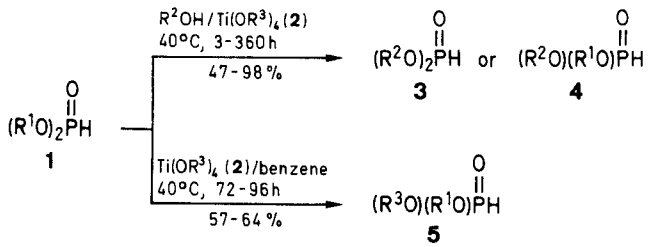
New Synthesis of Phosphorous and Phosphoric Acid Esters[1]

M. Froneman, T.A. Modro*
Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

Reaction of alcohols with dialkyl phosphites in the presence of titanium tetraalkoxides results in a displacement of both or one ester function(s) by the RO groups of the alcohol used. The mixed phosphites, $(R^3O)(R^1O)P(O)H$, prepared by this method can be used as substrates for the mixed phosphates, $(R^4O)(R^3O)(R^1O)PO$.

Transesterification of carboxylic esters[2] has been greatly improved by the application of titanium tetraalkoxides **2**,[3] ($Ti(OR^3)_4$), particularly for substrates sensitive to more conventional conditions. When phosphonic and carboxylic ester groups are present in the same molecule, the former is inert towards **2**, as demonstrated by the chemoselective transesterification of the triethyl ester of α-phosphonocinnamic acid.[4] Although esters of phosphorous acid **1**, $(R^1O)_2P(O)H$ undergo transesterification under thermal, or acid/base catalysis conditions,[5] our recent results on the exchange of the alkoxy functional groups in **1** for a dialkylamino group by means of titanium tetrakis(dialkylamides)[6] prompted us to investigate the effect of reagents **2** on the reaction of alcohols with esters **1**. We have found[1] that dialkyl phosphites **1** react smoothly with alcohols in the presence of titanium reagents **2**, yielding the products of the exchange of one **4** and **5**, or both ester groups **3**.



1	R^1	2	R^3
a	Me	a	*i*-Pr
b	Et	b	*t*-Bu
c	*i*-Pr	c	$PhCH_2$
d	Bu	d	2,3-[$OC(Me)_2O$]C_3H_5
e	$CH_3CH_2CH(Et)$		

3	R^1	4	R^1	R^2
a	i-Pr	a	Me	t-Bu
b	Bu	b	Et	*t*-Bu
c	Et	c	*i*-Pr	*t*-Bu
d	*c*-C_6H_{11}	d	Bu	*t*-Bu

5	R^1	R^3
a	Et	$PhCH_2$
b	Et	2,3-[$OC(Me)_2O$]C_3H_5
c	*i*-Pr	2,3-[$OC(Me)_2O$]C_3H_5
d	$CH_3CH_2CH(Et)$	*i*-Pr

The transesterification reaction can be carried out under mild and neutral conditions (alcohol to give **4** or benzene solution to give **5**, 40 °C) and involves simple and non-destructive workup procedures. The reaction offers therefore, a new and general route to dialkyl phosphites. With respect to the unsymmetrical (mixed) diesters, our procedure complements the limited available methods, based on the successive reactions of two alcohols with phosphorus trichloride,[7] on thermal disproportionation of two symmetrical phosphites,[8] or on the alkylation of the salts of monoesters of phosphorous acid.[9]

A series of symmetrical and mixed dialkyl phosphites were synthesized and characterised (Table 1). Structures

