HL
http://heteroletters.org
ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)
Vol. 1, special issue, July (2011), 31-34

UNPRECEDENTED STEREOSELECTIVITY OF β-LACTAM FORMATION VIA STAUDINGER REACTION WITH CONJUGATED IMINES DERIVED FROM POLYAROMATIC SYSTEMS

Robert Rodriguez and Bimal K. Banik*

Department of Chemistry, The University of Texas Pan American, 1250 West University Drive, Edinburg, Texas 7854, USA ; E-mail: banik@utpa.edu

Abstract: Synthesis of a few 3, 4-disubstitued β-lactams derived from polycyclic aromatic conjugated imines has been achieved following Staudinger reaction under classical conditions and Microwave-induced reaction. Unprecedented formation of *trans* β-lactams has been observed under microwave-induced reaction conditions and high temperature.

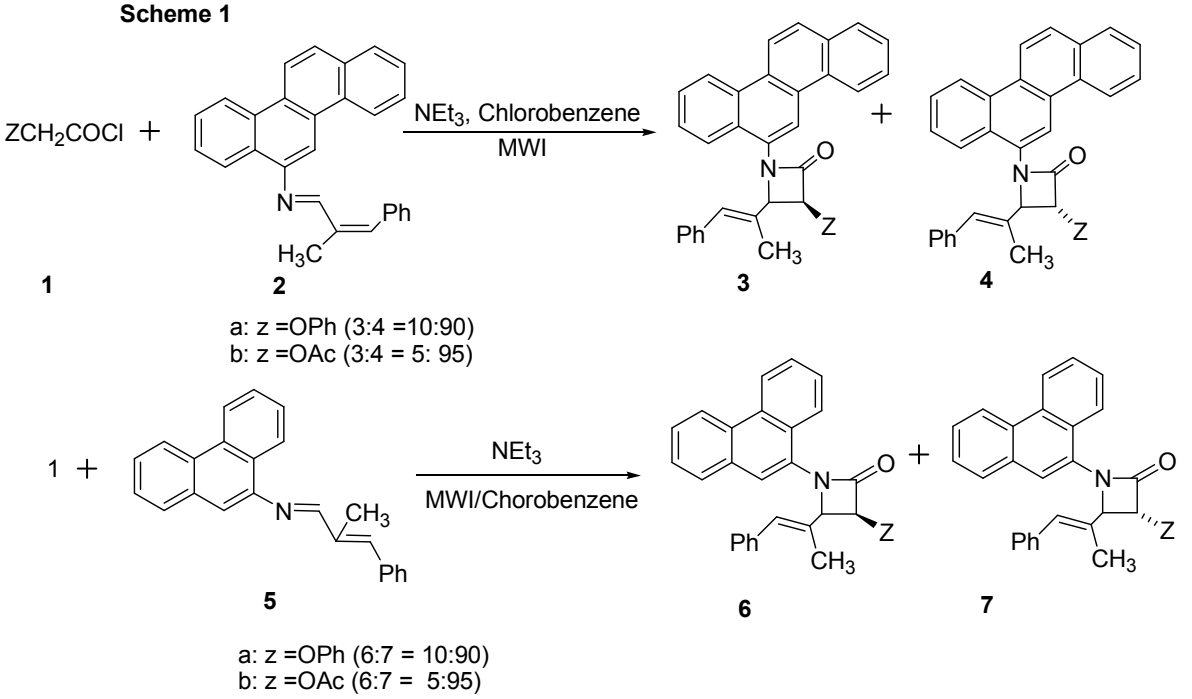
Keywords: β-lactams, Cycloaddition chemistry, Microwave irradiation method

Introduction: The impact of β-lactams has been very significant because of their medicinal applications.[1] For this reason, the research on useful β-lactams is one of the most attractive areas.[2] Our research has culminated in the synthesis of β-lactams[3,4,5] as anticancer agents.[6,7,8] Following our own method, we describe stereoselective synthesis of a few *trans* 3, 4-disubstituted β-lactams using polycyclic conjugated imines by cycloaddition chemistry.

