A Practical Synthesis of Cycloalkylphosphonates from Trichloromethylphosphonates

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Received 6 October 1994

Cycloalkylphosphonates **5** with ring size varying from 4 to 6 were synthesized in good overall yields, in two steps from trichloromethylphosphonates and ω-dibromoalkanes, via the corresponding α-trimethylsilyl cycloalkylphosphonates **4**.

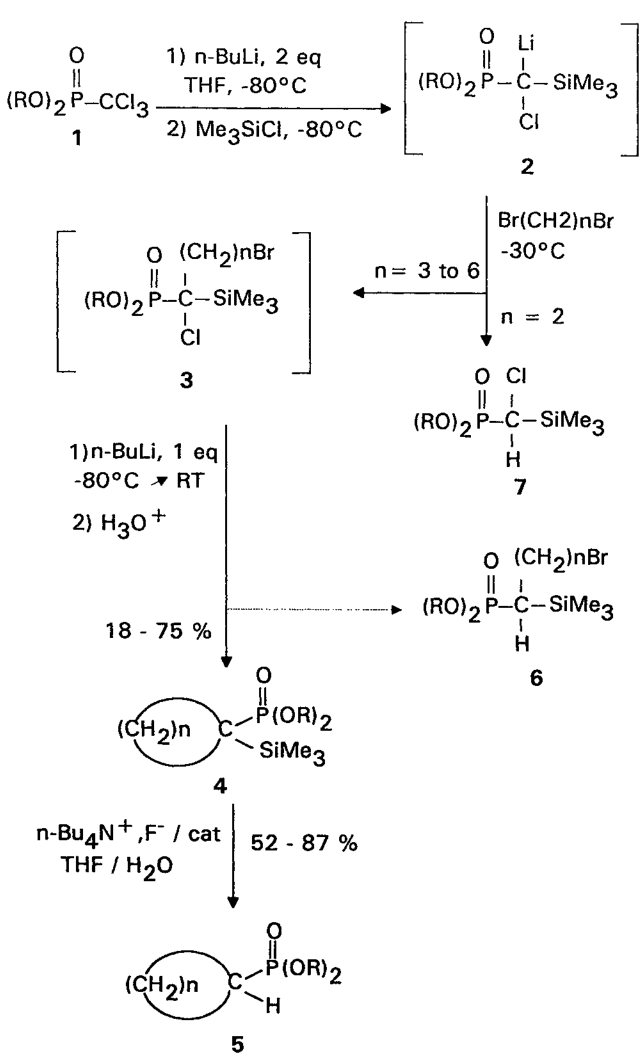
Owing to their biological properties, many phosphonate derivatives have found applications in the fields of pharmaceuticals and agrochemicals.[1,2] For some of these compounds, biological activity seems to be linked to the presence of a cyclic residue within their structure. This is the case, for example, for di-*n*-butyl α-(*n*-butylamino)cyclohexylphosphonate (the herbicide Trakephon[3]) and for α-aminocyclopentylphosphonic acid, which exhibits in vitro anti-leukaemic activity.[4]

In continuation of our studies on cycloalkylphosphonates,[5] we attempted to prepare unsubstituted cycloalkylphosphonates **5**, which are potentially interesting precursors of α-functionalized cycloalkylphosphonates.

Few examples of unsubstituted cycloalkylphosphonates **5** are found in the chemical literature. Cyclohexylphosphonates have been prepared, in moderate yields, by alcoholysis of either corresponding Kinnear–Perren chloroaluminate complexes,[6] or the phosphonochloridate which results from the reaction of oxygen, phosphorus trichloride and cyclohexane under forcing conditions.[7] Another route to these compounds involves the photophosphonylation of cycloalkanes in the presence of dialkyl or diaryl phosphites or phosphoryl chloride;[8,9] although good yields are obtained in the cyclohexane series,[8] the method is time consuming and lacks generality.

The peroxide initiated free-radical reaction of dialkyl phosphites with cycloalkenes leads to the expected cycloalkylphosphonates, but only in moderate yields.[10–16] Finally, Raney nickel desulfurization of the (1-alkylthio)cycloalkylphosphonates which result from the reaction of trialkyl phosphites with various cycloalkanedithiols, gives cycloalkylphosphonates in fairly good yields.[17]

