Microwave-Induced Stereocontrol of β-Lactam Formation with an *N*-Benzylidene-9,10-dihydrophenanthren-3-amine *via Staudinger* Cycloaddition

by **Debasish Bandyopadhyay** and **Bimal K. Banik***

Department of Chemistry, The University of Texas – Pan American, 1201 West University Drive, Edinburg, Texas 78539, USA (e-mail: banik@panam.edu)

The synthesis of 3-substituted 4-phenyl-1-(9,10-dihydrophenanthren-3-yl)azetidin-2-ones was achieved following *Staudinger* cycloaddition under microwave-induced conditions. The stereoselectivity of β-lactam formation depended on the power level of the microwave irradiation used in the experiments.

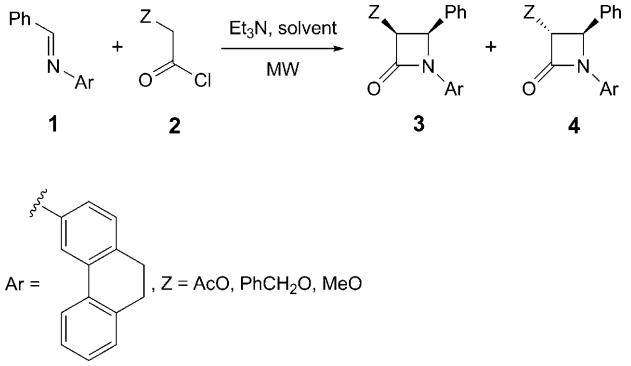
Introduction. – The significance of β-lactams in our practical life has been enormous and these azetidin-2-ones have many medicinal applications [1]. As a result, the searches for clinically useful β-lactams that are antibiotics and/or medically important will continue [2].

We have reported the first synthesis and biological evaluation of β-lactams [3] as anticancer agents [4]. We describe herein the stereocontrolled synthesis of a few novel 3-substituted 4-phenyl-1-(9,10-dihydrophenanthren-3-yl)azetidin-2-ones by means of a microwave-induced reaction. Syntheses of this type of β-lactams by cycloaddition chemistry or by any other method and their diasteroselectivity of formation have not been studied so far. Based on our current research on the anticancer β-lactams with polycyclic aromatic systems [4], we now explored the diastereoselectivity of their formation with different types of acid chloride and *N*-benzylidene-9,10-dihydrophenanthren-3-amine.

Results. – In general, the reaction of acyloxy, alkoxy, and N-containing acid chlorides with *N*-(arylmethylene)arenamines produce *cis*-β-lactams under *Staudinger* cycloaddition conditions. In contrast, our study identified different results on *Staudinger* cycloaddition. For example, reaction of polyaromatic formal imines [4] with acid chlorides in the presence of Et_3N at $-78°$ to room temperature produced *trans*-β-lactams. A few of our *trans*-(acetyloxy)-β-lactams derived from multicyclic aromatic compounds demonstrated anticancer activity *in vitro* and in an animal model [4]. In our earlier study, only angular polyaromatic systems at N(1) of the β-lactam ring demonstrated selective anticancer activity [4]. Therefore, further investigations of these types of β-lactams are necessary. Based on this exciting background, in this study, cycloaddition reaction of a formal imine derived from 9,10-dihydrophenanthren-3-amine was performed by means of an automated microwave oven. Despite huge success in β-lactam research for the past six decades, synthesis and biological evaluation of anticancer β-lactams has not been investigated [4].

Reaction of *N*-benzylidene-9,10-dihydrophenanthren-3-amine (**1**) with acid chlorides **2** in the presence of Et_3N was performed at 0° to room temperature, and a mixture of *cis*- and *trans*-β-lactams **3** and **4** was obtained in 70% overall yield. The microwave-induced method at low power settings produced a mixture of the two β-lactams **3** and **4** (80% yield) within 10 min [5][6] (*Scheme 1*).

Scheme 1



The ratio of the β-lactam formation depends on the nature of the acid chlorides, microwave-power settings, reaction temperature, and nature of the solvent (*Table*). In general, high temperature and high power settings favor the formation of the *trans*-β-lactam. Interestingly, nonpolar solvents favor also the formation of the *trans*-β-lactams, *e.g.*, the cycloaddition in toluene produced more *trans*-β-lactams.

