A convenient synthesis of perfluoroalkylated hydroxy- and dihydroxyphosphonates

Wenbiao Cen, Xuezhen Dai and Yanchang Shen*

Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai 200032 (China)

(Received July 15, 1992; accepted December 11, 1992)

Abstract

Perfluoroalkylated 1-hydroxyphosphonates may be easily synthesized in good yield by the reaction of the corresponding perfluoroalkyl aldehydes with dimethyl phosphite. Perfluoroalkylcarboxylic esters react with the phosphonate anion to give (perfluoroacyl)methylphosphonates, their tautomeric isomers (2-perfluoroalkyl-2-hydroxy)vinylphosphonates and their hydrates (2-perfluoroalkyl-2,2-dihydroxy)ethylphosphonates, which are reduced with sodium borohydride affording perfluoroalkylated 2-hydroxyphosphonates in 61–68% yield. Perfluoroalkylated dihydroxyphosphonates may be obtained by the reaction of the bisphosphonate anion with perfluoroalkyl aldehydes followed by oxidation with osmium tetraoxide in 54–68% yield.

Introduction

Hydroxyphosphonates and dihydroxyphosphonates are useful intermediates in organic synthesis; some of them are also biologically active [1, 2]. It has been shown that the introduction of fluorine, trifluoromethyl or perfluoroalkyl groups into organic compounds often brings about unique chemical and biological properties. Organofluorine compounds have been applied increasingly in materials science, pharmaceuticals, medical science and other fields [3]. However, little is known concerning the perfluoroalkylated hydroxyphosphonates and dihydroxyphosphonates [4]. We now wish to report the synthesis of hydroxyphosphonates and dihydroxyphosphonates containing perfluoroalkyl groups from commercially available starting materials.

Results and discussion

Our approach to the preparation of perfluoroalkylated 1-hydroxyphosphonates is based on the addition reaction of perfluoroalkyl aldehydes with dimethyl phosphite under basic catalytic conditions (Scheme 1). Gaseous perfluoroalkyl aldehydes were prepared before use and bubbled directly into the reaction mixture containing dimethyl phosphite. Perfluoroalkylated 1-hydroxyphosphonates **1** were thus obtained in good yield under mild reaction conditions.

*To whom all correspondence should be addressed.

$$R_fCH(OH)_2 \xrightarrow[95\ ^\circ C]{P_2O_5/H_2SO_4} R_fCHO \xrightarrow[0\text{–}75\ ^\circ C]{HP(O)(OMe)_2/Et_3N} R_f-\underset{\displaystyle OH}{\underset{|}{C}}HP(O)(OMe)_2 \quad (1)$$

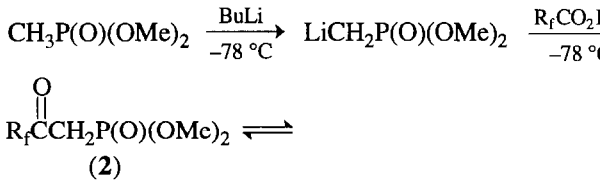
(a) $R_f = CF_3$; (b) $R_f = n\text{-}C_3F_7$

Scheme 1.

It was known previously that the phosphonate anion $(RO)_2(O)P\bar{C}HR$, in which R is H or alkyl, could react with carbonyl compounds to give 2-hydroxyphosphonates [5]. However, this was not applicable to the preparation of perfluoroalkylated 2-hydroxyphosphonates, since the reaction of a perfluoroalkyl aldehyde with the phosphonate anion leads to many by-products even at low temperatures. However, perfluoroalkyl carboxylic esters are readily available and exhibit a mild reactivity with nucleophilic reagents. Thus, perfluoroalkyl carboxylic esters react with the phosphonate anion to give a mixture of (perfluoroacyl)methyl phosphonates **2**, their tautomeric isomers (2-perfluoroalkyl-2-hydroxy)vinyl phosphonates **3** and their hydrates (2-perfluoroalkyl-2,2-dihydroxy)ethyl phosphonates **4**, as shown by ^{19}F NMR spectroscopy and by comparison with literature data [4]. The mixture of **2**, **3** and **4** was subsequently reduced by sodium borohydride to afford perfluoroalkylated 2-hydroxyphosphonates **5** in 61–68% yield (Scheme 2).