Table 1. Dialkyl Phosphites **3**, **4**, **5** Prepared

Substrate	Alcohol[a] R^2OH	$Ti(OR^3)_4$[b]	Reaction Time (h)	Product	Yield[c] (%)
1a	*i*-PrOH	**2a**	18	**3a**	91
1b	*i*-PrOH	**2a**	3	**3a**	95
1d	*i*-PrOH	**2a**	24	**3a**	76
1a	BuOH	**2a**	18	**3b**	67
1b	BuOH	**2a**	18	**3b**	56
1c	BuOH	**2a**	140	**3b**	53
1a	EtOH	**2a**	18	**3c**	62
1c	EtOH	**2a**	140	**3c**	63
1d	EtOH	**2a**	24	**3c**	66
1d	*c*-$C_6H_{11}OH$	**2a**	48	**3d**	98
1b	*c*-$C_6H_{11}OH$	**2a**	48	**3d**	81
1c	*c*-$C_6H_{11}OH$	**2a**	72	**3d**	85
1d	*c*-$C_6H_{11}OH$	**2a**	72	**3d**	50
1e	*c*-$C_6H_{11}OH$	**2a**	72	**3d**	47
1a	*t*-BuOH	**2b**	170	**4a**	68
1b	*t*-BuOH	**2b**	360	**4b**	50
1c	*t*-BuOH	**2b**	360	**4c**	61
1d	*t*-BuOH	**2b**	360	**4d**	61
1b	–[d]	**2c**[e]	72	**5a**	57
1b	–[d]	**2d**[e,f]	96	**5b**	64
1c	–[d]	**2d**[e,f]	96	**5c**	62
1d	–[d]	**2d**	96	**5d**	58

[a] Used as a solvent; molar excess ~ 20.
[b] Molar ratio **2**/**1** = 2.
[c] Not optimized.
[d] No alcohol was used; benzene as solvent.
[e] **2a**/**4** = 1.
[f] Bis[2,3-diisopropylidenedioxypropyl]phosphite was formed as a secondary product in addition to the mixed phosphite in 10% yield.
$C_{12}H_{23}O_7P$ (310.2) calc. C 46.45 H 7.42 found 46.00 7.20
IR (neat): ν = 2441, 1264, 1028 (br) cm^{-1}.
^{1}H-NMR ($CDCl_3$/TMS): δ = 1.31 (s, 6H), 1.38 (d, 6H, J = 1.0 Hz), 3.76 (m, 2H), 4.05 (m, 2H), 6.89 (d of t, 1H, J = 717.0, 2.0 Hz).
^{13}C-NMR ($CDCl_3$/TMS): δ = 25.1, 25.2, 26.2, 65.4 (d, J = 6.5 Hz), 65.73, 65.78, 65.81, 74.0, 71.4 (2 d, J = 5.9 Hz), 109.9, 110.0.
^{31}P-NMR ($CDCl_3$/Me_3PO_4): δ = 6.19, 6.46, 6.72.
MS: m/z (%) = 310 (M^+, 12).

Table 2. Physical and Spectroscopic Data of Compounds **3–5** Prepared[a]

Product	bp(°C)/Torr	Molecular Formula or Lit. bp(°C)/Torr	IR (neat)[b] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	^{31}P-NMR ($CDCl_3$/Me_3PO_4[d]), δ
3a	84/4[e]	79/14[15]			
3b	142–144/5	126–127/18[15]			
3c	50–51/2	73–74/14[15]			
3d	115/0.5	120/0.15[15]			
4a	–[f]	$C_5H_{13}O_3P$ (152.2)	2424, 1262, 980	1.52 (s, 9H), 3.77 (d, 3H, J = 12.2), 6.83 (d, 1H, J = 689.6)	0.58
4b	–[f]	$C_6H_{15}O_3P$ (166.2)	2418	1.34 (t, 3H, J = 7.1), 1.50 (s, 9H), 4.08 (d of q, 2H, J = 7.1, 10.6), 6.83 (d, 1H, J = 686.3)	−0.10
4c	–[f]	$C_7H_{17}O_3P$ (180.2)	2420	1.32 (d, 6H, 7.2), 1.51 (s, 9H), 4.68 (m, 1H), 6.84 (d, 1H, J = 684.7)	−1.93
4d	–[f]	$C_8H_{19}O_3P$ (194.2)	2416	0.92 (t, 3H, J = 7.2), 1.19–1.70 (m, 4H), 1.51 (s, 9H), 4.02 (d of t, 2H, J = 7.2, 10.6), 6.84 (d, 1H, J = 687.4)	−0.33
5a	105/0.05[d,e]	$C_8H_{13}O_3P$ (188.2)	2426, 1261, 978	1.31 (t, 3H, J = 7.0), 4.09 (d of q, 2H, J = 7.0, 9.2), 5.10 (d, 2H, J = 9.6), 6.86 (d, 1H, J = 698.9), 7.37 (m, 5H)	5.21
5b	–[f]	$C_8H_{17}O_5P$ (224.2)	2435, 1256, 1054, 970	1.27 (s, 3H), 1.28 (t, 3H, J = 7.0), 1.35 (s, 3H), 3.76 (m, 1H), 4.01 (m, 3H), 4.11 (d of q, 2H, J = 7.0, 8.7), 4.25 (quint, 1H, J = 7.0), 6.81 (d, 1H, J = 704.2)	5.63, 5.81
5c[g]	–[f]	$C_9H_{19}O_5P$ (238.2)	2431, 1250, 1050, 975	1.29 (s, 3H), 1.30 (d, 6H, J = 5.6), 1.37 (s, 3H), 3.76 (m, 1H), 4.01 (m, 3H), 4.26 (m, 1H), 4.71 (d of hept, 1H, J = 5.6), 6.81 (d, 1H, J = 701.5)	4.23, 4.40
5d	69–72/1.5	$C_8H_{19}O_3P$ (194.2)	2428, 1262, 980	0.92 (t, 6H, J = 7.6), 1.32 (d, 6H, J = 6.2), 1.62 (2d of q, 4H, $\Delta\delta$ 2 Hz, J = 7.6, 6.2), 4.29 (d of quint, 1H, J = 9.4, 6.2), 4.70 (d of hept, 1H, J = 6.2, 8.8), 6.82 (d, 1H, J = 687.7)	2.93