We report here a two-step synthesis of unsubstituted cycloalkylphosphonates **5** starting from trichloromethylphosphonate **1** which is easily and cheaply available on large scale by Michaelis–Arbuzov reaction.[18] In the first step (**1**–**4**), we effected the cyclization sequence by successive removal of the three chlorine atoms from **1** (Scheme). The carbanions **2** were quantitatively generated by simultaneous addition of **1** and chlorotrimethylsilane to a solution of butyllithium (2 equivalents) in tetrahydrofuran, at temperatures below – 80 °C, in order to avoid the formation of carbenes during the removal of the first chlorine atom.[19] The carbanions **2** are stabilized by the trimethylsilyl group and can be kept at room temperature and analysed by ^{31}P NMR spectroscopy [^{31}P(THF) $\delta = +44.6$ for R = Et and $+42.3$ for R = *i*-Pr]. Carbanions **2** were then alkylated by various ω-dibromoalkanes, at around – 30 °C, to give intermediate phosphonates **3** [NMR ^{31}P spectroscopy (THF), δ varing from 21 to 23] which were not isolated. Finally the cyclization of **3** into **4** was easily achieved by subsequent addition of a third equivalent of butyllithium to the mixture at – 80 °C. We observed only exchange of the third chlorine atom and intramolecular cyclization provided that the temperature was kept around – 80 °C. α-Trimethylsilylated cycloalkylphosphonates **4** were isolated after acidic treatment and purified by distillation (Table 1).



4, 5	a	b	c	d	e	f	g	h
R	Et	iPr	Et	iPr	Et	iPr	Et	iPr
n	3	3	4	4	5	5	6	6

Scheme

It appears that the facility of cyclization roughly decreased in the following order, according to n = 4 > 5 ~ 3 > > 6 as it is commonly observed for this process.[20] Although in each case, the formation of intermediate phosphonate **3** was quantitative, the cyclization was almost complete only when the geometry was favorable (n = 3, 4 and 5), and corresponding α-silylated cycloalkylphosphonates **4** were obtained in good yield. For n = 6 (**4g**, **4h**), the entropy effect of cyclization was less favorable, consequently the cyclization was imcomplete and the excess of anion derived from **3** was protonated during hydrolysis leading to phosphonate **6** [^{31}P NMR spectroscopy ($CDCl_3$), δ varing from 32 to 34].

Table 1. Synthesis of α-Trimethylsilyl Cycloalkylphosphonates **4**

Product[a]	^{31}P NMR ($CDCl_3$)	bp (°C)/Torr	Yield[b] (%)
4a	34.5	87/0.3	70
4b	33.0	75/0.1	75
4c	37.0	87/0.5	68
4d	35.7	82/0.1	72
4e	35.4	98/0.3	66
4f	33.7	95/0.1	65
4g	36.1	120/0.3	18
4h	34.4	126/0.3	23

[a] Satisfactory microanalysis obtained: C ±0.38, H ±0.43.
[b] Yield of distilled products.

For n = 2, we were not able to prepare the corresponding cyclopropylphosphonates by the proposed sequence; under our conditions carbanions **2** were quantitatively protonated by reaction with dibromoethane, giving the phosphonates **7** [^{31}P($CDCl_3$) δ = +20.4 for R = Et and +19.0 for R = *i*-Pr].

Removal of the trimethylsilyl group from **4** was achieved in the second step. Previously reported procedures (LiOH or EtONa in alcohol) for the desilylation of trimethylsilylated alkylphosphonates[19,21] failed when applied to phosphonates **4**. The use of potassium fluoride in refluxing dimethyl sulfoxide for several hours led to cycloalkylphosphonates **5** in moderate yields only. Finally, we found that stirring **4** with a wet solution of tetrahydrofuran containing about 30 %mol of tetrabutylammonium fluoride at 0 °C achieved complete desilylation of **4**, in a few minutes. The expected cycloalkylphosphonates **5** were isolated in good yields after purification by distillation (Table 2).

In conclusion, we propose an efficient two-step synthesis of cyclobutyl-, cyclopentyl- and cyclohexylphosphonates starting from readily available trichloromethylphosphonates and ω-dibromoalkanes. Further investigations, devoted to α-functionalization of these compounds, are in progress in our laboratories.

Table 2. Synthesis of Cycloalkylphosphonates **5**

Product[a]	^{31}P NMR ($CDCl_3$), δ	bp (°C)/Torr	Yield[b] (%)
5a	30.1	76/0.3	87
5b	28.2	80/0.1	68
5c	33.2	85/0.3	68
5d	31.1	87/0.2	72
5e	30.7	90/0.3[c]	77
5f	28.7	85/0.1	65
5g	32.9	93/0.3	58
5h	30.9	95/0.3	52

[a] Satisfactory microanalysis obtained: C ±0.49, H ±0.47.
[b] Yield of distilled products.
[c] Lit.[8] bp 127°/3.5 Torr.

NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for proton, 50.3 MHz for carbon and 81.01 MHz for phosphorus. ^{31}P downfield shifts (δ) are expressed with a positive sign, relative to external 85% H_3PO_4 in H_2O. ^{1}H and ^{13}C chemical shifts (δ) are reported relative to TMS as internal standard. Coupling constants (*J*) are given in Hertz. GC was performed on a Girdel 300 chromatograph equipped with a 2 m OV 17 column.

All reagents were of commercial quality or were purified before use. Organic solvents were purified by standard procedures. THF was distilled under an inert atmosphere from purple solutions of sodium/benzophenone ketyl. The synthesis of compounds **4** was carried out under dry inert gas.

α-Silylated Cycloalkylphosphonates 4; General Procedure:
To a stirred mixture of a 1.6 M hexane solution of BuLi (50 mL, 80 mmol) and anhydr. THF (100 mL) cooled to −80 °C were added dropwise trichloromethylphosphonate (40 mmol) and $ClSiMe_3$ (5.6 mL, 44 mmol) in THF (10 mL). Stirring was continued at −80 °C for about 15 min until formation of carbanion **2** was complete, as indicated by ^{31}P NMR spectroscopy [single peak at δ = ~43 (THF)]. Then the ω-dibromoalkane (44 mmol) in THF (5 mL) was added dropwise at −30 °C and the stirred mixture was allowed to warm to r.t. until formation of phosphonate **3** was complete, as proved by ^{31}P NMR spectroscopy [single peak at δ = ~21 or 23 (THF)]. The mixture was cooled to −80 °C and a solution of BuLi in hexane (25 mL, 40 mmol) was slowly added under stirring at this temperature. The resulting mixture was allowed to warm to r.t. and stirred until formation of phosphonate **4** was complete. The mixture was then acidified with 4 N HCl (20 mL) and separated. The aqueous layer was extracted with Et_2O (3 x 20 mL). The organic layers were dried ($MgSO_4$) and the solvents evaporated in vacuo to give the crude product which was purified by distillation under reduced pressure. (Tables 1 and 3).

Desilylation of 4 to Cycloalkylphosphonates 5; General Procedure:
To a solution of α-silylated cycloalkylphosphonate **4** (10 mmol) in THF (50 mL) at 0 °C was added $Bu_4NF \cdot 3H_2O$ (99 %, 3.8 g) or a commercial 1 M THF solution of Bu_4NF (3 mL, 3 mmol). The mixture was stirred for 1 h at 0 °C, then acidified with 4 N HCl and separated. The aqueous layer was extracted with Et_2O (3 x 20 mL). Organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to give the crude product which was purified by distillation under reduced pressure. (Tables 2 and 4).

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Table 3. ^1H and ^{13}C NMR Data of α-Trimethylsilyl Cycloalkylphosphonates **4**