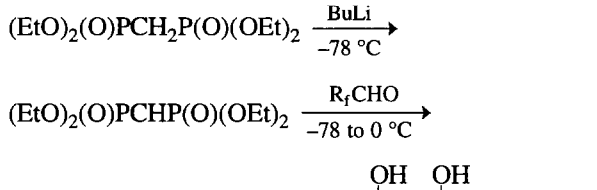
Dihydroxyphosphonates have attracted considerable interest because of their use in organic synthesis, their

0022-1139/93/$6.00



(a) $R_f = CF_3$; (b) $R_f = C_2F_5$; (c) $R_f = n\text{-}C_3F_7$

Scheme 2.



(a) $R_f = CF_3$; (b) $R_f = n\text{-}C_3F_7$

Scheme 3.

occurrence in biologically active compounds and their function as chelating agents [6]. To our knowledge, dihydroxyphosphonates bearing fluoroalkyl groups have not been reported previously. We report here a convenient route for the preparation of perfluoroalkylated dihydroxyphosphonates (Scheme 3).

The reaction of a bisphosphonate anion, generated from the corresponding bisphosphonate and butyllithium, with perfluoroalkyl aldehyde to give perfluoroalkylated α, β-unsaturated phosphonate, followed by oxidation with osmium tetraoxide afforded perfluoroalkylated dihydroxyphosphonates in 54–68% yield.

Experimental

All boiling points and melting points are reported uncorrected. The IR spectra of the liquid products were obtained as films and of the solid products as discs on a Shimadzu IR-440 spectrometer. NMR spectra ($CDCl_3$ as solvent, chemical shifts in ppm from TMS for ^1H NMR, from external TFA for ^{19}F NMR, positive for upfield shifts and from external 85% H_3PO_4 for ^{31}P NMR, positive for downfield shifts) were determined on Varian EM-360 (60 MHz), JEOL FX-90Q (90 MHz) or JEOL XL-200 (200 MHz) spectrometers. Mass spectra were recorded on a Finnigan GC–MS 4021 spectrometer.

Perfluoroalkyl aldehyde hydrates were prepared according to literature methods [7].

Typical procedure for the preparation of perfluoroalkylated 1-hydroxyphosphonates (1)

Crude trifluoroacetaldehyde hydrate (5.0 g) was added dropwise into a stirred mixture consisting of 2.2 g phosphorus pentoxide and 8 ml of concentrated sulfuric acid at 95 °C. The freshly produced gaseous trifluoroacetaldehyde was bubbled into a stirred mixture of dimethyl phosphite (2.2 g, 20 mmol), triethylamine (1.0 g, 10 mmol) and dry THF (20 ml) at 0 °C. After addition, the reaction mixture was allowed to warm to 70 °C and stirred for 0.5 h. Compound **1a** (2.8 g) was isolated by distillation *in vacuo*.

Dimethyl 1-hydroxy-2,2,2-trifluoroethylphosphonate (**1a**): Yield 67%, m.p. 53 °C. IR(KBr) (cm^{-1}): 3210 (s); 1240 (s); 1180 (s); 1060 (s). ^1H NMR δ: 3.88 (d, $J = 11$ Hz, 6H); 4.39 (m, 1H); 5.83 (s, 1H) ppm. ^{19}F NMR δ: −1.5 (s) ppm. ^{31}P NMR δ:16.5 (s) ppm. MS *m/e*: 209 ($M^+ + 1$); 189 ($M^+ - F$); 109 [$^+P(O)(OCH_3)_2$]. Analysis: Calc. for $C_4H_8F_3O_4P$: C, 23.08; H, 3.85%. Found: C, 23.25; H, 3.57%.

