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AN EFFICIENT β-AMINO ACID CYCLODEHYDRATION USING METHANESULFONYL CHLORIDE TO THIENAMYCIN INTERMEDIATE 3-[1-HYDROXYETHYL]-4-[METHOXY CARBONYLMETHYL]-AZETIDIN-2-ONE

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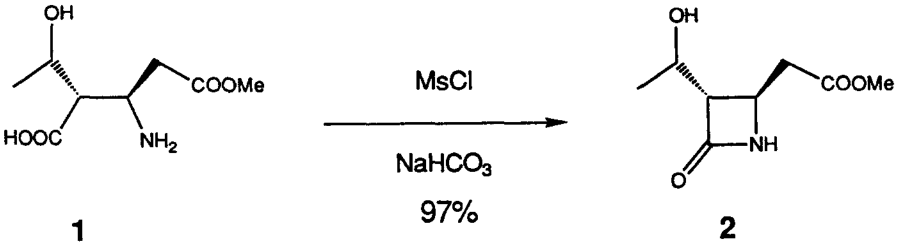
Summary: A new process for β-amino acid **1** cyclodehydration to β-lactam **2** using methanesulfonyl chloride/ sodium bicarbonate is described.

The broad spectrum β-lactam antibiotic thienamycin and its potent analogues have been the focus of numerous racemic and non-racemic synthetic strategies over the past decade.[1] The synthesis of (+)-thienamycin, developed in this laboratory and based on acetone-dicarboxylate (ADC), relies on ring closure of β-amino acid **1** to form the key carbapenem skeleton **2**[1d,e]. Recently, we re-examined the chemistry of this critical cyclodehydration step. Our investigation resulted in the development of a simplified, high yield method for the cyclodehydration of β-amino acid **1** to β-lactam **2** using methanesulfonyl chloride and sodium bicarbonate in a suitable solvent.



Numerous procedures are currently available for the cyclodehydration of β-amino acids to β-lactams[1,2], with several methods introduced since the initial thienamycin process development.[2] None of these methods fulfilled our strategy or yield expectations when evaluated on **1**, therefore, we sought a potentially simple, alternative method. To this end we explored the phase transfer catalytic (PTC) ring closure method developed by Mukaiyama that used inexpensive methanesulfonyl chloride as the cyclodehydrating reagent[3].

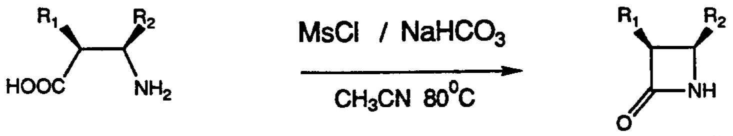
Application of the PTC method on **1** gave predominant methyl ester hydrolysis of **1** and less than 20% of **2**. Elimination of the aqueous phase precluded the ester hydrolysis and resulted in a moderate yield increase of **2**. Encouraged by that result, this system was probed in depth leading to the new cyclodehydration method which achieved a consistent 97% yield of high purity β-lactam **2** from β-amino acid **1** without N-substitution[2i], an aqueous phase, or the mediation of phase transfer catalysis.[4]

Typically, solid β-amino acid **1** was added over a two hour period to a rapidly stirred 45°C solution of methanesulfonyl chloride (1.05 equiv) in acetonitrile (0.2M in MsCl) containing suspended $NaHCO_3$[5] (6 equiv). Consumption of the starting material occurred within two hours of addition, after which time the fine suspension was cooled to 0°C and filtered. The resultant acetonitrile solution contained **2** in 97% yield (HPLC quantitative solution assay), and upon evaporation provided crystalline **2** of 97% purity (HPLC). Further purification was achieved by either recrystallization or chromatography and gave 99% pure **2** in 94-96% isolated yield. Additionally, this reaction was easily scaled from gram to kilogram quantities with equal success.

This method compared favorably with other β-lactamization methods applied on **1**, including DCC[1c], Ph_3P/2,2'Dibenzothiazyl disulphide[2b] and 2-chloro-N-methylpyridinium iodide[2c] which gave **2** in 88%, 90% and 93% yields respectively. It also has several clear advantages over these methods including ease of work-up (filtration) to obtain high purity (vide supra) β-lactam in solution.

To explore the generality of this procedure, simple substituted and unsubstituted β-amino acids were subjected to the cyclodehydration conditions and the resulting β-lactam yields were compared to at least two literature methods (table I). The yields of the isolated β-lactams ranged from moderate to good, while the simplest β-amino acid, β-analine (entry a), proved the most difficult to cyclodehydrate. The very low solubility in acetonitrile at 45°C of the highly polar, zwitterionic form of this and the other simple β-amino acids (entries a,b,c,e) was implicated for their modest cyclodehydration yields. Increasing the reaction temperature to 80°C improved their solubility and lead to a 50%

TABLE I. Cylcodehydration of Simple β-Amino Acids with Methanesulfonyl Chloride / $NaHCO_3$*



3(a-f)

4(a-f)

Entry	R_1	R_2	% yield **4** (%; **REF**)
a	H	H	36 (80;**2a**)(22;**1f**)
b	H	Me	57 (80;**2g**)(87;**2c**)(46;**1f**)
c	Me	H	58 (75;**2g**)(49;**1f**)
d	H	Ph	87 (88;**2g**)(89;**2c**)(97;**2a**)
e	H	CO_2Bn	38
f	CH_3HOCH-	CH_2CO_2Me	75^a

* All reactions were carried out in acetonitrile at 80°C using 1.1 eqiuv. Methanesulfonyl Chloride. [a]Reacted at 45°C.

increase in β-lactam yields. In contrast, the greater solubility of amino acid 3d in acetonitrile was reflected in a β-lactam yield comparable to the literature methods. The low yield normally observed with cis β-amino acid ring closure[1,2,3], a consequence of steric compression, was not observed with this method and the cis β-amino acid 3f was readily cyclodehydrated in 75% isolated yield.

Work is in progress to further clarify the intriguing nature of this cyclodehydration process, as well as, to evaluate its application to other β-amino acid and higher homologs.

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4) (a)Benzenesulfonyl chloride has been used in the preparation of benzanilide from benzoic acid and anilide, however, it reportedly resulted from the amine displacement on the symmetrical carboxylic anhydride. **J.AM.CHEM.SOC.** 1955,77,6214. (b) Toluenesulfonyl chloride was found to react with both the amine and carboxylate under these conditions. (see 4a for a similar observation.)

5) The use of high purity USP grade $NaHCO_3$ was critical for consistant results.

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