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The Preparation of Phosphonic Acids Having Labile Functional Groups

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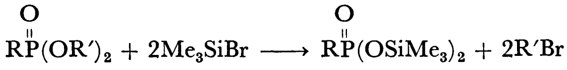
Synopsis. Phosphonic acids having labile functional groups have been prepared quantitatively by the hydrolysis of bis(trimethylsilyl) phosphonates, were prepared by the reaction under mild conditions of the corresponding dialkyl phosphonates with bromotrimethylsilane.

The biological activity of phosphonic acids has become of interest in recent years.[1)] Phosphonic acids may be capable of inhibiting or perturbing the regular metabolism.[2)] The phosphonic acid esters need reexamination as the corresponding acids which may be more readily assimilated by organisms. A convenient method for the preparation of phosphonic acids from dialkyl phosphonates (**1**) has been recently reported, which includes the reaction of **1** with chloro- or bromotrimethylsilane (**2**) and the subsequent hydrolysis under mild conditions of the resulting bis(trimethylsilyl) phosphonates (**3**).[3,4)] Dialkyl phosphonates react more readily with **2** to give **3** than with chlorotrimethylsilane. The limitation for silylation of **1** with **2** has not yet been reported. The conditions for silylation were investigated by the reaction of **1** having different labile functional groups with **2**, a modification of the procedures of Mckenna[3)] and Rabinowitz.[4)]

The silylation of **1** with double the molar quantity of **2** was carried out at room temperature for 1 h to give **3** in good yields. The reaction, which was monitored by the NMR of the reaction mixture, was completed within 1 h. The results are summarized in Table 1.



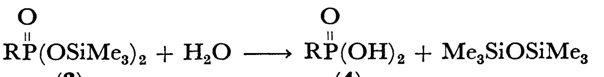
$$\mathrm{R\overset{O}{\overset{\|}{P}}(OR')_2} + \mathrm{2Me_3SiBr} \longrightarrow \mathrm{R\overset{O}{\overset{\|}{P}}(OSiMe_3)_2} + \mathrm{2R'Br}$$

(**1**) (**2**) (**3**)

1a	R=(MeO)$_2$CH, R'=Me	**1f**	R=MeOCO, R'=Et
1b	R=MeCO, R'=Et	**1g**	R=NCCH$_2$, R'=Et
1c	R=Me$_2$NCO, R'=Et	**1h**	R=H$_2$NCOCH$_2$, R'=Et
1d	R=MeOCOCH$_2$, R'=Et	**1i**	R=EtOCH=CH, R'=Me
1e	R=PhOCOCH$_2$, R'=Et		

For the silylation of **1h**, different conditions were required, namely, a slight excess of **2** (2.3 times). In the reaction of diethyl 2,3-epoxypropylphosphonate with an equimolar amount of **2**, diethyl 2-bromo-3-trimethylsiloxypropylphosphonate was produced instead of bis(trimethylsilyl) 2,3-epoxypropylphosphonate. The reaction appears to proceed *via* an onium type intermediate formed by the attack of phosphinyl sp^3 oxygen on the silicon atom of **2**, which in turn decomposes to the trimethylsilylated esters of phosphonic acid and alkyl bromide.

The hydrolysis of **3** was carried out with a water–ether mixture at room temperature for a few minutes to afford the phosphonic acids (**4**), which were isolated as the anilinium or cyclohexylammonium salts in good yields. These salts were recrystallized from a mixture of methanol–acetone. The results are summarized in Tables 2 and 3.



$$\mathrm{R\overset{O}{\overset{\|}{P}}(OSiMe_3)_2} + \mathrm{H_2O} \longrightarrow \mathrm{R\overset{O}{\overset{\|}{P}}(OH)_2} + \mathrm{Me_3SiOSiMe_3}$$

(**3**) (**4**)

Table 1. Yields and physical properties of **3**

	Yield (%)	Bp (°C/mmHg)	IR (cm^{-1})	^{1}H NMR δ in CCl$_4$ (ppm)
3a	99	116—119/10	1248(P=O)	3.14 (6H, s, CH$_3$O), 4.34 (1H, d, J=6.0 Hz, CHP), 0.26 (16H, s, OSiMe$_3$)
3b	91	60—62/0.1	1690(C=O) 1245(P=O)	2.38 (3H, d, J=4.8 Hz, CH$_3$C), 0.30 (18H, s, OSiMe$_3$)
3c	92	80—82/0.1	1616(C=O) 1240(P=O)	2.92 (3H, s, CH$_3$N), 3.30 (3H, s, CH$_3$N), 0.28 (18H, s, OSiMe$_3$)
3d	90	123—124/8	1732(C=O) 1244(P=O)	3.65 (3H, s, CH$_3$O), 2.74 (2H, d, J=21.6 Hz, CH$_2$P), 0.28 (18H, s, OSiMe$_3$)
3e	90	133—135/0.5	1760(C=O) 1256(P=O)	3.00 (2H, d, J=21.6 Hz, CH$_2$P), 7.23 (5H, m, C$_6$H$_5$), 0.29 (18H, s, OSiMe$_3$)
3f	91	60—62/0.1	1724(C=O) 1250(P=O)	3.78 (3H, s, CH$_3$O), 0.30 (18H, s, OSiMe)
3g	93	129—130/7	2250(C≡N) 1250(P=O)	2.84 (2H, d, J=21.6 Hz, CH$_2$P), 0.32 (18H, s, OSiMe$_3$)
3h	> 99[a)]	—	—	3.21 (2H, d, 21.0 Hz, CH$_2$P), 0.33 (18H, s, OSiMe$_3$)
3i	92	71—73/0.01	1600(C=C) 1245(P=O)	1.30 (3H, t, CH$_3$C), 3.84 (2H, q, CH$_2$O), 4.69 (1H, dd, J=9.6 Hz, CHP, J=13.2 Hz, HCCH), 7.02 (1H, t, J=13.2 Hz, HCCP), 0.26 (18H, s, OSiMe$_3$)

a) The reaction was carried out in CHCl$_3$ and the silyl ester was not isolated. Yield was estimated on the reaction mixture by NMR in CDCl$_3$. A broad signal of CONH$_2$ was observed at δ=6.5–8.0.