Diethyl 1-hydroxy-2,2,3,3,4,4,4-heptafluorobutylphosphonate (**1b**): Yield 71%, b.p. 131 °C/2 mmHg. IR(film) (cm^{-1}): 3220 (s); 1240 (s); 1190 (s); 1050 (s). ^1H NMR δ: 3.88 (d, $J = 11$ Hz, 6H); 4.46 (m, 1H); 6.35 (s, 1H) ppm. ^{19}F NMR δ: 4.2 (s, 3F); 40.2 and 46.4 (AB, $J = 291$ Hz, 2F); 49.5 (s, 2F) ppm. ^{31}P NMR δ: 17.2 (s) ppm. MS *m/e*: 309 ($M^+ + 1$); 289 ($M^+ - F$); 109 [$^+P(O)(OCH_3)_2$]. Analysis: Calc. for $C_6H_8F_7O_4P$: C, 23.23; H, 2.48%. Found: C, 23.38; H, 2.60%.

Typical procedure for the preparation of perfluoroalkylated 2-hydroxyphosphonates (5)

A dry flask equipped with a dropping funnel was charged with n-butyllithium (20 mmol in ether) and THF (30 ml) at −78 °C. A solution of dimethyl methylphosphonate (20 mmol, 2.5 g in 10 ml THF) was added slowly. After addition, the mixture generated was stirred for 10 min and a solution of ethyl trifluoroacetate (20 mmol, 2.8 g in 10 ml THF) was added slowly. The cooling bath was removed and the reaction mixture was quenched with 5 ml of 6 N HCl and extracted with ether. The organic phase was combined, and after drying and evaporation gave a yellow oil [mixture of intermediates **2**, **3** and **4** as ascertained by ^{19}F NMR spectra δ: 4.4 (**2a**), −0.2 (**3a**) and 10.1 (**4a**) ppm]. The yellow oil was dissolved in a solution of ethanol and water (1:1, 24 ml) at 0 °C and sodium borohydride (11 mmol, 0.42 g) was added in portions.

Upon complete addition, the mixture was stirred for 10 min, diluted with brine (50 ml) and extracted with ether (3×40 ml). The ether extracts were combined, washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated to give 3.1 g of crude product. Distillation *in vacuo* gave 2.7 g of **5a**.

Dimethyl 2-hydroxy-3,3,3-trifluoropropylphosphonate (**5a**): Yield 61%, b.p. 117 °C/1 mmHg. IR(film) (cm^{-1}): 3210 (s); 1220 (s); 1130 (s); 1040 (s). ^1H NMR δ: 2.14 (m, 2H); 3.76 (d, $J=11$ Hz, 6H); 4.35 (m, 1H); 5.44 (br s, 1H) ppm. ^{19}F NMR δ: 4.0 (s) ppm. ^{31}P NMR δ: 30.1 (s) ppm. MS *m/e*: 223 ($M^+ + 1$); 203 ($M^+ - F$); 153 ($M^+ - CF_3$); 109 [$^+P(O)(OCH_3)_2$]. Analysis: Calc. for $C_5H_{10}F_3O_4P$: C, 27.03; H, 4.50%. Found: C, 27.22; H, 4.79%.

Dimethyl 2-hydroxy-3,3,4,4,4-pentafluorobutylphosphonate (**5b**): Yield 63%, m.p. 48 °C. IR(KBr) (cm^{-1}): 3210 (s); 1220 (s); 1120 (s); 1040 (s). ^1H NMR δ: 2.10 (m, 2H); 3.75 (d, $J=11$ Hz, 6H); 4.42 (m, 1H); 5.45 (br s, 1H) ppm. ^{19}F NMR δ: 4.6 (s, 3F); 45.2 and 55.2 (AB, $J=273$ Hz, 2F) ppm. ^{31}P NMR δ: 30.1 (s) ppm. MS *m/e*: 273 ($M^+ + 1$); 253 ($M^+ - F$); 153 ($M^+ - C_2F_5$); 109 [$^+P(O)(OCH_3)_2$]. Analysis: Calc. for $C_6H_{10}F_5O_4P$: C, 26.47; H, 3.68%. Found: C, 26.44; H, 3.71%.

