Preparation of Oxoalkanephosphonic Acids

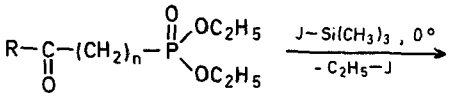
Jan ZYGMUNT, Paweł KAFARSKI, Przemysław MASTALERZ*

Institute of Organic and Physical Chemistry, Technical University (Politechnika), 50-370 Wrocław, Wybrzeże Wyspiańskiego 27, Poland

Recent evidence indicates that some oxoalkanephosphonic acids, particularly those with the oxo group at positions 1 or 2, are of considerable biochemical interest as structural analogs of phosphate esters[1] or oxoalkanecarboxylic acids[2-5].

It appears, however, that the preparation of free oxoalkanephosphonic acids has never been studied systematically and that the few specific examples which have been described so far[3-8] were prepared by various, usually not very efficient methods.

In this communication we describe the preparation of 1-oxoalkanephosphonic and 2-oxoalkanephosphonic acids by dealkylation of their readily available esters using the silylation procedure[9] and compare this method with those involving hydrolysis of esters and acidolysis with hydrobromic acid. Silylation with chlorotrimethylsilane or bromotrimethylsilane has been applied previously to prepare phosphonic acids, including one example of an oxoalkanephosphonic acid[8]. The more reactive iodotrimethylsilane has not yet been used to this purpose, although it was applied successfully to dealkylate esters of carboxylic acids[10]. We demonstrate that with iodotrimethylsilane it is possible to silylate oxoalkanephosphonic esters within minutes at 0° while bromotrimethylsilane requires about 1 h at room temperature[8]. Preparative yields of the silylated oxoalkanephosphonates are very good (Table 1 and 2).



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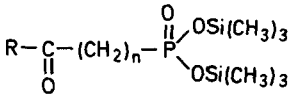

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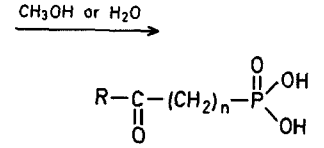

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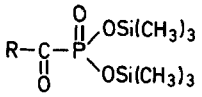
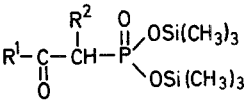
Table 1. *O,O*-Bis[trimethylsilyl] 1-Oxoalkanephosphonates (**2**, n = 0)



R	Yield [%]	b.p./torr	I.R. (film) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
CH_3	76	53–54°/0.3	1705 (C=O), 1270 (P=O), 1050 (Si—O), 865 (Si—C)	0.33 (s, 18H, $SiCH_3$); 2.49 (d, 3H, $^3J_{PH}$ = 5.0 Hz, P—C—CH_3)
C_2H_5	78	56–57°/0.3	1710 (C=O), 1265 (P=O), 1035 (Si—O), 860 (Si—C)	0.33 (s, 18H, $SiCH_3$); 1.11 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_2CH_3); 2.89 (q, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2CH_3)
n-C_3H_7	76	63–64°/0.3	1705 (C=O), 1270 (P=O), 1045 (Si—O), 860 (Si—C)	0.33 (s, 18H, $SiCH_3$); 0.95 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_2CH_3); 1.69 (sext, 2H, $^3J_{HH}$ = 7.5 Hz, $CH_2CH_2CH_3$); 2.84 (t, 2H, $^3J_{HH}$ = 7.5 Hz, $CH_2CH_2CH_3$)
i-C_3H_7	76	58–59°/0.3	1710 (C=O), 1275 (P=O), 1050 (Si—O), 870 (Si—C)	0.33 (s, 18H, $SiCH_3$); 1.19 [d, 6H, $^3J_{HH}$ = 7.0 Hz, $(H_3C)_2CH$]; 3.14 [hept. 1H, $^3J_{HH}$ = 7.0 Hz, $(H_3C)_2CH$]

Table 2. *O,O*-Bis[trimethylsilyl] 2-Oxoalkanephosphonates (**2**, n = 1)



