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A CONVENIENT METHOD FOR THE PREPARATION OF PHOSPHORIC DIESTERS AND ITS APPLICATION TO THE SYNTHESIS OF PHOSPHOLIPIDS

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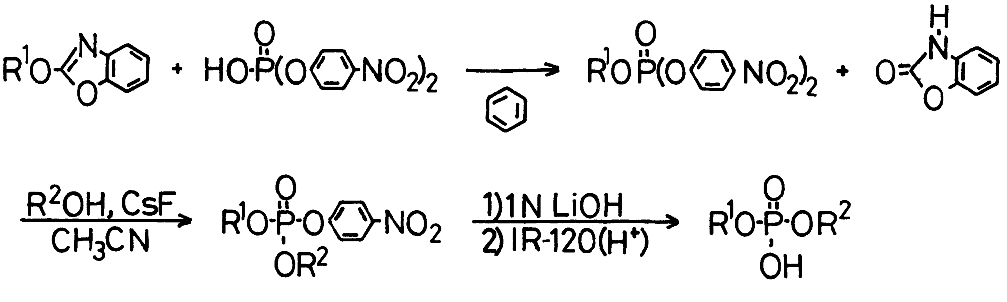
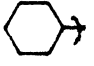
Treatment of 2-alkyloxybenzoxazoles with bis(p-nitrophenyl) hydrogen phosphate resulted in the formation of alkyl bis(p-nitrophenyl) phosphates. The phosphates were then converted by the application of various alcohols in the presence of cesium fluoride to dialkyl p-nitrophenyl phosphates, which, on treatment with alkali, gave dialkyl hydrogen phosphates in good overall yields. These sequential reactions were successfully applied to a synthesis of several phospholipids.

In the previous paper,1) we have described a new phosphorylation reaction by activating an alcohol with diphenyl hydrogen phosphate and 2-alkyloxybenzoxazoles. The alkyl diphenyl phosphates produced by the above reaction can be converted to alkyl dihydrogen phosphates by catalytic hydrogenation (Pt/H_2) or to alkyl phenyl hydrogen phosphates by a treatment with alkali under rather dradtic condition. Dialkyl phosphates can be obtained by phosphorylation of these alkyl phosphates with the second alcohols, however, reaction conditions to remove a phenoxy group from the phosphates are not suitable, especially in the cases where they have functional groups such as double bonds or alkali-sensitive groups. More effective process for the synthesis of dialkyl phosphates using 2-alkyloxybenzoxazoles have now been found by employing bis(p-nitrophenyl) hydrogen phosphate2) as a starting phosphate in place of diphenyl hydrogen phosphate. A preparation of dialkyl phosphates was performed by treating alkyl bis(p-nitrophenyl) phosphates, prepared by above mentioned reaction, with an alcohol in the presence of cesium fluoride3) and subsequent alkaline hydrolysis.



The following is a typical procedure for the preparation of dialkyl phosphates:

Table 1. Synthesis of dialkyl phosphates

R^1	R^2	Overall yield(%)a),b)
$\mathrm{Ph(CH_2)_2}$	$\mathrm{CH_3CH_2}$	74
$\mathrm{Ph(CH_2)_2}$	$\mathrm{CH_3O(CH_2)_2}$	80
$\mathrm{Ph(CH_2)_2}$	$\mathrm{HC{\equiv}CCH_2}$	76
$\mathrm{CH_3O(CH_2)_2}$		72
$\mathrm{CH_3O(CH_2)_2}$	$\mathrm{HC{\equiv}CCH_2}$	75

a) All compounds exihibited ir and nmr spectroscopic data in accordance with assigned structures.

b) Based on 2-alkyloxybenzoxazole.

