Heterocyclic Letters
Vol. 11| No.3|323-327|May-July|2021
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

BANIK'S CYCLOADDITION REACTION: ANTICANCER β-LACTAMS

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#Dedicated to the Dr. R. R. Gupta on the Occasion on his 80th Birthday

Abstract:
Bimal Krishna Banik has discovered a new reaction (Banik's Cycloaddition Reaction) of polyaromatic Schiff base with an acid chloride in the presence of an organic tertiary base to afford novel beta-lactams. This cycloaddition reaction is highly diastereoselective. The most probable mechanism of this reaction is advanced. Some of the resulting beta-lactams have demonstrated selective anticancer activities against several human cancer cell lines.

Definition:
Banik's cycloaddition reaction involves the reaction of polyaromatic imines and ketenes in triethylamine as base through a non-photochemical 2+2 cycloaddition and produces *trans*-β-lactams as the sole products[1–5].

New Discoveries in this Method:
Polyaromatic imines as the substrates; Unprecedented stereoselectivity; Electron withdrawing effects of the N-aryl groups in the intermediates; Selective anticancer activity of the beta-lactams.

Chemicals Required:
Polyaromatic Imine, Acid Chloride, and Tertiary Base

Solvents:
Dichloromethane/Dichloroethane/Chlorobenzene/DMF

Temperature:
Ice-Cold, 25^0C, or 100^0C

Time of the Reaction:
5 min to 20 h

Stereochemistry of the β--Lactam:
Trans at C-3 and C-4 Stereocenters

Mechanism of the Reaction:

The mechanism of Banik's cycloaddition reaction is postulated. The orientation of the polyaromatic imine concerning the plane of the ketene is crucial in determining the stereochemistry of the products. An attack of the polyaromatic imine over the top portion of the ketene and a conrotatory cyclization forms one trans isomer. On the other hand, an attack of the polyaromatic imine from the bottom side and a conrotatory ring closure forms the other trans-isomer**.** The bulkier electron-withdrawing polyaromatic group on N of imine results in the formation of thermodynamically stable trans-β-lactam. Therefore, no cis-compound is formed [6,7]. Optically active imines produce two trans beta-lactams in excellent yield.

Use of the Products:

Some of the beta-lactams prepared by Banik's reaction have demonstrated selective anticancer activities against breast, blood, skin, ovary, pancreas, prostate, and colon cancer cells [1-4].

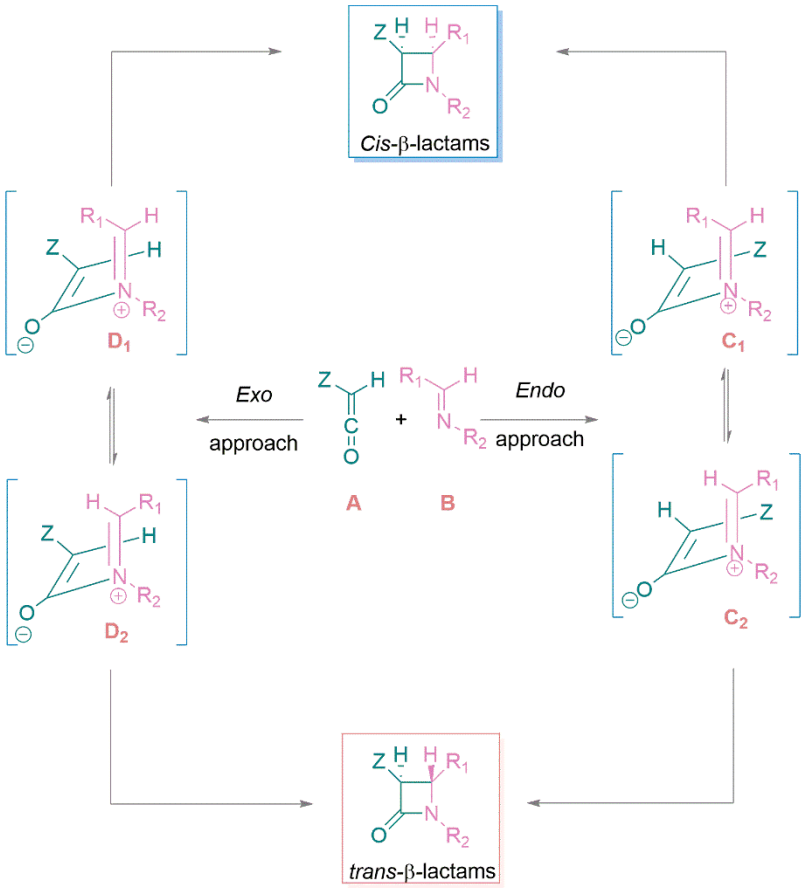


FIG. 1 Plausible reaction mechanism of β-lactam formation

Significance:

