STEREOSELECTIVITY OF 3, 3-DISUBSTITUTED β-LACTAM FORMATION VIA STAUDINGER REACTION

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Abstract

Synthesis of a few 3, 3-disubstitued β-lactams has been achieved following Staudinger reaction. The stereoselectivity of their formation has been rationalized through isomerization of the enolates formed during the reaction of acid chloride with imines in the presence of triethylamine.

Introduction

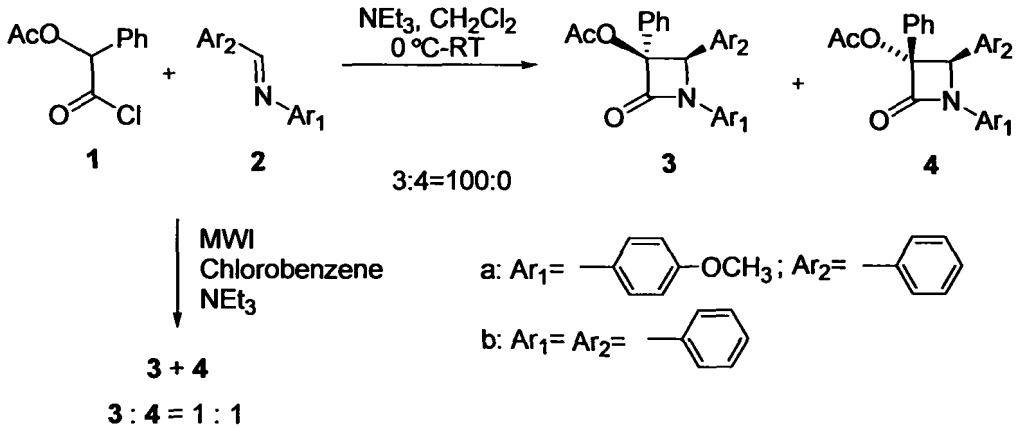
The impact of β-lactams has been enormous and this enchanted 4-membered cyclic amide has a number medicinal applications.[1] Because of the general trend of β-lactam use, the search for clinically useful β-lactams that are antibacterial or have other medically important properties will continue. [2]We have been actively engaged in the synthesis of β-lactams[3] as anticancer agents for the last two decades.[4]In continuation of our research, we describe herein stereocontrolled synthesis of a few 3, 3-disubstituted β-lactams. Syntheses of 3, 3-disubstituted β-lactams by cycloaddition chemistry and their diasteroselectivty of formation have not been explored systematically. Based on our current research on the anticancer polyaromatic β-lactams,[4] we have explored diasteroselectivity of their formation with a disubstituted acid chloride and the results are disclosed here.

Results and Discussion

The Staudinger reaction has been used extensively for the synthesis of β-lactams. This reaction requires an imine, a tertiary base, and acid chloride (or equivalent). It is known that the stereochemistry of β-lactams varies depending on the substituents present in the imine and acid chloride and the conditions of the reactions.[5] The reaction of acyloxy, alkoxy, and nitrogen-containing acid chloride with diaryl imine produces *cis*-β-lactams under Staudinger reaction conditions. In contrast, reaction of polyaromatic imines[4] with acid chloride in the presence of triethylamine at –78°C to room temperature produced *trans*-β-lactams. Furthermore, some of our *trans* acetoxy β-lactams have demonstrated selective anticancer activity against a number of human cancer cell lines *in vitro*.[4] Therefore, further synthetic and biological studies of these types of compounds are necessary.

