A Convenient Method for the β-Lactam Formation from β-Amino Acids Using Triphenylphosphine-Hexachloroethane-Triethylamine-Acetonitrile System

Bong Young Chung*, Kyu Cheol Paik, and Cha Soo Nah

Department of Chemistry, Korea University, Seoul 136-701

Received April 8, 1991

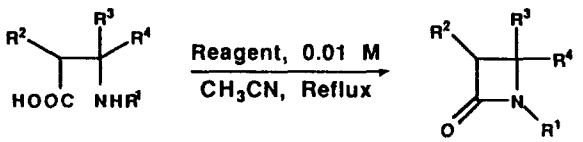
Hexachloroethane has been known to activate the carboxylic acid unit in the presence of triphenylphosphine and thus applied to the synthesis of simple peptides[1] or polypeptides[2]. Similar reagents such as triphenylphosphine-tetrachloromethane or triphenylphosphine-tetrabromomethane system have also been used for the synthesis of aziridines[3], Δ^2-oxazolines, Δ^2-oxazines, Δ^2-thiazolines, Δ^2-imidazolines[4], and for the conversion of carbonyl compounds into dichloroolefins[5], THP ethers into the corresponding bromides[6], alcohols into olefins[7], or carboxylic acids into esters[8]. In particular, the latter system has been utilized for the formation of β-lactams from 3-aminopropanoic acids[9] or from β-hydroxy amides[10] in good yields.

In connection with the β-lactam chemistry undergoing in this laboratory, we have applied the hexachloroethane-triphenylphosphine-triethylamine system to the synthesis of β-lactams from β-amino acids. With 3-benzylaminobutanoic acid as a model substrate, several solvents such as acetonitrile, tetrahydrofuran, dichloromethane, *N,N*-dimethylformamide and dimethyl sulfoxide were tested under various 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. When the reaction mixture was allowed to stand at room temperature for 15 hr, the same result was also realized.

The typical experimental procedure is as follows; To a stirred solution of triphenylphosphine (315 mg, 1.2 mmol), hexachloroethane (308 mg, 1.3 mmol) and triethylamine (263 mg, 2.6 mmol) in acetonitrile (100 m*l*) was added 3-benzylaminobutanoic acid (193 mg, 1.0 mmol) and the mixture was refluxed for 3 hr. Usual work-up and column chromatography of the resulting residue on silica gel using 3:1 ethyl acetate-hexane afforded 1-benzyl-4-methylazetidin-2-one in 87% yield (152 mg) as an oil.

Table 1 summarizes some of experimental results and illustrates the efficiency of the present method. β-Amino acids were cleanly cyclized into the corresponding β-lactams in high yields whether the amino group is secondary or primary. Even though the present method requires column chromatography to remove triphenylphosphine oxide, the reagents are readily available and inexpensive, and the system can be applicable to the β-amino acids of which the amino group is primary.

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



R^1	R^2	R^3	R^4	Yield(%)[a]
CH_2Ph	H	H	H	71
CH_2Ph	CH_3	H	H	92
CH_2Ph	H	CH_3	H	87
CH_2Ph	H	CH_3	CH_3	88
CH_2Ph	H	$COOCH_3$	H	76
$CH(CH_3)_2$	H	H	H	71
$CH(CH_3)_2$	CH_3	H	H	70
$CH(CH_3)_2$	H	CH_3	H	75
H	H	Ph	H	81
H	H	CH_3	H	70

[a]Isolated yields by column chromatography.

Acknowledgement. We gratefully acknowledge the financial supports from the Korea Science and Engineering Foundation and the Organic Chemistry Research Center sponsored by KOSEF.

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