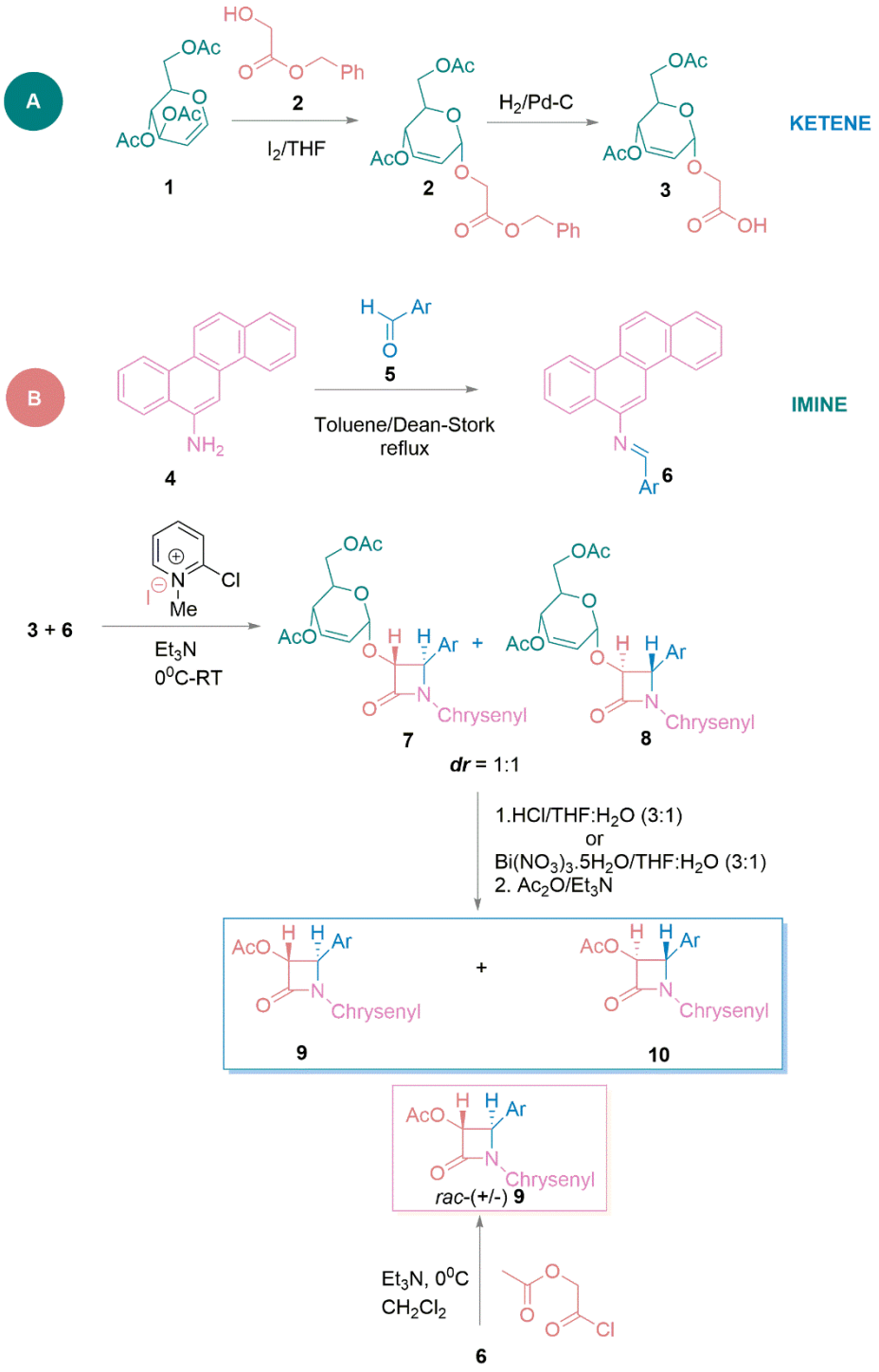
Because of the medicinal activity synthesis and biological studies of beta-lactams has been widely investigated for more than 100 years. A total synthesis led to the remarkable preparation of penicillin in 1940's. Since the discovery of penicillin, other members of β-lactam antibiotics had been possible. Their extensive use had continued to be a major action against infectious pathogens. Beta-lactams were used in other applications to human. For examples, these were used as inhibitors of serine protease and acyl coenzyme A cholesterol transferases. Many beta-lactams were used as starting compounds for the synthesis of numerous heterocycles. Hydroxy beta-lactam derivatives were used in the synthesis of Taxol and Taxotere. Studies of human leukocyte elastase inhibitory mechanisms of β -lactams were investigated.

Description of the Current Method:

Banik's reaction discovers a reaction between polyaromatic imines **6** and acid **3/** acetoxy acetyl chloride in the presence of Mukiyama reagent or triethylamine/N-methylmorpholine in dichloromethane/dichloroethane at various temperatures. The products are trans beta-lactams **7**, **8** and **9.** Acid **3** is a ketene equivalent in this reaction in the presence of an activator and a base. Different types of acid chlorides are used for this reaction. For example, acetoxy acetyl chloride, phenoxy acetyl chloride, methoxy acetyl chloride, phthalimido acetyl chloride and benzyloxy acetyl chloride are used. Similarly, imines are obtained from diverse aldehydes and polyaromatic amines. Benzaldehyde, susbstituted benzaldehydes, polyaromatic aldehydes and heterocyclic aldehydes are the choice. 6-Aminochrysene, 9-aminophenanthrene, 1-aminoanthracene and 2-aminonaphthalene are used with success.

The imine **6** is prepared by refluxing an equimolar solution of aldehyde and amines in toluene using a Dean-Stark water separator. After evaporation of toluene, imines are used for the next reaction. To the solution of imine in dichloromethane or dichloroethane and triethylamine, acid chloride is added at ice-cold temperature. After being stirred for overnight, the reaction is extracted and the trans beta lactam is obtained in 70-80% yield.

SCHEME 1 Banik's Cycloaddition reaction in synthesis of *trans*-β-lactams



This reaction is also performed in a domestic and automated microwave oven using chlorobenzene and DMF as the solvent. The desired beta lactam is obtained in good yield.

Other Methods:

A number of important strategies are available for the synthesis of the 2-azetidinone core ring

present in all *β*-lactams (Staudinger cycloaddition reaction, ester enolate-imine condensation, hydroxamate approach, alkene-isocyanate method and the alkyne-nitrone reaction) [8–11].

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Received on March 14, 2021.