

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

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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.

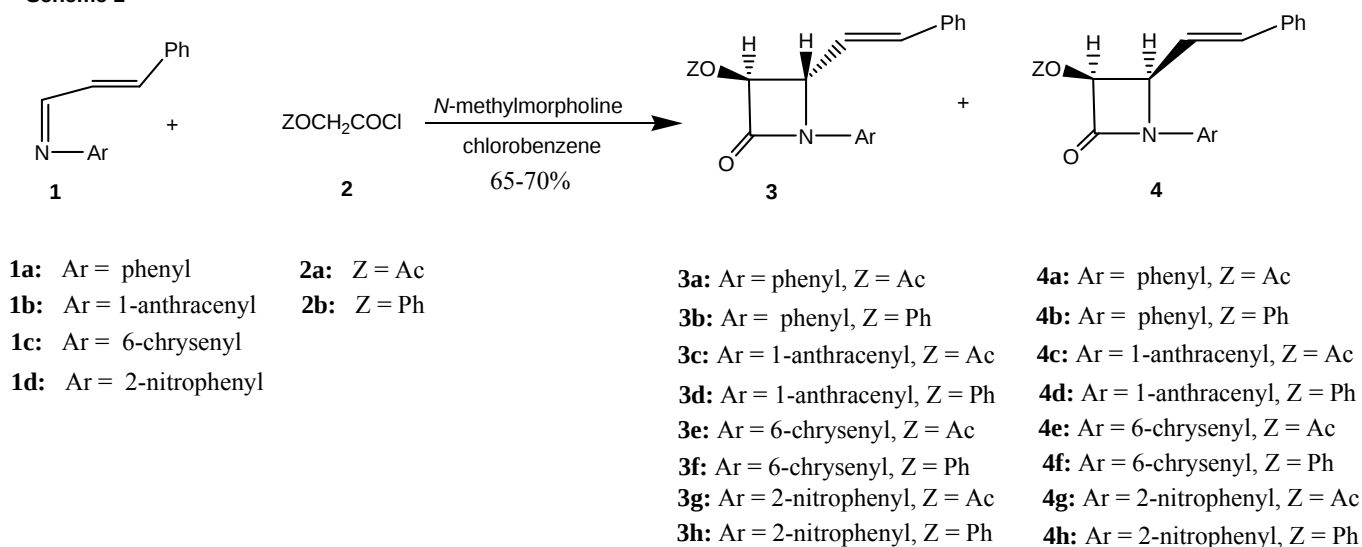
INTRODUCTION

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*-methyldmorpholine 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



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.

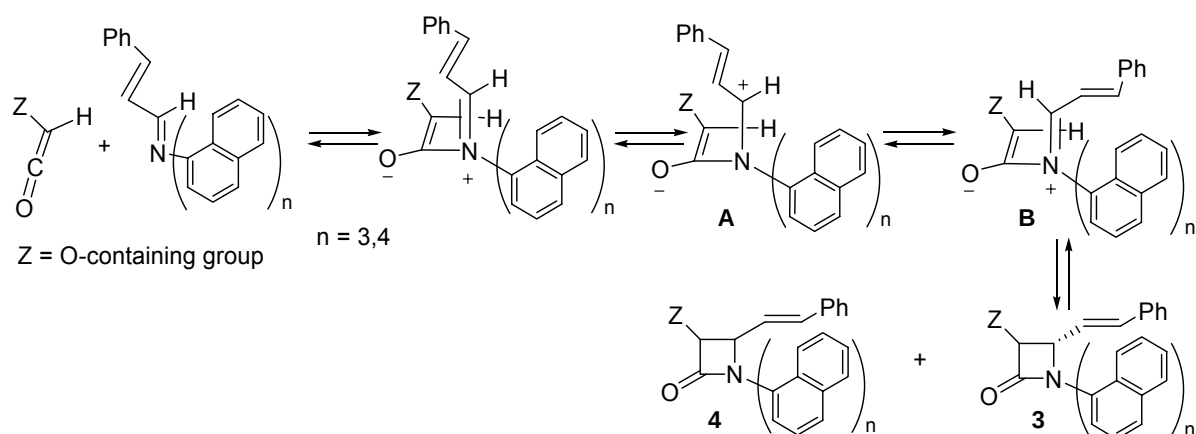
Table 1: Preparation of **3** and **4**:

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 C₄ 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).

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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. ^1H 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 %).