HETEROCYCLES, Vol. 71, No. 11, 2007, pp. 2321 - 2324. © The Japan Institute of Heterocyclic Chemistry
Received, 8th June, 2007, Accepted, 6th August, 2007, Published online, 7th August, 2007. COM-07-11134

# UNPRECEDENTED STEREOCONTROL OF β-LACTAM FORMATION DERIVED FROM *N*-CINNAMYLIDENEARYLAMINE

**Bimal K. Banik,* Hector Aguilar, and Daniel Cordova**

Department of Chemistry, The University of Texas- Pan American, 1201 West University Drive, Edinburg, Texas 78541, USA; Phone: 956-380-8741; Fax: 956-384-5006, E-mail: banik@panam.edu

**Abstract** – Formation of β-lactams by the reaction of acid chloride, *N*-cinnamylidenearylamine and a tertiary amine seems to involve multiple pathways. Microwave-induced irradiation and high temperature lead to preferential formation (95-100 %) of *trans* β-lactams derived from conjugated imines.

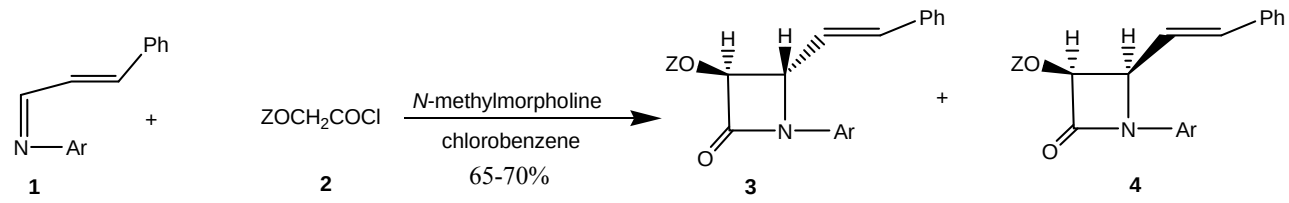
## INTRODUCTION

In earlier publications we have reported efficient preparation of anticancer β-lactams derived from polyaromatic imines.[1] Our current studies have now shown that it is possible to prepare *trans* β-lactams using a domestic and automated CEM microwave oven and at high temperature with polyaromatic imines derived from a conjugated aldehyde. This is one of the most exciting finding in β-lactam research since earlier reports have indicated formation of *cis* β-lactams as the only products with *N*-cinnamylidenearylamine.

## RESULTS AND DISCUSSION

In general, the reaction of acyloxy, alkoxy, and nitrogen-containing acid chloride with diaryl imines produces *cis* β-lactams under Staudinger reaction conditions.[2] Based on the anticancer activities of our β-lactams, further studies of these types of compounds are necessary.[1] For a study of the effect of microwave irradiation on the formation of α-hydroxy-β-lactams derivatives several Schiff bases and the high boiling tertiary amine *N*-methylmorpholine in place of lower boiling triethylamine were selected. Chlorobenzene was chosen as the reaction medium which absorbs microwave energy efficiently. Microwave-induced method produced a mixture of *cis* and *trans* products (**4** and **3**) from **1a**.[3] The stereochemistry of these isomeric structures was deduced from NMR data by a direct comparison. A systematic study was undertaken and the data shown in **Table 1** were collected. It was found that *cis* β-lactam **4a** formed at lower level of microwave irradiation and at room temperature. At about 112 °C

**Scheme 1**




**1a:** Ar = phenyl
**1b:** Ar = 1-anthracenyl
**1c:** Ar = 6-chrysenyl
**1d:** Ar = 2-nitrophenyl

**2a:** Z = Ac
**2b:** Z = Ph

**3a:** Ar = phenyl, Z = Ac
**3b:** Ar = phenyl, Z = Ph
**3c:** Ar = 1-anthracenyl, Z = Ac
**3d:** Ar = 1-anthracenyl, Z = Ph
**3e:** Ar = 6-chrysenyl, Z = Ac
**3f:** Ar = 6-chrysenyl, Z = Ph
**3g:** Ar = 2-nitrophenyl, Z = Ac
**3h:** Ar = 2-nitrophenyl, Z = Ph

**4a:** Ar = phenyl, Z = Ac
**4b:** Ar = phenyl, Z = Ph
**4c:** Ar = 1-anthracenyl, Z = Ac
**4d:** Ar = 1-anthracenyl, Z = Ph
**4e:** Ar = 6-chrysenyl, Z = Ac
**4f:** Ar = 6-chrysenyl, Z = Ph
**4g:** Ar = 2-nitrophenyl, Z = Ac
**4h:** Ar = 2-nitrophenyl, Z = Ph

final reaction temperature, there was more of the *trans* compound **3a** than the *cis* isomer **4a**.[4] However, with **2b** cis β-lactam **4b** was the predominant product at reflux temperature.

