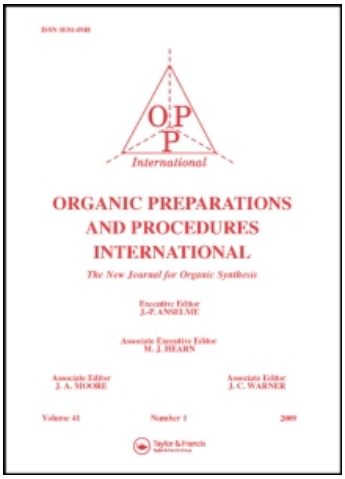

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AN IMPROVED SYNTHESIS OF MONOESTERS OF PHOSPHORIC ACID

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AN IMPROVED SYNTHESIS OF MONOESTERS OF PHOSPHORIC ACID

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Various methods are available[1] for the conversion of alcohols into their monophosphate esters. For those routes employing alcohols as substrates, direct phosphorylation with pyrophosphoric acid,[2] or phosphorous acid-Hg^{2+}-R_3N systems has been reported; in the former method, variable yields were observed while in the latter large excess of an alcohol is required. The phosphorylation of an alcohol *via* the nucleophilic cleavage of the P-Cl bond can be performed with a suitably protected reagent (e. g., *o*-phenylenephosphorochloridate[4]) or by a much simpler approach, in reaction with $POCl_3$, followed by selective hydrolysis of the monosubstituted intermediate. The first step (formation of **1**) can be successfully applied for primary alcohols and phenols, but selective hydrolysis of **1**, and the isolation of pure **2** can present problems. Cramer and Winter[6] reported the high-yield preparation of free acids **2** *via* the hydrolysis of **1** in aqueous acetonitrile in the presence of

$$ROH + P(O)Cl_3 \rightarrow \underset{\mathbf{1}}{ROP(O)Cl_2} \xrightarrow{2H_2O} \underset{\mathbf{2}}{ROPO_3H_2}$$

a) R = Me, b) R = Et; c) R = CF_3CH_2; d) R = *i*-Pr; e) R = *n*-Bu
f) R = *n*-C_8H_{17}; g) R = $PhCH_2CH_2$; h) R = Ph

silver oxide. We have found that under those conditions, the hydrolysis is in fact, non-selective and the product consists of a mixture of the expected **2** and orthophosphoric acid (as determined by ^{31}P NMR spectroscopy; δ_P in D_2O), ca. -10, and 0 ppm, respectively) in a ratio of about 1:2. The formation of the inorganic phosphate is a consequence of the highly basic conditions of the hydrolysis procedure.

We now report that pure **2,** free of any other phosphorus-containing by-products (within the accuracy of the ^{31}P NMR spectroscopy) can be easily prepared by a simple modification of Cramer's method,[6] involving the replacement of silver oxide by silver nitrate. Under these acidic conditions, the ester function does not undergo any appreciable hydrolysis, and nitric acid formed as a by-product can be removed under reduced pressure. The results of our modified procedure are summarized in Table 1. Although the hydrolysis step works equally well for secondary alkyl derivatives (fourth entry in Table 1), the limited availability of **1** from $POCl_3$ and secondary or tertiary alcohols, limits practically the procedure to primary alkyl and aromatic systems.[8]

Table 1. Alkyl Phosphorodichloridates (**1**) and Alkyl Phosphates (**2**)

		1			**2**	Anilinium Salt of **2**		
R	bp. (°C/mmHg)	Yield (%)	δ_P[a]	Yield (%)	δ_P	mp (°C)	Yield (%)	δ_P[b]
2a	44/77	47	9.15	94	1.39[a]	166-169.5 (lit.[2] 166-167)	85	2.25
2b	40/5	79	7.23	100	0.61[b]	165 (lit.[2] 164-165)	61	1.24
2c	22/20	88	5.40	78	0.71[a]	173-175	85	0.71
2d	36/5	20	6.28	96	1.05[a,c]	171-173 (lit.[2] 171)	77	0.26
2e	50/0.12	79	7.50	100	2.27[b]	142-144 (lit.[2] 144-148)	86	1.20
2f	99/0.13	79	7.11	100	0.60[a]	140-142 (lit.[3] 129-130)	79	0.22[d]
2g	150[e]/0.05	94	7.47	100	1.35[a]	171-172	100	1.06
2h	93/5	f	4.09	100	-3.78[b,g]	176-177 (lit.[2] 169-170)	100	-3.29

a) In $CDCl_3$. b) In D_2O. c) Crystalline, mp. 42-45°. d) In DMSO-d_6. e) Bulb to bulb distillation; oven temperature. f) Commercial substrate (Aldrich). g) Crystalline; mp. 93-94°, lit.[7] 99.5-100°.

