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MICROWAVE-INDUCED STEREOSELECTIVITY OF β -LACTAM FORMATION: EFFECTS OF SOLVENTS

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Abstract:

Synthesis of 3, 4-disubstituted 2-azetidiones has been achieved following Staudinger reaction under microwave-induced conditions. The stereoselectivity of β -lactam formation depends on the nature of the solvents used in the reaction.

Introduction:

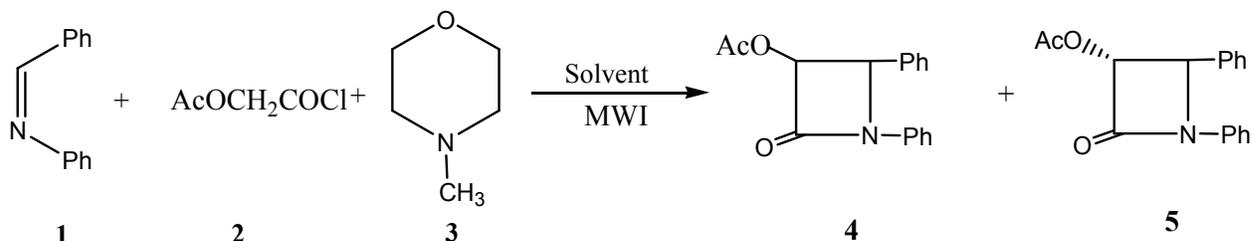
The significance of β -lactam in synthetic chemistry has no parallel.¹ Consequently, the searches for clinically useful β -lactams that are antibiotics and/or are medically important properties have received intense pursuit.² We describe herein stereocontrolled synthesis of a 3,4-disubstituted-2-azetidines using microwave-induced reaction. Based on our current research on the anticancer β -lactams³ we have explored automated microwave-induced reaction to study the diastereoselectivity with a simple imine following stringent conditions.

Results and Discussion:

The reaction of acyloxy and alkoxy acid chlorides with diaryl imines produced *cis*- β -lactams under Staudinger reaction conditions. In contrast, reaction of polyaromatic imines with acid chlorides in the presence of triethylamine produced *trans*- β -lactams. Although microwave-induced β -lactam synthesis has been investigated, however, precise maintenance of temperature and pressure inside the reaction mixtures in presence of different solvents has been proved to be difficult process. Because of the technological development in recent years, it has been possible to maintain these parameters accurately which are found to be very crucial in controlling the stereochemistry of β -lactams and other organic compounds.

Reaction of diarylimine **1** with acetoxy acetyl chloride **2** in the presence of N-methylmorpholine was performed using CEM automated microwave and a mixture of *cis* and *trans* β -lactams **3** and **4** was obtained in 70% yield. Microwave-induced method at low power settings produced a mixture of two β -lactams **3** and **4** within 10 minutes (**Scheme 1**). Reaction of **1** and **2** at -78°C to room temperature afforded only **4** as the only product irrespective of the solvent used.

Scheme 1:



The ratio of the β -lactam formation **3** and **4** depends on microwave power settings, temperature of the reactions and nature of the solvent (**Table 1**). High temperature and high power settings favor the formation of the *trans* β -lactam. Notably, non-polar solvent favors the formation of the *trans* β -lactams. For example, cycloaddition has produced *trans* β -lactams predominantly in benzene. In this context, it is important to note that even non polar benzene can produce β -lactams. Earlier attempts to prepare β -lactam in benzene with reasonable yields were not successful using domestic microwave oven. It was believed that benzene cannot absorb microwave energy because of its low dipole moment and therefore, it is not a good solvent in microwave-induced reactions. It was hypothesized that only polar solvents can accelerate microwave-induced reactions. According to our knowledge, no paper has been published using domestic microwave with non polar solvents. However, we have observed formation of β -lactam in good yield using automated microwave even in the presence of benzene. Moreover, it has been observed that the *trans* β -lactam is the major product in benzene. It has been found that high temperature reaction in benzene favors the formation of the *trans* isomer when the power settings remain constant. High temperature reaction in dichloroethane also favors the formation of this isomer. Importantly, *trans* isomer is the major product in benzene compared with dichloroethane when temperature and power settings remain the same. The reason for this selectivity is not established. However, this suggests that the initial iminium ion intermediate is more stabilized in polar solvent whereas the iminium ion that results in through the rotation of the C-N bond is more stabilized in non polar solvent. The first iminium produces *cis* β -lactam and the second iminium ion (through rotation of the C-N bond) produces the *trans* β -lactam through a cycloaddition reaction.

Table 1:

Solvents	Temperature/Time/Power Level	Ratio of 4 and 5
Benzene	100 °C, 10 min., 300 μ	10:90
1,2-Dichloroethane	100 °C, 10 min., 300 μ	25:75
Benzene	50 °C, 10 min., 300 μ	30:70
1,2-Dichloroethane	50 °C, 12 min., 300 μ	40:60
Benzene	20 °C, 20 min., 300 μ	40:60
1,2-Dichloroethane	20 °C, 20 min., 300 μ	50:50

Experimental:

A representative experimental procedure is given below. Acid chloride (1.5 mmol) was added to imine (1 mmol) and N-methylmorpholine (3 mmol) in a solvent as mentioned in **Table 1**. The reaction mixture was then irradiated in a CEM automated microwave oven according to **Table 1**, washed with saturated sodium bicarbonate solution (10 mL), dilute hydrochloric acid (10%, 10 mL), brine (10 mL), dried with anhydrous sodium sulfate and evaporated. NMR data was collected to calculate the ratio of the isomeric β -lactams. The pure product was then isolated via column chromatography over silica gel using ethyl acetate-hexanes (1: 4) as the solvent.

Conclusion:

This study suggests that it is not only the structure of the imine, but also the nature of the solvent plays a significant role in determining the stereochemistry of β -lactams. Non polar solvents can be used in the cycloaddition reaction with equal success. It is possible to control the stereochemistry of the products by adjusting the conditions of the experiments.

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