A mixture of 2-phenethyloxybenzoxazole (239 mg, 1.0 mmol) and bis(p-nitrophenyl) hydrogen phosphate (408 mg, 1.2 mmol) in benzene (10 ml) was refluxed for 2 hours under an argon atmosphere. After cooling, ether was added and the solution was washed with water (3 times), filtered, and evaporated under reduced pressure. The residue was thoroughly dried on phosphorus pentoxide under reduced pressure and dissolved in acetonitrile (10 ml). The solution was added to 2-methoxyethanol (91 mg, 1.2 mmol) in acetonitrile (10 ml) and cesium fluoride4) (180 mg, 1.2 mmol), and the reaction mixture was stirred for 10 minutes at room temperature. After adding ether, the solution was washed with water (3 times), filtered, and evaporated under reduced pressure. The residue was dissolved in acetonitrile (10 ml) and treated with 4.5 ml of 1 N lithium hydroxide solution for 30 minutes at room temperature. After removal of acetonitrile, the pH of the aqueous solution was adjusted to pH 5 with acetic acid, and water (about 30 ml) was added. The aqueous solution was washed with ether (4 times), concentrated, and freed from lithium ions by passage through a 1.4×10 cm column of IR-120(H^+) resin. The effluent and washings were evaporated under reduced pressure and dried in vacuo to give spectoscopically and chromatographically pure 2-methoxyethyl phenethyl hydrogen phosphate (209 mg, 80% yield) as colorless oil.

In a similar manner, various dialkyl phosphates were obtained in good overall yields as listed in Table 1. Thus, various mixed dialkyl phosphates are prepared efficiently without isolation of any synthetic intermediates by the following three steps; 1) phosphorylation using 2-alkyloxybenzoxazolyl derivatives of various alcohols to alkyl bis(p-nitrophenyl) phosphates, 2) direct convertion to dialkyl p-nitrophenyl phosphates by application of alcohols in the presence of cesium fluoride,5) 3) removal of the residual p-nitrophenoxy group by treating with weak alkaline solution.6)

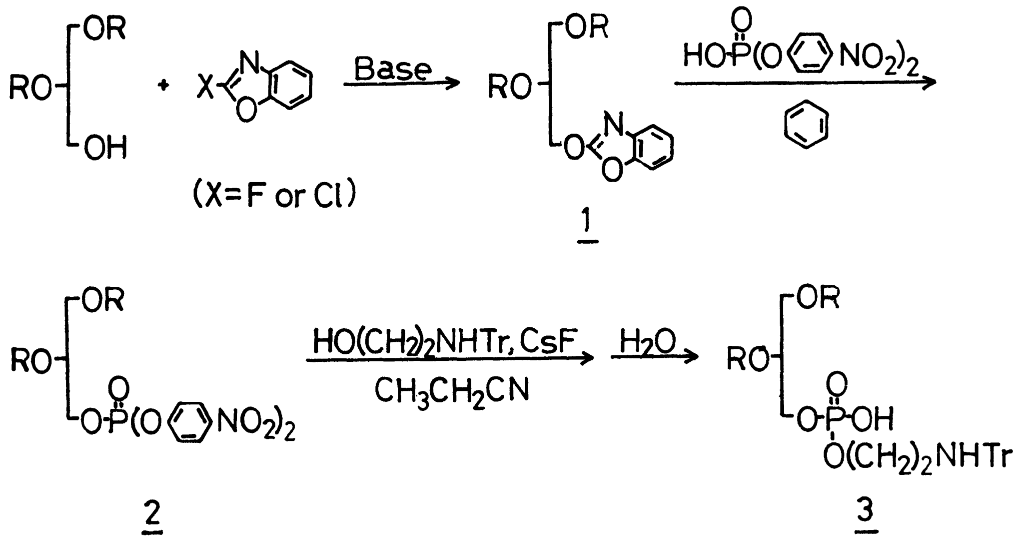
In the next place, we have successfully applied the present method to synthesis of phospholipids as illustrated in the following scheme.

