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ESTER ENOLATE-IMINE CONDENSATION TO BETA LACTAM: MECHANISM OF THE REACTION

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Abstract
An ester enolate condensation with an imine produces substituted β-lactam. The mechanism of the process is advanced to explain the stereoselectivity. This reaction gives similar stereochemical results in the presence of organic base (HMPA).

Keywords: Enolate-Imine, 2-azitidinone, LDA

Introduction:
A new compound of carbapenem group was isolated as thienamycin in late 1970 [1, 2]. Synthetic approaches for this antibiotics is known [3]. Penicillin and cephalosporin have C5α-C6α structures their azetidine nucleus **1-3**. Thienamycin has *trans*-configuration C6β-C5α [4]. The synthesis of (+/)-thienamycin was available in 1978 [5]. The compounds in this group can be converted to another by some manipulations. Monocyclic ring is actually elaborated to the bicyclic ring. The side can functional group can be installed in the beginning of the synthetic approaches. It can also be inserted after the two ring formation through an aldol type of reaction. However, to introduce the functional groups at the five-membered ring requires significant efforts.

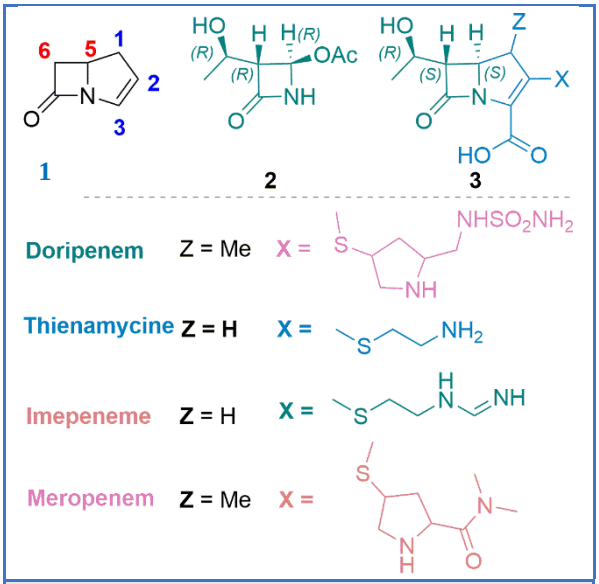
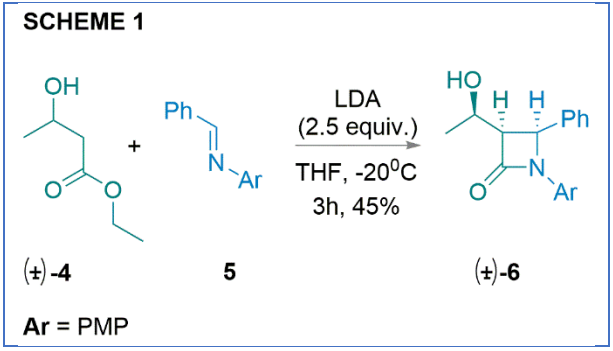


FIG.1 Core structure of Thienamycin Group of antibiotics

We report herein a lithium disoproylamide-induced reaction of hydroxybutyrate and diaryl imine for the preparation of the 1-hydroxyethyl side chain of thienamycin. Only a single diaryl imine is shown here. However, the reaction proceeds with similar diamines derived from other amines and carbonyl compounds.

Result and Discussion:

Lithium dianion of ester-enolate with *p*-anisylaldimine **5** produced *cis*-β-lactam **6** in 50% yields as a single stereoisomer. The temperature of the reaction has significant effects on the stereochemistry of the product (Scheme 1). An organic base in molar proportion (HMPA) is found to act positively in this reaction. An excess amount of LDA is required for the success of this reaction. An average of 3h is required for the completion of this reaction. This reaction can be performed at -78^{0}C as well. But, the reaction needs a longer time (approximately 6h) for completion. This reaction proceeds well with racemic as well as optically active hydroxybutyrate. No elimination products of the side chain (alkene-substituted) is found.



The stereochemistry of the products depends on the configuration of the lithium enolate (Z/E) and spatial nature of the substituent of the imine in the transition state. This reaction may produce numerous products as it is a sensitive reaction. However, we obtained a *cis* product. The formation of the *cis* isomer was due to the production of stabilized transition state through an E-enolate (Scheme 2). The stabilization can be enhanced by the co-solvent HMPA. The yield of the product goes down in the absence of HMPA.

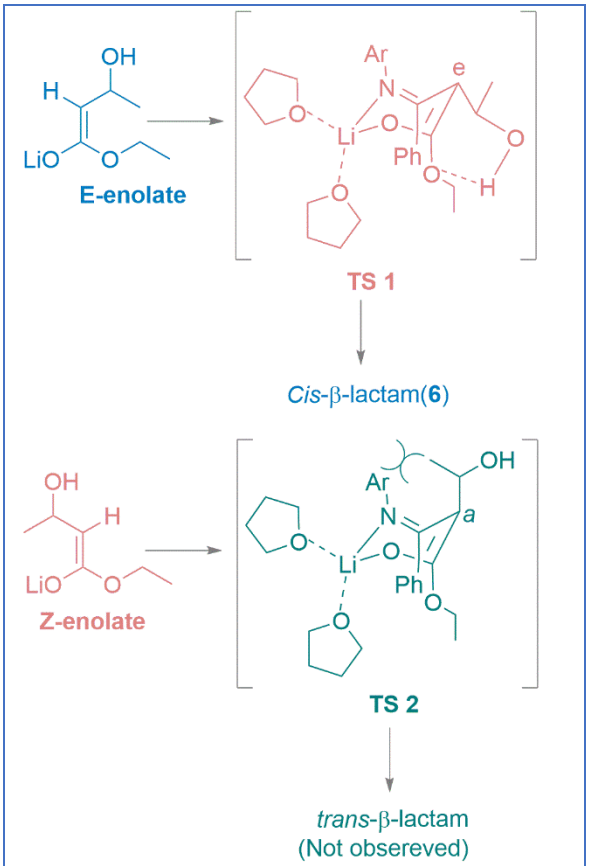


FIG.2 Plausible T.S for the formation *Cis*-β-lactam

A *trans*-β-lactam was possible from the Z-enolate and this was not observed. The driving force for the transition state was due to stabilization through remote hydrogen bonding between the hydroxyethyl part and ester of butyrate functionality. This suggested that the E-enolate reacts faster and delivers the product exclusively. The *cis*-β-lactam **6** was isolated through column chromatography and was then fully characterized. An inversion of the TS 2 is not noted. TS1 is stabilized in the presence of HMPA. A treatment of the cis isomer with a base at room temperature does not invert the stereochemistry. However, prolonged exposure of the hydroxyl compound in the presence of base decomposed it since dehydration to other products is feasible.

Conclusion:

Reaction of ethyhydroxybutyrate and an imine in the presence of LDA was performed to produce a *cis*-β-lactam, a fragment present in thienamycin. A mechanism of the process is advanced.

Acknowledgment:

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