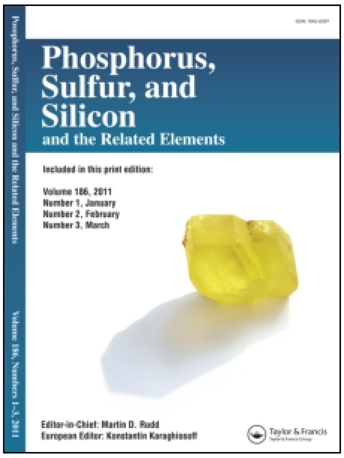

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# TRANSESTERIFICATION OF TRIS(*p*-NITROPHENYL) PHOSPHATE WITH SODIUM ALKOXIDES: BIS(*p*-NITROPHENYL) METHYL PHOSPHATE, BIS(*p*-NITROPHENYL) BENZYL PHOSPHATE, BIS(*p*-NITROPHENYL) *n*-BUTYL PHOSPHATE

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# TRANSESTERIFICATION OF TRIS(*p*-NITROPHENYL) PHOSPHATE WITH SODIUM ALKOXIDES: BIS(*p*-NITROPHENYL) METHYL PHOSPHATE, BIS(*p*-NITROPHENYL) BENZYL PHOSPHATE, BIS(*p*-NITROPHENYL) *n*-BUTYL PHOSPHATE

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Transesterification of tris(*p*-nitrophenyl) phosphate by sodium alkoxides, in dichloromethane at 0°, provides a convenient synthetic route to diaryl alkyl phosphates which are produced in a high state of purity and in moderate to high yields. The procedure is used to prepare bis(*p*-nitrophenyl) methyl phosphate, bis(*p*-nitrophenyl) benzyl phosphate and bis(*p*-nitrophenyl) *n*-butyl phosphate.

## INTRODUCTION

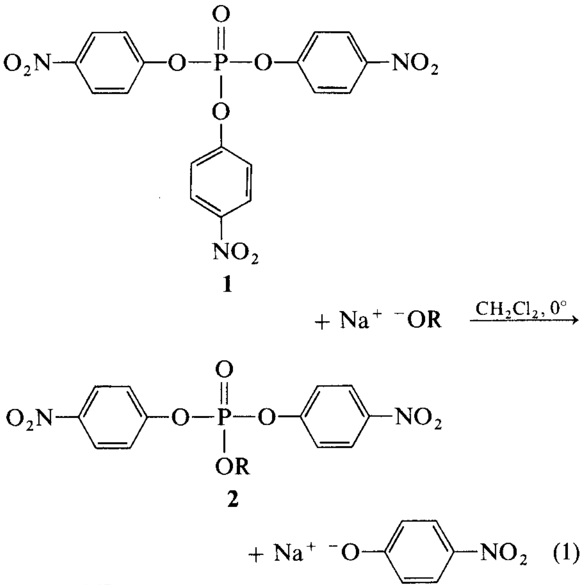
Activated triesters of phosphoric acid are of considerable value in examining the active-site chemistry of the serine hydrolases.[1–3] Work on the synthesis and resolution of the first optically active triester of phosphoric acid, asymmetric only at the phosphorus atom, methyl *n*-butyl *p*-nitrophenyl phosphate,[4] drew our attention to the fact that although there are several procedures available for the synthesis of these compounds, none of them is entirely satisfactory with respect to the number of synthetic steps, yield, or general applicability. This situation is exemplified by a comparison of the procedures available for the synthesis of bis(*p*-nitrophenyl) methyl phosphate (**2a**).

Ketelaar and Gersmann first obtained this compound in a yield of approximately 22% by treatment of one equivalent of phosphorus oxychloride with two equivalents of sodium *p*-nitrophenoxide followed by one equivalent of sodium methoxide.[5] An improvement in this type of synthesis involves the reaction of monosubstituted phosphorodichloridates and disubstituted phosphorochloridates with alcohols in anhydrous pyridine,[6] a procedure which still requires the synthesis and purification of the desired substituted phosphorochloridates and phosphorodichloridates. The two other literature procedures for synthesis of **2a** require the synthesis of bis(*p*-nitrophenyl) hydrogen phosphate by treatment of tris(*p*-nitrophenyl) phosphate (**1**) with hydroxide ion. Moffatt and Khorana[7] synthesized **2a** by the phosphorylation of methanol with tetra-*p*-nitrophenyl pyrophosphate, generated *in situ* by reaction of bis(*p*-nitrophenyl) hydrogen phosphate with di-*p*-tolylcarbodiimide. The yield for the phosphorylation reaction cannot exceed 50% based on bis(*p*-nitrophenyl) hydrogen phosphate, since phosphorylation yields **2a** and bis(*p*-nitrophenyl) hydrogen phosphate. The observation of Corby *et al.*[8] that the phosphorylating power of symmetrical pyrophosphates is a function of the acid strength of the parent acid, suggests that this type of reaction may not be applicable to the synthesis of less activated phosphate triesters. Dudman and Zerner[4] improved the yield for conversion of bis(*p*-nitrophenyl) hydrogen phosphate to **2a** to approximately 80% by alkylation with diazomethane in ether. Reaction of methyl *p*-nitrophenyl hydrogen phosphate, from the alkaline hydrolysis of **2a**, with diazobutane gave methyl *n*-butyl *p*-nitrophenyl phosphate in 83% yield.

