

## ASYMMETRIC SYNTHESIS OF $\beta$ -LACTAM USING S-CITRONELLAL

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**Abstract:** Stereocontrolled synthesis of optically active  $\beta$ -lactams using S-Citronellal via the Staudinger cycloaddition reaction has been achieved.

**Keywords:**  $\beta$ -lactams, Citronellal, Enantioselectivity

### **Introduction:**

$\beta$ -Lactams are well known for their medical applications. For example, penicilins and cephalosporins are  $\beta$ -lactams antibiotics. The need for more potent and effective  $\beta$ -lactam has driven scientists to create new analogues. These compounds have been used in the medical field as therapeutic agents for lowering plasma cholesterol levels. It has been discovered that specific  $\beta$ -lactams have anticancer properties.

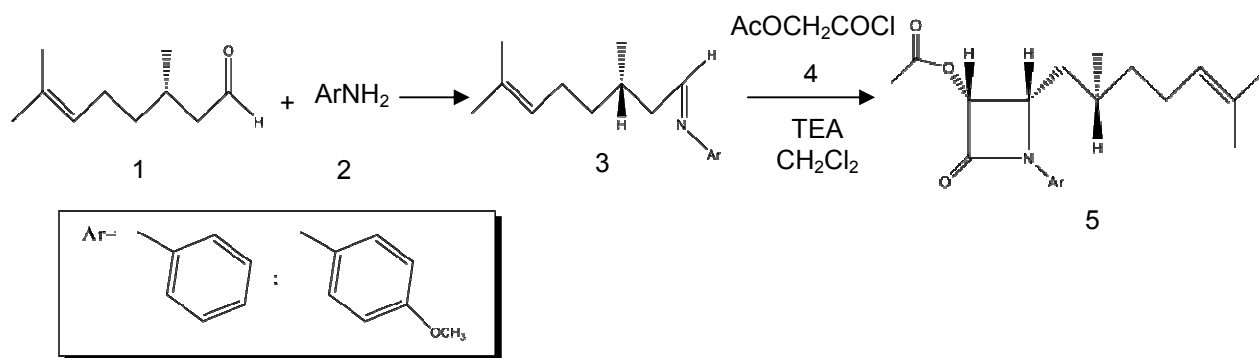
The synthesis of  $\beta$ -lactams has been carried following the Staudinger cycloaddition reaction.<sup>1</sup> Also known as a [2+2] ketene-imine cycloaddition reaction, this reaction is considered as one of the most fundamental methods for the synthesis of  $\beta$ -lactams.<sup>2</sup> The reaction process consists primarily in a stepwise cycloaddition reaction. The reaction itself is initiated by creation of an imine which can undergo a nucleophilic attack to a ketene. A conrotatory electrocyclic ring-closure of the intermediate from the previous reaction results in the final  $\beta$ -lactam. The reaction of a monosubstituted ketene with an acyclic imine produces two stereogenic centers. On this basis two  $\beta$ -lactams may result in from this reaction as the *cis* or *trans* isomer.

In some other studies, experimental results have provided a comprehensive understanding of the pathway for the formation of the *cis* and *trans*  $\beta$ -lactam. It has been demonstrated that the stereoselectivity depends on a number of factors: structure of the imine and the acid chloride, order of addition of the reagents, nature of the solvent and temperature of the reaction. In this paper, optically active S-citronellal has been used to introduce chirality in  $\beta$ -lactam as one of the imine components.

## Results and Discussion:

All reactions were carried under strictly dry conditions using a balloon full with nitrogen to create an inert atmosphere. Anhydrous solvents were obtained from commercial sources but were further dried by distillation methods. Reactants were as well obtained from commercial sources without making any further treatment before using them in the reactions. The rate of the reactions was monitored by Thin Layer Chromatography (TLC) using pre-coated silica gel plastic plates containing fluorescence indicator. Imine **3** was prepared from *s*-citronellal (**1**) and aromatic amine **2** in the presence of molecular sieves in dichloromethane. Reaction of **3** with acetoxyacetyl chloride (**4**) in the presence of triethylamine produced a  $\beta$ -lactam **5** in approximately 50% yield. Proton NMR was used to determine the presence and structure of the  $\beta$ -lactam.

### Scheme 1:



$\beta$ -Lactam preparation using an chiral aldehyde in which the chiral carbon is one carbon away has been known. However, in this example, the chiral carbon is two carbons away from the aldehyde functionality. It has been hypothesized that the absolute stereochemistry of the  $\beta$ -lactam ring in **5** follows earlier observation.<sup>3</sup> Structure **5** is highly functionalized and therefore, several chemical manipulations can be performed for the preparation of important compounds.

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