TABLE 2. YIELDS AND PHYSICAL PROPERTIES OF SALTS OF **4**

	Yield (%)	Mp (°C)	^1H NMR δ in D_2O (ppm)
4a	96	135—137 (dec)	3.47 (6H, s, CH_3O), 4.45 (1H, d, J=4.2 Hz, CHP), 7.50 (5H, m, C_6H_5N)
4b	92	159—162 (dec)	2.34 (3H, d, J=4.2 Hz, CH_3C)
4c	93	148—150	2.91 (3H, s, CH_3N), 3.32 (3H, s, CH_3N), 7.44 (5H, m, C_6H_5N)
4d	94	145—146	3.68 (3H, s, CH_3O), 2.84 (2H, d, J=19.2 Hz, CH_2P), 7.45 (5H, m, C_6H_5N)
4e	89	157—159	3.21 (2H, d, J=19.8 Hz, CH_2P), 7.52 (10H, m, C_6H_5O, C_6H_5N)
4f	95	160—162	3.72 (3H, s, CH_3O), 7.30 (10H, m, C_6H_5N)
4g	97	172—174	2.85 (2H, d, J=19.2 Hz, CH_2P), 7.50 (5H, m, C_6H_5N)
4h	92	131—133	2.74 (2H, d, J=20.4 Hz, CH_2P), 7.51 (5H, m, C_6H_5N)
4i	90	164—167 (dec)	1.23 (3H, t, CH_3C), 3.85 (2H, q, CH_2O), 4.90 (1H, dd, J=9.6 Hz, CHP, J=13.8 Hz, HCCH), 6.84 (1H, dd, J=11.4 Hz, HCCP)

TABLE 3. ELEMENTAL ANALYSIS OF SALTS OF **4**

	Formula	Found (%)				Calcd (%)			
		C	H	N	P	C	H	N	P
4a	$C_9H_{16}O_5NP$a)	43.64	6.64	5.80	12.17	43.37	6.43	5.62	12.45
4b	$C_{14}H_{31}O_4N_2P$d)	48.85	9.58	8.98	9.89	52.17	9.63	8.70	9.63
4c	$C_9H_{15}O_4N_2P$a)	44.08	6.31	11.37	12.51	43.90	6.10	11.38	12.60
4d	$C_9H_{14}O_5NP$a)	43.69	5.88	5.73	12.34	43.72	5.67	5.67	12.55
4e	$C_{14}H_{16}O_5NP$a)	54.04	5.50	4.81	10.12	54.37	5.18	4.53	10.03
4f	$C_{14}H_{19}O_5N_2P$b)	51.70	6.03	8.69	9.24	51.53	5.83	8.59	9.51
4g	$C_8H_{11}O_3N_2P$a)	45.12	5.37	13.13	14.90	44.86	5.14	13.08	14.49
4h	$C_8H_{13}O_4N_2P$a)	41.30	5.94	12.23	13.10	41.38	5.60	12.07	13.36
4i	$C_{10}H_{22}O_4NP$c)	47.90	9.13	5.81	12.46	47.81	8.76	5.58	12.35

a) Monoanilinium salt. b) Dianilinium salt. c) Monocyclohexylammonium salt. d) Dicyclohexylammonium salt.

Experimental

All the melting and boiling points are uncorrected. NMR spectra were obtained by a JNM-TS-100 spectrometer with TMS or DSS as an internal reference. IR spectra were obtained by a Shimadzu IR-400.

*Preparation of Dialkyl Phosphonates (**1**).* The phosphonates (**1b**—**1h**) were prepared by the Arbuzov reaction of the corresponding chlorides with triethyl phosphite. The phosphonate (**1a**) was prepared from PCl_3 and trimethyl orthoformate accroding to the method of Gross and Freiberg.5) The phosphonate (**1i**) was prepared from ethyl vinyl ether and PCl_5 according to the method of Anisimov and Nesmeynov.6)

*Preparation of Bromotrimethylsilane (**2**).* Bromotrimethylsilane (**2**) was prepared from hexamethyldisiloxane and PBr_3 according to the method of Gilliam *et al.*7)

*Preparation of Bis(trimethylsilyl) Phosphonates (**3**).* Bromotrimethylsilane (**2**) (20 mmol) was added dropwise to **1** (10 mmol) with stirring at room temperature for 1 h. After the removal of the resulting methyl or ethyl bromide, **3** was obtained by distillation.

*Preparation of Phosphonic Acids (**4**).* Compound **3** (10 mmol) was dissolved in ether (50 ml) and the solution extracted with three portion of water (3×30 ml). The combined aqueous solution was neutralized by the addition of aniline or cyclohexylamine (20 mmol) and concentrated to dryness under reduced pressure to give a solid. The solid was recrystallized from a mixture of methanol-acetone (1:5 v/v) to afford the salt of **4**.

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