CHEMISTRY LETTERS, pp. 895-898, 1979. Published by the Chemical Society of Japan

AN EFFICIENT METHOD FOR THE SYNTHESIS OF MIXED DIESTERS OF PHOSPHORIC ACID

Teruaki MUKAIYAMA, Naoya MORITO, and Yutaka WATANABE
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

The reaction of 2-alkyloxybenzoxazoles with bis(p-nitrophenyl) hydrogen phosphate, and subsequent removal of one of two p-nitrophenoxy groups in the resulting alkyl bis(p-nitrophenyl) phosphate gave alkyl p-nitrophenyl phosphates. These were then converted to mixed dialkyl hydrogen phosphates in good overall yields by repetition of the above two-step procedure. The stepwise removal of two p-nitrophenoxy groups was successfully accomplished by the use of tetrabutylammonium acetate under very mild conditions.

In the previous communications,[1)] we reported a new phosphorylation method which consists of the reaction of 2-alkyloxybenzoxazole, readily derived from the corresponding alcohol and 2-halobenzoxazole, with diaryl hydrogen phosphate. Since the reaction is based on the activation of alcohol moiety, no pyrophosphate forms essentially and phosphoric triesters can be obtained in excellent yields starting from nearly stoichiometric amounts of 2-alkyloxybenzoxazoles and phosphoric diesters.

We now wish to report here an efficient synthetic method for the preparation of mixed diesters of phosphoric acid by the sequencial use of two different 2-alkyloxybenzoxazoles derived from primary alcohols. The reaction of 2-phenethyloxybenzoxazole derived from phenethyl alcohol and 2-fluorobenzoxazole with bis(p-nitrophenyl) hydrogen phosphate afforded bis(p-nitrophenyl) phenethyl phosphate which, without isolation, was treated with 1N lithium hydroxide solution giving p-nitrophenyl phenethyl hydrogen phosphate in 88% yield. The diester thus obtained

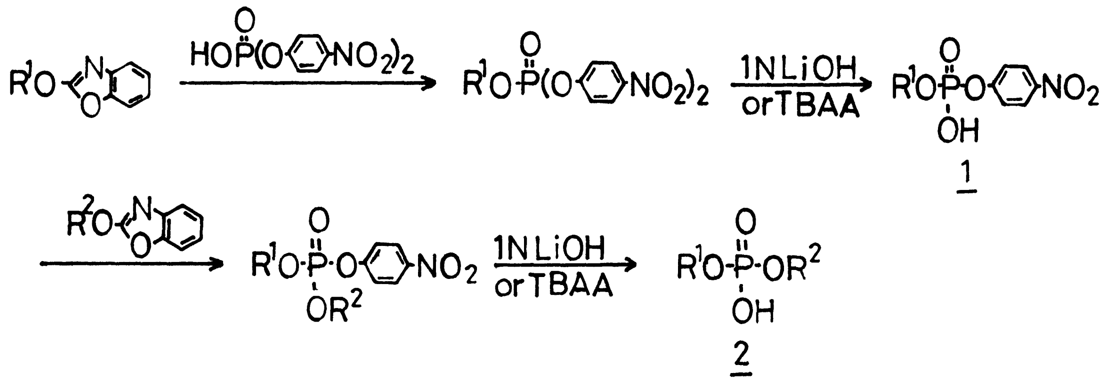


Table. Synthesis of dialkyl phosphates

R^1	R^2	Deblocking[a] method	Yield(%) of 1[b),c)]	Yield(%) of 2[b),d)]
$CH_3O(CH_2)_2$	CH_3CH_2	A	81	94
$Ph(CH_2)_2$	CH_3CH_2	A	88	82
$HC{\equiv}CCH_2$	$CH_3O(CH_2)_2$	A	94	91
CH_3CH_2	$Ph(CH_2)_2$	B	88	75
$CH_3O(CH_2)_2$	$Ph(CH_2)_2$	B	83	83

