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A Convenient Method for β-Lactam Formation from β-Amino Acids using Diphenylphosphinic Chloride

Sunggak Kim,* Phil Ho Lee, and Tai Au Lee

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 130–012, Korea

Diphenylphosphinic chloride is found to be very effective in promoting β-lactam formation from β-amino acids.

A new method for preparing β-lactams from β-amino acids is of particular interest in connection with the synthesis of β-lactam antibiotics,[1] and several efficient reagents such as triphenylphosphine/di-2-pyridyl disulphide[2] and 2-chloro-1-methylpyridinium iodide[3] have been reported in recent years.[4] Although organophosphinic chlorides have been successfully utilized in peptide synthesis,[5] as far as we are aware their application in forming β-lactams from β-amino acids has not been reported. We have found that diphenylphosphinic chloride in acetonitrile is very effective for inducing β-lactam formation from β-amino acids.

Among the solvents tested, acetonitrile gave the best

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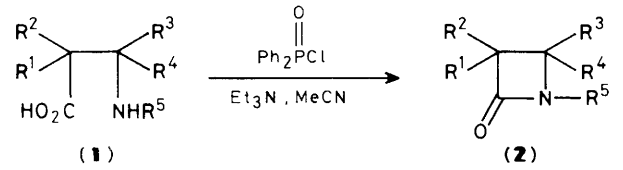

	R^1	R^2	R^3	R^4	R^5
a	H	H	H	Me	CH_2Ph
b	H	H	Me	Me	CH_2Ph
c	H	H	H	Pr^n	CH_2Ph
d	H	H	H	Me	cyclo-C_6H_{11}
e	H	H	H	Me	C_8H_{17}
f	Me	H	H	H	CH_2Ph
g	Me	H	H	H	cyclo-C_6H_{11}
h	Me	OPh	H	Ph	Ph
i	H	SPh	H	Ph	Ph
j	Me	OPh	H	Ph	CH_2Ph
k	OPh	H	H	Ph	CH_2Ph
l	H	H	H	Ph	H

results, although dichloromethane and tetrahydrofuran were also effective.

Using *N*-benzyl-3-aminobutyric acid as a model compound with diphenylphosphinic chloride and triethylamine under high dilution conditions (0.01 M), 78% of *N*-benzyl-4-methyl-azetidin-2-one was obtained in acetonitrile at 80 °C in 10 h, whereas 61 and 68% of the same β-lactam were obtained in dichloromethane and tetrahydrofuran, respectively. In a typical experiment, diphenylphosphinic chloride (1.2 equiv.) and triethylamine (1.2 equiv.) were added to a suspension of the β-amino acid in acetonitrile (0.01 M) and the reaction mixture was stirred at 80 °C for 10 h. After work-up with Na_2CO_3 solution and solvent removal, the crude product was purified by passing through a short column of silica gel.

As shown in Table 1, *N*-substituted β-amino acids were cleanly cyclized into the corresponding β-lactams in high yields. However, yields were poor when the amino group is primary. In case of β-amino acids (**1h**)—(**1k**),[6] it is noteworthy that the stereochemistry of the β-amino acids was preserved in the cyclization.

Table 1. Synthesis of β-lactams from β-amino acids.

β-Lactam	% Yield	β-Lactam	% Yield
(**2a**)	78	(**2g**)	81
(**2b**)	94	(**2h**)	85[a]
(**2c**)	80	(**2i**)	88[b]
(**2d**)	78	(**2j**)	98[c]
(**2e**)	70	(**2k**)	96[d]
(**2f**)	72	(**2l**)	31

[a] Mixture of diastereoisomers (2:3). [b] Mixture of *cis*- and *trans*-isomers (1:5). [c] Pure single isomer. [d] *cis*-Isomer from pure *threo*-(**1k**).

In conclusion, the present method offers several advantages over previous methods: the reagent is readily available, and the β-lactams are easily separated, and formed in high yields.

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