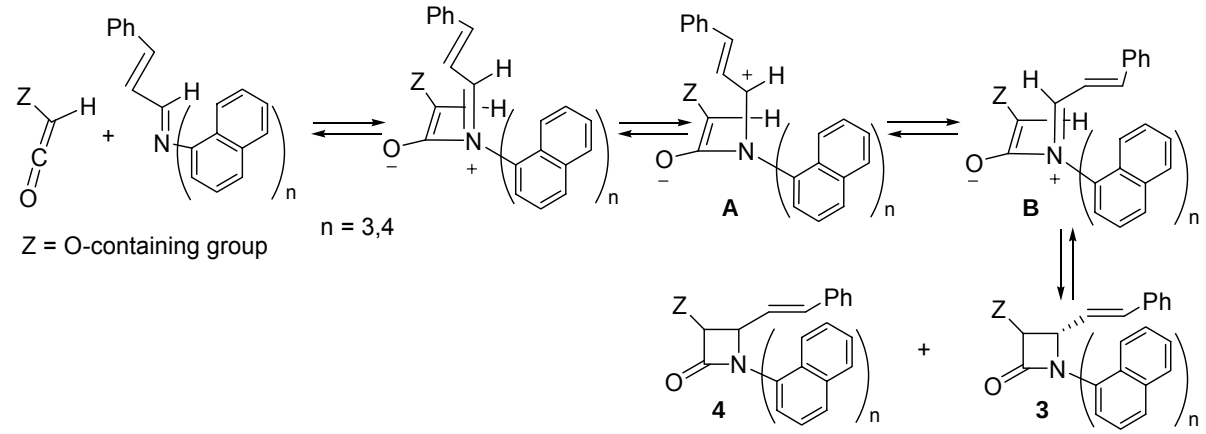
Table 1: Preparation of **3** and **4**:

| **1** | **2** | Method | Product Ratio (3:4) | % Yield |
|---|---|---|---|---|
| **1a** | **2a** | microwave [i] | 50 : 50 **(3a : 4a)** | 66 |
| **1a** | **2a** | microwave [ii] | 55 : 45 **(3a : 4a)** | 65 |
| **1a** | **2a** | microwave [iii] | 60 : 40 **(3a : 4a)** | 66 |
| **1a** | **2a** | microwave [iv] | 60 : 40 **(3a : 4a)** | 65 |
| **1a** | **2a** | reflux [v] | 90 : 10 **(3a : 4a)** | 68 |
| **1a** | **2b** | microwave [iv] | 45 : 55 **(3b : 4b)** | 66 |
| **1a** | **2b** | reflux [v] | 0 : 100 **(3b : 4b)** | 68 |
| **1b** | **2a** | reflux [v] | 100 : 0 **(3c : 4c)** | 65 |
| **1b** | **2b** | reflux [v] | 95 : 5 **(3d : 4d)** | 68 |
| **1c** | **2a** | microwave [iv] | 98 : 2 **(3e : 4e)** | 70 |
| **1c** | **2a** | reflux [v] | 100 : 0 **(3e : 4e)** | 70 |
| **1c** | **2b** | microwave [iv] | 95 : 5 **(3f : 4f)** | 69 |
| **1c** | **2b** | reflux [v] | 95 : 5 **(3f : 4f)** | 70 |
| **1d** | **2a** | reflux [v] | 98 : 2 **(3g : 4g)** | 68 |
| **1d** | **2b** | reflux [v] | 95 : 5 **(3h : 4h)** | 68 |

**i**: 200 mg imine with acid chloride (1.5 eq) and *N*-methylmorpholine (3 eq) were reacted in microwave for 8 min at a power of 200 watts and temperature of 80 °C; **ii** 200 mg imine with acid chloride (1.5 eq) and *N*-methylmorpholine (3 eq) were reacted in microwave for 8 min at a power of 300 watts and temperature of 80 °C; **iii**: 200 mg imine with acid chloride (1.5 eq) and *N*-methylmorpholine (3 eq) were reacted in microwave for 8 min at a power of 200 watts and temperature of 100 °C; **iv**: 200 mg imine with acid chloride (1.5 eq) and *N*-methylmorpholine (3 eq) were reacted in microwave for 8 min at a power of 300 watts and temperature of 100 °C; **v**: 200 mg imine and *N*-methylmorpholine (3 eq) was refluxed for 10 min before adding the acid chloride (1.5 eq). The reaction was then refluxed for another 10 min.