R^1	R^2	Yield [%]	b.p./torr	I.R. (film) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
CH_3	H	84	66–67°/0.4	1720 (C=O), 1260 (P=O), 1040 (Si—O), 855 (Si—C)	0.28 (s, 18H, $SiCH_3$); 2.31 (s, 3H, H_3C—CO); 3.04 (d, 1H, $^2J_{PH}$ = 24.0 Hz, P—CH_2); 3.07 (d, 1H, $^2J_{PH}$ = 23.0 Hz, P—CH_2)
CH_3	CH_3	77	74–75°/0.7	1715 (C=O), 1255 (P=O), 1030 (Si—O), 850 (Si—C)	0.27 (s, 18H, $SiCH_3$); 1.05–1.50 (m, 3H, CH—CH_3); 2.29 (s, 3H, H_3C—CO); 2.75–3.50 (m, 1H, CH—CH_3)
i-C_3H_7	H	82	83–84°/0.7	1715 (C=O), 1255 (P=O), 1030 (Si—O), 850 (Si—C)	0.24 (s, 18H, $SiCH_3$); 1.06 [d, 6H, $^3J_{HH}$ = 7.0 Hz, $(H_3C)_2CH$]; 2.60–3.00 [m, 1H, $(H_3C)_2CH$]; 3.02 (br d, 2H, $^2J_{PH}$ = 23.0 Hz, P—CH_2)
t-C_4H_9	H	79	85–86°/0.7	1710 (C=O), 1255 (P=O), 1030 (Si—O), 850 (Si—C)	0.28 (s, 18H, $SiCH_3$); 1.15 (s, 9H, *t*-C_4H_9); 3.08 (d, 1H, $^2J_{PH}$ = 23.0 Hz, P—CH_2); 3.11 (d, 1H, $^2J_{PH}$ = 22.0 Hz, P—CH_2)

Table 3. Dicyclohexylammonium Salts of 1-Oxoalkanephosphonic Acids **3** (n = 0)

R	Yield [%]	m.p.	Molecular formula[a]	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (D_2O/HMDS) δ [ppm]
CH_3	96	197–208°	$C_{14}H_{28}NO_4P$ (305)	3200–2000 ($PO_3H^{\ominus}$, $H_2N^{\oplus}$, CH), 1685 (C=O), 1610 ($H_2N^{\oplus}$), 1170, 1080 ($PO_3H^{\ominus}$)	1.25–2.60 (br, CH_2, 20H); 2.68 (d, 3H, $^3J_{PH}$ = 4.5 Hz, H_3C—CO); 3.30–3.85 (m, 2H, >CH—N)
C_2H_5	90	209–212°	$C_{15}H_{30}NO_4P$ (319)	3200–2000 ($PO_3H^{\ominus}$, $H_2N^{\oplus}$, CH), 1685 (C=O), 1610 ($H_2N^{\oplus}$), 1165, 1075 ($PO_3H^{\ominus}$)	1.31 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_2CH_3); 1.35–2.70 (br, CH_2, 20H); 3.20 (q, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2CH_3); 3.25–3.90 (m, 2H, >CH—N)
n-C_3H_7	99	206–211°	$C_{16}H_{32}NO_4P$ (333)	3200–2000 ($PO_3H^{\ominus}$, $H_2N^{\oplus}$, CH), 1680 (C=O), 1605 ($H_2N^{\oplus}$), 1170, 1070 ($PO_3H^{\ominus}$)	insoluble
i-C_3H_7	85 (97)[b]	208–212°	$C_{16}H_{32}NO_4P$ (333)	3200–2000 ($PO_3H^{\ominus}$, $H_2N^{\oplus}$, CH), 1680 (C=O), 1605 ($H_2N^{\oplus}$), 1165, 1085 ($PO_3H^{\ominus}$)	1.47 [d, 6H, $^3J_{HH}$ = 7.5 Hz, $(H_3C)_2CH$]; 1.35–2.60 (br, CH_2, 20H); 3.30–3.80 [m, 3H, >CH—N + $(H_3C)_2CH$]

[a] All products gave satisfactory microanalyses (P ±0.15, N ±0.25).
[b] By methanolysis of the silyl ester.

Silylation followed by hydrolysis appears to be the method of choice for the preparation of 1-oxoalkanephosphonic acids (Table 3) as it is much faster than dealkylation with sodium iodide described by Kluger et al.[4,5]. We were unable to obtain 1-oxoalkanephosphonic acids from their esters upon hydrolysis or treatment with hydrobromic acid, observing

Table 4. Dicyclohexylammonium Salts of 2-Oxoalkanephosphonic Acids **3** (n = 1)

