Facile Synthesis of Trifluoromethylated α-Hydroxyphosphonates

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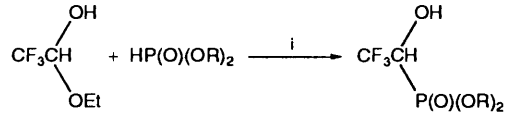
A facile synthesis of trifluoromethylated α-hydroxyphosphonates starting from commercially available stable 1-ethoxy-2,2,2-trifluoroethanol under mild conditions in 35–91% yields is described.

α-Hydroxyalkanephosphonates have attracted much interest since they can serve as useful intermediates in organic synthesis; some of them are also biologically and pharmaceutically active.[1,2] It is well known that the introduction of fluorine, as a trifluoromethyl group, into organic molecules usually increases the biological activities of these compounds significantly.[3,4] Therefore the development of a convenient method for the synthesis of trifluoromethylated analogues would be valuable. Recently it has been reported that perfluoroalkylated α-hydroxyphosphonates can be synthesised by the reaction of the corresponding perfluoroalkyl aldehyde with dimethyl phosphite.[5] However, the starting material, for example trifluoroacetaldehyde, is very unstable and not easy to handle.[6] Trifluoroacetaldehyde ethyl hemiacetal (1-ethoxy-2,2,2-trifluoroethanol) is commercially available and stable[6] and can be employed as a useful intermediate in the synthesis of fluorine containing molecules.[7] We now report a facile synthesis of trifluoromethylated α-hydroxyphosphonates starting from this commercially available stable hemiacetal under mild conditions in 35–91% yields.

Results and Discussion

1-Ethoxy-2,2,2-trifluoroethanol reacted with diethyl phosphite when catalysed by a variety of bases with or without solvent at room temperature and exposed to the air; no reaction occurs in the absence of base even at higher temperatures (see Table 1). Triethylamine seems to be a more suitable base than potassium carbonate or diisopropylethylamine, and the addition of solvent (THF) does not confer any advantages on this reaction.



1 2 3

Reagent and conditions: i, base catalysis, air, room temp.

The results of the reaction of a variety of dialkyl phosphites with 1-ethoxy-2,2,2-trifluoroethanol catalysed by triethylamine are shown in Table 2. High to excellent yields are obtained with most dialkyl phosphites. However, the reaction of dimethyl phosphite with 1-ethoxy-2,2,2-trifluoroethanol gave low yields (35%), accompanied by some unidentifiable by-products (GC–MS). It has been reported that dimethyl phosphite can be used as an alkylating reagent.[8] It is probable that an alkylation reaction resulted in the formation of by-products and caused the low yield.

If a further portion of 1-ethoxy-2,2,2-trifluoroethanol (1 equiv.) was added, the reaction proceeded slowly (5 h, 17% conversion; 2 days, 53%, conversion). It may be rationalized that the reaction is in equilibrium and that the addition of a further portion of 1-ethoxy-2,2,2-trifluoroethanol causes the backward reaction.

Table 1 Reaction of diethyl phosphite with **1**[a]

Entry	Base (mol%)	Time (h)	Conversion (%)[b]
1		20	0
2[c]		10	0
3	Pr^i_2NEt (25)	5	71.4
4	Et_3N (25)	5	87.5
5	Et_3N (50)	5	91.3
6	Et_3N (50)	10	93.1
7[d]	Et_3N (50)	5	50
8	K_2CO_3 (25)	5	81

[a] The reactions were carried out under air at 25 °C unless otherwise mentioned, with 1 mol of **1** and **2** and without solvent (except entry 7). [b] Conversion of **1** into **3** according to ^{19}F NMR spectroscopy. [c] Reaction at 60 °C. [d] THF (1 cm^3) as solvent.

Table 2 Preparation of compounds **3**[a]

Entry	Compound **3**	R	Time (h)	Yield (%)[b]
1	**3a**	Et	10	90
2[c]	**3b**	Me	5	35
3	**3c**	Pr	12	88
4	**3d**	Pr^i	10	91
5	**3e**	Bu	14	85
6	**3f**	n-C_6H_{13}	16	83

[a] The reactions were carried out on a 2 mmol scale (**1**:**2**:Et_3N = 1.1:1:0.5) except for entry 2. [b] Isolated yields. [c] 10 mmol scale (**1**:**2b**:Et_3N = 1:1:0.5), isolated yield based on the weight of distilled product.

Unfortunately, the reaction of diphenyl phosphite with the hemiacetal resulted in the formation of many by-products. GC–MS showed that the desired product was contaiminated with eight by-products (for example: phenol, M^+, 94; ethyl phenyl 2,2,2-trifluoro-1-hydroxyethylphosphonate, M^+, 284). Attempts to purify the crude product (~ 50%) failed. Therefore, this methodology is not applicable to the preparation of trifluoromethylated diphenyl α-hydroxyphosphonates.