Dimethyl 2-hydroxy-3,3,4,4,5,5,5-heptafluoropentylphosphonate (**5c**): Yield 68%, m.p. 59 °C IR(KBr) (cm^{-1}): 3210 (s); 1240 (s); 1120 (s); 1040 (s). ^1H NMR δ: 2.20 (m, 2H); 3.77 (d, $J=11$ Hz, 6H); 4.55 (m, 1H); 5.50 (br s, 1H) ppm. ^{19}F NMR δ: 4.3 (s, 3F); 43.0 and 51.6 (AB, $J=279$ Hz, 2F); 48.8 (s, 2F) ppm. ^{31}P NMR δ: 30.2 (s) ppm. MS *m/e*: 323 ($M^+ + 1$); 303 ($M^+ - F$); 153 ($M^+ - C_3F_7$); 109 [$^+P(O)(OCH_3)_2$] ppm. Analysis: Calc. for $C_7H_{10}F_7O_4P$: C, 26.09; H, 3.10%. Found: C, 26.13; H, 2.92%.

Typical procedure for the preparation of perfluoroalkylated α, β-unsaturated phosphonates (6)

To a dry flask charged with tetraethyl methylenediphosphonate (20 mmol) and 30 ml of dry ether at −78 °C was added butyllithium (20 mmol in ether) and the mixture stirred for 0.5 h. Freshly produced gaseous trifluoroacetaldehyde (20 mmol) was then bubbled slowly into the stirred mixture at −78 °C and the stirring continued for 0.5 h. After this period, the mixture was allowed to warm slowly to 0 °C and 15 ml of water added. The water layer was separated and extracted with ether, the ether layers were combined, dried ($MgSO_4$), filtered, concentrated and distilled *in vacuo* to give 2.6 g of **6a**.

Diethyl 3,3,3-trifluoropropenylphosphonate (**6a**): Yield 57%, b.p. 82 °C/8 mmHg. IR(film) (cm^{-1}): 1260 (s); 1130 (s); 1030 (s); 975 (m). ^1H NMR δ: 1.33 (t, $J=7$ Hz, 6H); 4.13 (m, 4H); 6.42–6.72 (m, 2H) ppm. ^{19}F NMR δ: −9.8 (s) ppm. ^{31}P NMR δ: 12.5 (s) ppm. MS *m/e*: 233 ($M^+ + 1$); 205 ($M^+ + 1 - C_2H_4$); 177 ($M^+ + 1 - 2C_2H_4$): 163 ($M^+ - CF_3$). Analysis: Calc. for $C_7H_{12}F_3O_3P$: C, 36.21; H, 5.17%. Found: C, 36.40; H, 5.26%.

Diethyl 3,3,4,4,5,5,5-heptafluoropentenylphosphonate (**6b**): Yield 75%, b.p. 52 °C/2 mmHg. IR(film) (cm^{-1}): 1240 (s); 1120 (s); 1030 (s); 975 (m). ^1H NMR δ: 1.35 (t, $J=7$ Hz, 6H); 4.15 (m, 4H); 6.40–6.84 (m, 2H) ppm. ^{19}F NMR δ: 3.8 (t, $J=8$ Hz, 3F); 38.5 (q, $J=8$ Hz, 2F); 50.8 (s, 2F) ppm. ^{31}P NMR δ: 12.2 (s) ppm. MS *m/e*: 333 ($M^+ + 1$); 305 ($M^+ + 1 - C_2H_4$); 277 ($M^+ + 1 - 2C_2H_4$); 163 ($M^+ - C_3F_7$). Analysis: Calc. for $C_9H_{12}F_7O_3P$: C, 32.53; H, 3.61%; Found: C, 32.23; H, 3.76%.