The alkaline hydrolysis of *p*-nitrophenyl-substituted triesters proceeds rapidly and yields *p*-nitrophenol and the corresponding phosphate diester.[7] Moffatt and Khorana[7] further report that in the presence of 3.1 molar equivalents of sodium benzoxide in benzyl alcohol, **2a** was rapidly transesterified to dibenzyl methyl phosphate. These two observations suggested that the reaction of equimolar amounts of an aryl-substituted phosphate triester and a sodium alkoxide would lead to the selective displacement of an aryl substituent by an alkyl substituent.[9]

## DISCUSSION

The reaction of equimolar amounts of **1** and a sodium alkoxide in dichloromethane (Eq. 1) illustrates a simple, convenient method for transesterification of triesters of phosphoric acid, with the replacement of a *p*-nitrophenyl group by an alkyl substituent, to give moderate-to-high yields of product of high purity.



**a**, R = $CH_3$
**b**, R = $CH_2Ph$
**c**, R = $(CH_2)_3CH_3$

The high purity of product is confirmed by elemental analysis of once-crystallized product, the lack of anomalous peaks in the $^1$H nmr, and by the observed stoichiometric release of 100 ± 1 % of the theoretically expected quantity of *p*-nitrophenoxide in 0.1 N NaOH. The lack of an appreciable reaction of **2a** with sodium methoxide to give dimethyl *p*-nitrophenyl phosphate under the experimental conditions is confirmed by the near quantitative yield of crude **2a** and the high purity of the once-crystallized product. Sodium butoxide has previously been shown to react with triethyl phosphate under forcing conditions to give mixed ethyl butyl phosphates.[10] Transesterification of alkyl functions is therefore unlikely in the reaction of bis(*p*-nitrophenyl) alkyl and dialkyl *p*-nitrophenyl phosphates with sodium alkoxides. The successful conversion of bis(*p*-nitrophenyl) alkyl phosphates to mixed alkyl phosphates has already been demonstrated by Moffatt and Khorana,[7] and the present work clearly indicates that reaction of a bis(*p*-nitrophenyl) alkyl phosphate with a stoichiometric amount of a different sodium alkoxide will yield the mixed alkyl *p*-nitrophenyl phosphate in good yield.

Further, the facile alkaline hydrolysis of this class of phosphate triesters, with removal of one *p*-nitrophenyl group, provides in addition a convenient route to the corresponding alkyl-substituted phosphate diesters.[7]

## EXPERIMENTAL

The following experimental procedure illustrates the general method of synthesis of bis(*p*-nitrophenyl) alkyl phosphates from tris(*p*-nitrophenyl) phosphate (**1**).[11]

