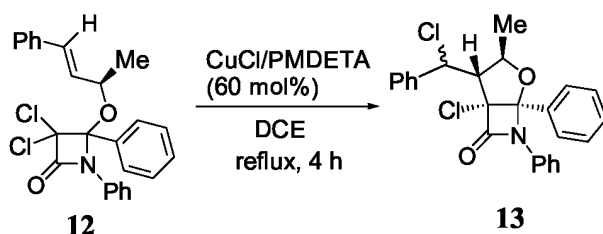
β -Lactams are important antibiotics, inhibitors of β -lactamases and other mammalian enzymes and synthetic intermediates. Therefore, they are important synthetic targets. Chapter 3 describes a new synthetic route to chlorinated C-fused tetrahydrofuro[3,2-c]azetidin-2-one using HATRC as the key step, as shown in **Scheme 4**. The allylic imidates **9** were prepared by reaction of easily accessible imidoyl chlorides with allylic alcohols in the presence of NaH in quantitative yields.

The allylic imidates **9** on Staudinger reaction with dichloroketene afforded the 3,3-dichloro- β -lactams **10** in good yields. After screening some ligands, such as bpy, TMEDA and PMDETA, the HATRC of **10** could be realized with 60 mol% each of CuCl and PMDETA in DCE at reflux under a N₂ atmosphere for 4 h in a highly regioselective and diastereoselective manner to furnish the bicyclic C-fused tetrahydrofuro- β -lactams **11** in high yields through 5-*exo-trig* HATRC.



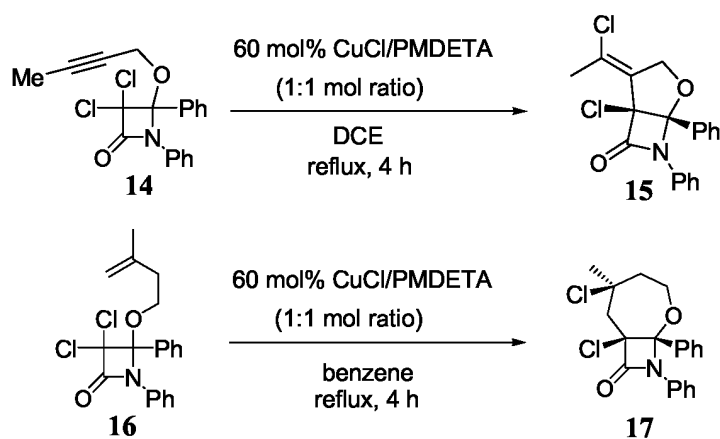
Scheme 4

The β -lactam **12** (Scheme 5) was successfully cyclized with CuCl/PMDETA (60 mol%, 1:1 mol equiv mixture) in DCE under reflux for 4 h by 5-*exo-trig* radical cyclization in a highly diastereoselective manner to afford the bicyclic β -lactams **13**, in good yield.



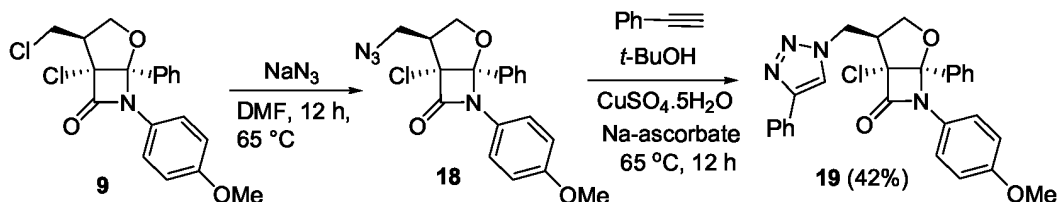
Scheme 5

In most of the cases, only one diastereomer was isolated. Single crystal X-ray diffraction of **9** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$) and **9** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{Ph}$) showed *cis*-ring fusion and *trans* relationship between the bridge-head chlorine atom and the adjacent side-chain on the tetrahydrofuran ring. The similarity of their NMR spectra with those of the other bicyclic β -lactams **11** indicated that probably all the bicyclic β -lactams **11** had similar stereostructures. Single crystal X-ray diffraction also revealed that the monocyclic β -lactam **12** was obtained as *RR* and *SS* enantiomeric mixture of a single diastereoisomer by highly diastereoselective Staudinger reaction which on HATRC furnished a 78:22 mixture of two not easily separable diastereomers **13**. However, the side chain in these diastereomers was arguably oriented *cis* to the bridge-head chlorine as suggested by considerably different values of the vicinal coupling constants (1.8-3.5 as against 10.8-7.5 Hz in **11**) between the tetrahydrofuran ring protons, probably due to difference in the puckering of the THF ring. The cyclization of the β -lactam **14** (Scheme 6) having an alkynic radical trap occurred exclusively by 5-*exo-dig* radical cyclization to afford the β -lactam **15** with an *E*-exocyclic double bond. The cyclization of **16** (Scheme 6) having a substituted homoallylic group as the radical trap was carried out in benzene under reflux. The bicyclic β -lactam **17** was isolated as a single diastereomer in 62% yield. The 7-*endo-trig* cyclization was probably favored due to steric hindrance for the 6-*exo-trig* cyclization. The stereostructures of the bicyclic β -lactams **15** and **17** were also supported by X-ray diffraction spectroscopy.



