A New Method for the Preparation of Bis(1-hydroxyalkyl)-phosphinic Acids

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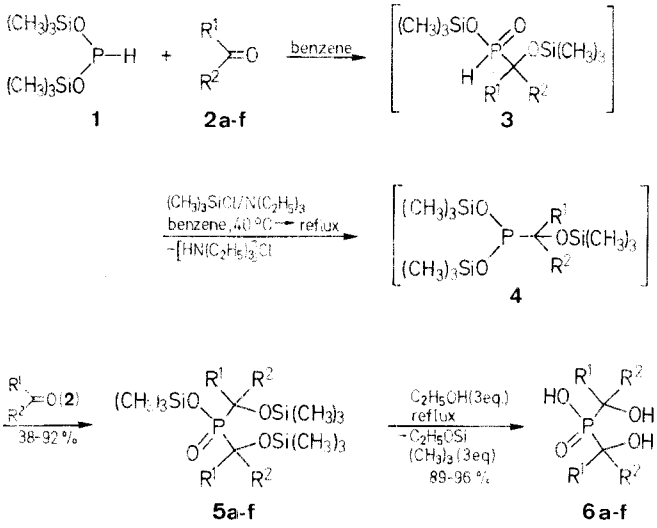
Bis(1-hydroxyalkyl)phosphinic acids **6** have been conveniently obtained by addition of bis(trimethylsiloxy)phosphine **1** to aldehydes or ketones **2** in the presence of chlorotrimethylsilane and triethylamine, followed by ethanolysis of the resulting trimethylsilyl bis(1-trimethylsiloxyalkyl)-phosphinates **5**.

Bis(1-hydroxyalkyl)phosphinic acids **6** are of interest as compounds of potential biological activity and as useful starting materials for the synthesis of bis(chloromethyl)phosphinic acid.[1] A relatively simple and convenient approach to **6** is the reaction of phosphinous acid with two equivalents of the corresponding carbonyl compound.[2] This reaction requires, however, long heating of substrates in water solution (8 h, 90–95 °C), and therefore cannot be applied when the respective carbonyl compounds are sensitive to moisture and/or acids.

Looking for a new, more effective and convenient synthesis of the acids **6**, we turned our attention to the relatively readily available bis(trimethylsiloxy)phosphine (**1**)[3] as a starting material. The phosphine **1** could be expected to react with two equivalents of the corresponding aldehyde or ketone **2**. Known addition of **1** to the first equivalent of **2** would produce the corresponding (1-trimethylsiloxyalkyl)phosphinates **3**,[4] which would subsequently react with a second equivalent of **2**. The latter was anticipated to be more effective if the phosphinates **3** were transformed into the corresponding trimethylsilyl ester **4**. We supposed that this transformation could be performed *in situ* if the addition sequence were carried out in the presence of a silylating reagent.

Indeed, the reaction of **1** with two equivalents of carbonyl compound **2** in the presence of one equivalent of chlorotrimethylsilane and one equivalent of triethylamine in refluxing benzene affords trimethylsilyl bis(1-trimethylsiloxyalkyl)phosphinates **5**, usually in excellent yields (exception: **5c**). The phosphinates **5**, can be easily purified by distillation *in vacuo*. Physical constants and spectroscopic data of the phosphinates **5** are presented in Table 1. In the case of benzaldehyde (**2a**), furaldehyde (**2b**) and acetaldehyde (**2c**) three possible diastereoisomers **5a, b, c** are obtained, depending on the chirality of the two carbon atoms bonded to the phosphorus atom of **5** and the pseudoasymmetric properties of this phosphorus



2, 6	R^1	R^2	2, 6	R^1	R^2
a	C_6H_5	H	d	H	H
b	2-furyl	H	e	CH_3	CH_3
c	CH_3	H	f	$CH(OH)CH_2OH$	H

5a–e: see **6a–e**

5f: R^1 =  , R^2 = H

atom. The ratio of diastereoisomers in **5a, b, c** was established by means of ^{31}P-NMR spectroscopy (see Table 1). The phosphinates **5** can be efficiently converted into bis(1-hydroxyalkyl-) phosphinic acids **6** by refluxing in ethanol. After evaporation of solvent, the acids **6** are obtained in analytically pure state (Table 2, exception: **6b**). The structure of new compounds **6b, c, f** was confirmed by IR and NMR spectroscopy. According to ^{31}P-NMR and ^{1}H-NMR data the acids **6a, b, c** consist of two diastereoisomers in the ratio 1 : 1.

