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SYNTHESIS OF VINYL β-LACTAMS: INSIGHTS ON THE MECHANISM OF THEIR FORMATION

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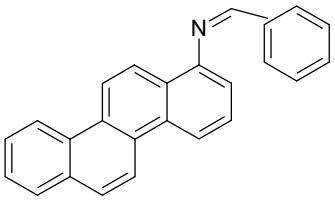
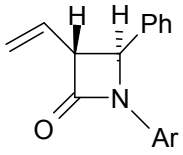
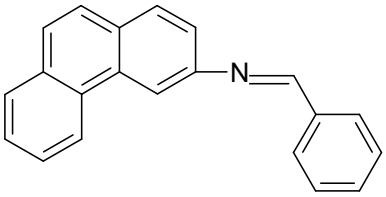
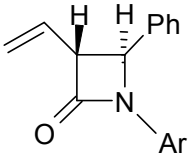
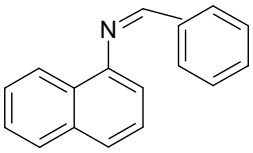
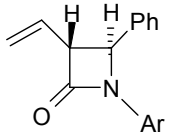
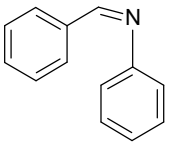
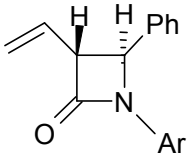
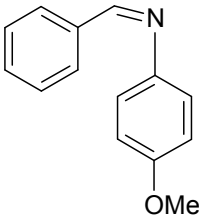
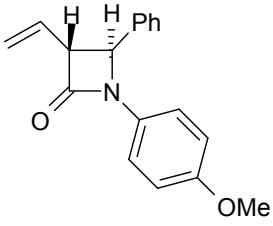
Abstract: Synthesis of vinyl β-Lactams has been realized. The mechanism of their formation has been explained.

Keywords: β-Lactams, Mechanism, Rearrangement

Introduction: β-Lactam antibiotics cover a wide range of compounds that includes penicillin, penams (which are pencilin derivatives), cephalosporins, carbapenems, and any antibiotic agent that contains a 2-azetidinone ring. Since the discovery of penicillin this field has grown immensely with β-lactams showing antimicrobial as well as antibacterial properties. Synthesis of vinyl β-lactams is important objective because the olefinic group can be converted to other functional moieties. We have been conducting research on β-lactams that have polyaromatic groups at the nitrogen. Our research has also demonstrated notable anticancer activities of some of the β-lactams.[1] During the course of this investigation, we became interested in the preparation of vinyl β-lactams derived from polyaromatic imines as well as imines derived from monocyclic benzene derivatives. In this communication, we describe that synthesis of vinyl β-lactams from polyaromatic systems is a problematic procedure. In addition, we would like to focus on the mechanism of formation of vinyl β-lactams. Despite huge success of the β-lactam chemistry, mechanism of vinyl β-lactam formation remains unexplored. [2]

Experimental: Reaction of *trans* crotonyl chloride was performed with imines derived from chrysene. Unfortunately β-lactam from this reaction was isolated in very low yield (approximately 5%).[3] To examine the validity of our method, we attempted other similar imines. We performed this reaction with smaller polyaromatic ring systems bound to the nitrogen of the imines such as the phenyl, naphthalenyl and the phenanthrenyl and the results are shown in **Table 1**. These reactions yielded a vinyl β-lactam for naphthalene imine and phenanthrene imine in low yields and the products were extremely difficult to isolate. In contrast, the reaction proceeded well with smaller aromatic imines derived from monocyclic benzene derivatives.[4]

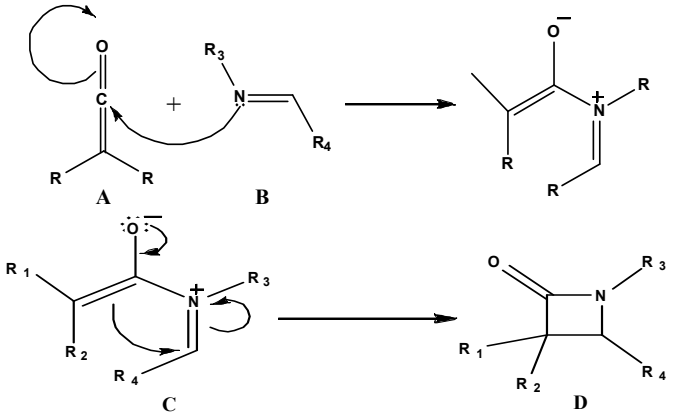
Table1: Synthesis of vinyl β-lactams

IMINES	β-LACTAMS	% Yield
	 **Ar = Chrysenyl**	**5**
	 **Ar =Phenenrneyl**	**10**
	 **Ar = 1-Naphthyl**	**10**
	 **Ar = Phenyl**	**70**
		**75**

