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SYNTHESIS OF HETEROCYCLES THROUGH BETA LACTAMS RING RUPTURE

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Abstract:

Many Beta lactams are widely used as medicines. The 4-membered ring present in the beta lactams is under strain and therefore, it can undergo cleavage reactions to diverse compounds. Chemical manipulation of the resulting products affords numerous molecules of interest. In this perspective, some examples developed at our laboratory are discussed.

Introduction:

Synthesis of beta lactams is one of most active areas of research because of the applications of many compounds belong to this class [1] Extreme precaution is taken for the preparation of these types of compounds because these 4-membered heterocyclic compounds undergo diverse chemical pathways because of the strain present in this system. Hydrolysis, hydrogenolysis, and rearrangement are very common reactions in beta lactam chemistry. However, products obtained from these reactions are crucial since they can be used for the preparation of racemic and optically active heterocycles.

Results and Discussions:

Method 1: Hydrolysis of the 1, 2-bond in beta lactams

Beta lactams are cyclic 4-membered amides and therefore, hydrolysis of the 1, 2 amide bond is highly possible. In fact, hydrolysis in beta lactam is more facile than other related amides. The presence of electron withdrawing groups at the nitrogen help to cleave the 1, 2 bond easily. The 1, 2-bond breakages in beta lactam with a hydroxy nucleophilic reagent produces an amino acid. This suggests that other nucleophilic agents also can break the 1, 2-bond in beta lactams. Depending upon the nature of the nucleophilic regent, products can be categorized. For example, if the nucleophilic reagent is methoxide ion, the product is an amino methyl ester. Surprisingly, if the nucleophilic agent is a cyanide ion, the product is not the amino ketocyanide. The product from this reaction is amino ester/amino acid depending upon the solvent used. Hydrolysis of the 1, 2-bond is also performed by

Lewis and Bronsted acids. In general, groups present at the nitrogen of the beta lactam ring controls the hydrolysis rate. Electron donating groups at the nitrogen retards hydrolysis while electron withdrawing groups accelerates hydrolysis. The presence of aromatic ring at the nitrogen of the beta lactam ring helps the hydrolysis slower compared to the presence of aliphatic and arylalkyl groups at the nitrogen. For example, N-benzyl and N-allyl beta lactams undergo faster hydrolysis than N-phenyl and 4-methoxyphenyl beta lactams. N-Phenyl beta lactam undergoes slower hydrolysis than 4-nitrophenyl beta lactam under identical conditions. Steric hindrance also plays a role in controlling the hydrolysis of the beta lactam ring. More sterically crowded beta lactam rings are slowly hydrolyzed than less sterically crowded beta lactam rings. These observations are unique regardless of the mechanism of the hydrolysis. The products (amino ester or amino acid) are suitable starting materials for the preparation of heterocycles using the functionalities that are present at the other positions of the resulting products. Most of the salts (NaCl, NaBr, KCl) are unable to hydrolyze the beta lactam rings. The hydrolysis seems to take place equally well regardless of the stereochemistry of the beta lactam ring.

A suitably oriented halogen substituted beta lactam can be rearranged to a pyrrolidine or piperidine heterocycles through 1, 2 bond cleavage of the beta lactam ring and subsequent rearrangement [2].

Sugar containing beta lactam form lactones upon hydrolysis provided the resulting acid/ester can participate with a free hydroxyl group in the same molecule [3a].

Method 2: Reduction of the 1, 2-bond in the beta lactam ring

Reduction of the 1, 2 bond in beta lactam with lithium aluminum hydride produces amino alcohol. This reduction is independent of the stereochemistry of the ring junction. Electronic distribution of the groups and the substituents present at the nitrogen of the ring system has some roles in this reduction. However, these are not as prominent as seen in the hydrolysis reaction. This is confirmed by the fact that the reduction is more drastic in nature. The amino alcohols are very important molecules as they can be used for the synthesis of amino acids and amino aldehydes. This method has applications for the enantiospecific synthesis of polyhydroxyamino acids and amino sugar [3a]. Interestingly, during reduction, no changes of relative or absolute stereochemistry of the products have noted.

Method 3: Hydrogenolysis of the 1, 4-bond in the beta lactam ring

The 1, 4-bond in C-4 aromatic substituted beta lactam ring is cleaved under reductive hydrogenation conditions. The 1, 4-bond in all monocyclic beta lactam rings that have an aromatic group at C-4 position can be ruptured by hydrogen gas in 10% Pd/C and catalytic transfer hydrogenation method. A number of reagents are used for this type of cleavage reactions. For example, ammonium formate, sodium formate, cyclohexene, and formic acid in the presence of Pd/C in ethanol at approximately 75^0C are good combination to break the N-C-4 bond in beta lactams. The ring rupture in beta lactam does not take place if there is an aliphatic group present at the C-4 position of the ring. However, if the aromatic group is not directly connected to the C-4 of the ring, but 2-carbons away (for example, styrene system), partial cleavage of the N-C-4 bond is observed [4].

Method 4: Cleavage of the 1, 2-bond in the beta lactam ring and subsequent rearrangement

If there is a 1, 2-bond cleavage by acid or base-induced process (protic acid and nitrogen containing bases), a suitably substituted group can attack the resulting amines or acids/esters. This process can be used for the preparation of heterocycles. The 1, 2 bond cleavage and subsequent rearrangement can also be facilitated through a co-ordination with metals or their salts to the carbonyl group of the beta lactam and thereby an increasing chance of a nucelophilic attack is feasible. Indium metal can coordinate with the carbonyl group of the beta lactam ring and a suitably substituted aromatic amino group can attack the 1, 2-bond of the ring. This process finally produces oxazines [5].

Conclusions:

Beta lactams rings are cleaved by different types of reactions and the generated products without isolation are converted to diverse heterocycles.

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