SYNTHESIS OF SOME CHLORINATED HETEROATOM RICH MONOCYCLIC, BICYCLIC AND TRICYCLIC β-LACTAMS AND β-LACTAM GLYCOCONJUGATES

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BY

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Dedicated to my parents

Certificates

This is to certify that the thesis entitled "**Synthesis of Some Chlorinated Heteroatom Rich Monocyclic, Bicyclic and Tricyclic β-Lactams and β-Lactam Glycoconjugates**", being submitted by **Ms. Nisha Dawra**, 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 her. Ms. Nisha Dawra 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.

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ABSTRACT

β-Lactams (azetidin-2-one) occupy an important place in chemistry and medicine. They are useful kits in the tool-box of synthetic organic chemists. More significantly, they constitute what are famously known as β-lactam antibiotics, the predominant therapeutic agents for the treatment of diseases caused by pathogenic microorganisms. Some molecules containing the β-lactam ring are β-lactamase inhibitors, the co-drugs that negate one of the important ways of resistance developed by bacteria towards the β-lactam antibiotics. Recently, β-lactams have been reported to inhibit several mammalian enzymes implicated in various non-microbial diseases. Therefore, synthesis of β-lactams has maintained a high level of interest. In the present scenario, when new resistant strains of bacteria are emerging with alarming rate, the synthesis of β-lactams has assumed more importance as never before, in order to ensure regular supply of new β-lactams for the development of more potent antibiotics not encountered by bacteria so far.

Incorporation of a chlorine substituent at the C-3 position of the β-lactam ring is expected to increase its chemical reactivity and potentiate its biological activity. A vast majority of bioactive molecules and clinical drugs are rich in heteroatoms. Therefore, the contribution of heteroatoms towards the bioactivity of a molecule is difficult to undermine. In view of this, the present thesis describes the synthesis of some chlorinated monocyclic, C-fused bicyclic and tricyclic β-lactams and β-lactam glycoconjugates rich in heteroatoms (N, O, S, Cl) in chapters 2-4 following an introductory chapter on some relevant aspects of β-lactams and halogen atom transfer radical cyclization. The present work uses Staudinger reaction for constructing the β-lactam ring. For the synthesis of fused bicyclic and tricyclic β-lactams, free radical cyclization strategy on to the preformed β-lactam motif was preferred over the ionic methods of annulation in view of the sensitivity of the β-lactam

ring to ionic reaction conditions. Of the radical methods, Cu(I)-catalyzed chlorine atom transfer radical cyclization (ATRC) was preferred over the tin hydride method, because amongst other benefits, it has proven to be a useful method for the preparation of chlorinated compounds.

In chapter 2, a methodology to access some heteroatom rich α,α-dichloro-β-N,β-S-disubstituted monocyclic β-lactams by Staudinger reaction of acyclic *S*-alkylisothioureas with dichloroketene has been described. The acyclic *S*-alkylisothioureas needed for the Staudinger reaction were synthesized by reaction of trisubstituted thioureas with alkyl bromides in refluxing acetone using potassium carbonate as a base in 88-98% yields. The trisubstituted thioureas required for the preparation of *S*-alkylisothioureas were synthesized in quantitative yields by reaction of alkyl/aryl isothiocyanates with secondary amines in ethanol at room temperature (25-30 ˚C). Staudinger reaction of the *S*-alkylisothioureas with dichloroketene generated *in situ* from dichloroacetyl chloride (1 equiv) and triethylamine (2 equiv) in DCM at 0 ˚C under a nitrogen atmosphere for 5 minutes provided the desired α,α-dichloro-β-N,β-S-disubstituted monocyclic β-lactams in 52-69% yields. The synthesis is fairly general. The reaction conditions are mild and the starting materials used are inexpensive and easily accessible. The work up and purification procedures are very simple, not requiring chromatographic methods. These monocyclic β-lactams being rich in heteroatoms like N, O, S and Cl have the ability to interact with biological targets in multiple ways, so they may serve as interesting targets for biological studies.

