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Studies on Substituted Beta Lactams Towards Ring Opening: Elimination Versus Rearrangement

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Abstract

Beta lactams and products obtained from them through rearrangement reactions are extremely useful compounds of diverse interests. During the course of study of vinyl beta lactams and rearrangement of beta lactams, it has been observed that elimination reaction becomes much faster than rearrangement when substituted bromo beta lactam alcohol is exposed under nucleophilic reaction conditions.

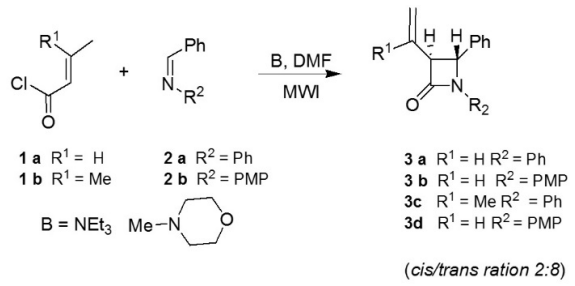
Keywords: Bromo alcohol; Beta lactam; Base-induced reaction; Elimination; Rearrangement

Introduction

Because of their medicinal activity and remarkable use as important molecules, synthesis and pharmacological investigations of beta-lactams have been performed for the past many decades [1-7]. A variety of work has been pursued by scientists to demonstrate the immense interest in beta lactam research [8-16]. Specifically, beta lactams are widely used as starting materials for the synthesis of numerous heterocyclic compounds. During the course of study of synthesizing pyrrolidines, an interesting observation regarding the base-induced pathways on substituted beta lactam is occurred to us [17]. This study describes an elimination reaction of substituted bromo beta lactam alcohol or bromo beta lactam acetate via a sodium ethoxide-induced reaction [18].

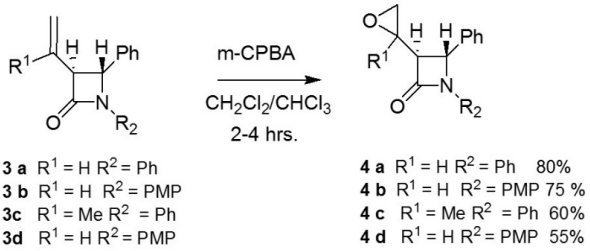
Results and Discussion

Synthesis of vinyl beta lactams was achieved successfully [18,19]. The stereochemistry of vinyl beta lactam formation was unpredictable. The olefinic groups in beta lactams was then manipulated to many other chemical transformations: oxidation, reduction and rearrangement [17]. For example, acid chloride 1 on reaction with imine 2 in the presence of a tertiary base afforded a mixture of cis and trans beta lactam 3. This reaction was accelerated by microwave-induced reactions (Scheme 1). Triethylamine or N-methylmorpholine was used as the base. A number of 1,2,3-trisubstituted beta lactams were prepared by this method.



Scheme 1: Synthesis of α Vinyl β-lactam via [4+2] Staudinger Ketene-Imine cycloaddition reaction.

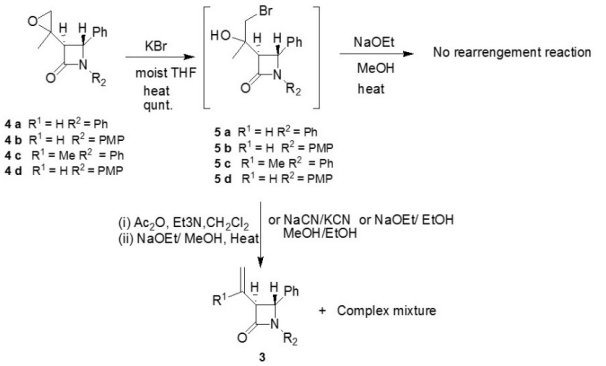
The alkene group in 3 was then oxidized to epoxide 4 by m-chloroperbenzoic acid in excellent yield (Scheme 2). Treatment of 4 with aqueous potassium bromide produced the bromo alcohol 5.



Scheme 2: Epoxidation of α-Vinyl β-lactam with meta-choloroperoxybenzoic acid.

An analogue of 4 without the hydroxyl group was converted to pyrrolidine derivative by treatment with sodium ethoxide or potassium cyanide in methanol/ethanol [17]. This was possible because of a nucleophilc reaction to the carbonyl group of the beta lactam ring and subsequent rearrangement reaction.

However, a similar reaction of the bromo alcohol derivative 5 did not produce hydroxy-susbtituted pyrrolidine compound. Instead the product was the vinyl beta lactam 3. Similarly, the acetate on the same reagent treatment produced vinyl beta lactam 3 under a one-pot operation (Scheme 3).



Scheme 3: Ring opening of Epoxide with Neucleophile and base inducedring expansion study.

The hydroxyl or acetate group present in compound 5 acted as the leaving group due to base-induced E2 elimination reaction when the bromine was removed. Therefore, the nucleophile was unable to attack the beta lactam carbonyl in 5 and rearrangement was not occurred. The whole procedure was tested with four compounds, 5a-5d.

Conclusion

Although the idea was to prepare hydroxyl/aceate-substituted pyrrolidines through a simple method, however, it confirms other factors become much more predominant in this process. This study suggests that to prepare 1,2,3-trisubstituted pyrrolidines, beta lactam rearrangement is not a suitable method. Perhaps, it is necessary to use 1,2-disubstituted pyrrolidine for hydroxylation at the site-3 of the pyrrolidine ring by other methods for this purpose. Our laboratory has shown an access of 1,2-disubstituted pyrrolidine through molecular rearrangement reaction [17,20].

Acknowledgements

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