[a] Satisfactory microanalyses obtained: C ± 0.5, H ± 0.3.
[b] Recorded on a Beckman 4250 spectrophotometer.
[c] Obtained on a superconducting FT Bruker AC 300 spectrometer. Assignments were made by the use of the 2D COSY and HECTOR experiments.
[d] Trimethyl phosphate.
[e] "Bulb to bulb" distillation using a Kugelrohr apparatus; oven temperature indicated.
[f] Partial decomposition occured upon distillation.
[g] For detailed analysis of NMR spectra, see reference 13.

Table 3. ^{13}C-NMR and MS Data of Selected Compounds **5**

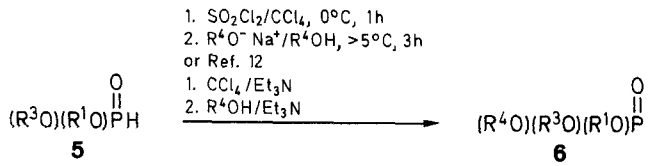
Product	^{13}C-NMR ($CDCl_3$/TMS)[a] δ, J (Hz)	MS[b] m/z (%)
5b[c]	16.1 (d, J = 6.0), 25.0, 25.1, 26.6, 61.8 (d, J = 5.4), 65.2, 65.5, (2d, J = 6.2), 65.72, 65.75, 74.0, 74.1, (2d, J = 6.4), 109.8, 109.9	224 (M^+, 8), 196 (7)
5c[c]	23.7, 23.9 (2d, J = 4.6), 25.1, 25.6, 26.6, 65.0, 65.4 (2d, J = 6.1), 65.8, 65.9, 71.2 (d, J = 6.0), 74.0, 74.1 (2d, J = 6.3), 109.8, 109.9	238 (M^+, 10), 198 (15), 196 (25), 124 (12)
5d	9.17, 9.33, 23.63, 23.82 (2d, J = 4.5), 27.48, 27.71 (2d, J = 4.0), 70.53 (d, J = 6.2), 80.51 (d, J = 6.6)	194 (M^+, 1.5), 179 (2), 165 (7), 152 (1o), 124 (54), 82 (100)

[a] See Table 2, footnote [c].
[b] Recorded on a VG Micromass 16 F spectrometer.
[c] For detailed analysis of NMR spectra, see Ref. 13.

of products were confirmed by NMR (^{1}H, ^{31}P, and, in some cases, ^{13}C), IR, and (in some cases) mass spectrometry (Tables 2 and 3). All new compounds gave satisfactory elemental analyses for C, H.

