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NEW METHODS FOR β-LACTAM FORMATION FROM β-AMINO ACIDS WITH ORGANOPHOSPHOROUS COMPOUNDS

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Summary: Ethyl dichlorophosphate, phenyl dichlorophosphate and phenylphosphonic dichloride are found to be very effective for β-lactam formation from β-amino acids.

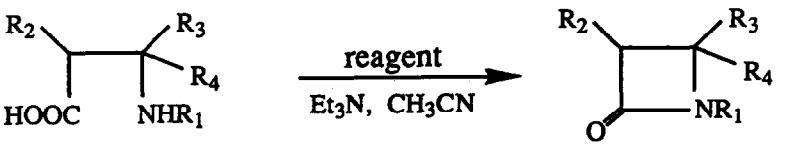
After diphenylphosphinic chloride was found to be very effective in promoting β-lactam formation from β-amino acids,[1] we have examined the effectiveness of other similar types of commercially available organophosphorus compounds. After much experimentation, ethyl dichlorophosphate, phenyl dichlorophosphate and phenylphosphonic dichloride have been found to be very effective for β-lactam formation from β-amino acids under mild conditions.

In a model study using N-benzyl-3-aminobutyric acid with ethyl dichlorophosphate and triethylamine, several noteworthy features have been found. First, the reaction proceeded smoothly at room temperature and was complete within 3 h. Secondly, among the solvents tested, acetonitrile gave the best results, although tetrahydrofuran and dichloromethane were also effective. Under high dilution conditions (0.01 M), 98% of N-benzyl-4-methylazetidin-2-one was obtained in acetonitrile, whereas 92% and 62% of the same β-lactam were obtained in tetrahydrofuran and dichloromethane, respectively. Finally, high dilution conditions were beneficial for optimal yields. 60% and 70% of the β-lactam were obtained in acetonitrile at room temperature under 0.1 M and 0.05 M. Thus, remaining reactions were carried out with 1.2 equiv of ethyl dichlorophosphate and triethylamine in acetonitrile at room temperature for 3 h under 0.01 M (Method A).

Phenyl dichlorophosphate and phenylphosphonic dichloride gave similar results but they were less effective than ethyl dichlorophosphate. Using N-benzyl-3-aminobutyric acid with phenyl dichlorophosphate and triethylamine in acetonitrile under 0.01 M, 57% of N-benzyl-4-methylazetidin-2-one was obtained at room temperature in 10 h, whereas 89% of the same β-lactam was obtained in acetonitrile at reflux for 3 h. Similar results were realized with phenylphosphonic dichloride. Thus, remaining reactions were carried out with 1.2 equiv of phenyl dichlorophosphate or phenylphosphonic dichloride and triethylamine in acetonitrile at reflux for 3 h under 0.01 M (Method B).

Table 1 summarizes some of experimental results and illustrates the efficiency and the scope of the present methods. N-Substituted β-amino acids were cleanly cyclized into the corresponding β-lactams in high yields. However, the yields were generally poor when

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



β-amino acid				isolated yield (%) of β-lactams		
R_1	R_2	R_3	R_4	$EtOP(O)Cl_2$[a]	$PhOP(O)Cl_2$[b]	$PhP(O)Cl_2$[b]
c-C_6H_{11}	H	H	H	81		
c-C_6H_{11}	CH_3	H	H	82	86	83
c-C_6H_{11}	H	H	CH_3	80	95	91
$PhCH_2$	H	H	H	96		
$PhCH_2$	CH_3	H	H	96	81	88
$PhCH_2$	H	H	CH_3	98	89	84
$PhCH_2$	H	CH_3	CH_3	99	95	96
$PhCH_2$	H	H	$COOCH_2Ph$	99	84	87
CH_3	c-C_6H_{11}	Ph	H	95[c]	96[c]	95[c]
$PhCH_2CH_2$	H	H	CH_3	78		
$PhCH_2CH_2$	H	CH_3	CH_3	99		
H	H	H	Ph	76[b]	0	37
H	H	H	CH_3	30[b]	0	[d]

[a]Method A. [b]Method B. [c]cis-Isomer from erythro β-amino acid[2]. [d]less than 5%.

the amino group is primary. It is noteworthy that the stereochemistry of the β-amino acid was retained in the β-lactam formation.[2]

In conclusion, the present method offers several advantages over previously known methods.[3] The reagents are readily available, and the β-lactams are easily separated by aqueous workup and obtained in high yields under mild conditions.[4]

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