Results: According to Lopez et al [5] the Staudinger reaction between a ketene and in imine undergoes a [2+2] cycloaddition reaction that is not concerted but rather under goes a stepwise reaction. It is further elaborated by their calculations that confirm that the Staudinger reaction undergoes a two-step process through the formation of the zwitterionic intermediate then it undergoes the ring closure step (A to D; **Scheme 1**). Their calculations further elaborate that the geometry of the β-lactam not only depends on the size of the substituent (steric hindrance) but also their nature i.e. the electron donating groups favor the con-rotatory ring closure via an outward rotation that favors *cis*-

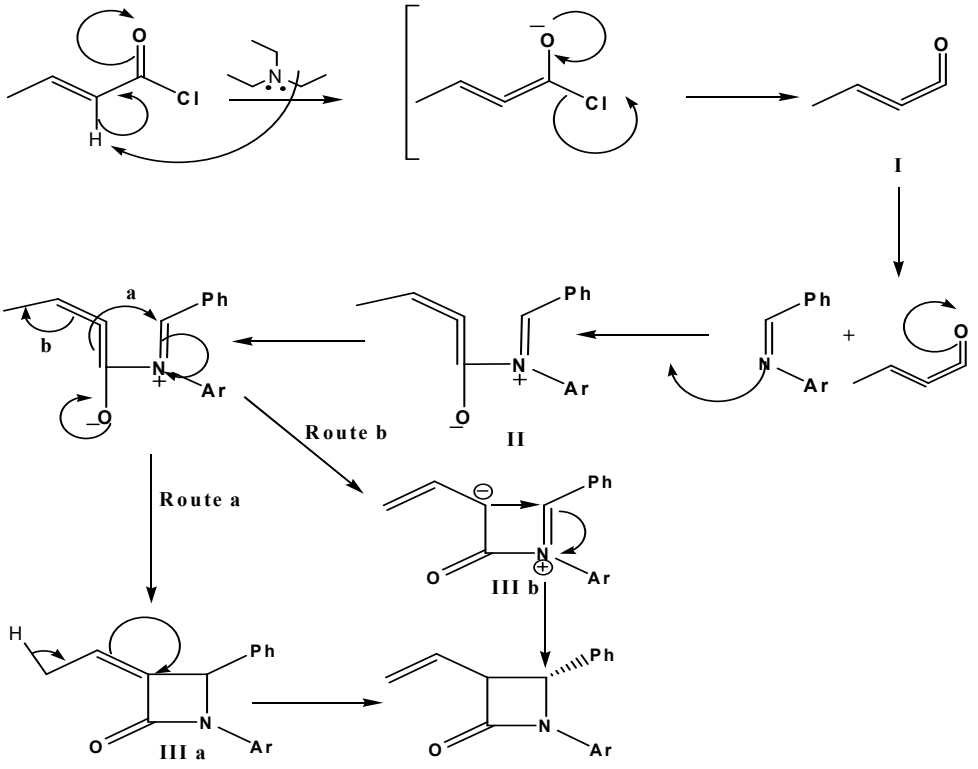
stereochemistry, whereas electron-withdrawing groups favor an inward rotation leading to *trans*-stereochemistry. This mechanism explains most of the β-lactam formation reaction. However, it seems there is a significant gap when unstaturated acid chloride was used. According to this mechanism, products from this reaction should be conjugated unsaturated β-lactams. However, this present study and confirmed that this reaction produced non-conjugated β-lactams. Although we have not investigated the mechanism of this reaction in detail, we could explain the formation of the product as described below. In fact, literature revealed that no mechanism has been investigated on the synthesis of vinyl β-lactams.

Scheme-1



This mechanism can be divided into four intermediate steps (**Scheme-2**). The first step is the formation of the α, β-unsaturated ketene **I**. This formation of ketene has been postulated by many authors.[3,4]

Scheme-2



The imine acts as the nucleophile and attacks the carbonyl carbon of the ketene forming the zwitterionic intermediate **II**. The formation of this type of intermediate is established in the literature.
The zwitterionic intermediate **II** undergoes ring closure forming the β-lactam with an exocylic double bond **IIIa**. This suggests that the product should be a conjugated β-lactams **IIIa (**route **a)**. Moreover, conjugated system should be the preferred product. But, in reality, the actual products are found to be non-conjugated **IV**. To explain this product, we hypothesize a rearrangement reaction that can produce thermodynamically more stable *trans* β-lactam **IV**. This exocyclic double bond in **III** undergoes rearrangement to yield a vinyl β-lactam **IV**. Although not clear, however, it seems that the conjugated product is under severe strain because of the size of the β-lactam ring. Alternatively, enolate **II** can form **IIIb** through route **b** and this method then can form non-conjugated *trans* β-lactam **IV**. It appears that the presence of polyaromatic ring at the nitrogen makes the intermediates unstable and consequently, preparation of β-lactams proved to be extremely difficult. It may be stated here with oxygen- and nitrogen-containging acid chlorides, the reaction proceeded well with polyaromatic imines.[1] These observations clearly indicate that vinyl β-lactam formation is an extremely complex process regardless of the structure of the imines.

Conclusion

In conclusion, the difficulty in synthesizing vinyl β-lactam has been addressed here with polyaromatic imines. An attempt has also been made to explain the formation of the vinyl β-lactams through an extension of the existing knowledge in this area.[1,2]

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