The reaction follows second-order rate law (first-order with respect to both, the phosphite **1**, and the titanate **2**), as demonstrated for the reaction between dimethyl phosphite and titanium tetraisopropoxide **(2a)** in benzene-d_6 at 40 °C. The rate of the first substitution (formation of the mixed methyl isopropyl phosphite) could be conveniently measured by ^{31}P-NMR spectroscopy (disappearance of the substrate's signal at δ = 7.0, and the appearance of the mixed phosphite's signal at δ = 4.5), and gave the rate constant, $k_2 = 1.1 \times 10^{-4}\ M^{-1}s^{-1}$ (R^2 = 0.994). The exchange reaction shows a high degree of chemoselectivity with respect to various types of esters of phosphorus acids. Triethyl phosphite and phosphate, as well as diethyl benzyl-, or α-hydroxybenzylphosphonate,[10] were recovered (> 95%) after incubation with titanium tetraalkoxide **2** for 72 hours at 40 °C. For simple alcohols used in the transesterification reactions, the reactivity in the exchange of the alkoxy groups, as measured by reaction yields and required times, decreases in the order: 2° > 1° > > 3°. We believe that this order results from the superimposition of two effects; steric hindrance vs the form of **2** in solution. Although steric hindrance increases from the primary to the tertiary system, hence reactivity should decrease in that order, it has been found[11] that titanate reagents derived from primary alcohols exist in solution as dimers and tetramers, while secondary and tertiary derivatives exist in a monomeric form, more available for exchange reaction. For the titanates **2** where R = *t*-Bu or $PhCH_2$, the exchange of only one group in the parent phosphite could be achieved. When the R groups in the reagent **2** are too

bulky, no exchange at phosphorus takes place. For example, when diethyl or diisopropyl phosphite, **1b** and **1c** respectively, were treated with **2** derived from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, no reaction was observed at 40 °C after as much as four weeks.



6	R^1	R^3	R^4
a	Et	$PHCH_2$	i-Pr
b	$CH_3CH_2CH(Et)$	*i*-Pr	Me
c	$CH_3CH_2CH(Et)$	*i*-Pr	Bu
d	$CH_3CH_2CH(Et)$	*i*-Pr	*t*-Bu
e	Et	2,3-$[OC(Me)_2O]C_3H_5$	*i*-Pr
f	Et	2,3-$[OC(Me)_2O]C_3H_5$	Bu

Since dialkyl phosphites can be easily converted into phosphoric acid triesters via phosphorochloridates,[12] the mixed phosphites **5** prepared were used for the synthesis of mixed phosphates **5** [$(R^4O)(R^3O)(RO)PO$]. Two methods, depending on the stability of the phosphite substrate, were used for the preparation of compounds **6**: (A) treatment of the phosphite with sulfuryl chloride followed by addition of the sodium salt of the required alcohol; (B) stirring the phosphite in a tetrachloromethane/triethylamine mixture followed by the addition of the required alcohol. The results of those preparations are listed in Table 4.

Table 4. Mixed Phosphates **6** Prepared

Substrate	Alcohol R^4OH	Method	Product	Yield (%)	^{31}P-NMR ($CDCl_3$/Me_3PO_4), δ
5a	*i*-PrOH	A	**6a**	71	−4.12
5d	MeOH	A	**6b**	95	−3.43
5d	BuOH	A	**6c**	51	−4.40
5d[a]	*t*-BuOH	A	**6d**	41	−4.95
5b	*i*-PrOH	B	**6e**	63	−4.26
5c	EtOH	B	**6e**	67	
5b[b,c]	BuOH	B	**6f**	73	−3.24

[a] (*i*-PrO)$(CH_3CH_2CH(Et)O)P(O)OH$ (53%; ^{31}P-NMR ($CDCl_3$/Me_3PO_4: $\delta = -2.13$) was also formed by hydrolysis of the intermediate phosphorochloridate

[b] Reaction of the intermediate phosphorochloridate with aniline yield [2,3-$(O,C(Me)_2O)C_5H_7O$] (*i*-PrO)(PhNH)PO in 90% yield [bp 125 °C/0.15 Torr: ^{31}P-NMR ($CDCl_3/Me_3PO_4$): $\delta = -0.47$]