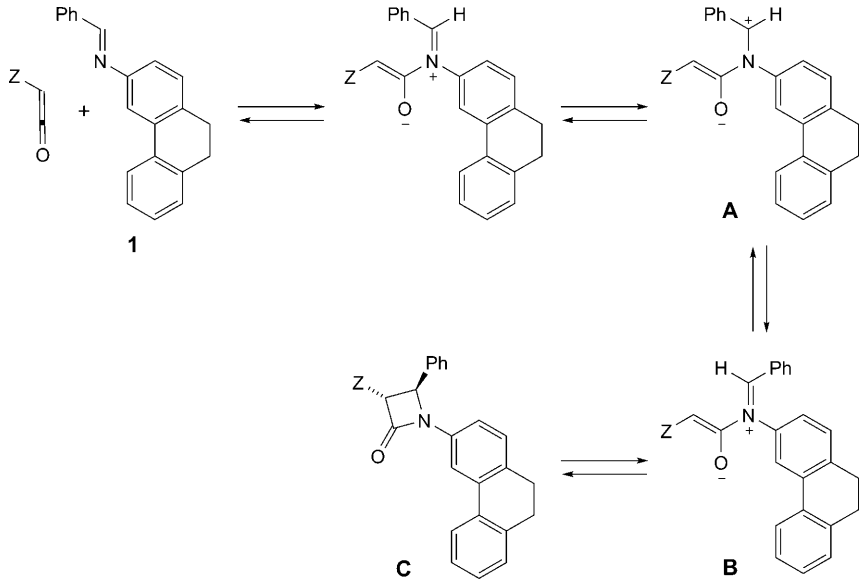
Table. *Microwave-Assisted Reaction of* N-*Benzylidene-9,10-dihydrophenanthren-3-amine* (**1**) *with Various Acid Chlorides*[a])

Acid chloride	Solvent	Temp.	Power	*cis/trans* Ratio (**3/4**)
$AcOCH_2COCl$	CH_2Cl_2	50°	300 W	50 : 50
$AcOCH_2COCl$	CH_2Cl_2	50°	100 W	75 : 25
$PhCH_2OCH_2COCl$	CH_2Cl_2	50°	300 W	40 : 60
$PhCH_2OCH_2COCl$	CH_2Cl_2	50°	100 W	80 : 20
$MeOCH_2COCl$	CH_2Cl_2	50°	300 W	90 : 10
$MeOCH_2COCl$	CH_2Cl_2	50°	100 W	95 : 5
$AcOCH_2COCl$	CH_2Cl_2	100°	300 W	15 : 85
$AcOCH_2COCl$	CH_2Cl_2	100°	100 W	40 : 60
$AcOCH_2COCl$	CH_2Cl_2	100°	300 W	5 : 95
$AcOCH_2COCl$	CH_2Cl_2	100°	100 W	10 : 90
$PhCH_2OCH_2COCl$	toluene	100°	100 W	50 : 50
$PhCH_2OCH_2COCl$	toluene	100°	300 W	40 : 60
$MeOCH_2COCl$	toluene	100°	100 W	40 : 60
$MeOCH_2COCl$	toluene	100°	300 W	30 : 70

[a]) Pressure in all experiments: 15 – 30 psi; time: 10 min.

Discussion. – In our earlier studies, formal imines derived from phenanthrene produced exclusively *trans*-β-lactams, irrespectively of the temperature, solvent, or acid chloride [4]. This suggests that the nature of the *N*-aryl group is crucial in controlling the stereochemistry of the β-lactam formation. It has been proposed that cycloaddition of the imine occurs from the least hindered side of the ketene, a process that generates zwitterionic intermediates; conrotatory cyclization of these intermediates can then provide β-lactams (*Scheme 2*) [4][7].

Scheme 2



The formation of *cis*- and *trans*-β-lactams **3** and **4** with 9,10-dihydrophenanthren-3-amine **1** can be explained through isomerization of the enolates (*Scheme 2*, **A** to **B**) [4][9]. Our experimental finding is supported by the following hypothesis. The electron-withdrawing dihydrophenanthrene group at the N-atom can stabilize the iminium ion through a rotation of the bond (**A** to **B**), and this results in the formation of **C**. The electron-withdrawing effect of the dihydrophenanthrene system at the N-atom of **1** is the dominating factor under high-power microwave-induced conditions. On the other hand, it appears that the iminium ion acquires sufficient stability in the presence of a polar solvent (CH_2Cl_2) and low-power microwave irradiation and thus isomerization of the enolate becomes a slow process. The formal phenanthrenylimine corresponding to **1** produces *trans*-β-lactams, irrespective of the conditions of the experiment (with or without microwave irradiation, low temperature, room temperature, and high temperature, in the presence of benzene, toluene, CH_2Cl_2, and chlorobenzene as solvents) probably due to its high electron-withdrawing capacity compared to the dihydrophenanthrenyl system [10].