2-(1,2-Distearoylglyceryl)benzoxazole was prepared by the reaction of 2-fluorobenzoxazole and 1,2-distearoylglycerol7) in the presence of triethylamine in 91% yield and 2-(1,2-dialkylglyceryl)benzoxazoles were obtained by treatment of the

Table 2. Synthesis of phospholipids

R	Step 1			Step2		
	Reaction conditions time (h)	temp.	Yield(%)[a] of 2	Reaction conditions time (h)	temp.	Yield(%)[a] of 3
Stearyl	10	refl.	79	2	60°C	73
Oleyl	10	refl.	73	2	r.t.	76
Stearoyl	1.5	refl.	81	2	40°C	75

a) Each product gave satisfactory spectral data.



potassium salts of the corresponding alcohols[8)] with 2-chlorobenzoxazole in 61% (R=stearyl) and 80% (R=oleyl) yields, respectively. These benzoxazolyl derivatives 1 thus obtained were converted smoothly by the reaction with bis(p-nitrophenyl) hydrogen phosphate to phosphoric triesters 2.[9)] These phosphates were in turn treated with N-trityl-2-aminoethanol in the presence of cesium fluoride in propionitrile[10)] and with water giving N-tritylated phospholipids 3. In these cases, the residual p-nitrophenoxy group was removed very smoothly by just treating with water different from the typical procedure using alkaline solution. N-Trityl derivatives can be converted to 1,2-diacyl- and 1,2-dialkylglycero-3-phosphorylethanolamines according to the method of Billimoria and Lewis.[11)]

It should be noted that the present procedure provides an efficient method for the preparation of dialkyl phosphates with respect to mildness of reaction conditions, simplicity of the procedure, and yield. And the wide applicability of the present method was realized partly by the synthesis of several phospholipids.

References and Notes

1) Y. Watanabe and T. Mukaiyama, Chem. Lett., 1978, 349.
2) J. G. Moffatt and H. G. Khorana, J. Am. Chem. Soc., 79, 3741 (1957).
3) Ogilvie et al. reported recently the preparation of mixed trialkyl phosphates by the transesterification assisted by large excess of cesium fluoride: K. K.

Ogilvie, S. L. Beaucage, N. Theriault, and D. W. Entwistle, J. Am. Chem. Soc., 99, 1277 (1977); K. K. Ogilvie and S. L. Beaucage, J. Chem. Soc. Chem. Comm., 1976, 443.

4) Prior to the reaction, cesium fluoride was dried by utilizing a toluene azeotrope.

5) Recently, Skaric et al. reported that the reaction of nucleoside bis(p-nitrophenyl) phosphates with the sodium salts of nucleoside derivatives gave the corresponding dinucleoside p-nitrophenyl phosphates in moderate yields; V. Skaric, M. Hohnijec, and D. Skaric, Croat. Chem. Acta, 49, 851 (1977), [Chem. Abstr., 90, 6640p (1979).]. As mentioned in the present communication, however, the transesterification using free alcohols is synthetically advantageous because of the simple procedure and mild conditions.

6) Typically, 1N lithium hydroxide solution (r. t.) was used, however, the use of 0.2N lithium hydroxide solution (0°C) gave similar results.

7) E. Bear and M. Kates, J. Am. Chem. Soc., 72, 942 (1950).

8) W. J. Baumann and H. K. Mangold, J. Org. Chem., 31, 498 (1966).

9) Similar results were obtained when the reaction was carried out without isolation of phosphoric triesters 2. For example, N-trityl-1,2-distearoylglycero-3-phosphorylethanolamine was obtained in 48% overall yield based on the starting material, 2-benzoxazolyl derivative.

10) Employment of propionitrile in place of acetonitrile gave better results presumably because the phosphoric triesters 2 containing long chain alkyl residues are scarecely soluble in acetonitrile.

11) J. D. Billimoria and K. O. Lewis, J. Chem. Soc. (C), 1968, 1404.

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