R^1	R^2	Yield [%] by Method[a] A	B	C	m.p.	Molecular formula[b]	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (D_2O/HMDS) δ [ppm]
CH_3	H	89[c]	87	91	173–175°	$C_{15}H_{30}NO_4P$ (322)	3500–2000 ($PO_3H^{\ominus}$, $H_2N^{\oplus}$, CH), 1705 (C=O), 1615 ($H_2N^{\oplus}$), 1150, 1060 ($PO_3H^{\ominus}$)	1.40–2.60 (br, CH_2, 20H); 2.64 (s, 3H, CH_3); 3.38 (d, 2H, $^2J_{PH}$ = 21.0 Hz, P—CH_2); 3.25–3.80 (m, 2H, >CH—N)
CH_3	CH_3	97[c]	—	—	170–175°	$C_{16}H_{32}NO_4P$ (336)	3500–2000 ($PO_3H^{\ominus}$, $H_2N^{\oplus}$, CH), 1705 (C=O), 1600 ($H_2N^{\oplus}$), 1160, 1075 ($PO_3H^{\ominus}$)	1.35–2.60 (br, CH_2 + P—C—CH_3, 23H); 2.67 (s, 3H, H_3C—CO); 3.35–4.10 (m, 3H, >CH—N + P—CH_2)
i-C_3H_7	H	100[c]	86	89	168–162°	$C_{17}H_{34}NO_4P$ (350)	3500–2000 ($PO_3H^{\ominus}$, $H_2N^{\oplus}$, CH), 1695 (C=O), 1605 ($H_2N^{\oplus}$), 1160, 1070 ($PO_3H^{\ominus}$)	1.32 [d, 6H, $^3J_{HH}$ = 7.0 Hz, $(H_3C)_2CH$]; 1.35–2.75 (br, CH_2, 20H); 3.35 (d, 2H, $^2J_{PH}$ = 22 Hz, P—CH_2); 3.10–3.90 [m, 3H, >CH—N + $(H_3C)_2CH$]
t-C_4H_9	H	93	88	84	175–178.5°	$C_{18}H_{36}NO_4P$ (364)	3500–2000 ($PO_3H^{\ominus}$, $H_2N^{\oplus}$, CH), 1695 (C=O), 1615 ($H_2N^{\oplus}$), 1170, 1070 ($PO_3H^{\ominus}$)	1.43 (s, 9H, CH_3); 1.40–2.55 (br, CH_2, 20H); 3.42 (d, 2H, $^2J_{PH}$ = 20.5 Hz, P—CH_2); 3.25–3.70 (m, 2H, >CH—N)

[a] Method A—silylation; Method B—hydrolysis; Method C—acidolysis with hydrobromic acid in acetic acid.

[b] All products gave satisfactory microanalysis (P ±0.15, N ±0.25).

[c] From distilled silyl ester **2**.

instead the cleavage of the P—C bond. Dealkylation of 2-oxoalkanephosphonates can be accomplished with comparable effort and yields using any of the three procedures, i.e. silylation, hydrolysis, or acidolysis with hydrobromic acid (Table 4).

Desilylation proceeds smoothly with water or methanol but methanolysis is not recommended for the preparation of 1-oxoalkanephosphonic acids as it is complicated by formation of 1,1-dimethoxy derivatives. In the case of *O,O*-bis[trimethylsilyl] 1-oxoethanephosphonate, methanolysis yielded 1,1-dimethoxyethanephosphonic acid as sole reaction product.

Bromomethyl ketones were prepared according to the literature[11,12] and were reacted with potassium iodide to give iodomethyl ketones[13] which were used for the preparation of diethyl 2-oxoalkanephosphonates by Arbuzov reaction[14]. Yields ranged within 70–95%. Diethyl 1-methyl-2-oxopropanephosphonate was obtained by alkylation of diethyl 2-oxopropanephosphonate with methyl iodide[14,15]. Diethyl 1-oxoalkanephosphonates were prepared as described Connell[16]. Iodotrimethylsilane was prepared using the described method[17].

Preparation of *O,O*-Bis[trimethylsilyl] Oxoalkanephosphonates (2):

To the diethyl oxoalkanephosphonate **1** (0.05 mol) in dry carbon tetrachloride (20 ml), iodotrimethylsilane (0.1 mol) is added dropwise at 0° over 20 min with stirring under dry nitrogen. The cooling bath is then removed and after 20 min the mixture is evaporated under reduced pressure. The resultant residue is vacuum fractionated yielding **2** as dense, colorless liquids (Table 1 and 2).

Methanolysis of *O,O*-Bis[trimethylsilyl] Oxoalkanephosphonates:

The silyl ester **2** (0.01 mol) is dissolved in methanol (50 ml) and ~30 ml of methanol are distilled off under atmospheric pressure to remove the resultant trimethylsilanol. The remaining methanol is then removed on a rotary evaporator at 50°, the resultant oil is dissolved in acetone (10 ml) and treated with dicyclohexylamine (0.02 mol) in acetone (5 ml). The mixture is left overnight in a refrigerator. The white, crystalline precipitate is isolated by filtration yielding **3** (Table 4). For analytical purposes the salts are crystallized from acetone/water.