Results and Discussion: The cycloaddition reaction has been extensively investigated for the preparation of β-lactams. It is established that the stereochemistry of β-lactams depends on the substituents present in the imine and acid chloride and the conditions of the reactions.[9] For example, the reaction of acyloxy, alkoxy, and nitrogen-containing acid chloride with diaryl imine produces *cis*-β-lactams. However, the reaction of polyaromatic imines[6,7,8] with acid chloride produces *trans*-β-lactams. Importantly imines derived from conjugate carbonyl compounds always produce *cis*-β-lactams as the only products. Some of the *trans* acetoxy β-lactams have demonstrated anticancer activity *in vitro*.[6,7,8] Therefore, further synthetic and biological studies of these types of compounds are necessary.

Reaction of diarylimine **2** with acid chloride **1** was performed at 0°C-room temperature and a single β-lactam **3** was obtained in 70% yield.[10] But, microwave-induced method produced a mixture of two β-lactams **3** and **4** in a ratio of 1:9 (70% yield).[11,12,13,14] High temperature reaction also produced an identical mixture of products **3** and **4** in comparable yield (**Scheme 1**).

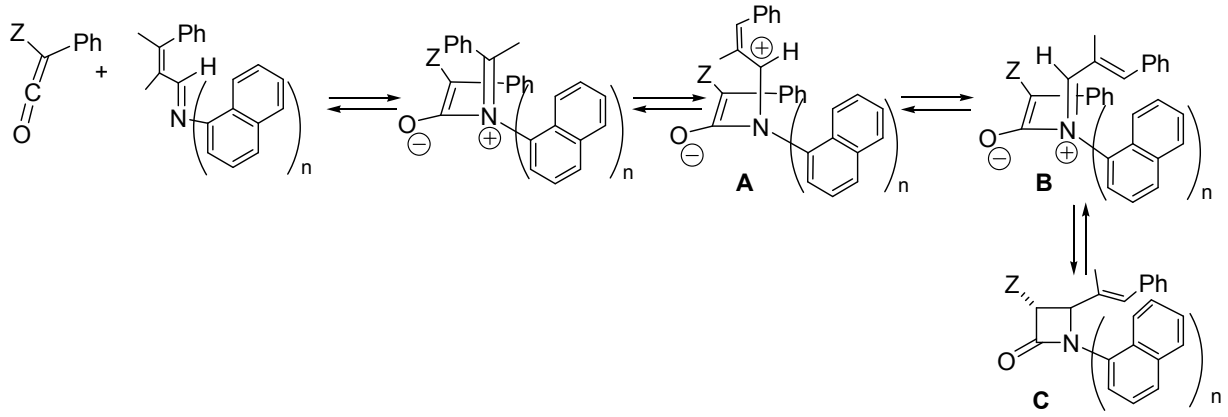
Scheme 1



When irradiated in a microwave oven using chlorobenzene and triethylamine, *cis* β-lactam **3** and **6** did not isomerize to *trans* β-lactams **4** and **7**. Isomerization could not be detected when *cis* β-lactams were heated at thigh temperature (80℃) using chlorobnezene at triethylamine. These experiments confirmed that there was no isomerization of the *cis* β-lactams during reaction at a high temperature and / or under microwave irradiation.

The results observed in this present study are new and support our hypothesis.[6,7,8] It has been demonstrated that cycloaddition of the imine occurs from the least hindered side of the ketene and generates zwitterionic intermediates. Conrotatory cyclization of these intermediates is responsible for the formation of β-lactams (**Scheme 2**).

Scheme 2



The formation of compounds *trans* compounds can be explained through an isomerization of the enolate (**Scheme 2**, **A** to **B**).[6,7,8,15] The electron-withdrawing polyaromatic group at the nitrogen stabilizes the iminium ion. This stabilization allows a rotation of the bond (**A** to **B**) and an intermediate **C** can be formed. The significant electron withdrawing effects of the polyaromatic system at nitrogen is the predomination force at high temperature and under microwave-induced conditions. This results in the formation of a *trans* β-lactam even with conjugated imines derived from polyaromatic systems. The classical condition using imine follows the usual cycloaddition route as reported in the literature and this gives *cis*-type of compounds. In this case, stabilization of the iminium by the conjugated system present in imine appears to be more significant and this results in *cis* β-lactam formation. Microwave radiation and high temperature proves to be responsible to alter the structure of the intermediate presumably through a rotation of the bond and these results in the formation of *trans* β-lactams with conjugate polyaromatic systems.[16-19]

Structurally, these β-lactams are similar to our anticancer compounds.[6,7,8] The presence of the conjugated system in these β-lactams can be used to prepare a variety of other compounds through oxidative cleavage. An availability of these compounds may therefore, prove to be useful for our structure-activity study.[6,20]

Conclusion: The unprecedented stereochemical results along with the mechanism of the Staudinger reaction with polyaromatic conjugated imines will offer additional opportunities to use β-lactams in the synthesis of new compounds having anticancer properties.

