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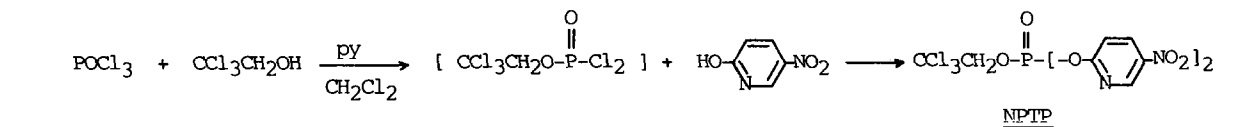
A NEW CONVENIENT METHOD FOR β-LACTAM FORMATION FROM β-AMINO ACIDS USING BIS(5'-NITRO-2'-PYRIDYL) 2,2,2-TRICHLOROETHYL PHOSPHATE

Sunggak Kim,* Suk Bok Chang, and Phil Ho Lee
Department of Chemistry
Korea Advanced Institute of Science and Technology, Seoul 131, Korea

Summary: Bis(5'nitro-2'-pyridyl) 2,2,2-trichloroethyl phosphate is found to be a new efficient condensing agent for β-lactam formation from β-amino acids in acetonitrile.

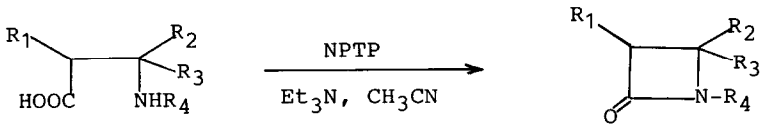
Although many synthetic methods for β-lactam formation have been developed,[1] one of the most important methods is β-lactam formation via the dehydration of β-amino acids. Thus, several efficient condensing agents such as triphenyl phosphine/2,2'-dipyridyl disulfide[2] and 2-chloro-1-methylpyridinium iodide[3] have been reported in recent years.[4] Although organophosphate types of condensing agents have attracted a great deal of interest in the peptide synthesis,[5] as far as we are aware, no successful report has appeared for their applications to form β-lactams from β-amino acids by intramolecular condensation. We wish to report that bis(5'-nitro-2'-pyridyl) 2,2,2-trichloroethyl phosphate is very effective for the β-lactam formation from β-amino acids.



The reagent was conveniently prepared by the reaction of phosphorous oxychloride with 1 equiv of 2,2,2-trichloroethanol and 3 equiv of pyridine in dichloromethane at 0 °C for 1.5 h and then at room temperature for 30 min followed by the addition of 2 equiv of 2-hydroxy-5-nitropyridine and subsequent stirring at room temperature for 2 h. The reagent was obtained in 75% yield as stable white crystalline solids.[6]

Among the solvents tested in this study, acetonitrile gave the best results and is generally recommended, although dichloromethane and tetrahydrofuran were also effective to some extent. In a typical experiment, 3-benzylaminobutyric acid was suspended in acetonitrile (0.01M solution), the reagent (1.1 equiv) and triethylamine (2.1 equiv) were added, and the mixture was stirred at room temperature for 10 h.[7] After aqueous workup with Na_2CO_3 solution and removal of the solvent in vacuo, the crude product was further 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 in acetonitrile at room temperature in most cases. However, the present method appeared to be less effective in the formation of β-lactams from N-unsubstituted β-amino acids. Although clear conclusions regarding the reaction mechanism await further study, the reaction may proceed via the intermediacy of a carboxylic-phosphoric mixed anhydride.

The noteworthy features of the present method include (i) a successful application of a new organophosphate condensing agent for β-lactam formation from β-amino acids, (ii) easy separation of β-lactams from the reaction mixture, (iii) mild conditions, and (iv) high yields for N-substituted β-lactams.



I II

a, $R_1=R_2=R_3=H$; $R_4=CH_2C_6H_5$
b, $R_1=R_2=H$; $R_3=CH_3$; $R_4=CH_2C_6H_5$
c, $R_1=CH_3$; $R_2=R_3=H$; $R_4=CH_2C_6H_5$
d, $R_1=H$; $R_2=R_3=CH_3$; $R_4=CH_2C_6H_5$
e, $R_1=R_2=H$; $R_3=n\text{-}C_3H_7$; $R_4=CH_2C_6H_5$
f, $R_1=R_2=H$; $R_3=CH_3$; $R_4=$cyclohexyl
g, $R_1=CH_3$; $R_2=R_3=H$; $R_4=$cyclohexyl
h, $R_1=R_2=H$; $R_3=CH_3$; $R_4=n\text{-}C_8H_{17}$
i, $R_1=R_2=R_4=H$; $R_3=n\text{-}C_3H_7$
j, $R_1=R_4=H$; $R_2=R_3=CH_3$

Table 1. Synthesis of β-Lactams from β-Amino Acids[a]

β-lactam	time, h	isolated yield, %	β-lactam	time, h	isolated yield, %
IIa	5[b]	70	IIf	6	91
IIb	10	84	IIg	6	87
IIc	10	84	IIh	5	80
IId	14	93	IIi	12[b]	44
IIe	6	85	IIj	12[b]	40

[a]The reaction was carried out with an 1:1 mixture of β-amino acids and the reagent in the presence of 2 equiv of triethylamine in acetonitrile (0.01M solution at room temperature. [b] The reaction was done at reflux.

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6. mp 158-160 °C; ^{1}H-NMR($CDCl_3$)δ 5.05 (d, 2H, J=8 Hz), 7.23 (d, 2H, J=8 Hz), 8.60 (m, 2H), 9.25 (d, 2H, J=4 Hz); IR(KBr) 1475, 1360, 1255 cm^{-1}.
7. The reagent may be converted into 5'-nitro-2'-pyridyl 2,2,2-trichloroethyl phosphoric acid after the reaction, although its structure was not determined by isolation.

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