Scheme 6

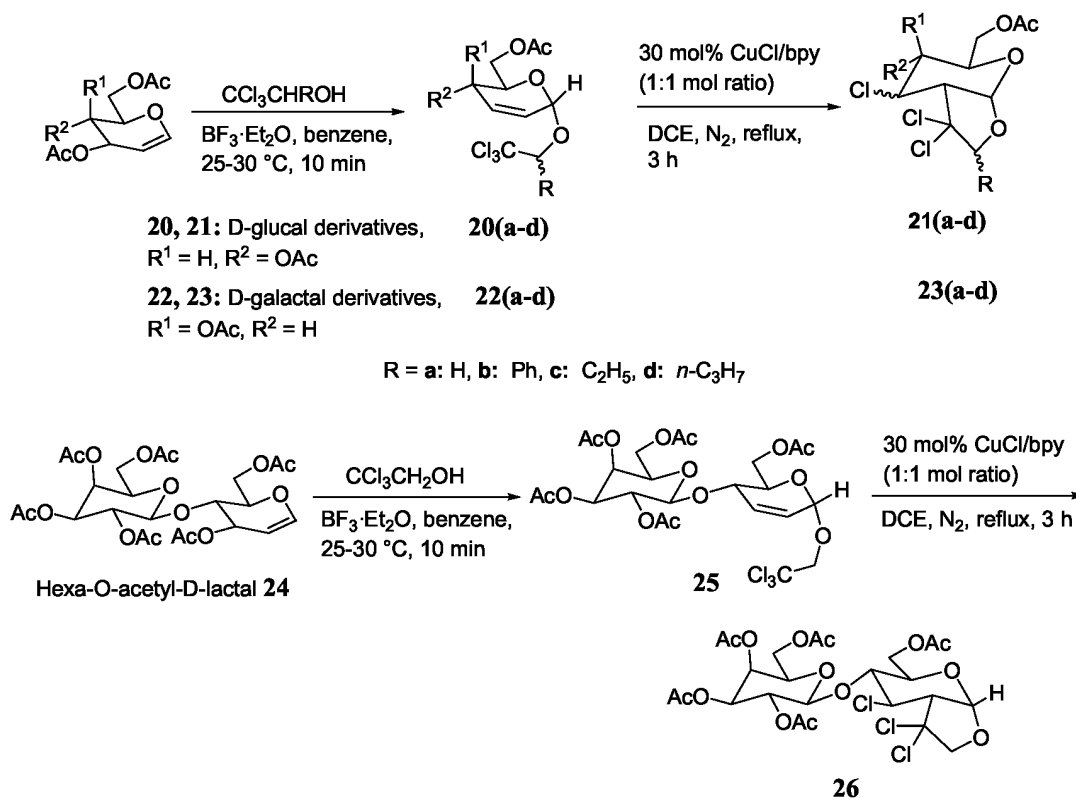
In order to demonstrate the application of the side-chain chlorine atom in further elaboration of the bicyclic β -lactams, the β -lactam **9** ($R^1 = 4\text{-MeOC}_6\text{H}_4$, $R^2 = R^3 = \text{H}$) was converted to the azide **18** (**Scheme 7**) by treatment with sodium azide which on copper(I)-catalyzed azide-alkyne click reaction with phenylacetylene furnished the triazolyl β -lactam **19** in 42% yield.



Scheme 7

Application of the CuCl/bpy-catalyzed HATRC to sugar-derived unsaturated trichloroethyl acetals offered a simple and convenient route for the preparation of sugar-based chlorinated fused bicyclic acetals, which is described in chapter 4. This type of fused bicyclic structure is frequently found in nature as a structural sub-unit of many biologically active natural products. They are also useful building blocks for the synthesis and modification of sugar templates. Thus, the trichloroethyl acetals **20(a-d)** (**Scheme 8**), **22(a-d)** and **25** were prepared by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed Ferrier reaction of

tri-*O*-acetyl-D-glucal **20**, tri-*O*-acetyl-D-galactal **22** and hexa-*O*-acetyl-D-lactal **24** with primary and secondary 2,2,2-trichloroethanols in benzene at 25-30 °C. After work up and purification of the crude residual mass by column chromatography, an epimeric mixture (in the case of reaction with secondary trichloroethanols) of α -anomer was isolated in acceptable yields. The reaction was generally highly diastereoselective, giving one epimer in major amounts. The Ferrier rearrangement furnished the α -anomers selectively with chiral recognition for the *S*-enantiomer of the racemic trichloroethanols in the case of tri-*O*-acetyl-D-glucal and for the *R*-enantiomer in the case of tri-*O*-acetyl-D-galactal. Copper(I)/bpy-catalyzed HATRC of the Ferrier products **20**, **22** and **25** (Scheme 8) using 30 mol% each of CuCl and bpy in DCE at reflux under a nitrogen atmosphere for 4 h furnished the perhydrofuro[2,3-*b*]pyrans **21**, **23** and **26** by 5-*exo-trig* HATRC in a highly diastereoselective manner.



Scheme 8

The stereo-structures of the products were determined by ^1H NMR spectroscopy. In the case of solid compounds **21a**, **21b**, **23c** and **23d** the stereochemistry was further supported by single crystal X-ray diffraction spectroscopy. The two rings were found to be *cis*-fused to each other and in most of the cases, the chlorine atom in the sugar ring was found to be placed at equatorial position in the six membered ring.

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