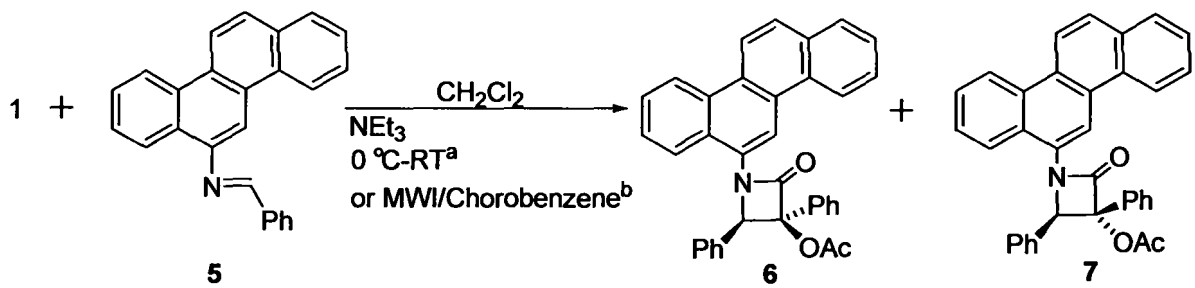
Reaction of diarylimine **1** with O-acetylmandelic chloride **2** in the presence of triethylamine was performed at 0°C-room temperature and a single β-lactam **3** was obtained in 70% yield.[6] The hydrogens of the acetate group and the C-4 hydrogen of the β-lactam ring in **3** resonate at δ 1.6 and δ 5.7 respectively. Microwave-induced method, however, produced a mixture of two β-lactams **3** and **4** in a ratio of 1:1.2 (70% yield).[7, 8] High temperature reaction also produced an identical mixture of products **3** and **4** in comparable yield. The hydrogen of the acetate group and the C-4 hydrogen of the β-lactam ring in **4** resonate at δ 2.2 and δ 5.67 respectively (**Scheme 1**).

Scheme 1

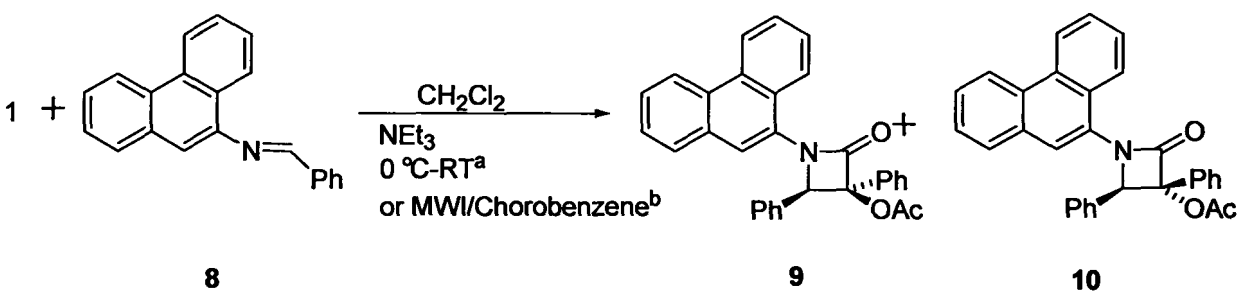


Cycloaddition of imine **5** derived from a multicyclic aromatic amine at 0°C-room temperature afforded two β-lactams **6** and **7** in a ratio of 7: 3. Microwave irradiation, however, produced a mixture of two products **6** and **7** in a ratio of 2: 8 (**Scheme 2**). The hydrogen of the acetate group and C-4 hydrogen in **6** resonate at δ 2.17 and δ 5.95 respectively. The acetate and C-4 hydrogen in **7** resonate at δ 2.33 and 6.46 respectively. Similar observation was obtained with imine **8** derived from phenanthrene system.

Scheme 2



a: (**6** : **7** = 7 : 3); b: (**6** : **7** = 2 : 8)