Acknowledgment: We gratefully acknowledge the financial support for this research project from National Institutes of Health-SCORE (2SO6GM008038-37) and NCI-P20.

References:

(1) A. K. Bose, M. S. Manhas, B. K. Banik and V. Srirajan, *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Material Science* in A.Greenberg, C. M. Breneman, J. F. Liebman (Eds); Wiley-Interscience, New York, p. 157-214 (2000)
(2) M. Suffness, *Taxol Science and Applications*, CRC Press, Boca Raton, FL (1995)
(3) S. K. Dasgupta and B. K. Banik, *Tetrahedron Lett*, **43**, 9445 (2002)
(4) B. K. Banik, S. Samajdar and I. Banik, *Tetrahedron Lett.*, **44**, 1699 (2003)
(5) B. K. Banik, I. Banik and L. Hackfeld, L *Heterocycles*, **59**, 505 (2003)
(6) I. Banik, F. F. Becker and B. K. Banik, B. K., *J. Med. Chem.,* **46**, 12 (2003)
(7) B. K. Banik, F. F. Becker and I. Banik, *Bioorg. Med. Chem,* **12**, 2523 (2004)
(8) B. K. Banik, I. Banik, I. And F. F. Becker, *Bioorg. Med. Chem.,* **13**, 3611 (2004)
(9) G. I. Georg and V. T. Ravikumar, *The Organic Chemistry of β-Lactams* in G. I. Georg (Ed.),VCH publishers, New York (1992)
(10) A. K. Bose, B. Lal, B. Dayal and M. S. Manhas, *Tetrahedron Lett.,* **30**, 2633 (1974)
(11) L. Perreux and A. Loupy, *Tetrahedron,* **57,** 9199 (2001)
(12) P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron,* **57**, 9225 (2001)
(13) A. K. Bose, M. S. Manhas, S. N. Ganguly, A. H. Sharma and B. K. Banik, *Synthesis*, 1578 (2002)

(14) B. K. Banik, K. J. Barakat, D. R. Wagle, M. S. Manhas and A. K. Bose, *J. Org. Chem*., ***64***, 5746-5753 (1999)
(15) B. K. Banik, B. Lecea, A. Arrieta, A. Cozar and F. P. Cossio, *Angew. Chem.,* **46,** 3028 (2007)
(16) B. Alcaide and A. Vicente-Rodriguez, *Tetrahedron Lett., **40***, 2005 (1999)
(17) A. Afonso, S. B. Rosenblum, M. S. Puar and A. T. McPhail, *Tetrahedron Lett., **39***, 7431(1998)
(18) M. Endo and R. Droghini, *Bioorg. & Med. Chem. Lett.*, ***3***, 2483 (1993)
(19) A. K. Bose, B. K. Banik, B. K and M. S. Manhas, *Tetrahedron Lett*., ***36***, 213 (1995)
(20) A representative experiment procedure is given below. A solution consisting of acid chloride (1.5 mmol) in chlorobenzene (2 mL) was added to imine (1 mmol) and triethylamine (3 mmol). The reaction mixture was then heated at 80℃ for 1h, washed with saturated sodium bicarbonate solution (10 mL), dilute hydrochloric acid (10%, 10 mL), brine (10 mL), dried with anhydrous sodium sulfate and evaporated to obtain the crude product. Proton NMR was performed to calculate the ratio of the isomeric β-lactams. The pure *trans* product was then obtained via column chromatography over silica gel using ethyl acetate-hexanes (1:4) as the solvent. Microwave-Assisted Preparation of the *trans* β-Lactam: An identical amount of the imine, acid chloride, and triethylamine in chlorobenzene (2 mL) was placed in an Erlenmeyer flask (125 mL capacity). The flask was then capped with a glass funnel and placed in a microwave oven (G. E. Model, 1450 W). A 500 mL beaker containing 200 mL of water was placed in the oven next to the reaction flask to serve as a heat sink. The mixture was irradiated for 6 min at intervals of 1 minute each. After the usual work up and purification as described above, the *trans* β-lactam was isolated.