EXPERIMENTAL SECTION

Commercially available substrates were purified and dried by standard methods immediately before use. NMR spectra were recorded on a Bruker AC 300 MHz spectrometer and the chemical shift values are given relative to TMS (^{1}H) and 85% phosphoric acid (^{31}P).

Preparation of Phosphorodichloridates (1). General Procedure.- The alcohol (1 mol equiv.) was added dropwise with stirring and cooling at 0° to $POCl_3$ (1 mol equiv.). The mixture was then stirred at 0° for 1 hr. and dry air was passed through the solution at 0° for 30 min. Crude **1** was purified by distillation under reduced pressure.

Preparation of Monophosphate Esters, (2). General Procedure.- A solution of **1** (1 mol equiv.) in acetonitrile (0.5 mL per mmol of **1**) was added dropwise with stirring and cooling at 0-5° to a solution of $AgNO_3$ (2 mol-equiv.) in water/acetonitrile (1:1, v/v, 1. 5 mL per g of $AgNO_3$). The mixture was stirred for additional hour at 0-5°, and left overnight in a refrigerator. The precipitate (AgCl) was filtered off, and the residue was evaporated under reduced pressure. If the yield of AgCl was below 100%, some ethanol was added to the residue which caused complete precipitation of the salt. After filtration and evaporation, acid **2** was obtained (as colorless syrups or solids) and were dried under reduced pressure. In all cases, ^{31}P NMR spectra indicated that only one phosphorus-containing product was present, and ^{1}H NMR spectra showed only the presence of signals expected for a given product.

Conversion of acids **2** into their monoanilinium salts was achieved by mixing ethanolic solutions of equimolar quantities of **2** and aniline. The precipitated product was collected and dried. The anilinium salts were usually analytically pure without further purification, and their melting points did not increase after crystallization from ethanol. Analytical data obtained for the salts are given in Table 2.

Table 2. Elemental Analyses of Anilinium Salts of **2**

Cmpd	Formula	Calcd			Found		
		C	H	N	C	H	N
2a	$C_7H_{12}NO_4P$	41.0	5.9	6.8	40.9	5.9	6.7
2b	$C_8H_{14}NO_4P$	43.9	6.4	6.4	43.8	6.5	6.4
2c	$C_8H_{11}F_3NO_4P$	35.2	4.1	5.1	35.1	4.0	5.1
2d	$C_9H_{16}NO_4P$	46.3	6.9	6.0	46.4	6.8	6.1
2e	$C_{10}H_{18}NO_4P$	48.9	7.3	5.7	49.0	7.5	5.6
2f	$C_{14}H_{26}NO_4P$	55.4	8.6	4.6	55.5	8.7	4.7
2g	$C_{14}H_{18}NO_4P$	57.9	6.1	4.7	57.7	6.0	4.7
2h	$C_{12}H_{14}NO_4P$	54.9	5.3	5.2	55.0	5.3	5.1

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8. With benzyl and *tert*-butyl alcohol as substrates, treatment with $POCl_3$ (with or without a tertiary amine) led to the formation of the corresponding chloroalkane as the only isolable organic product. With cyclohexanol, high yield of cyclohexene was obtained. We believe that the spontaneous decomposition of the product **1** involves fragmentation to the corresponding carbonium ion and of the metaphosphate species, $ClPO_2$.[9]

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REACTION OF THIONYL BROMIDE WITH KETONES

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Thionyl bromide reacts with aromatic aldehydes to yield either the acid bromides, the benzalbromides or the corresponding acid in the case of 2-anisaldehyde.[1] It has also been reported that benzoin (**1**) reacts with thionyl bromide to produce α,α-dibromodesoxybenzoin (**2**) as the major product along with small amounts of benzil.[2] We now report that thionyl bromide reacts with