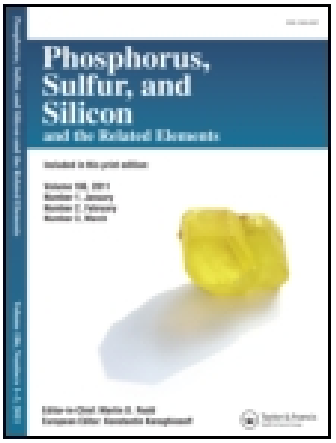

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Triethylphosphate/Phosphorus Pentoxide as an Efficient Reagent for the Phosphorylation of Phenols

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TRIETHYLPHOSPHATE/PHOSPHORUS PENTOXIDE AS AN EFFICIENT REAGENT FOR THE PHOSPHORYLATION OF PHENOLS

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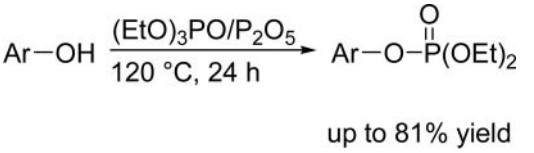
GRAPHICAL ABSTRACT



Abstract *A simple, efficient, and novel method has been developed for the phosphorylation of phenols. Treatment of phenols with a mixture of triethylphosphate/phosphorus pentoxide gives the corresponding phosphate derivatives in good yields. This method is easy, rapid, and offers good yields for the phosphorylation of phenols. The reaction of triethylphosphate with phosphorus pentoxide was also studied by variable-temperature ^{31}P-NMR spectroscopy.*

Keywords Phosphorylation; phenols; phosphorus pentoxide; triethylphosphate

INTRODUCTION

The organic chemistry of phosphorus compounds has became increasingly useful and important in organic synthesis. Phosphate esters are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[1] The synthesis of phosphate esters is an important objective in organic synthesis, because their wide use in the preparation of biologically active molecules as diverse as nucleic acids, proteins, carbohydrates, lipids, coenzymes, and steroids as well as in the reduction of phenols to aromatic hydrocarbons.[2] Many effective methods have been developed for the preparation of phosphates.[3] These methods involve: (1) the reaction of a dialkyl phosphite with phenol in the presence of triethylamine in carbon tetrachloride,[4] (2) phosphorylation of phenols with diethyl cyanophosphonate in the presence of triethylamine,[5] (3) phosphorylation of phenols *via* the activation of trialkyl phosphate with molecular iodine,[6] and (4) the use of a phosphoramidite

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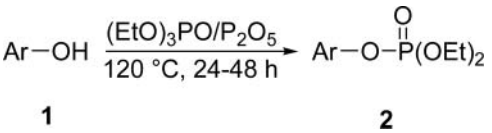
reagent to form the phosphate triester, followed by oxidation to the phosphate ester.[7] However, these methods have problems, including the use of chlorinated solvents and strong bases, low yields, and side-reactions. In addition, some of the starting materials have to be synthesized, and cleavage of a Et-O-P bond of the phosphorylating agent occurred in the phosphorylation of phenols using of diethyl chlorophosphate.[8] Recently, phosphorylation of alcohols and phenols with *N*-phosphoryl 5,5′-diphenyl oxazolidinones in the presence of copper (II) triflate and *N,N*-ethylene bis(benzaldimine) as a ligand has been reported.[9]

We have previously reported alternative strategies to achieve the phosphoryl transfer employing a chlorophosphate as the phosphate source in solvent-free condition in the presence of magnesia and alumina.[10] The development of simple and general synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. As part of our efforts for the synthesis of organophosphorus compounds,[11] we now report a new and efficient method for the synthesis of phosphate esters from the reaction of a mixture of triethyl phosphate and phosphorus pentoxide with phenols producing good yields of phosphate esters.

RESULTS AND DISCUSSION

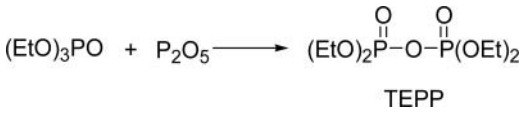
The phosphorylation of phenol (**1a**), chosen as a model compound, was studied in the presence of triethyl phosphate (Scheme 1). The progress of the reaction was monitored by (thin layer chromatography) TLC, and the experimental data for the screening conditions are listed in Table 1. Treatment **1a** with triethyl phosphate failed to give the corresponding phosphate adduct **2a** after 24 h at 50–120 °C (Entries 1–4). When the reaction was carried out at 70 °C in the presence of a mixture of triethyl phosphate and phosphorus pentoxide (4:1 w/w), compound **2a** was obtained in 36% isolated yield after 24 h (Entry 5). The phosphorylation of **1a** with a mixture of triethyl phosphate and phosphorus pentoxide proceeded smoothly at 120 °C for 24 h and gave **2a** in 78% isolated yield (Entry 6).



Scheme 1

Under the above optimized conditions, phenols were employed in the phosphorylation reactions (Scheme 1). The obtained results are summarized in Table 1. The phosphorylation of different substituted phenols gave the corresponding adducts in 46–81% isolated yields (Entries 7–14). The phosphorylation of benzyl alcohol also gave the corresponding adduct in a lower yield (41%), which was possibly due to low acidity (Entry 15). It was also possible to carry out this reaction for 1-naphthol and gave the corresponding phosphorylated adduct in a lower yield (42%), which was possibly due to the steric effect (Entry 16). Thus, the conditions reported herein tolerate a phosphorylation reaction of a wide variety of phenols.

