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ULTRASOUND-MEDIATED STEREOSELECTIVITY OF Β-LACTAMS FORMATION WITH POLYAROMATIC IMINES

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Abstract: A few 3, 4-disubstitued β-lactams obtained from polyaromatic conjugated imines has been synthesized using ultrasound. The formation of *trans* β-lactams was observed under this reaction condition exclusively.

Keywords: Polyaromatic β-Lactams, Cycloaddition, Ultrasound

Introduction:

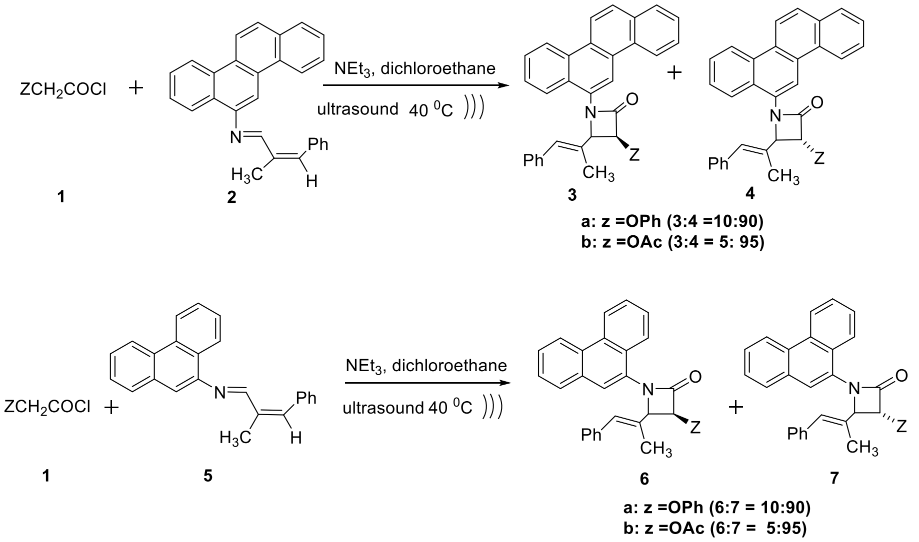
The β-lactam skeleton has gained significant interest among synthetic as well as medicinal chemists over the years, mainly because it represents the core structure of synthetic and natural β-lactam antibiotics. The importance of the β-lactam unit as a synthon has been recognized in the synthesis of a variety of biologically active β-lactam and non β-lactam derivatives[1]. The constant need for new drugs displaying broader antibacterial activity and the necessity for new β-lactam antibiotics to combat microorganisms that have built up resistance against traditional drugs have maintained the interest of organic chemists for decades [2]. Here, we have reported the synthesis of anticancer *trans*-β-lactams agents[3]. A highly stereoselective ultrasound-mediated synthesis of a *trans* 3, 4-disubstituted β-lactams using polyaromatic conjugated Schiff base by Staudinger (2+2) cycloaddition is described here.

Results and Discussion:

The cycloaddition reaction has been studied for the synthesis of β-lactams for more than a century. The stereochemistry of β-lactams formed in this reaction depends on the substituents present in the Schiff bases and acid chloride (equivalents) and the conditions of the process[9]. The acyloxy, alkoxy, and nitrogen-containing activated acid chloride with diaryl Schif bases gives *cis*-β-lactams. On the other hand, the reaction of polyaromatic Schiff base with acid chloride generates *trans*-β-lactams.[6,7,8] Notably, Schiff bases derived from conjugate carbonyl compounds produce *cis*-β-lactams.

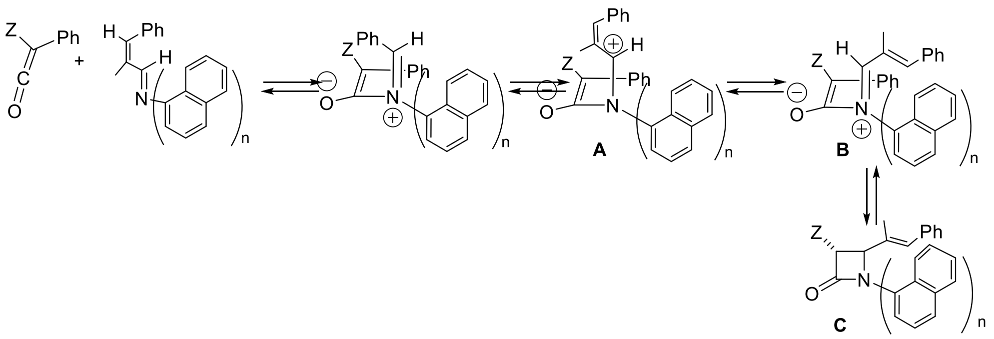
Diarylimine **2** on reaction with acid chloride **1** at 0 °C-room temperature produced a single β-lactam **3** [10]. But ultrasound-induced process produced two β-lactams **3** and **4** in a ratio of 1:9 (75% yield).[11] (**Scheme 1**).

Scheme-1



The *cis* β-lactam produced from this study did not isomerize to *trans* β-lactams upon ultrasonic exposure. Moreover, isomerization was not seen when *cis* β-lactams were heated at thigh temperature (at 80 ºC) in toluene and triethylamine. So, there was no isomerization of the *cis* β-lactams under the reaction conditions.[12] The cycloaddition of the Schiff base started from the least hindered part of the ketene and generated zwitterionic species. A conrotatory cyclization process of these intermediates gave β-lactams (**Scheme 2**).[13]

Scheme-2



The formation of *trans*-isomer was realized through an isomerization of the intermediate enolate (**Scheme 2**, **A** to **B**). The electron-withdrawing multicyclic aromatic groups at the nitrogen was able to stabilize the iminium ion. The stabilization was able to rotate the bond in **A** to **B** and this helped to form an intermediate **C**. The electron withdrawing effects of the multicyclic aromatic system at nitrogen became prominent under ultrasound exposure. As a result, *trans* β-lactams with conjugated imines were formed. The normal condition using this imine produced the *cis*-compounds· A stabilization of the iminium was high under normal conditions and therefore, *cis* β-lactam was formed. Ultrasound was able to alter the intermediate structure presumably through a rotation of the bond. This alteration was responsible for the formation of the *trans*-isomers.

Conclusions:

The stereochemical observation with conjugated multicyclic compounds is new because ultrasound was never used to alter the stereochemistry of β-lactams. Therefore, this principle can be extended to diverse research activities.

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14. Representative experiment procedure is given below. A solution consisting of acid chloride (1.5 mmol) in dichloroethane (2 mL) was added to imine (1 mmol) and triethylamine (3 mmol). The reaction mixture was then sonicated in a sonication at 40 ^{o}C for 10 min. It was then washed with sodium bicarbonate solution (5 mL), dilute hydrochloric acid (10%, 5 mL), brine (5 mL), dried with anhydrous sodium sulfate and evaporated. The proton NMR was taken to know the ratio of the isomeric products. The pure *trans* isomer was obtained through column chromatography over silica gel using ethyl acetate-hexanes.

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