A New Route to α-Fluoromethyl- and α-Fluoroalkyl-phosphonates

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α-Fluoroalkylphosphonates are prepared by double-halogen exchange of 1,1,1-dibromofluoroalkylphosphonates with *n*-butyllithium–trimethylchlorosilane (2 : 1) followed by alkylation and ethanolysis.

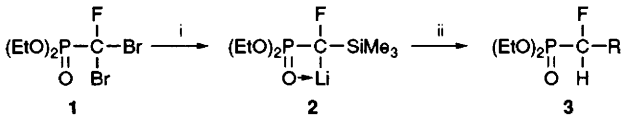
It is increasingly recognised that phosphonic acids structurally related to natural phosphates possess particularly interesting properties.[1] In this field α-fluoroalkylphosphonates are finding growing applications in the synthesis of 'unnatural products' and biologically active compounds. The implication of an isosteric relationship between a natural phosphate and a phosphonic acid requires close consideration for the design of specific compounds. Blackburn[2] and Chambers[3] have shown that α-fluoroalkylphosphonates lead to good correspondence because the CHF or CF_2 group can both sterically and electronically mimic the binding oxygen atom of the ester group.

A few methods have been described in the literature for the preparation of α-fluorinated alkylphosphonates.[4] One approach is based on the reaction of a dialkyl phosphite anion with a fluorobromomethane (Michaelis–Becker reaction[5]) or reaction of a trialkyl phosphite with fluorotribromomethane (Michaelis–Arbuzov reaction[6,7]). Another is based on the fluorination of phosphonate carbanions by action of sources of positive fluorine, such as $FClO_3$[8] or $(RSO_2)_2NF$[7] or by the action of sources of nucleophilic fluorine, such as Et_2NSF_3 (DAST) upon α-hydroxyphosphonates.[9] However, these methods often suffer from low yields and side-reactions, and involve potentially hazardous fluorinating agents.

We now describe a novel, facile and practical method for the preparation of a range of α-fluoroalkylphosphonates from fluorodibromomethylphosphonate **1**.

Compound **1** was readily obtained in high yield (95%) by the action of triethyl phosphite on tribromofluoromethane[10] in refluxing tetrahydrofuran (THF).† The ease of access to **1** on a large scale allowed a detailed investigation of the reactivity of this α-fluorophosphonate.

† At the temperature of refluxing THF, the ethyl bromide produced does not react with triethyl phosphite.



Scheme 1 *Reagents and conditions*: i, Bu^nLi (2 equiv.), $ClSiMe_3$, THF, −78 °C; ii, R = H: (*a*) EtOH, −78 °C, (*b*) 2 mol l^{-1} HCl 0 °C; R ≠ H: (*a*) RI, −78 °C, (*b*) EtOH–EtOLi, 0 °C, (*c*) 2 mol l^{-1} HCl, 0 °C

Table 1 One-pot conversion of carbanion **2** to α-fluorophosphonates **3**[a]

	R	Isolated yield (%)[b]	B.p., *t*/°C at 16 mmHg[c]	δ(^{31}P)/$CDCl_3$(d) ($^2J_{PF}$/Hz)
3a	H	93	135–140	17.0 (63.5)
3b	Me	96	135–140	19.3 (73.8)
3c	Et	93	140–145	18.6 (76.0)
3d	Pr^n	96	145–150	19.0 (75.7)
3e	Bu^n	95	160–165	18.8 (75.7)
3f	$CH_2CH{=}CH_2$	91	165–170	18.0 (74.2)
3g	$CH_2CH{=}CHMe$	92	160–165	18.3 (75.9)
3h	*n*-C_5H_{11}	93	175–180	19.0 (74.9)
3i	$[CH_2]_3Cl$	87	195–200	18.0 (76.7)

[a] All compounds were fully characterised by ^{31}P and ^{1}H NMR spectroscopy,§ and in the case of known compounds displayed spectra in accordance with literature data. [b] 40 mmol scale preparations. [c] Compounds **3** were purified in a kugelrohr bulb-to-bulb distillation apparatus.

