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BANIK'S CYCLOADDTION REACTION TOWARDS BETA LACTAMS: MECHANISTIC INSIGHTS

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Abstract:
Banik's cycloaddition describes the stereospecific synthesis of β-lactams starting from polyaromatic imines and acid chlorides in the presence of a tertiary base. The N-polyaromatic substituent has a crucial role that controls the synthesis of thermodynamically stable *trans*-*N*-azetidin-2-one. A probable mechanism of this process is advanced based upon the available literature.

Key words: Beta Lactams, ketenes, polyaromatic imines, cycloaddition, mechanisms

Introduction

The *β*-lactams have been used for the synthesis of biologically active other *β*-lactam and non *β*-lactam compounds [1]. There has been a need for new *β*-lactam antibiotics to fight microorganisms [2]. Therefore, many methods for the preparation of *β*-lactam have been developed [3]. The common method for the synthesis of the *β*-lactam ring is the cycloaddition known as the Staudinger reaction [4]. This method has proved to be attractive for the synthesis of *β*-lactams derived from amines of smaller ring sizes. However, cycloaddition reaction of imines derived from polyaromatic amines has not been investigated by any group except that of Banik's group. Banik has invented stereospecific cycloaddition of imines with acid chlorides for the synthesis of polyaromatic *β*-lactams. Some of Banik's *β*-lactams have demonstrated anticancer activity against diverse cancer cell lines *in vitro* and *in vivo*. Therefore, Banik's reaction has been considered as an active area of research [5, 6]. Asymmetric synthesis of *β*-lactams has been studied extensively investigated using [2+2] cycloaddition reaction [7]. Importantly, Banik has also investigated asymmetric cycloaddition reaction toward chiral *β*-lactams [8, 9]. The results obtained by Staudinger cycloaddition and Banik's cycloaddition are different. On this basis, a focus on the mechanism of these two important reactions is necessary.

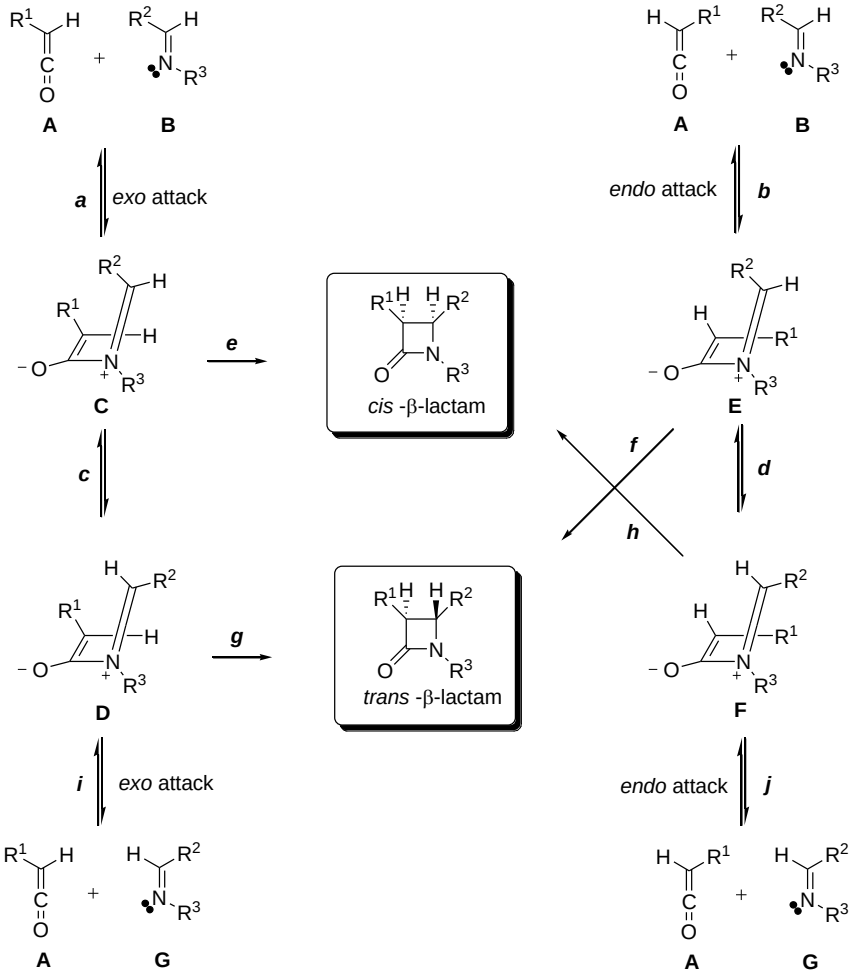
Results and Discussion:

The optically active *β*-lactams has been prepared using [2+2] cycloaddition reaction of chiral compounds (aldehydes, amines, and acid halides). An excellent stereospecificity was observed if the *β*-carbon of the chiral aldehyde has a hetero atom. Many chemists reported methods to prepare chiral *β*-lactams with predictable absolute configuration [10]. Deshmukh *et al.* [11] studied this subject and obtained *cis β*-lactams. The stereochemical fate was depended upon the group present on the Schiff bases. Imines with alkyl or electron-withdrawing groups produced *cis* or *cis* and *trans*-*β*-lactam mixtures.