*bis*(p-*Nitrophenyl*) *methyl phosphate* (**2a**). A 3-1 Erlenmeyer flask containing a teflon-coated magnetic stirring bug was fitted with a two-hole rubber stopper, a 250-ml dropping funnel and a glass tube, both fitted with $CaSO_4$ drying tubes. To 2,300 ml of dichloromethane[12] was added 46.1 g (0.10 mol) of **1**,[13] and the solution was magnetically stirred and cooled to 0° in an ice bath. A methanolic solution of sodium methoxide [2.30 g (0.10 mol) of sodium per 150 ml of methanol[14]] was added dropwise over 6.5 h to the vigorously stirred reaction mixture.[15] The dense, orange reaction mixture was stirred for a further 45 min, and the precipitated sodium *p*-nitrophenoxide filtered off. The pale yellow filtrate was reduced in volume to 500 ml and a further small quantity of sodium *p*-nitrophenoxide filtered off. The filtrate was washed with 200 ml of water, and dried over anhydrous $Na_2SO_4$. Removal of solvent gave 35.0–35.1 g (99 %) of crude **2a**. The round-bottomed flask containing the crude triester was fitted with a condenser and $CaSO_4$ drying tube; 150 ml of chloroform[16] and a porcelain chip were added, and the mixture brought to reflux on a water bath.[17] Norit (0.6 g) was added, and the hot solution was filtered through a double layer of fluted Whatman 542 filter paper, and the paper was washed with 10 ml of hot chloroform. Hot carbon tetrachloride (300 ml) was added and the pale yellow solution was cooled gradually to −20°. The white needles which separated were filtered off, washed with a little cold carbon tetrachloride and dried *in vacuo* for 24 h, to give 25.5–27.8 g (72.0–78.5 %) of **2a**, mp 142.0–143.0°, lit. mp 142–143°.[7] The spectral properties of the product are as follows: ir, cm$^{-1}$: 1285 (P=O); 1201, 1165 (P—O—C$_{aryl}$); 1054 (P—O—C$_{alkyl}$): $^1$H nmr, $\delta$ (multiplicity, number of protons): 4.06 (singlet split by $^{31}$P coupling, 3); 7.42 (multiplet, 4); 8.28 (multiplet, 4). *Anal.* Calcd. for $C_{13}H_{11}N_2O_8P$: C, 44.08; H, 3.13; N, 7.91; P, 8.7. Found: C, 44.11; H, 3.44; N, 7.88; P, 8.6.

bis(*p*-Nitrophenyl) benzyl phosphate (**2b**), crystallized from carbon tetrachloride, mp 98.3–100.3°, lit. mp 101–102°,[7] and bis(*p*-nitrophenyl) *n*-butyl phosphate (**2c**), crystallized from carbon tetrachloride, mp 59.0–59.5°, were similarly prepared in yields of 67 % and 65 %, respectively. For **2c**, *Anal.* Calcd. for

$C_{16}H_{17}N_2O_8P$: C, 48.49; H, 4.32; N, 7.07; P, 7.8. Found: C, 48.36; H, 4.36; N, 6.98; P, 7.4. The spectral properties of **2c** are as follows: ir, $cm^{-1}$: 1293 (P=O); 1205, 1167 (P—O—$C_{aryl}$); 1040 (P—O—$C_{alkyl}$): $^1H$ nmr, $\delta$ (multiplicity, number of protons): 0.94 (triplet showing unresolved fine splitting, 3); 1.42 (sextet showing unresolved fine splitting, 2); 1.78 (quintet showing unresolved fine splitting, 2); 4.37 (triplet split by $^{31}P$ coupling, 2); 7.43 (multiplet, 4); 8.28 (multiplet, 4).

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8. N. S. Corby, G. W. Kenner, and A. R. Todd, *J. Chem. Soc.*, 1234 (1952).
9. The work described here results from a detailed study of a procedure used in the synthesis of a radioactive derivative (Ref. 2).
10. W. H. C. Rueggeberg and J. Chernack, *J. Amer. Chem. Soc.*, **70**, 1802 (1948).
11. Melting points were determined using open capillaries and are uncorrected. Infrared spectra (KBr discs) were recorded on a Pye Unicam SP1000 spectrometer, calibrated with polystyrene. Only the bands for P=O and P—O—C are reported. $^1H$ nmr spectra were determined on a Jeol JNM-PS-100 spectrometer using chloroform-*d* as solvent and TMS as reference. All removals of solvent were carried out on a Büchi rotary evaporator. The elemental analyses were performed by the Australian Microanalytical Service, Melbourne.
12. Mallinckrodt AR dichloromethane was dried for 24 h over Linde 4A molecular sieve and filtered through oven-dried Whatman 542 filter paper before use.
13. tris(*p*-Nitrophenyl) phosphate (Aldrich) was recrystallized from boiling acetone, mp 156–158°.
14. Commercial, redistilled methanol was dried using magnesium activated by iodine and fractionated, b.p. 64.6°; A. I. Vogel, *A Textbook of Practical Organic Chemistry* (Longman Group Limited, London, 1956), 3rd ed., p. 169.
15. The dichloromethane solution of **1** showed immediate turbidity on addition of the first drop of sodium methoxide. An orange precipitate of sodium *p*-nitrophenoxide was clearly evident after several minutes.
16. Freshly fractionated chloroform and carbon tetrachloride were used for the crystallizations.
17. Purification of **2a** was impeded when solid **2a** was heated significantly higher than ~95°. Such heating caused the formation of a highly insoluble by-product presumed to contain pyro- or poly-phosphate derivatives of **2a** (Ref. 2).