Product	^1H NMR ($CDCl_3$, 200 MHz) δ, J (Hz)	^{13}C {^1H} NMR ($CDCl_3$, 50 MHz) δ, $J_{C,P}$ (Hz)
4a	0.08 [s, 9H, $Si(CH_3)_3$], 1.24 (t, $J = 7$, 6H, $\underline{CH_3}CH_2O$), 1.88–2.60 (m, 6H, $\underline{H}$ring), 4.06 (dq, $J = 7, 9$, 4H, $CH_3\underline{CH_2}O$)	−3.0 [s, $Si(CH_3)_3$], 16.2 (d, $J = 5.6$, CH_3), 17.6 (d, $J = 9.8$, C_3), 23.0 (d, $J = 7.4$, C_2, C_4), 26.6 (d, $J = 130$, C_1), 61.2 (d, $J = 7.3$, OCH_2)
4b	0.10 [s, 9H, $Si(CH_3)_3$], 1.26 [d, $J = 6$, 12H, $(\underline{CH_3})_2CHO$], 1.80–2.60 (m, 6H, $\underline{H}$ring), 4.63 [m, 2H, $(CH_3)_2\underline{CH}O$]	−3.2 [s, $Si(CH_3)_3$], 17.9 (d, $J = 10.5$, C_3), 23.1 (d, $J = 7.7$, C_2, C_4), 23.8 (d, $J = 3.9$, CH_3), 23.9 (d, $J = 5.3$, CH_3), 26.3 (d, $J = 129$, C_1), 69.2 (d, $J = 7.6$, OCH)
4c	0.07 [s, 9H, $Si(CH_3)_3$], 1.25 (t, $J = 7$, 6H, $\underline{CH_3}CH_2O$), 1.35–2.20 (m, 8H, $\underline{H}$ring), 4.04 (dq, $J = 7, 9$, 4H, $CH_3\underline{CH_2}O$)	−2.7 [s, $Si(CH_3)_3$], 16.3 (d, $J = 6.1$, CH_3), 27.3 (d, $J = 3.6$, C_3, C_4), 29.6 (d, $J = 4.7$, C_2, C_5), 30.6 (d, $J = 128$, C_1), 61.0 (d, $J = 7.4$, OCH_2)
4d	0.04 [s, 9H, $Si(CH_3)_3$], 1.24 [d, $J = 6$, 12H, $(\underline{CH_3})_2CHO$], 1.40–2.12 (m, 8H, $\underline{H}$ring), 4.63 [m, 2H, $(CH_3)_2\underline{CH}O$]	−2.5 [s, $Si(CH_3)_3$], 23.8 (d, $J = 3.0$, CH_3), 23.9 (d, $J = 5.0$, CH_3), 27.7 (d, $J = 3.6$, C_3, C_4), 29.9 (d, $J = 4.5$, C_2, C_5), 31.0 (d, $J = 127$, C_1), 69.2 (d, $J = 7.4$, OCH)
4e	0.07 [s, 9H, $Si(CH_3)_3$], 1.28 (t, $J = 7$, 6H, $\underline{CH_3}CH_2O$), 1.40–2.12 (m, 10H, $\underline{H}$ring), 4.08 (dq, $J = 7, 9$, 4H, $CH_3\underline{CH_2}O$)	−2.3 [s, $Si(CH_3)_3$], 16.3 (d, $J = 6.1$, CH_3), 22.5 (d, $J = 2.8$, C_3, C_5), 25.8 (s, C_4), 26.6 (d, $J = 3.7$, C_2, C_6), 27.7 (d, $J = 124$, C_1), 60.7 (d, $J = 7.3$, OCH_2)
4f	0.02 [s, 9H, $Si(CH_3)_3$], 1.25 [d, $J = 6$, 12H, $(\underline{CH_3})_2CHO$], 1.27–2.0 (m, 10H, $\underline{H}$ring), 4.63 [m, 2H, $(CH_3)_2\underline{CH}O$]	−2.0 [s, $Si(CH_3)_3$], 22.4 (d, $J = 3.2$, C_3, C_5), 23.8 (d, $J = 3.6$, CH_3), 24.0 (d, $J = 4.9$, CH_3), 25.8 (s, C_4), 26.6 (d, $J = 3.4$, C_2, C_6), 27.4 (d, $J = 127$, C_1), 68.7 (d, $J = 7.4$, OCH)
4g	0.00 [s, 9H, $Si(CH_3)_3$], 1.19 (t, $J = 7$, 6H, $\underline{CH_3}CH_2O$), 1.27–2.10 (m, 12H, $\underline{H}$ring), 3.97 (dq, $J = 7, 9$, 4H, $CH_3\underline{CH_2}O$)	−1.9 [s, $Si(CH_3)_3$], 16.2 (d, $J = 6.0$, CH_3), 25.3 (d, $J = 7.2$, C_3, C_6), 29.1 (d, $J = 4.8$, C_2, C_7), 29.6 (d, $J = 122$, C_1), 31.1 (s, C_4, C_5), 60.9 (d, $J = 7.5$, OCH_2)
4h	0.00 [s, 9H, $Si(CH_3)_3$], 1.20 [d, $J = 6$, 12H, $(\underline{CH_3})_2CHO$], 1.30–2.1 (m, 12H, $\underline{H}$ring), 4.56 [m, 2H, $(CH_3)_2\underline{CH}O$]	−1.6 [s, $Si(CH_3)_3$], 23.7 (d, $J = 5.0$, CH_3), 23.9 (d, $J = 3.4$, CH_3), 25.3 (d, $J = 7.3$, C_3, C_6), 29.2 (d, $J = 4.4$, C_2, C_7), 29.3 (d, $J = 124$, C_1), 31.3 (s, C_4, C_5), 69.0 (d, $J = 7.7$, OCH)