Methanolysis of *O,O*-bis[trimethylsilyl] 1-oxoethanephosphonate gives 1,1-dimethoxyethanephosphonic acid monodicyclohexylammonium salt; yield: 90%; m.p. 194–198°.

$C_{16}H_{35}NO_5P$	calc.	N 3.99	P 8.83
(352.4)	found	4.04	8.96

I.R. (KBr): ν_{max} = 3200–2000 ($PO_3H_9^{\ominus}$, $H_2N^{\oplus}$, CH); 1680, 1610 ($H_2N^{\oplus}$); 1160, 1060 ($PO_3H^{\ominus}$); 1035 cm^{-1} (C—O).

^{1}H-N.M.R. (D_2O/HMDS): δ = 1.30–2.75 (br, CH_2, 20H); 2.71 (d, 3H, $^3J_{PH}$ = 4.5 Hz, P—C—CH_3); 3.62 (s, 6H, OCH_3); 2.90–3.90 ppm (m, 2H, CH).

Methanolysis of *O,O*-bis[trimethylsilyl] 1-oxopropanephosphonate gives a mixture of 1,1-dimethoxy derivative and the oxoalkanephosphonic acid in a ratio of 3:7 (by N.M.R.).

Methanolysis of *O,O*-bis[trimethylsilyl] 1-oxobutanephosphonate gives a similar mixture (2:8). Formation of the 1,1-dimethoxy-derivative is not observed in the case of *O,O*-bis[trimethylsilyl] 1-oxo-2-methylpropanephosphonate.

Hydrolysis of *O,O*-Bis[trimethylsilyl] 1-Oxoalkanephosphonates:

The silyl ester **2** (0.007 mol) is shaken with water (50 ml) for 1 h at room temperature. The resultant mixture is extracted with dichloromethane (3 × 20 ml) and the aqueous layer is evaporated leaving a dense, colorless oil which is dissolved in acetone (50 ml). To the acetone solution of phosphonic acid thus obtained, dicyclo-

hexylamine (0.014 mol) in acetone (20 ml) is added and the mixture is left for 12 h in the refrigerator. The white, crystalline precipitate is collected by filtration, the products obtained are chemically pure and are not crystallized for analysis (Table 3).

Hydrolysis of Diethyl 2-Oxoalkanephosphonates by Concentrated Hydrochloric Acid:

The diethyl ester **1** (0.01 mol) is heated under reflux in concentrated hydrochloric acid (50 ml) for 8 h followed by evaporation on a rotary evaporator. The oily residue is mixed with toluene (30 ml) and repeatedly evaporated. The resultant product is dissolved in acetone (10 ml) and the dicyclohexylammonium salt is precipitated by addition of dicyclohexylamine (0.02 mol) in acetone (5 ml) (Table 4).

Hydrolysis of diethyl 2-oxo-3,3-dimethylbutanephosphonate gives the corresponding phosphonic acid which is recrystallized from carbon tetrachloride, yield: 81 %; m.p. 101–103°.

$C_6H_{13}O_4P$	calc.	P 17.22
(180.1)	found	17.12

I.R. (KBr): ν_{max} = 3200–2000 ($PO_3H^{\ominus}$, CH); 1690 (C=O); 1020 cm^{-1} ($PO_3H^{\ominus}$).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.16 (s, 9H, CH_3); 3.33 (d, 2H, $^2J_{PH}$ = 20.5 Hz, CH_2P); 8.95 ppm (s, 2H, PO_3H_2).

Acidolysis of Diethyl 2-Oxoalkanephosphonates with 45 % Hydrobromic Acid in Acetic Acid:

The diethyl ester **1** (0.01 mol) is heated at 50–60° in 45 % hydrobromic acid in acetic acid (20 ml) for 0.5 h (even after 24 h at room temperature the reaction is not complete). After evaporation, the residue is dissolved in methanol (20 ml) and repeatly evaporated. Evaporation is repeated twice and the resultant, dense oil is mixed with toluene and evaporated once more. The yellow oil thus obtained is dissolved in acetone (10 ml) and the dicyclohexylammonium salt is precipitated as above (Table 4).

Disodium salts of oxoalkanephosphonic acids can be easily obtained by addition of equimolar amounts of sodium hydroxide solution to the free acid **3** obtained after dealkylation by the silyl procedure and evaporation.

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