This methodology is an interesting example of carbon–phosphorus bond formation by reaction of a hemiacetal with dialkyl phosphites, and provides a convenient synthesis of trifluoromethylated α-hydroxyphosphonates suitable for large scale preparations.

Experimental

All m.p.s are uncorrected. IR spectra of all products were obtained as films on a Perkin-Elmer 983G spectrometer. ^1H and ^{31}P NMR spectra were recorded on a Bruker AM-300 spectrometer, ^{19}F spectra were taken on a Varian EM-360L spectrometer (δ in ppm from tetramethylsilane, external trifluoroacetic acid and external 85% phosphoric acid for ^1H, ^{19}F and ^{31}P NMR, respectively, positive for downfield shifts) in $CDCl_3$. J Values are given in Hz. Mass spectra were measured on a HP 5989a spectrometer.

Diethyl 2,2,2-Trifluoro-1-hydroxyethylphosphonate **3a**. *General Procedure.*—1-Ethoxy-2,2,2-trifluoroethanol (2.2 mmol, 0.26 cm^3), diethyl phosphite (2.0 mmol, 0.26 cm^3) and triethylamine (1.0 mmol, 0.14 cm^3) were mixed at room temperature under air and then stirring was continued until most of 1-ethoxy-2,2,2-trifluoroethanol had been converted into the product as shown by ^{19}F NMR. The reaction mixture was concentrated to give a residue, which was purified by flash column chromatography on silica gel with light petroleum (b.p. 60–90 °C)–acetone (20 : 1) as eluent to give the pure product **3a**, as a white solid, m.p. 62–63 °C; $\nu(CHCl_3)/cm^{-1}$ 3225, 1267, 1229 and 1052; *m/e* 237 ($M^+ + 1$), 207 and 109; δ_H 5.80 (1 H, br), 4.21–4.29 (5 H, m) and 1.36 (6 H, t, *J* 7.1); δ_F 5.1 (s); δ_P 14.93 (s) (Found: C, 30.8; H, 5.0. Calc. for $C_6H_{12}F_3O_4P$: C, 30.51; H, 5.08%).

Dimethyl 2,2,2-trifluoro-1-hydroxyethylphosphonate **3b** was similarly prepared on a 10 mmol scale; the crude product was purified by distillation at reduced pressure, and the pure product gave satisfactory analyses which were identical with those reported in the literature.[5]

Dipropyl 2,2,2-trifluoro-1-hydroxyethylphosphonate **3c**. Colourless oil; ν/cm^{-1} 3234, 1266, 1228 and 1015; *m/e* 265 ($M^+ + 1$), 221 and 43; δ_H 5.75 (1 H, br), 4.23–4.37 (1 H, m), 4.08–4.19 (4 H, m), 1.66–1.78 (4 H, m) and 0.96 (6 H, t, *J* 7.4); δ_F 5.0 (s); δ_P 14.87 (s) (Found: C, 36.3; H, 6.0. Calc. for $C_8H_{16}F_3O_4P$: C, 36.36; H, 6.06%).

Diisopropyl 2,2,2-trifluoro-1-hydroxyethylphosphonate **3d**. White solid, m.p. 46–47 °C; $\nu(CHCl_3)/cm^{-1}$ 3231, 1267, 1226 and 1005; *m/e* 265 ($M^+ + 1$), 221 and 43; δ_H 6.10 (1 H, br), 4.76–4.89 (2 H, m), 4.19–4.26 (1 H, m), 1.36 (12 H, dd, *J* 6.1, 3.5); δ_F 5.3 (s); δ_P 12.94 (s) (Found: C, 36.0; H, 5.9. Calc. for $C_8H_{16}F_3O_4P$: C, 36.36; H, 6.06%).

Dibutyl 2,2,2-trifluoro-1-hydroxyethylphosphonate **3e**. Colourless oil; ν/cm^{-1} 3242, 1267, 1226 and 1027; *m/e* 293 ($M^+ + 1$), 237 and 57; δ_H 5.80 (1 H, br), 4.27–4.34 (1 H, m), 4.12–4.23 (4 H, m), 1.63–1.70 (4 H, m), 1.37–1.47 (4 H, m) and 0.91–0.97 (6 H, m); δ_F 5.0 (s); δ_P 14.88 (s) (Found: C, 41.0; H, 6.9. Calc. for $C_{10}H_{20}F_3O_4P$: C, 41.10; H, 6.85%).

Dihexyl 2,2,2-trifluoro-1-hydroxyethylphosphonate **3f**. Colourless oil; ν/cm^{-1} 3246, 1267, 1226 and 1017; *m/e* 349 ($M^+ + 1$), 265 and 85; δ_H 5.80 (1 H, br), 4.26–4.33 (1 H, m), 4.11–4.21 (4 H, m), 1.64–1.73 (4 H, m), 1.31–1.42 (12 H, m) and 0.89 (6 H, t, *J* 6.8); δ_F 5.2 (s); δ_P 14.91 (s) (Found: C, 48.3; H, 8.0. Calc. for $C_{14}H_{28}F_3O_4P$: C, 48.28; H, 8.04%).

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