One-pot conversion of **1** to α-fluoromethylphosphonate **3a** (R = H) was achieved by the action of *n*-butyllithium (2 equiv.) in THF solution at −78 °C in the presence of chlorotrimethylsilane (1 equiv.).[11] The double metal-halogen exchange (Li–Br) was instantaneous and complete at low temperature as gauged by ^{31}P NMR spectroscopy. The presence of two bromine substituents allowed complete reaction control. Upon completion of the addition of reagents, the reaction mixture containing α-lithiated α-fluorotrimethylsilylmethylphosphonate carbanion **2** was treated at low temperature with absolute ethanol, then allowed to warm to 0 °C. Subsequent acidic work-up gave a pale yellow organic layer from which **3a** was isolated by distillation (Scheme 1).

Reaction time and quenching temperature required careful control, since heating or prolonged stirring resulted in partial reaction of **2** with *n*-butyl bromide (produced by the metal–halogen exchange), as deduced from ^{31}P NMR spectra. Use of ethanol free from water is essential. Addition of ethanol generates EtOLi which is responsible for C–Si bond cleavage by specific attrack of the silicon atom; addition of water produces LiOH which concurrently attacks at phosphorus and silicon, yielding a mixture of products which is difficult to separate.

The transformation appeared to be compatible with a variety of electrophiles, and carbanion **2** reacted successfully with alkyl iodides to afford α-fluoroalkylphosphonates **3b–i** in good to excellent yield. The alkylating agent‡ was added at −78 °C, and the reaction mixture was brought to 0 °C before ethanolysis (Table 1). These examples of the reaction of **2** with alkyl iodides illustrate the great potential of the method.

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§ ^{1}H NMR ($CDCl_3$) δ (*J* in Hz): **3a** 12.37 (t, 6 H, J_{HH} 7), 4.2 (dq, 4 H), 4.67 (dd, 2 H, $^2J_{PH}$ 4.7, $^2J_{FH}$ 46.8); **3b** 1.35 (t, 6 H), 1.60 (ddd, 3 H, J_{HH} 7, J_{PH} 16.6, J_{FH} 23.8), 4.20 (m, 4 H), 4.85 (ddq, 1 H, J_{PH} 2.3, J_{FH} 46.2); **3c** 1.00 (t, 3 H), 1.26 (t, 6H), 1.7–2.0 (m, 2 H), 4.10 (m, 4 H), 4.55 (m, 1 H, J_{FH} 46.7); **3d** 0.92 (t, 3 H), 1.35 (t, 6 H), 1.40–2.15 (m, 4 H), 4.20 (m, 4 H), 4.70 (m, 1 H, J_{FH} 46.7); **3e** 0.90 (t, 3 H), 1.33 (t, 6 H), 1.40–2.10 (m, 6 H), 4.19 (m, 4 H), 4.70 (m, 1 H, J_{FH} 46.6); **3f** 1.35 (t, 6 H), 2.5–2.8 (m, 2 H), 4.21 (m, 4 H), 4.72 (m, 1 H, J_{FH} 46.6), 5.18 (m, 2 H), 5.84 (m, 1 H); **3g** 1.35 (t, 6 H), 1.67 (t, 3 H), 2.25–2.75 (m, 2 H), 4.19 (m, 4 H), 4.70 (m, 1 H, J_{FH} 46.7), 5.43–5.72 (m, 2 H); **3h** 0.90 (t, 3 H), 1.36 (t, 6 H), 1.20–2.10 (m, 8 H), 4.19 (m, 4 H), 4.70 (m, 1 H, J_{FH} 46.9); **3i** 1.36 (t, 6 H), 1.83–2.35 (m, 4 H), 3.60 (t, 3 H), 4.22 (m, 4 H), 4.71 (m, 1 H, J_{FH} 46.6).

‡ In the case of **3e** (R = Bu^n), no alkylating agent was introduced; *in situ*-generated Bu^nBr sufficed for complete alkylation of the carbanion **2** on warming to 0 °C.

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