Chapter 3 presents the synthesis of heteroatom rich bicyclic C-fused azidotetrahydrofurano-β-lactams and their glycoconjugation by Cu(I)-catalyzed azide-alkyne click reaction with propargyl glycosides to access several heteroatom rich triazolyl β-lactam glycoconjugates. The azido β-lactams needed for the click reaction were prepared by nucleophilic substitution of side chain chlorine atoms of the chlorinated

tetrahydrofurano fused bicyclic β-lactams by azido group. The chlorinated bicyclic tetrahydrofurano-β-lactams, themselves were prepared by Cu(I)-catalyzed ATRC as reported by this laboratory. The propargyl glycosides were synthesized diastereoselectively from D-sugars (D-glucose, D-galactose and D-mannose) by glycosylation of sugars with propargyl alcohol through known procedures. The Cu(I)-catalyzed azide-alkyne click reaction of the bicyclic azidotetrahydrofurano-β-lactams and propargyl glycosides using 0.5 equiv each of CuCl and PMDETA in DCE at room temperature (25-30 ˚C) under a nitrogen atmosphere provided the desired β-lactam glycoconjugates in 65-92% yields. The method used readily accessible inexpensive starting materials and is quite general for the synthesis of a variety of heteroatom rich β-lactam glycoconjugates. The triazolyl β-lactam glycoconjugates synthesized in the present work represent a rare and interesting assembly of a β-lactam ring, a tetrahydrofuran ring, a sugar moiety and a triazole ring. Therefore, they are good candidates for their further study and biological evaluation.

Chapter 4 describes the application of Cu(I)/PMDETA-catalyzed ATRC in the synthesis of chlorinated, heteroatom rich and differently fused tricyclic β-lactams starting from 1-substituted-3,4-dihydropyrimidine-2(1H)-thiones. The dihydropyrimidinethiones needed for the synthesis were prepared by the three component Biginelli reaction using substituted thioureas, aromatic aldehydes and 1,3-dicarbonyl compounds. The allylation/alkylation of Biginelli adducts provided 2-alkyl/allylthio-1,4-dihydropyrimidines in excellent yields. These molecules contained a cyclic thiourea moiety which was exploited in Staudinger β-lactam synthesis. Staudinger reaction of these 2-alkyl/allylthio-1,4-dihydropyrimidines with *in situ* generated dichloroketene in DCM at 0 ˚C provided the bicyclic dichloro-β-lactams as a single diastereomer. The bicyclic dichloro-β-lactams bearing *S*-allyl group were successfully cyclized by ATRC method using CuCl/PMDETA (1:1 mol ratio, 60 mol%) as the catalyst in DCE at room temperature (25-

30 ˚C) under a nitrogen atmosphere to provide tricyclic β-lactams in 69-91% yields as a single diastereomer. The bicyclic dichloro-β-lactams bearing *N*-allyl group on ATRC under similar reaction conditions using CuCl/PMDETA (1:1 mol ratio, 20 mol%) provided another series of chlorinated, differently fused and heteroatom rich tricyclic β-lactams as mixtures of two diastereomers in 64-86% combined yields. Intramolecular competition between the *N*-allyl group and the *S*-allyl group for the cyclization revealed that the *S*-allyl group was more reactive than the *N*-allyl group, contrary to what appeared otherwise, probably due to lower strain involved in the cyclization through the *S*-allyl group. The methodology used Cu(I)-catalyzed ATRC for the synthesis of tricyclic β-lactam for the first time. It also demonstrated the application of Cu(I)-catalyzed ATRC to sulphur compounds for constructing tetrahydrothiophene ring for the first time. The method used easily accessible and inexpensive starting materials and is quite general for the synthesis of a variety of tricyclic β-lactams. The tricyclic β-lactams thus synthesized have interesting structural features, so they may elicit the attention of computational and medicinal chemists for their further studies.

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