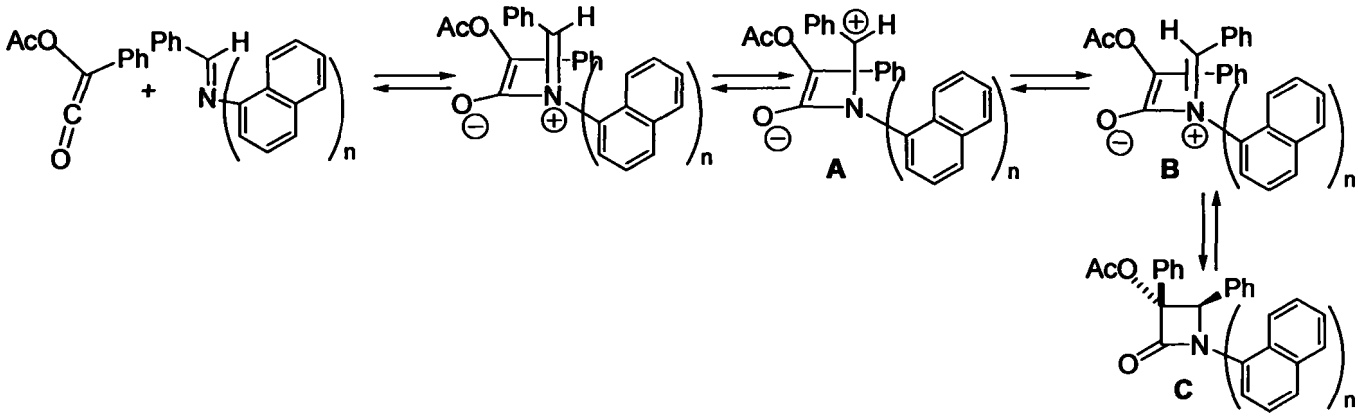


a: (**9** : **10** = 7 : 3); b: (**9** : **8** = 2 : 8)

When irradiated in a microwave oven using chlorobenzene and triethylamine, β-lactam **3**, **6** and **9** did not isomerize to **4**, **7** and **10** respectively. The β-lactams **3**, **6** and **9** also did not produce to **4**, **7** and **10** when they were refluxed in ethylene dichloride and triethylamine. These experiments established that there were no isomerization of the β-lactams **3**, **6** and **9** during reaction at a high temperature and / or under microwave irradiation.

The results observed in this present study are interesting and support our hypothesis.[4] It has been expalined 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 may then produce β-lactams (**Scheme 3**).

Scheme 3



The formation of compounds **4**, **7** and **10** can be rationalized through an isomerization of the enolate (**Scheme 3**, **A** to **B**).[4, 9]The electron-withdrawing polyaromatic group at the nitrogen stabilizes the iminium ion greatly. As a result, this process allows rotation of the bond (**A** to **B**) and formation of an intermediate **C** is possible. The significant electron withdrawing effects of the polyaromatic system at nitrogen is the dominating factor at high temperature and under microwave-induced conditions. This results in the formation of a β-lactam in which C-4 phenyl and C-3 acetoxy groups are *trans* to each other in the predominant product. Just *et al.* described the formation of a *trans* β-lactam with electron-withdrawing nitro-substituted imines.[10, 11] The classical condition using imine **1** follows the usual cycloaddition route as reported in the literature and this gives *cis*-type of compounds (C-3 acetoxy and C-4 H are *trans* to each other). However, drastic energy through microwave radiation altered the structure of the intermediate presumably through a rotation of the bond and these results in the formation of **4**, **7** and **10** in major proportion in three different cases.

Structurally, these β-lactams (**6**, **7** and **9**, **10**) are similar to our anticancer compounds.[4]The hydrophobicity of the phenyl group in these β-lactams **6**, **7**, **9** and **10** may alter their anticancer activities compared to our previous compounds and therefore, availability of these compounds may prove useful for our structure-activity study.[12]

Conclusion

The stereochemical results of the Staudinger reaction particularly with polyaromatic imines as reported herein will offer our laboratory and others many additional opportunities to use β-lactams in the synthesis of new compounds having anticancer properties. Despite tremendous interest among synthetic as well as medicinal chemists over the past six decades on β-lactams, the synthesis and biological evaluation of these agents as anticancer molecules has been investigated very poorly. On this basis, synthetic and medicinal studies of polyaromatic β-lactams will be useful, challenging and timely.

Acknowledgment

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References and notes

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(12) A representative experiment procedure is given below. A solution consisting of acid chloride (1.5 mmol) in dichloromethane (10 mL) was added drop wise to a stirred solution containing imine (1 mmol) and distilled triethylamine (3 mmol) in dry dichloromethane (10 mL) at 0 to 78°C. The reaction mixture was then stirred overnight at room temperature, 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 □-lactams. The pure product was then isolated via column chromatography over silica gel using ethyl acetate-hexanes (1 : 4) as the solvent.

Microwave-Assisted Preparation of the □-Lactam: The same 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 β-lactam was isolated.

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