Cycloaddition of imines (**1b-c**) derived from a multicyclic aromatic amine at high temperature and microwave-induced conditions afforded *trans* products (**3c-f**) as the major isomer (more than 95-100 %). To explain the unprecedented stereochemistry we propose a cycloaddition of the imine from the least hindered side of the ketene, a process that generates zwitterionic intermediate; conrotatory cyclization of this intermediate can then provide *cis*- and *trans*-β-lactams (**Scheme 2**).

**Scheme 2**




The formation of a *trans*-isomer as observed can be explained through isomerization of the enolates (**Scheme 2**, **A** to **B**).[1,5] The electron-withdrawing polyaromatic group at the nitrogen stabilizes the iminium ion. This process allows rotation of the bond (**A** to **B**) and results in formation of *trans* β-lactam.[3] The electron withdrawing effects of the polyaromatic system is the dominating factor at high temperature and microwave-induced method. Just *et al* demonstrated synthesis of *trans* β-lactam with electron-withdrawing nitro-substituted imines.[6] Drastic energy through microwave radiation altered the structure of the intermediate presumably through a rotation of the bond and this results in the formation of a *trans* compound in major proportion. The formation of a *cis*-β-lactam having a polyaromatic group at nitrogen and a cinnamyl group at $C_4$ of the imine at room temperature prompted us to develop a hypothesis of an extended conjugation of the system.[1,2] This observation is supported by the formation of donor-acceptor complex. At 0 °C – room temperature, the stabilization of acyliminium ion force is more predominant and this results in *cis*- β-lactam.

On the basis of the observations described above, it appears that the cyclization reaction involves multiple pathways some of which are highly accelerated by microwave irradiation (and/or higher temperature). The energy exerted by microwave and or high temperature presumably is sufficient to alter the intermediate structure of A to B with polyaromatic compounds. This suggests a dual effect (electron withdrawing power of the multicyclic rings or the presence of a nitro group and energy associated with the microwave irradiation and or high temperature) is necessary for the preparation trans β-lactam derived

from conjugated imines (e.g. cinnamyl imines). The unprecedented stereochemical outcome of the Staudinger reaction as reported herein will offer our laboratory and others additional opportunities to use β-lactams in the synthesis of new compounds of medicinal significance including novel anticancer agents.

**ACKNOWLEDGEMENTS**

We gratefully acknowledge the financial support for this research project from National Institutes of Health-SCORE (2SO6GM008038-36). We also grateful to the Welch Foundation departmental grant (BG0017).

**REFERENCES AND NOTES**

1. B. K. Banik, I. Banik, and F. F. Becker, *Bioorg. Med. Chem.,* 2005, **13**, 3611 and references cited therein.
2. G. I. Georg and V. T. Ravikumar, *The Organic Chemistry of β-Lactams*, ed. by G. I. Georg, VCH Publisher, New York, 1992.
3. (a) P. Lidstrom, J. Tierney, B. Wathey, and J. Westman, *Tetrahedron,* 2001, **57**, 9225. (b) For our endeavor on microwave-induced reactions, see; B. K. Banik, K. J. Barakat, D. R. Wagle, M. S. Manhas, and A. K. Bose, *J. Org. Chem*., 1999, **64**, 5746.
4. B. Alcaide and A. A. Vicente-Rodriguez, *Tetrahedron Lett.,* 1999, **40**, 2005.
5. B. K. Banik, B. Lecea, A. Arrieta, A. Cozar, and F. P. Cossio, *Angew Chem. Int. Ed.,* 2007, **46**, 3028.
6. G. Just, A. Ugolini, and R. Zamboni, *Synth. Commun*., 1979, **9**, 117.
7. Microwave-Assisted preparation of the β-lactam: Imine (1 mmol), acid chloride (1.5 mmol), and *N*-methylmorpholine (3 mmol) in chlorobenzene (2 mL) was placed in a reaction vessel (10 mL capacity). The reaction vessel was then capped and placed in a microwave (Discover Labmate, 120 V). The mixture was irradiated for 8 min at different power and temperature. The reaction mixture was then extracted with $CH_2Cl_2$ (25 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), diluted HCl (10 %, 10 mL), brine (10 mL), dried with anhydrous sodium sulfate and evaporated to obtain the crude product. $^1$H NMR was taken to calculate the ratio of the isomeric β-lactams. The pure product was then isolated via column chromatography over silica gel using EtOAc-hexanes (1 : 4) as the solvent (65-70 %).