HIGHLY STEREOSELECTIVE β-LACTAM SYNTHESIS VIA THE STAUDINGER REACTION USING POLYAROMATIC IMINES#

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#Dedicated to the memory of Dr. R. R. Gupta

Abstract

Highly stereoselective synthesis of a few *trans* 3-phthalimido substituted β-lactams has been achieved following Staudinger reaction.

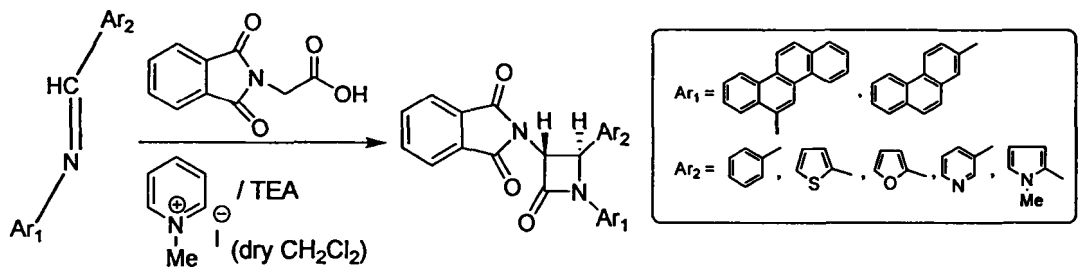
Introduction

We have been actively engaged in the synthesis of β-lactams as anticancer agents for the last two decades. In continuation of our research, we describe herein stereocontrolled synthesis of a few 3-substituted β-lactams using polyaromatic imines. Syntheses of these types of β-lactams by cycloaddition chemistry and their diasteroselectivty of formation have not been explored. Based on our current research on the anticancer polyaromatic β-lactams, we have explored diasteroselectivity of their formation with activated phthalimido acetic acid chloride.

Staudinger 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. In contrast to the existing literature, reaction of polyaromatic imines[4] with acid chloride in the presence of triethylamine produced *trans*-β-lactams. 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.

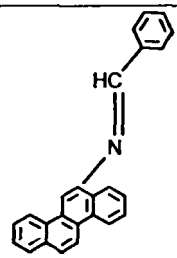
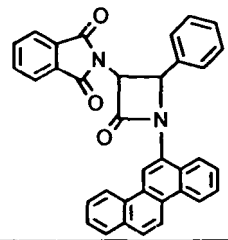
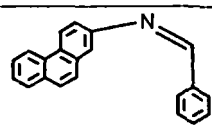
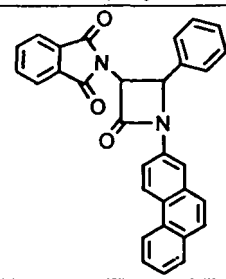
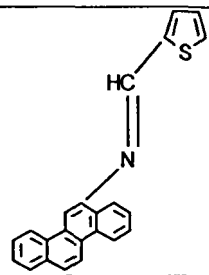
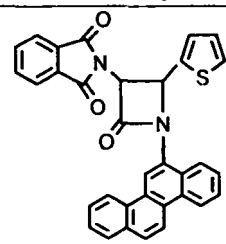
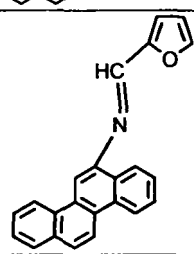
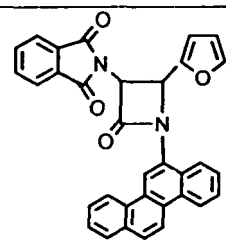
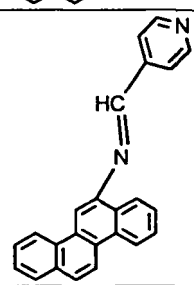
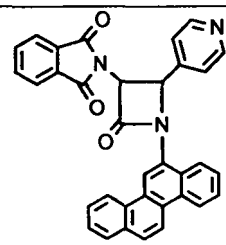
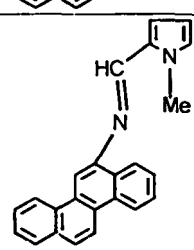
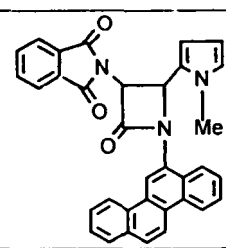
Results and Discussion

Reaction of chrysenyl- and phenanthrenyl imine **1** with phthalimidoacetic acid **2** in the presence of



Scheme 1

Table 1: Synthesis of Phthalimido β-lactams from Imines

Entry	Imine	Phthalimido β-lactam	Yield (%)
1			76
2			79
3			82
4			85
5			83
6			78

triethylamine and N-methylpyridinium iodide was performed at 0°C-room temperature and a single trans β-lactam **3** was obtained in 76-85% yield. High temperature reaction also produced an identical mixture of products **3** in comparable yield (**Scheme 1**). The reaction proceeded well with diverse imines that have different types of aromatic groups (**Table 1**).

The results observed in this present study are interesting and support our hypothesis.

Conclusion

The formation of *trans* isomer can be rationalized through an isomerization of the enolate. Polyaromatic group at the nitrogen stabilizes the iminium ion greatly.

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.

Acknowledgment

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References and notes

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(9) A representative experiment procedure is given below. A solution consisting of phthalimidoacetic acid (1.5 mmol) in dichloromethane (10 mL) was added 2-iodo-N-methylpyridine (2 mmol) and triethylamine (6 mmol) at ice-cold temperature. This mixture was stirred for 1h. Imine (1 mmol) in dry dichloromethane (10 mL) was then to it at

0°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 indicated the presence of *trans* was □-lactams only. The pure product was then isolated via column chromatography over silica gel using ethyl acetate-hexanes (1: 4) as the solvent. All the compounds have been characterized by IR, NMR and MS analyses.

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