Notes

Diethyl Bromophosphate as a New Condensing Reagent for the Formation of β-Lactams from β-Amino Acids

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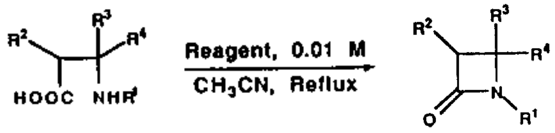
Received April 8, 1991

One of the most common synthetic methods for the formation of β-lactams is based on the intramolecular condensation of β-amino acids in the presence of suitable condensing reagents[1]. Among various condensing reagents developed so far, triphenylphosphine/ 2,2'-dipyridyl disulfide[2] and 2-chloro-1-methylpyridinium iodide[3] have been most frequently utilized. Recently, new organophosphate-type condensing reagents have been introduced[4] for the formation of β-lactams, and thus we wish to report that the very simple and readily available organophosphate, diethyl bromophosphate, is also very effective for the formation of β-lactams from β-amino acids.

Diethyl bromophosphate can easily be prepared by Arbuzov-type bromination of commercially available triethyl phosphite with bromine at −78℃ and has been successfuly applied to the peptide synthesis[5]. Thus, with 3-benzylaminobutanoic acid as a model substrate, we have examined the β-lactam formation using diethyl bromophosphate-triethylamine system. Among the solvents tested, acetonitrile gave the best results, even though dichloromethane and tetrahydrofuran were also effective, under high dilution (0.01 M) and reflux condition.

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



R^1	R^2	R^3	R^4	Isolated Yield(%)
CH_2Ph	H	H	H	65
CH_2Ph	CH_3	H	H	74
CH_2Ph	H	CH_3	H	71
CH_2Ph	H	CH_3	CH_3	89
CH_2Ph	H	$COOCH_3$	H	73
$CH(CH_3)_2$	H	H	H	76
$CH(CH_3)_2$	CH_3	H	H	72
$CH(CH_3)_2$	H	CH_3	H	71
H	H	Ph	H	33
H	H	CH_3	H	25

A representative experimental procedure is as follows; To a solution of diethyl bromophosphate (260 mg, 1.2 mmol) in acetonitrile (100 m*l*) was added triethylamine (121 mg, 1.2 mmol) followed by 3-benzylaminobutanoic acid (193 mg, 1.0 mmol). The mixture was refluxed for 5 hr and the solvent removed in vacuo. The residue was dissolved in dichloromethane and washed with 10% aqueous sodium bicarbonate followed by brine. Drying and solvent removal afforded pure 1-benzyl-4-methylazetidin-2-one in 80% yield (140 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 the corresponding β-lactams in moderate to high yields whereas N-unsubstituted β-amino acids gave poor results.

In conclusion, the present method offers several advantages over the previously known methods. The reagent is readily available and inexpensive, and the products are easily separated by simple aqueous work-up in high yields.

Acknowledgement. This research was financially supported by the Korea Science and Engineering Foundation and the Organic Chemistry Research Center sponsored by KOSEF.

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