Banik and his group have been investigating the synthesis of *trans*-*β*-lactams using ketenes and polyaromatic imines. His group synthesized *trans*-*β*-lactams such as 1-*N*-chryseneyl and 1-*N*-phenanthrenyl 3-acetoxy-4-aryl-2-azetidinones [12]. These compounds have demonstrated potent anticancer activity.

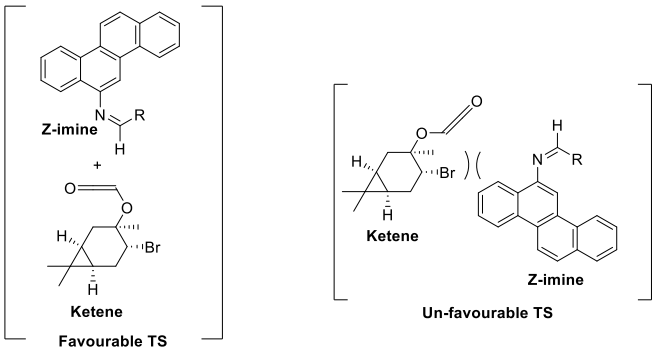
An attack of the imine to the top face of the ketene and a conrotatory ring cyclization produced an enantiomer. An attack of the Schiff base from the bottom face and a conrotatory ring cyclization produced another enantiomer. Since two chiral centers were formed, four isomeric forms of the products were possible (two *cis* and two *trans* isomers). Xu *et al.* advanced a study to identify the stereoselectivity on the kinetic pathway of the *cis*/*trans* ratio of *β*-lactams [13]. We demonstrated the effects of the bulkier electron withdrawing polyaromatic substituent on N(1) position of imine that results in *trans*-*β*-lactam. Notably, we reported the synthesis of a single *trans*-*β*-lactam starting from (+)-carene as the acid chloride component [12]. It seemed that the approach of the imine is orthogonal to the ketene. The stereochemical results depended on the geometry of the imine. The *Z*-imine on reaction with the ketene through an *exo*-pathway produced the *trans* compound. In contrast, the *E*-imine on reaction with the ketene through an *endo*-mode gave *cis* compound (**Scheme 1**).

Scheme 1



The two *trans-β*-lactams were formed by the isomerization of Transition state (TS) TS-F to an energetically favorable TS-D followed by a conrotatory ring formation process. The polyaromatic imines were more stable in *Z*-form since it has crowded electron withdrawing aromatic groups on N-1 position and phenyl groups on C-4 position. The Z imines on reaction from *exo* or *endo* side to the chiral ketene afforded *trans-β*-lactams. In reality, two *trans-β*-lactam diastereoisomers were expected. However, a single optically active *trans-β*-lactam was formed with carene. Similar cycloaddition with sugar ketenes produced two chiral *trans*-isomers [8, 9]. The probable mechanism was believed to occur through an *exo*-mode attack of Z-imine with ketene. The addition was occurred through an *exo* route from the opposite of side of the bromine on the ketene and this resulted in thermodynamically more stable *trans-β*-lactam. The diastereoisomer of *trans-β*-lactam was not formed. The ketene and imine failed to react through an *endo* mode because of steric hindrance (from the parallel side of bromine group) with bromine group (**Scheme 2**). The observed stereoselectivity in Banik's cycloaddtion remained consistent when the methods were performed under microwave irradiation [14]. In contrast, the stereochemistry of *β*-lactam formation reaction remained unprecedented when the reactions were performed following regular and microwave method. The involvement of ketene was confirmed rather than an acylated intermediate of the imine. An IR spectra of the solution of the acid chloride and triethyl amine gave a peak around 2200 cm.$^{-}$ This peak was due to a ketene group.

Scheme 2



Conclusions: In summary, the mechanism described above can explain the stereochemical distribution of the *trans-β*-lactams formation that are observed during Banik's cycloaddition reaction. Nevertheless, the mechanism of *β*-lactam formation with polyaromatic imines may require additional investigations.

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