Table 4. ^1H and ^{13}C NMR Data of Cycloalkylphosphonates **5**

Product	^1H NMR ($CDCl_3$, 200 MHz) δ, J (Hz)	^{13}C {^1H} NMR ($CDCl_3$, 50 MHz) δ, $J_{C,P}$ (Hz)
5a	1.31 (t, $J = 7$, 6H, $\underline{CH_3}CH_2O$), 1.96–2.51 (m, 6H, $\underline{H}$ring), 2.70 (m, 1H, HCP), 4.05 (dq, $J = 7, 9$, 4H, $CH_3\underline{CH_2}O$)	16.1 (d, $J = 5.7$, CH_3), 19.8 (d, $J = 18.6$, C_3), 22.1 (d, $J = 6.6$, C_2, C_4), 29.2 (d, $J = 146$, C_1), 61.3 (d, $J = 6.7$, OCH_2)
5b	1.20 [d, $J = 6$, 12H, $(\underline{CH_3})_2CHO$], 1.90–2.36 (m, 6H, $\underline{H}$ring), 2.55 (m, 1H, HCP), 4.66 [m, 2H, $(CH_3)_2\underline{CH}O$]	19.7 (d, $J = 18$, C_3), 22.3 (d, $J = 6.4$, C_2, C_4), 23.8 (d, $J = 4.1$, CH_3), 30.3 (d, $J = 148$, C_1), 69.4 (d, $J = 6.3$, OCH)
5c	1.21 (t, $J = 7$, 6H, $\underline{CH_3}CH_2O$), 1.35–2.18 (m, 9H, $\underline{H}$ring), 3.99 (dq, $J = 7, 9$, 4H, $CH_3\underline{CH_2}O$)	16.2 (d, $J = 5.8$, CH_3), 26.0 (d, $J = 12$, C_3, C_4), 26.7 (d, $J = 2.4$, C_2, C_5), 34.7 (d, $J = 146$, C_1), 61.1 (d, $J = 6.8$, OCH_2)
5d	1.10 [d, $J = 6$, 12H, $(\underline{CH_3})_2CHO$], 1.23–2.0 (m, 9H, $\underline{H}$ring), 4.42 [m, 2H, $(CH_3)_2\underline{CH}O$]	23.8 (d, $J = 3.5$, CH_3), 23.9 (d, $J = 4.7$, CH_3), 26.1 (d, $J = 12$, C_3, C_4), 26.9 (d, $J = 2.6$, C_2, C_5), 35.7 (d, $J = 148$, C_1), 69.3 (d, $J = 6.9$, OCH)
5e	1.20 (t, $J = 7$, 6H, $\underline{CH_3}CH_2O$), 1.42–2.0 (m, 11H, $\underline{H}$ring), 3.97 (dq, $J = 7, 9$, 4H, $CH_3\underline{CH_2}O$)	16.1 (d, $J = 5.8$, CH_3), 25.4 (d, $J = 4.3$, C_3, C_5), 25.7 (d, $J = 5.3$, C_2, C_6), 25.9 (s, C_4), 35.2 (d, $J = 143$, C_1), 61.3 (d, $J = 6.9$, OCH_2)
5f	1.26 [d, $J = 6$, 12H, $(\underline{CH_3})_2CHO$], 1.27–2.0 (m, 11H, $\underline{H}$ring), 4.63 [m, 2H, $(CH_3)_2\underline{CH}O$]	23.8 (d, $J = 4.8$, C_3, C_5), 23.85 (d, $J = 4.7$, CH_3), 23.9 (d, $J = 3.5$, CH_3), 25.7 (d, $J = 5.0$, C_2, C_6), 26.2 (s, C_4), 36.4 (d, $J = 144$, C_1), 69.3 (d, $J = 7.0$, OCH)
5g	1.17 (t, $J = 7$, 6H, $\underline{CH_3}CH_2O$), 1.30–2.20 (m, 13H, $\underline{H}$ring), 3.95 (dq, $J = 7, 9$, 4H, $CH_3\underline{CH_2}O$)	16.2 (d, $J = 5.8$, CH_3), 27.1 (d, $J = 1.4$, C_3, C_6), 27.2 (d, $J = 17.6$, C_2, C_7), 27.9 (s, C_4, C_5), 36.5 (d, $J = 136$, C_1), 61.1 (d, $J = 6.9$, OCH_2)
5h	1.22 [t, $J = 6$, 12H, $(\underline{CH_3})_2CHO$], 1.28–2.05 (m, 13H, $\underline{H}$ring), 4.58 [m, 2H, $(CH_3)_2\underline{CH}O$]	23.7 (d, $J = 4.2$, CH_3), 23.8 (d, $J = 3.3$, CH_3), 27.2 (d, $J = 2.5$, C_3, C_6), 27.4 (d, $J = 17.6$, C_2, C_7), 27.9 (s, C_4, C_5), 37.2 (d, $J = 138$, C_1), 69.2 (d, $J = 7.0$, OCH)

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