^{1}H-NMR spectra were measured at 80 MHz with a Tesla BS 487 C spectrometer. ^{31}P-NMR spectra were measured at 24.3 MHz with a Jeol JNM-C-60HL spectrometer using a Heteronuclear Spin Decoupler, JNM-SD-HC, or at 36.43 MHz with a Bruker HFX 90 spectrometer.

Bis(trimethylsiloxy)phosphine was prepared by adaptation of know a procedure;[3] yield 81%; b.p. 76–77°C/25 torr (Lit.[3] b.p. 51–52°C/11 torr.)

^{31}P-NMR (C_6H_6, 36.43 MHz): δ = 141.5 ppm (d, J_{PH} = 176 Hz).

^{1}H-NMR (C_6D_6/C_6H_{6int}): δ = 0.1 (s, 18H, CH_3Si); 7.55 ppm (d, 1H, J_{PH} = 176 Hz, PH).

Trimethylsilyl Bis(1-trimethylsiloxyalkyl)phosphinates 5; General Procedure:

Bis(trimethylsiloxy)phosphite (**1**; 3 g, 14.4 mmol) is added from a syringe to a stirred solution of chlorotrimethylsilane (1.55 g, 14.4 mmol), triethylamine (1.47 g, 14.4 mmol), and benzene (35 ml). To the resultant mixture a solution of carbonyl compound **2** (28.8 mmol) in benzene (5 ml) is gradually added dropwise with stirring at such rate that the temperature does not exceed 45°C. The reaction mixture is stirred at 40–45°C for 15 min and than refluxed for 2 h. After the mixture has cooled to room temperature, dry ether (20 ml) is added and the resultant mixture cooled to 0°C. The precipitated trimethylamine hydrochloride is filtered off, the filtrate evaporated, and the residue distilled *in vacuo* to give analytically pure **5**. See Table 1.

Bis(1-hydroxyalkyl)phosphinic Acids 6; General Procedure:

The phosphinate **5** (10 mmol) is dissolved in ethanol (20 ml), and the resulting solution is refluxed for 10 min. The solvent is then evaporated

Table 1. Trimethylsilyl-Bis(1-trimethylsiloxyalkyl)phosphinates **5**

5	Yield (%)	b.p. (°C)/torr	Molecular Formula[a]	^{31}P-NMR (C_6H_6/H_3PO_{4ext}) δ (ppm)	^{1}H-NMR (solvent/TMS_{int})[b] δ (ppm)
a	92	122–125/0.3	$C_{23}H_{39}O_4PSi_3$ (494.75)	28.8; 30.0; 30.2 (5 : 2 : 3)[c,d]	(CCl_4): 0.36, 0.43, 0.45, 0.49, 0.56 (5s, 27H, $Si(CH_3)_3$); [5.29 (d, $^2J_{PH}$ = 7 Hz) + 5.60 (d, $^2J_{PH}$ = 7 Hz) + 5.70 (d, $^2J_{PH}$ = 8 Hz), 2H, CHP(O)]; 7.5–8.0 (m, $10H_{arom}$)
b	89	119–124/0.3	$C_{19}H_{35}O_6PSi_3$ (474.7)	24.6; 26.1; 26.3 (1 : 2 : 1)[c,d]	(CCl_4): 0.4 (br s, 27H, $Si(CH_3)_3$); [5.35 (d, $^2J_{PH}$ = 8 Hz) + 5.38 (d, $^2J_{PH}$ = 8 Hz) + 5.52 (d, $^2J_{PH}$ ≃ 10 Hz), 2H, CHP(O)]; 6.7–7.2 (m, $4H_{arom}$); 7.85 (br s, $2H_{arom}$)
c	38	80/0.4	$C_{13}H_{35}O_4PSi_3$ (370.6)	38.0; 40.0; 41.7 (3 : 2 : 1)[c,d]	(C_6D_6): 0.007, 0.010, 0.015, 0.025 (4s, 27H, $Si(CH_3)_3$); 1.0–1.8 (m, 6H, CH_3CP); 4.0–4.5 (m, 2H, CHP)
d	91	80–81/0.55	$C_{11}H_{31}O_4PSi_3$ (342.6)	32.8[d]	(C_6D_6): 0.1 (s, 18H, $COSi(CH_3)_3$); 0.25 (s, 9H, $POSi(CH_3)_3$); 3.9 (d, 4H, $^2J_{PH}$ = 7 Hz, PCH_2)
e	87	110/0.5	$C_{15}H_{39}O_4PSi_3$ (398.7)	38.0[d]	(C_6D_6): 0.15 (s, 18H, $COSi(CH_3)_3$); 0.25 (s, 9H, $POSi(CH_3)_3$); 1.55, 1.65 (2d, 12H, $^3J_{PH}$ = 13 Hz, $(CH_3)_2CP$)
f	88	122–130/0.15	$C_{21}H_{47}O_8PSi_3$ (542.8)	32.8; 33.4; 35.1; 35.5; 36.9; 37.3 (10 : 2 : 4 : 5 : 1 : 4)[e,f]	(C_6D_6): 0.22, 0.26, 0.30, 0.35, 0.38 (5s, 27H, $Si(CH_3)_3$); 1.36, 1.40, 1.48, 1.52 (4s, 12H, $C(CH_3)_2$); 3.8–5.0 (overlapped multiplets, 8H, $PCHCHCH_2$)

