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A New Method for the β-Lactam Formation from β-Amino Acids Using *N,N*-Bis[2-oxo-3-oxazolidinyl]phosphorodiamidic Chloride

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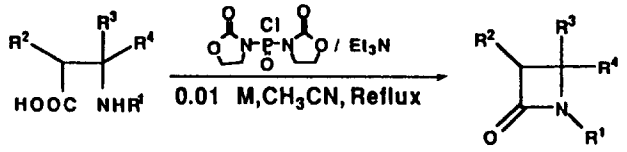
One of the most fundamental approaches to the construction of β-lactam rings is the dehydration of β-amino acids and numerous reagents have been introduced for this purpose[1]. In this paper, we wish to report that *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride[2] cyclizes β-amino acids into β-lactams in the presence of triethylamine. This reagent has been known to activate carboxyl group and thus applied to the peptide synthesis, esterification, and anhydride formation[2,3]. In particular, this reagent has once been utilized for the β-lactam formation from carboxylic acids and imines[4]; which consists of [2+2] cycloaddition of ketenes with imines.

With 3-benzylaminobutanoic acid as a model substrate, several solvents such as acetonitrile, dichloromethane, tetrahydrofuran and *N,N*-dimethylformamide were tested under various substrate concentrations (0.1, 0.05, 0.01 and 0.005 M) at room temperature or at refluxing condition. The best result was obtained in case of the substrate concentration of 0.01 M in acetonitrile with refluxing for 3 hr. Further dilution (0.005 M) or prolonged refluxing had no marked effects on yields.

A typical experimental procedure is as follows; To a solution of *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (305 mg, 1.2 mmol) in acetonitrile (100 m*l*) was added triethylamine (124 mg, 1.2 mmol) followed by 3-benzylaminobutanoic acid (193 mg, 1.0 mmol). The mixture was refluxed for 3 hr and the solvent removed in vacuo. Usual aqueous work-up and column chromatography on silica gel using 3:1 ethyl acetate-hexane afforded 1-benzyl-4-methylazetidin-2-one in 92% yield (161 mg).

Table 1 summarizes some of experimental results and illustrates the efficiency of the present method. N-Substituted β-amino acids were cleanly cyclized into β-lactams in excellent yields although 3-cyclohexylaminopropanoic acid and 3-benzylaminopropanoic acid gave moderate results due to the poor solubility. N-Unsubstituted β-amino acids were also cyclized in moderate yields.

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



R^1	R^2	R^3	R^4	Yield(%)[a]
C_6H_{11}	H	H	H	62
C_6H_{11}	CH_3	H	H	80
C_6H_{11}	H	CH_3	H	82
C_6H_{11}	H	CH_3	CH_3	87
CH_2Ph	H	H	H	63
CH_2Ph	CH_3	H	H	92
CH_2Ph	H	CH_3	H	90
CH_2Ph	H	CH_3	CH_3	98
CH_2Ph	H	$COOCH_3$	H	75
H	H	Ph	H	68
H	H	CH_3	H	61

[a] Isolated yields by column chromatograpy.

In conclusion, the present method offers several advantages over the previously known methods. The reagents are readily available and applicable to the β-amino acids of which the amino group is primary, and β-lactams are obtained in high yields under relatively mild condition.

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