Conclusion. – This study suggests that it is not only the structure of the imine but also the nature of the solvent and power level of microwave irradiation that plays a significant role in determining the configuration of several unique β-lactams. Structurally, the β-lactams **3** and **4** are similar to our anticancer compounds. Therefore, an availability of these compounds may prove useful for our structure – activity study [4].

Experimental Part

Representative Experimental Procedure. Acid chloride (1.5 mmol) was added to amine **1** (1 mmol) and Et_3N (3 mmol) in a solvent (1 ml) as mentioned in the *Table*. The mixture was irradiated in a *CEM* automated microwave oven according to the *Table*, then washed with sat. $NaHCO_3$ soln. (10 ml), 10% HCl soln. (10 ml), and brine (10 ml). The org. phase was dried (Na_2SO_4) and concentrated to obtain the crude product. A ^{1}H-NMR spectrum was performed to calculate the ratio of the isomeric β-lactams. The pure products were then isolated *via* column chromatography (silica gel, AcOEt/hexanes 1:4).

REFERENCES

[1] A. K. Bose, M. S. Manhas, B. K. Banik, V. Srirajan, in 'The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Material Science', Eds. A. Greenberg, C. M. Breneman, and J. F. Liebman, Wiley – Interscience, New York, 2000, Vol. 157, Chapt. 7.
[2] M. Suffness, in 'Taxol Science and Applications', CRC Press, Boca Raton, FL 1995.
[3] S. K. Dasgupta, B. K. Banik, *Tetrahedron Lett*. **2002**, *43*, 9445; B. K. Banik, S. Samajdar, I. Banik, *Tetrahedron Lett.* **2003**, *44*, 1699; I. Banik, L. Hackfeld, B. K. Banik, *Heterocycles* **2003**, *59*, 505.
[4] I. Banik, F. F. Becker, B. K. Banik, *J. Med. Chem.* **2003**, *46*, 12; B. K. Banik, F. F. Becker, I. Banik, *Bioorg. Med. Chem.* **2004**, *12*, 2523; B. K. Banik, I. Banik, F. F. Becker, *Bioorg. Med. Chem.* **2005**, *13*, 3611.
[5] L. Perreux. A. Loupy, *Tetrahedron* **2001**, *57*, 9199; P. Lidström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron* **2001**, *57*, 9225; A. K. Bose, M. S. Manhas, S. N. Ganguly, A. H. Sharma, B. K. Banik, *Synthesis* **2002**, 1578; A. K. Bose, B. K. Banik, N. Lavlinskaia, M. Jayaraman, M. S. Manhas, *Chemtech* **1997**, *27*, 18.
[6] B. K. Banik, K. J. Barakat, D. R. Wagle, M. S. Manhas, A. K. Bose, *J. Org. Chem*. **1999**, *64*, 5746.
[7] G. I. Georg, V. T. Ravikumar, in 'The Organic Chemistry of β-Lactams', Ed. G. I. Georg, VCH Publishers, New York, 1992.
[8] B. K. Banik, B. Lecea, A. Arrieta, A. de Cózar, F. P. Cossío, *Angew Chem., Int. Ed.* **2007**, *46*, 3028.
[9] G. Just, A. Ugolini, R. Zamboni, *Synth. Commun*. **1979**, *9*, 117.
[10] B. Alcaide, A. Rodríguez-Vicente, *Tetrahedron Lett.* **1999**, *40*, 2005; A. Afonso, S. B. Rosenblum, M. S. Puar, A. T. McPhail, *Tetrahedron Lett.* **1998**, *39*, 7431; M. Endo, R. Droghini, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2483; A. K. Bose, B. K. Banik, M. S. Manhas, *Tetrahedron Lett*. **1995**, *36*, 213.

Received June 4, 2009