Typical procedure for the preparation of perfluoroalkylated dihydroxyphosphonates (7)

Compound **6a** (0.46 g, 2 mmol) and 0.5 g of osmium tetraoxide (2 mmol) were dissolved in 8 ml of pyridine and stirred at room temperature for 24 h to give a dark-brown mixture. To this mixture was added a solution consisting of 0.9 g sodium bisulfite, 15 ml of water and 10 ml of pyridine. The mixture was stirred for 0.5 h and then extracted thoroughly with chloroform. The chloroform layer was dried over potassium carbonate, evaporated *in vacuo* to give a crude product, which was purified by chromatography on silica gel eluting with dichloromethylene/acetone (3:1) to give 0.28 g of **7a**.

Diethyl 1,2-dihydroxy-3,3,3-trifluoropropylphosphonate (**7a**): Yield 54%, m.p. 38 °C. IR(KBr) (cm^{-1}): 3380 (s); 3240 (s); 1240 (s); 1160 (s); 1060 (s). ^1H NMR δ: 1.33 (t, $J=7$ Hz, 6H); 4.01–4.42 (m, 6H); 4.63 (br s, 2H) ppm. ^{19}F NMR δ: −0.5 (d, $J=12$ Hz, 3F) ppm. ^{31}P NMR δ: 20.6 (s) ppm. MS *m/e*: 267 ($M^+ + 1$); 239 ($M^+ + 1 - C_2H_4$); 211 ($M^+ + 1 - 2C_2H_4$); 138 [$^+P(OH)(OC_2H_5)_2$]. Analysis: Calc. for $C_7H_{14}F_3O_5P$: C, 31.58; H, 5.26%. Found: C, 31.42; H, 5.56%.

Diethyl 1,2-dihydroxy-3,3,4,4,5,5,5-heptafluoropentylphosphonate (**7b**): Yield, 68%, m.p. 52 °C. IR(KBr) (cm^{-1}): 3380 (s); 3220 (s); 1240 (s); 1140 (s); 1040 (s). ^1H NMR δ: 1.33 (t, $J=7$ Hz, 6H); 3.93–4.52 (m, 6H); 5.19 (br s, 1H); 5.53 (br s, 1H) ppm. ^{19}F NMR δ: 4.0 (t, $J=12$ Hz, 3F); 42.7 and 49.9 (AB, $J=284$ Hz, 2F); 49.9 (d, $J=12$ Hz, 2F) ppm. ^{31}P NMR δ: 20.7 (s) ppm. MS *m/e*: 367 ($M^+ + 1$); 339 ($M^+ + 1 - C_2H_4$); 311 ($M^+ + 1 - 2C_2H_4$); 138 [$^+P(OH)(OC_2H_5)_2$]. Analysis: Calc. for $C_9H_{14}F_7O_5P$: C, 29.51; H, 3.83%. Found: C, 29.77; H, 3.61%.

Acknowledgement

The authors wish to thank the National Natural Science Foundation of China and Academia Sinica for financial support.

References

1 F. Texier-Boullet and A. Foucaud, *Synthesis,* (1982) 165.
2 T. Nagase, T. Kawashima and N. Inamato, *Chem. Lett.,* (1984) 1997.
3 R. Filler and Y. Kobayashi, *Biomedical Aspects of Fluorine Chemistry,* Elsevier Biomedical, Amsterdam, 1982.
4 T.E. Nickson, *J. Org. Chem., 53* (1988) 3870.
5 M. Mikolajczyk and P. Balczewski, *Synthesis,* (1984) 691.
6 A. Pondaven-Raphalen and G. Sturtz, *Phosphorus, Sulfur, 29* (1987) 329.
7 M. Braid, H. Iserson and F.E. Lawlor, *J. Am. Chem. Soc., 76* (1954) 4027.