

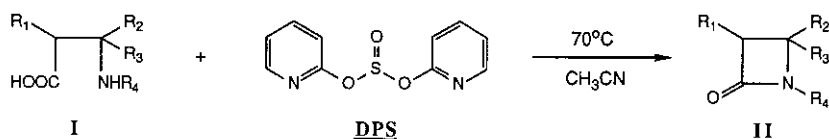
PREPARATION OF  $\beta$ -LACTAMS FROM  $\beta$ -AMINO ACIDS  
WITH DI-2-PYRIDYL SULFITE

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Abstract —  $\beta$ -Lactams are conveniently prepared in high yields by the reaction of  $\beta$ -amino acids with di-2-pyridyl sulfite in acetonitrile under very mild conditions.

Since  $\beta$ -lactams are known to be key components of many biologically active compounds such as penicilin and cephalosporin antibiotics, the importance of  $\beta$ -lactam formation in organic synthesis has been well recognized. Although there are a variety of methods for the construction of  $\beta$ -lactam ring,<sup>1</sup> one of the most fundamental approaches is based on dehydration of  $\beta$ -amino acids with condensing agents.<sup>2</sup> However, most known methods suffer from several limitations such as dependence on substrates, requirement of basic or acidic conditions, and difficulty of separation. Among various condensing agents currently available, triphenylphosphine/2,2'-dipyridyl disulfide<sup>3</sup> and 2-chloro-1-methylpyridinium iodide<sup>4</sup> might be most efficient. Recently we have reported new methods for  $\beta$ -lactam formation from  $\beta$ -amino acids with phosphorous-related condensing agents.<sup>5</sup> In the course of studies on the synthetic utility of di-2-pyridyl sulfite (DPS),<sup>6</sup> we have had an occasion to study the possibility of  $\beta$ -lactam formation from  $\beta$ -amino acids. It has been found that DPS is very effective for  $\beta$ -lactam formation in acetonitrile.

In order to find out optimum conditions, we have examined several reaction conditions by using 3-benzylaminobutyric acid as a model compound. The reaction proceeded smoothly and cleanly in acetonitrile at 70°C without addition of triethylamine, yielding N-benzyl-4-methyl-2-azetidinone in 72% yield, although the



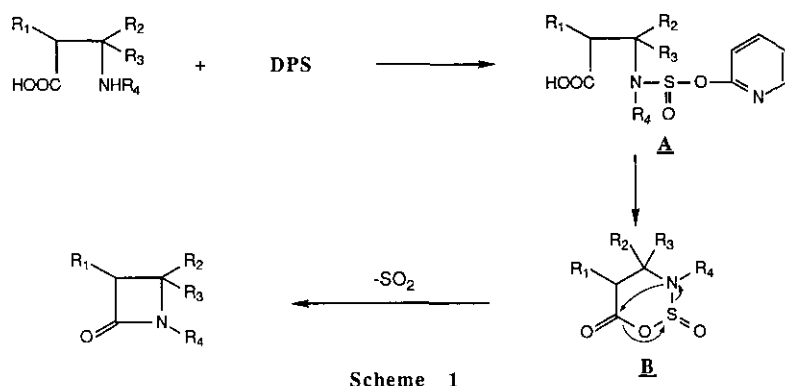
- |   |   |
|---|---|
| a. $R_1=R_2=H$ ; $R_3=CH_3$ ; $R_4=CH_2Ph$      | f. $R_1=CH_3$ ; $R_2=R_3=H$ ; $R_4=CH_2Ph$      |
| b. $R_1=R_2=H$ ; $R_3=CH_3$ ; $R_4=C-C_6H_{11}$ | g. $R_1=CH_3$ ; $R_2=R_3=H$ ; $R_4=C-C_6H_{11}$ |
| c. $R_1=R_2=H$ ; $R_3=CH_3$ ; $R_4=n-C_8H_{17}$ | h. $R_1=R_2=R_4=H$ ; $R_3=CH_3$                 |
| d. $R_1=R_2=H$ ; $R_3=n-C_3H_7$ ; $R_4=CH_2Ph$  | i. $R_1=R_2=R_3=R_4=H$                          |
| e. $R_1=H$ ; $R_2=R_3=CH_3$ ; $R_4=CH_2Ph$      |   |