We were interested to study the role of phosphorus pentoxide by the reaction of triethyl phosphate with phosphorus pentoxide by variable-temperature ^{31}P-NMR spectroscopy (Scheme 2). The ^{31}P-NMR spectrum of the mixture at 70 °C shows two completely resolved peaks at δ −10.23 (triethyl phosphate) and −22.33 ppm in a ratio of 1:0.7 respectively



Scheme 2

(Figure 1a). The peak at −22.33 is due to the tetraethyl pyrophosphate (TEPP).[12] The ratio of the TEPP to triethyl phosphate increases with increasing temperature to 120 °C (Scheme 2 and Figure 1b).

We also examined the reaction of thiophenol in the presence of a mixture of triethyl phosphate and phosphorus pentoxide. The reaction failed to give phosphorylated product and no other product was detected after 48 h at 120 °C.

In summary, we have developed a simple and practical method for the phosphorylation alcohols. Phosphorylation of phenols using very inexpensive and air stable reagents, can be synthesized in moderate to good yields. In addition, the other advantages of this environmentally benign and safe protocol include a simple reaction setup, not requiring specialized equipment, and gives moderate to good yields of products.

EXPERIMENTAL

All chemicals were commercial products and was distilled or recrystallized before use. NMR spectra were taken with a 400 Brucker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. The chemical shift data for each signal in ^{1}H NMR are given in units of δ relative to $CHCl_3$ ($\delta = 7.26$) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ and DMSO are recorded relative to the $CDCl_3$ resonance ($\delta = 77.0$). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 ($\delta = 0$) with broadband ^{1}H decoupling. Silica gel column chromatography

Table 1 Phosphorylation of phenols with a mixture of phosphorus pentoxide in triethyl phosphate at 120 °C

Entry	R	Reaction temperature (°C)	Time (h)	Yield%
1	C_6H_5-	50[a]	24	–
2	C_6H_5-	70[a]	24	–
3	C_6H_5-	90[a]	24	–
4	C_6H_5-	120[a]	24	–
5	C_6H_5-	70	24	36
6	C_6H_5-	120	24	78
7	*o*-MeC_6H_4-	120	48	75
8	*m*-MeC_6H_4-	120	24	81
9	*m*-FC_6H_4-	120	48	48
10	*m*-ClC_6H_4-	120	48	63
11	*m*-BrC_6H_4-	120	48	65
12	*m*-$NO_2C_6H_4$-	120	48	46
13	*p*-MeC_6H_4-	120	24	78
14	3,4-di-Me-C_6H_3-	120	24	78
15	$PhCH_2$-	100	48	41
16	α-Naphthyl	120	36	42
17	β-Naphthyl	120	24	54

[a]Reaction carried out without addition of phosphorus pentoxide.

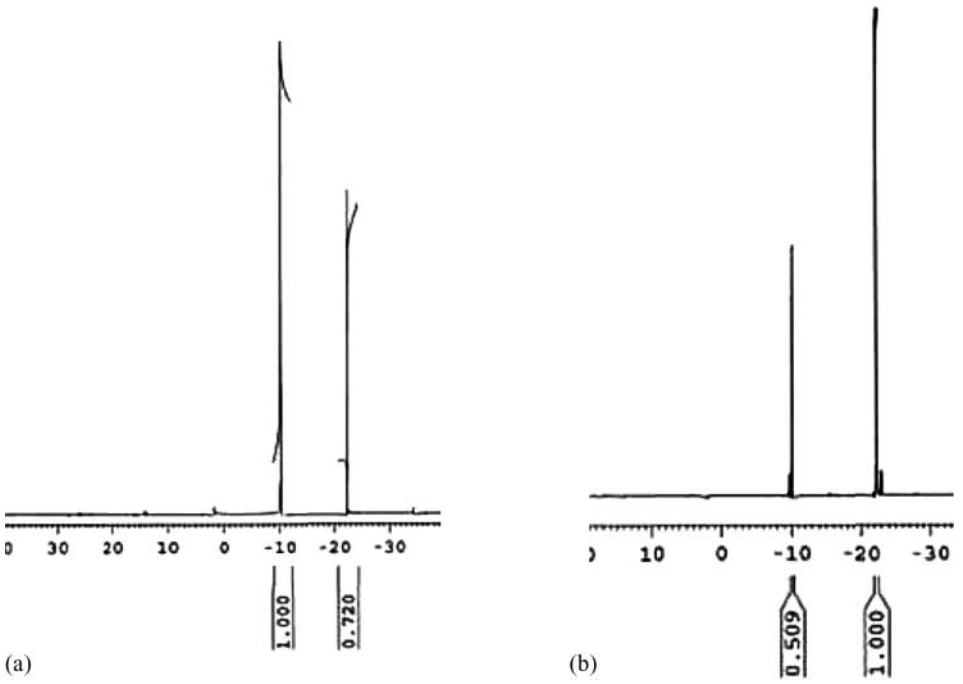


Figure 1 ^{31}P-NMR spectrum of the reaction of triethyl phosphate with phosphorus pentoxide (a) 70 °C and (b) 120 °C.

was carried out with Silica gel 100 (Merck no. 10184). Merck Silica-gel 60 F254 plates (no. 5744) were used for the preparative TLC.

General Procedure for the Phosphorylation of Phenols (2)

The phenol (5 mmol) was added to a mixture of triethyl phosphate (**4 g**) and phosphorus pentoxide (**1 g**) at 120 °C. The reaction mixture was stirred for the time reported in Table 1. The reaction mixture was poured into water, extracted with diethyl ether (3 × 25 mL), washed with brine (2 × 25 mL), and evaporated. The crude product was purified by simple filtration chromatography through a short plug of silica gel, eluting with EtOAc/*n*-hexane (2:8), and evaporation of the solvent under reduced pressure gave pure products in 41–81% yields. All products gave satisfactory spectral data in accord with the assigned structures and literature reports.[5–7,10]

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