[c] Hydrolysis of the intermediate phosphorochloridate in the precense of Et_3N gave [2,3-$(OC(Me)_2O)C_3H_5O$] (*i*-PrO)PO_2^- Et_3NH^+ in 83% yield [^{31}P-NMR ($CDCl_3/Me_3PO_4$: $\delta = -3.86$]

Structures of the products were established by NMR (^1H, ^{31}P, and ^{13}C) and IR spectroscopy, MS, and elemental (C, H, N) analysis. The NMR assignments were made on the basis of the 2D COSY and HETCOR experiments, as well as according to the characteristic H–P and C–P coupling constants.[14] Mass spectra of the mixed phosphates enabled us to establish the relative susceptibility of the individual RO groups to the electron impact induced fragmentations.

Elemental analyses were performed using a Heraeus Universal Combustion analyser. All reagents and solvents were dried and purified according to the conventional procedures immediately before use. All reactions were carried out in an atmosphere of dry nitrogen to avoid any decomposition of **2**.

Titanium tetraalkoxides (**2**) were synthesized by adding the required alcohol to titanium tetrakis(diethylamide), $Ti(NEt_2)_4$, either prepared independently, or generated in situ from $TiCl_4$. Two general procedures were used:

(i) Diethylamine (11.7 g, 160 mmol) is added dropwise with stirring to BuLi in hexane (1.6 M, 100 mL, 160 mmol) below −20 °C. The mixture is stirred at 0 °C for 2 h, cooled to −60 °C, and the solution of $TiCl_4$ (7.6 g, 40 mmol) in benzene (15 mL) is added dropwise with stirring below −20 °C. The mixture is allowed to warm up to r.t., stirred for 18 h, cooled, and the required alcohol (160 mmol) is added dropwise keeping the temperature below 0 °C. The mixture is warmed up to r.t., stirred for 4 h, volatile components are removed under reduced pressure, and the crude product is either purified by distillation, or used as prepared.

(ii) The alcohol (65 mmol) dissolved in benzene (15 mL) is added dropwise with stirring and keeping the temperature below 0 °C to the solution of $Ti(NEt_2)_4$ (prepared according to Ref. 6, 5.4 g, 16 mmol) in benzene (15 mL). The mixture is then stirred at r.t. for 2 h, and worked-up as in procedure (i).

2a: 85–87%; bp 65–68 °C/0.3 Torr; ^1H-NMR ($CDCl_3$): $\delta = 1.26$ (d, 24 H, $J = 6.1$ Hz, 8 × Me), 4.53 (quint, 4 H, $J = 6.1$ Hz, 4 × OCH); ^{13}C-NMR ($CDCl_3$): $\delta = 32.21$ (Me), 79.78 (CH).

2b: 81–84%; bp 69–72 °C/0.15 Torr; ^1H-NMR ($CDCl_3$): $\delta = 1.30$ (s, 12 × Me); ^{13}C-NMR ($CDCl_3$): $\delta = 32.21$ (Me), 79.74 (C_{quart}).

2c: 92%; dec. upon distillation; ^1H-NMR ($CDCl_3$): $\delta = 5.15$ (s, 8 H, CH_2), 7.36 (br s, 20 H, 4 × Ph).

2d: 85%; viscous oil; dec. upon distillation; ^1H-NMR ($CDCl_3$): $\delta = 1.32$ (s, 12 H, 4 × Me), 1.39 (s, 12 H, 4 × Me), 3.71 (d of d, 4 H, $J = 7.7$, 6.2 Hz, 4 × H-3), 4.02 (d of d, 4 H, $J = 7.7$, 6.2 Hz, 4 × H-3), 4.27 (m, 8 H, 8 × H-1), 4.38 (m, 4 H, 4 × H-2); ^{13}C-NMR ($CDCl_3$): $\delta = 25.33$ (4 × Me), 26.82 (4 × Me), 66.84 (C-3), 76.27 (br, C-1), 77.04 (C-2).

All reagents **2** gave satisfactory elemental analyses for C, H.