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.25, P ±0.30.
[b] Benzene was also used as an internal standard to obtain the chemical shift of the trimethylsilyl groups.
[c] The ratio of diastereoisomers.
[d] The spectra were measured at 24.3 MHz.
[e] Presumably the observed spectral lines show all stereoisomers that are formed from the ten possible. This can be concluded from the observation that the stereoisomeric phosphinate mixture **5f** form, on ethanolysis, three diastereoisomeric acids (see Table 2, **6f**).
[f] The spectra were measured at 36.43 MHz.

Table 2. Bis(1-hydroxyalkyl)phosphinic acids **6**[a]

6	Yield (%)	m.p. (°C) (solvent)	Molecular Formula[a] or Lit. m.p. (°C)	^{1}H-NMR (CD_3OD/TMS_{int})[b] δ (ppm)	^{31}P-NMR (CH_3OH/$H_3PO_{4\,ext}$) δ (ppm)
a	95	165–178	230 (from 165)[2a]	[5.1 (d, $^2J_{PH}$ = 6 Hz) + 5.4 (d, $^2J_{PH}$ = 7 Hz), 2H, CHP];[c] 7.2–7.5 (10 H_{arom})	36.5; 38.0 (1:1)[d,e]
b	89	syrup	$C_{10}H_{11}PO_6$ (258.2)	[5.2 (d, $^2J_{PH}$ = 8 Hz) + 5.4 (d, $^2J_{PH}$ = 8 Hz), 2H, CHP];[c] 6.5–6.8 (m, 4 H_{arom}); 7.65 (br s, 2 H_{arom})	34.0; 35.4 (1:1)[d,e]
c	95	oil	$C_4H_{11}PO_4$ (154.1)	1.58 (dd, 6H, $^3J_{PH}$ = 15 Hz, $^3J_{HH}$ = 7 Hz, CH_3CP); 4.3 (quin, 2H, $^2J_{PH} \simeq {}^3J_{HH}$ = 7 Hz, CHP)	45.0; 46.3 (1:1)[d,e]
d	94	oil	oil[5]	3.9 (d, 4H, $^2J_{PH}$ = 5.5 Hz, CH_2P)	44.0[e] (Lit.[6], 45.8)
e	96	181–183 (methanol)	185[2a]	1.45 (d, 12H, $^3J_{PH}$ = 13 Hz, $(CH_3)_2CP$)	46.6[e]
f	95	syrup	$C_6H_{15}PO_8$[g] (246.15)	3.4–4.7 (overlapped multiplets, 8H, CH_2CHCHP)	51.3; 43.4; 42.2 (1:5:3)[d,f]

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.25, P ± 0.30; exception **6b**, C + 0.57%. All compounds show IR (KBr or film) absorption bands characteristic for a dialkylphosphinic acid moiety P(O)OH:[7] weak broad bands between 2725–2525, 2350–2080 and 1740–1600 cm^{-1} (Specord 71 IR C. Zeiss spectrophotometer).

[b] The singlet signals of the hydroxylic protons: 3H or 7H, respectively for **6a–e** and **6f** were observed at 5.2 ppm.

[c] The intensity ratio of these two signals corresponding to the ratio diastereoisomers is 1:1.

[d] The ratio of diastereoisomers.

[e] The spectra were measured at 24.3 MHz.

[f] The spectra were measured at 36.43 MHz.

[g] Obtained after hydrolysis (5 min, reflux).

and the residue kept at 40°C/0.2 torr for 30 min in order to remove traces of volatile impurities. Almost all of the phosphinic acids **6** thus obtained are analytically pure. See Table 2.

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