PREPARATION OF β-LACTAMS FROM β-AMINO ACIDS WITH DI-2-PYRIDYL SULFITE

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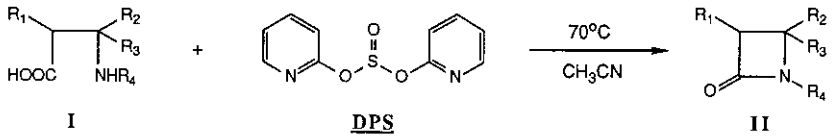
Abstract —— β-Lactams are conveniently prepared in high yields by the reaction of β-amino acids with di-2-pyridyl sulfite in acetonitrile under very mild conditions.

Since β-lactams are known to be key components of many biologically active compounds such as penicilin and cephalosporin antibiotics, the importance of β-lactam formation in organic synthesis has been well recognized. Although there are a variety of methods for the construction of β-lactam ring,[1] one of the most fundamental approaches is based on dehydration of β-amino acids with condensing agents.[2] 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[3] and 2-chloro-1-methylpyridinium iodide[4] might be most efficient. Recently we have reported new methods for β-lactam formation from β-amino acids with phosphorous-related condensing agents.[5] In the course of studies on the synthetic utility of di-2-pyridyl sulfite (DPS),[6] we have had an occasion to study the possibility of β-lactam formation from β-amino acids. It has been found that DPS is very effective for β-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



I DPS II

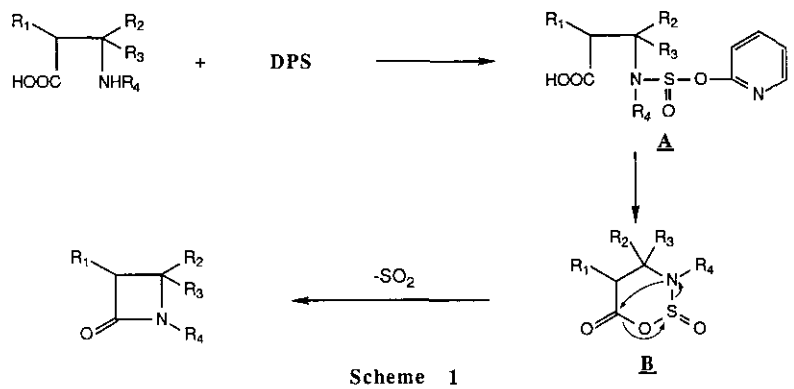
a. R_1=R_2=H; R_3=CH_3; R_4=CH_2Ph
b. R_1=R_2=H; R_3=CH_3; R_4=c-C_6H_{11}
c. R_1=R_2=H; R_3=CH_3; R_4=n-C_8H_{17}
d. R_1=R_2=H; R_3=n-C_3H_7; R_4=CH_2Ph
e. R_1=H; R_2=R_3=CH_3; R_4=CH_2Ph
f. R_1=CH_3; R_2=R_3=H; R_4=CH_2Ph
g. R_1=CH_3; R_2=R_3=H; R_4=c-C_6H_{11}
h. R_1=R_2=R_4=H; R_3=CH_3
i. R_1=R_2=R_3=R_4=H

Table 1. Synthesis of β-Lactams from β-Amino Acids

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

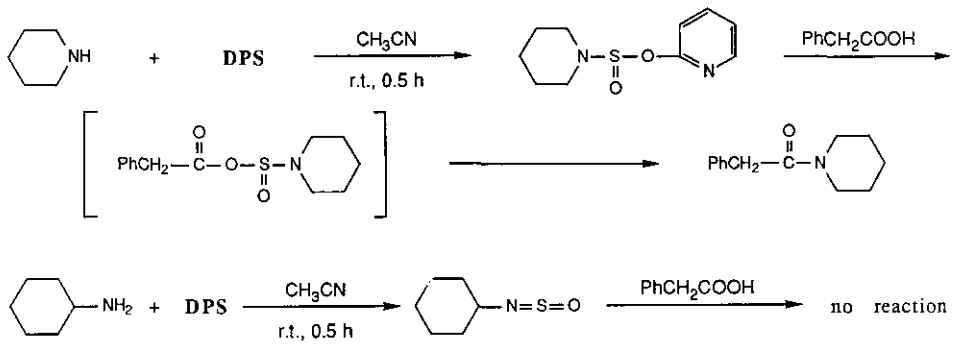
reaction occurred equally well in the presence of 1 equiv. of triethylamine (65% yield). The reaction took place at room temperature but 42% of the desired product was isolated together with 8% of 8-membered dimeric peptide in 10 h. Furthermore, it has been found that high dilution (0.01M) is necessary to obtain maximum yields of β-lactams.[7] Thus, other reactions were generally carried out with equimolar amounts of β-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 β-amino acids. For example, 3-cyclohexyl-aminobutyric acid and 2-methyl-3-benzylaminopropioinic acid were cyclized to the corresponding β-lactams in 83% and 79% yield, respectively. However, this method reaches a limit with N-unsubstituted β-amino acids and no β-lactams were obtained under the present conditions.



Scheme 1

Although clear conclusions regarding reaction mechanism await further study, the reaction may proceed via an intermediate A, as shown in Scheme 1. Cyclization ot 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 β-amino acids do not cyclize to give -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-phenylacetylpiperidine was obtained in 71% yield. Furthermore, it is noteworthy that the cyclization of β-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 β-amino acid chloride *hydrochloride salts.*[8] 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 β-lactams are easily separated, and formed in high yields under very mild conditions.

ACKNOWLEDGMENT

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