Preparation of Dialkyl Phosphites 3 and Mixed Dialkylphosphites 4 and 5; General Procedure:

Dialkyl phosphite **1** (5.5 mmol) is added to the solution of the titanium tetraalkoxide **2** (11 mmol) in the required alcohol (10 mL) (for 3 and 4) or **1** (5.5 mmol) is added to a solution of **2** (11 mmol) in benzene (15 mL)/(or **5**), and the solution is incubated at 40 °C for the required period of time. The mixture is poured into water, extracted with CH_2Cl_2 (3 × 10 mL), the organic solution is dried ($MgSO_4$), and solvent and volatile components removed under reduced pressure. The products are then purified and characterised, as shown in Tables 1–3. All phosphites **3**, **4** and **5** gave satisfactory elemental analyses for C, H.

Preparation of Phosphoric Acid Esters (5); General Procedure:

Method A: SO_2Cl_2 dissolved in CCl_4 is added dropwise to the solution of **4** in CCl_4 keeping the temperature below 0 °C. After one hour of stirring, the volatile components are removed under reduced pressure at low temperature, leaving the crude, colorless phosphorochloridate. This product is dissolved in the required alcohol and the solution is added dropwise, below 5 °C, to the solution of the equimolar amount of the corresponding sodium alkoxide in the same alcohol. The mixture is stirred for 3 h, filtered through the layer of $MgSO_4$, water is added, and the mixture is extracted with benzene (3 × 5 mL). After drying ($MgSO_4$) and

evaporating under reduced pressure, the crude phosphates are purified by "bulb to bulb" distillation using a Kugelrohr apparatus; oven temperature (°C)/Torr: **6a**, 110/0.02; **6b**, 70/0.08; **6c**, 110/0.1; ***6d***, *85*/0.07.

Method B: Phosphites **5** were converted into phosphoric acid esters **5** by reaction with CCl_4 in the presence of Et_3N, followed by the required alcohol in Et_3N.[12] The products **6** were identified and characterised according to their spectroscopic and elemental analysis data.

Financial assistance from the University of Pretoria and the Foundation for Research Development (CSIR) is gratefully acknowledged.

Received: 18 September 1989; revised: 18 December 1989

(1) Preliminary communication: Froneman, M.; Modro, T.A. *Tetrahedron Lett.* **1988**, *29*, 3327.
(2) March, J. *Advanced Organic Chemistry*, 3rd Ed., J. Wiley, New York, 1985, p. 351.
(3) Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer-Verlag, 1986.
(4) Reference 3, chapter 1, p. 10.
(5) Sasse, K., in: *Houben-Weyl*, 4th Ed., Vol. XII/2, Georg Thieme Verlag, Stuttgart, 1964, p. 35
Regitz, M., *ibid.* 1982, p. 326.
(6) Vather, S.M.; Modro, T.A. *Phosphorus Sulfur* **1986** *26*, 383.
(7) Sehring, R.; Zeile, K. *German Patent* 1078558 (1958), C.H. Boehringer Sohn; *C.A.* **1961**, *55*, 14308.
(8) Collin, R.; Schrader, G. *German Patent* 1059425 (1957), Farb. Bayer; *C.A.* **1962**, *56*, 11446.
(9) Kluba, M.; Zwierzak, A. *Synthesis*, **1978**, 134.
Kluba, M.; Zwierzak, A. *Tetrahedron* **1973**, *29*, 1089.
(10) Froneman, M.; Modro, T.A.; Qaba, L.; Vather, S.M. *Tetrahedron Lett.* **1987**, *28*, 2979.
(11) Bradley, D.C.; Holloway, C.E. *J. Chem. Soc. A.* **1968**, 1316.
Holloway, C.E. *J. Chem. Soc. Dalton. Trans.* **1976**, 1050.
(12) Steinberg, G.M. *J. Org. Chem.* **1950**, *15*, 637.
(13) Froneman, M.; Modro, T.A. *Tetrahedron Lett.* **1989**, *30*, 5469.
(14) Froneman, M. Ph.D. Thesis, University of Pretoria, 1989.
(15) Sasse, K., in: *Houben-Weyl*, 4th Ed., Vol. XII/2, Georg Thieme Verlag, Stuttgart, 1964, p. 24.