Table 1. Synthesis of  $\beta$ -Lactams from  $\beta$ -Amino Acids

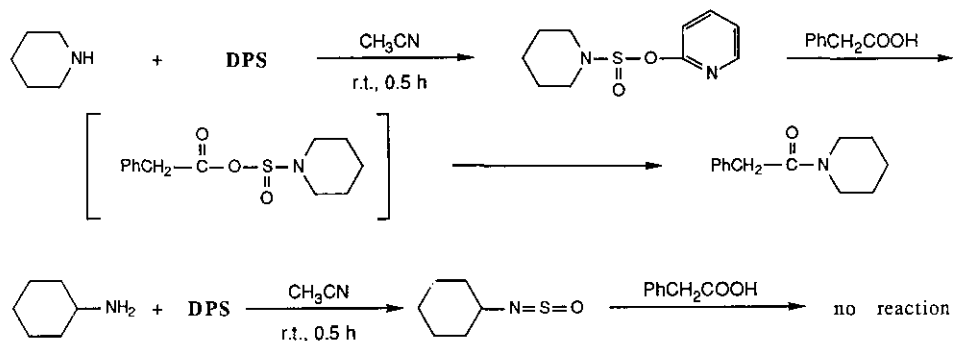
$\beta$ -lactam	isolated yield, %	$\beta$ -lactam	isolated yield, %
IIa	72	IIf	79
IIb	83	IIg	78
IIc	76	IIh	0
IId	73	IIi	0
IIe	91		

reaction occurred equally well in the presence of 1 equiv. of triethylamine (65% yield). The reaction took place at room temperature but 42% of the desired product was isolated together with 8% of 8-membered dimeric peptide in 10 h. Furthermore, it has been found that high dilution (0.01M) is necessary to obtain maximum yields of  $\beta$ -lactams.<sup>7</sup> Thus, other reactions were generally carried out with equimolar amounts of  $\beta$ -amino acids and DPS in acetonitrile at 70°C for 2 h under high dilution.

As shown in Table 1, the present method was successfully applied to various structurally different N-substituted  $\beta$ -amino acids. For example, 3-cyclohexylaminobutyric acid and 2-methyl-3-benzylaminopropionic acid were cyclized to the corresponding  $\beta$ -lactams in 83% and 79% yield, respectively. However, this method reaches a limit with N-unsubstituted  $\beta$ -amino acids and no  $\beta$ -lactams were obtained under the present conditions.



Although clear conclusions regarding reaction mechanism await further study, the reaction may proceed via an intermediate A, as shown in Scheme 1. Cyclization of the intermediate A into the 6-membered heterocycle B and the subsequent evolution of sulfur dioxide might give azetidinone derivatives. The proposed mechanism explains why N-unsubstituted  $\beta$ -amino acids do not cyclize to give  $\beta$ -lactams under the present conditions. As shown in Scheme 2, the reaction of cyclohexylamine with DPS in acetonitrile gave N-sulfinylcyclohexylamine, which did not react with phenylacetic acid. However, when 2-pyridyloxy-N-sulfinylpiperidine, generated from equimolar amounts of piperidine and DPS in acetonitrile, reacted with phenylacetic acid, N-phenylacetyl piperidine was obtained in 71% yield. Furthermore, it is noteworthy that the cyclization of  $\beta$ -amino acids using thionyl chloride and triethylamine has been reported in a limited number of cases, in which the reaction proceeds via an intermediacy of  $\beta$ -amino acid chloride hydrochloride salts.<sup>8</sup> Thus, the present method seems to be mechanistically different from the known method using thionyl chloride.



Scheme 2

In conclusion, the present method offers several advantages over previous methods: the reagent is easily prepared in a high yield, and the  $\beta$ -lactams are easily separated, and formed in high yields under very mild conditions.

#### ACKNOWLEDGMENT

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