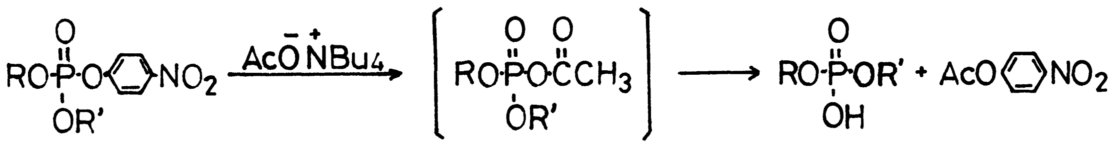
a) A: Treatment with 1N LiOH at room temperature.
B: Treatment with TBAA at room temperature.
b) All compounds exhibited ir and nmr spectroscopic data in accordance with assigned structures.
c) Based on 2-alkyloxybenzoxazole.
d) Based on alkyl p-nitrophenyl hydrogen phosphate.

was subjected to the reaction with 2-ethoxybenzoxazole, followed by alkaline hydrolysis to give ethyl phenethyl hydrogen phosphate in 82% yield. In a similar manner, some mixed diesters were prepared in high yields.

The removal of the p-nitrophenoxy group by treating with alkaline solution mentioned above is not always satisfactory, especially in the case where phosphoric triester has base-sensitive functional groups such as a carboxylic ester group in the same molecule. In order to remove of a p-nitrophenoxy group under nearly neutral condition, a new deblocking method was investigated. The selective removal of one of two p-nitrophenoxy groups in phenethyl bis(p-nitrophenyl) phosphate was effected by treatment with tetrabutylammonium acetate (TBAA)[2)] at room temperature for 10 minutes, and quantitative yield of phenethyl p-nitrophenyl hydrogen phosphate was obtained.[5)] The similar reaction of p-nitrophenyl diphenethyl phosphate with TBAA proceeded successfully to give diphenethyl phosphate in quantitative yield. Furthermore, bis(p-nitrophenyl) 2-stearoyloxyethyl phosphate 4a[6)] was quantitatively converted into the desired phosphoric diester 4b keeping the carboxylic ester group intact, while by treating with alkaline solution the carboxylic ester was competitively hydrolyzed. Even the acetyl group which is relatively reactive among common acyl groups was not also injured during the reaction of the 3α-acetyl-24-bis(p-nitrophenyl) phosphoryl derivative 5a[7)] with TBAA. The nonhydrolytic removal of the p-nitrophenoxy group is accomplished by way of a highly reactive acetyl phosphate 3 as sketched below. The intermediate acetyl phosphate derivative formed in situ is converted to the phosphoric diester and p-nitrophenyl acetate by the attack of the p-nitrophenoxide ion on the carbonyl carbon atom.[8)]

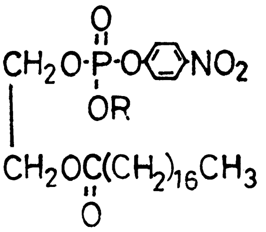
By repetition of the present phosphorylation and deblocking methods, ethyl phenethyl and 2-methoxyethyl phenethyl esters of phosphoric acid were prepared in high overall yields.

The following is a typical procedure for the preparation of dialkyl phosphates using TBAA in the removal of the p-nitrophenoxy group: A mixture of 2-(2-methoxyethoxy)benzoxazole (193 mg, 1.0 mmol) and bis(p-nitrophenyl) hydrogen phosphate (408 mg, 1.2 mmol) in benzene (10 ml) was refluxed for 3 hours under an argon atmosphere.



