

**MICROWAVE-INDUCED STEREOSPECIFIC SYNTHESIS OF β -LACTAMS
DERIVED FROM POLYAROMATIC IMINES: INFLUENCE OF THE MULTICYCLIC
RINGS AT THE NITROGEN**

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Abstract: Microwave-induced stereospecific synthesis of β -Lactams derived from polyaromatic imines has been realized.

Introduction:

The synthesis and biological evaluation of new β -lactams is perhaps the most explored area in organic chemistry and medicinal chemistry.¹ Research on polyaromatic β -lactams is very challenging because of their anticancer activities.² Microwave-induced cycloaddition reaction of imines derived from multicyclic rings produces *cis* β -lactams which is in sharp contrast to earlier observations. Clearly, the formation of β -lactams depends on a number of factors that need to be investigated in more detail.

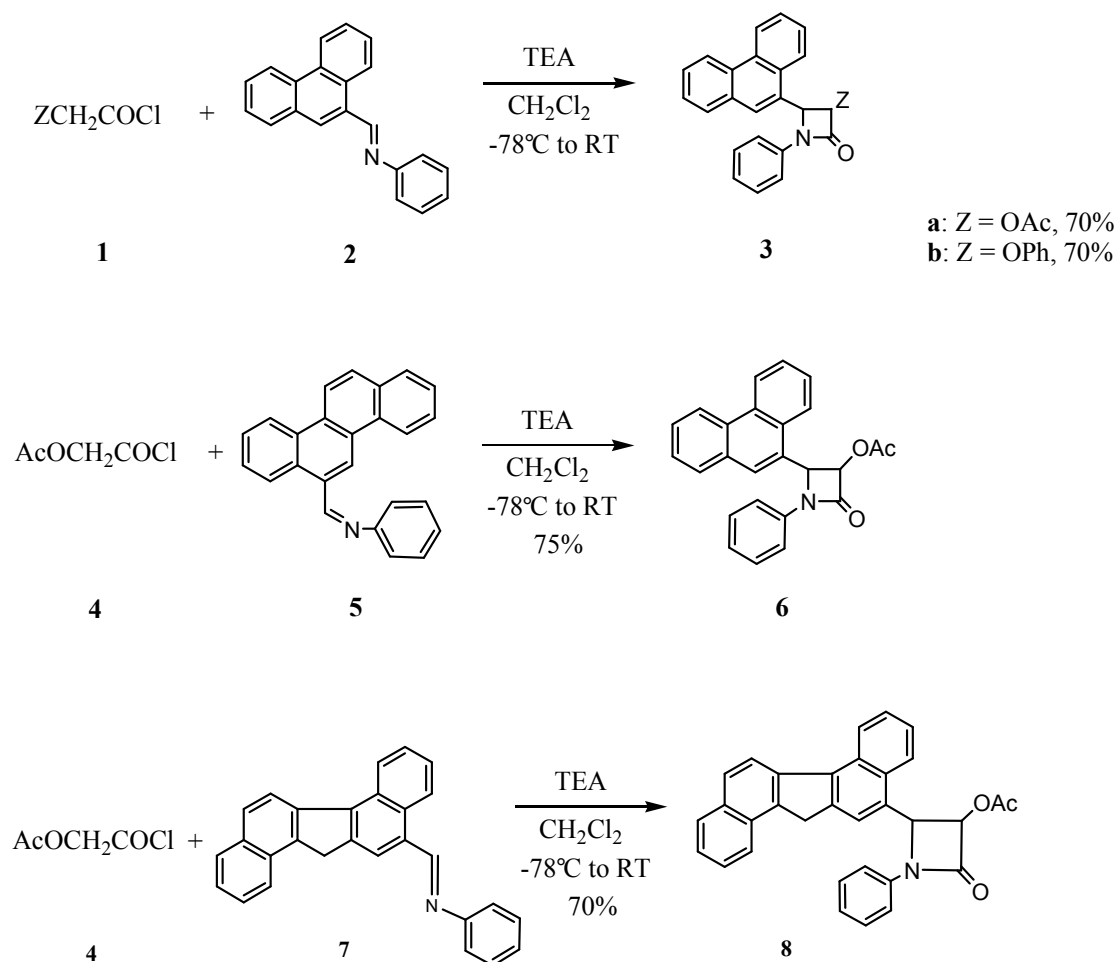
Results and Discussion:

Our research on imines derived from polyaromatic amines resulted in the formation of *trans* β -lactams as the only isolated products.² A similar reaction following the Staudinger reaction using specific imines derived from polyaromatic aldehydes, however, produced *cis* β -lactams. The *trans* and *cis* stereochemistry of the products have been verified by NMR data. The coupling constant at the C₃ and C₄ hydrogens in the *cis*-compounds is higher than that in the *trans*-compounds. Microwave-induced reaction produced *trans* β -lactams with imines derived from polyaromatic amines and conjugated carbonyl compounds as the main products. The unusual formation of *trans* products with conjugated carbonyl compounds is a fascinating observation. These results were explained based on the hypothesis that a rotation of the intermediate iminium ion is possible because of the presence of a polyaromatic aromatic system at nitrogen of the imines. Microwave-irradiation can favor the alteration of the transition state. The energy exerted by microwave is believed to be higher than the stabilizing effects that are possible with a conjugated system due to the formation of a donor-acceptor complex. Our results on imines derived from polyaromatic aldehydes following microwave-induced method are highly interesting since they do not produce *trans* β -lactams. The products from these imines are always found to be *cis* despite the conditions of the experiments.

Microwave-induced organic synthesis is well established.³ This method is very interesting because the unconventional set up for conducting the reaction takes advantage of the specific nature of microwave energy. Irradiation of a solution of imines **2**, **5**, and **7** with acid chlorides **1** and **4** in chlorobenzene using a domestic microwave oven afforded *cis*- β -lactams **3**, **6** and **8**, in excellent yield (**Scheme 1**).

A large Erlenmeyer flask was the reaction vessel in an unmodified domestic microwave oven. Chlorobenzene was used as solvent. The boiling point of chlorobenzene is higher than the projected temperature of the reaction. The temperature of the reaction mixture was kept below 75°C by the proper adjustments of the on-off cycle and a 'heat sink' (a beaker containing 200 mL of water). This heat sink can absorb sufficient amount of microwave energy and thereby the temperature of the reaction mixture can be maintained. Microwave energy is absorbed by all of the polar molecules and therefore, a stirrer and a reflux condenser are not required. When irradiated in a microwave oven using chlorobenzene and triethylamine, *cis*- β -lactams **3**, **6** and **8** did not isomerize to the *trans*- β -lactams.

Scheme 1:



Therefore, the present study clearly indicates that microwave irradiation can accelerate the synthesis of β -lactams with comparable yield. The reactions were performed in unmodified

domestic microwave ovens in a matter of minutes using very limited amounts of solvents. The results described herein clearly suggest that the presence of a multicyclic aromatic ring at the nitrogen of the imines is highly essential for the preparation of the *trans* β -lactams. The presence of this type of ring at the carbon of the imine has no effect in the stereochemical outcome of the standard cycloaddition reaction and therefore, *cis*-isomers are the only products obtained even in the presence of microwave irradiation. This study also confirms that multicyclic benzene derivatives can be used very successfully for the preparation of *cis* β -lactams. Based on the results, it seems that electronic effects of the substituents present in the imines have more control in the stereochemical distribution of the products than the steric nature of the groups present in them.

Conclusion: A simple microwave-induced method for the preparation of *cis* β -lactams has been demonstrated using imines starting from polyaromatic aldehydes.

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