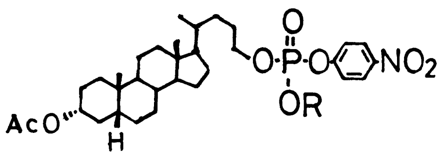
3

R'= alkyl, or p-$NO_2C_6H_4$



4

(4b; 96%)



5

(5b; 93%)

a; R = p-$NO_2C_6H_4$
b; R = H

After cooling, ether was added and the solution was washed with water (3 times), filtered, and evaporated under reduced pressure. The residue was dried on phosphorus pentoxide under reduced pressure and dissolved in tetrahydrofuran (THF) (5 ml), and the solution of tetrabutylammonium acetate (362 mg, 1.2 mmol) in THF (5 ml) was added. The reaction mixture was stirred for 10 minutes at room temperature, and water (40 ml) was added. The aqueous solution was washed with ether (4 times), concentrated, and freed from tetrabutylammonium ions by passage through a column of IR-120(H^+) resin. The effluent and washings were evaporated under reduced pressure and dried in vacuo to give crystalline 2-methoxyethyl p-nitrophenyl hydrogen phosphate (229 mg, 83%), mp 79.5-82°C (from ether). A benzene (5 ml) solution of 2-methoxyethyl p-nitrophenyl hydrogen phosphate (139 mg, 0.5 mmol) thus obtained and 2-phenethyloxybenzoxazole (144 mg, 0.6 mmol) was refluxed for 8 hours under an argon atmosphere. Work-up was carried out similarly to that described in the first step and the mixture obtained was then treated with tetrabutylammonium acetate (301 mg, 1.0 mmol) at room temperature for 7 hours and subsequently with IR-120(H^+) to give spectroscopically and chromatographically pure 2-methoxyethyl phenethyl hydrogen phosphate (108 mg, 83%) as colorless oil.

The present reaction using tetrabutylammonium acetate is a highly efficient method for unblocking p-nitrophenyl-protected phosphoric esters with respects to mildness of reaction conditions and yield. The phosphorylation reaction using 2-alkyloxybenzoxazoles proceeds smoothly under mild conditions. Consequently, the present sequence of the reactions provides a widely applicable method for the synthesis of mixed diesters of phosphoric acid.

References and Notes

1) Y. Watanabe and T. Mukaiyama, Chem. Lett., 1978, 349.
T. Mukaiyama, N. Morito, and Y. Watanabe, ibid., 1979, 531.

2) B. Iselin et al.3) utilized the reaction of tris(p-nitrophenyl) phosphite with carboxylic acids for preparing the p-nitrophenyl carboxylates. There have been, to our knowledge, no preparative method for unblocking aryl-protected phosphoric ester with acetate, although mechanistic studies on carboxyl-assisted hydrolysis4a) and alcoholysis4b) of phosphoric ester derivatives are known.

3) B. Iselin, W. Rittel, P. Sieber, and R. Schwyzer, Helv. Chim. Acta, 40, 373 (1957).

4) a) S. S. Simons, Jr., J. Am. Chem. Soc., 96, 6492 (1974), and references cited therein.
b) F. Ramirez and J. F. Marecek, Tetrahedron Lett., 1976, 3791.

5) Potassium acetate in the presence of 18-crown-6 brought about the same reaction to yield p-nitrophenyl phenethyl phosphate quantitatively, but it took six days to complete the reaction.

6) The phosphoric triester was obtained according to the typical procedure described in the text and used without isolation. 2-(2-Stearoyloxyethoxy)-benzoxazole was prepared by the reaction of the corresponding alcohol with 2-fluorobenzoxazole in the presence of triethylamine in 90% yield.

7) The phosphoric triester was prepared as described in the text. Namely, the mixture of it and 2-benzoxazolinone was allowed to react with TBAA. The 3α-acetyl-24-benzoxazolyl derivative was obtained by the reaction of the corresponding diol with 2-fluorobenzoxazole in the presence of triethylamine (97% yield), follwed by acetylation (83% yield). It should be noted that benzoxazolylation takes place exclusively on the hydroxyl group at C-24.

8) When phenethyl bis(p-nitrophenyl) and diphenethyl p-nitrophenyl phosphates were used, p-nitrophenyl acetate was obtained in quantitative yield in both cases. Since, according to the present method preparing dialkyl esters, the triesters formed in the phosphorylation steps are directly treated with TBAA, 2-benzoxazolinone as well as the p-nitrophenoxide ion attacks the acetyl group competitively.

(Received May 15, 1979)