Journal of Organometallic Chemistry, 340 (1988) 93–99
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

A simple synthesis of monofluoromethylene bisphosphonic acid

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(Received August 3rd, 1987)

Abstract

A simple synthesis of monofluoromethylene bisphosphonic acid has been devised, starting with an Arbusov reaction between fluorotribromomethane and triisopropyl phosphite to give diisopropyl dibromofluoromethylphosphonate. A Michaelis–Becker reaction between the latter and an excess of the sodium salt of diisopropyl phosphite yields tetraisopropyl bromofluoromethylene bisphosphonate, which is not isolated but undergoes nucleophilic debromination and protonation during the reaction and subsequent work up to produce tetraisopropyl monofluoromethylene bisphosphonate. De-esterification of the tetraester with bromotrimethylsilane followed by hydrolysis and cation exchange chromatography gives di(triethylammonium)monofluoromethylene bisphosphonate, which is converted into the free acid by further ion exchange chromatography.

Introduction

Halogenated methylene bisphosphonic acids, e.g. **1** are isopolar and isosteric analogues of pyrophosphoric acid in which the P–O–P bond has been replaced by the hydrolytically more stable P–C–P bond [1]. These bisphosphonic acids have been shown to possess antiviral activity [2] and to affect bone resorption and

$(HO)_2P(O)CXYP(O)(OH)_2$
(1)

(X = halogen, Y = halogen or H)

mineralisation [3]. Simple syntheses of dibromo- and dichloro-methylene bisphosphonic acids have been reported [4–6], and procedures developed for the monodehalogenation of the tetraesters of these acids [7,8]. Fluorination of tetraalkyl methylene bisphosphonates can be achieved with perchloryl fluoride [9,10], but there are hazards associated with the latter reagent which may make difficult the

0022-328X/88/$03.50

preparation of fluorinated methylene bisphosphonates on a large scale. In addition, tetraethyl difluoromethylene bisphosphonic acid has been prepared from diethyl bromodifluoromethylphosphonate via a Michaelis–Becker reaction with sodium diethyl phosphite [11]. We have adapted this synthetic route, and prepared tetraisopropyl difluoromethylene bisphosphonate in 40% yield by treating dibromodifluoromethane with two equivalents of sodium diisopropyl phosphite in dry hexane at low temperature.

$$CF_2Br_2 + 2Na^+(i\text{-}PrO)_2P{-}O^- \rightarrow (i\text{-}PrO)_2P(O)CF_2P(O)(i\text{-}PrO)_2 + 2NaBr$$

We now report the synthesis of tetraisopropyl monofluoromethylene bisphosphonate (in 50% yield by ^{31}P NMR) from diisopropyl dibromofluoromethylphosphonate by use of an excess of the sodium salt of diisopropyl phosphite.

$$(i\text{-}PrO)_2P(O)CFBr_2 + Na^+(i\text{-}PrO)_2P{-}O^- \rightarrow (i\text{-}PrO)_2P(O)CHFP(O)(i\text{-}PrO)_2$$

This reaction appears to involve the intermediate formation of the bromofluoromethylene bisphosphonate, which undergoes nucleophilic debromination during the reaction.

Results and discussion

The first step in our reaction sequence is an Arbusov reaction between tribromofluoromethane and triisopropyl phosphite, which gives the diisopropyl dibromofluoromethylphosphonate in ca. 70% yield

$$(i\text{-}PrO)_3P + CFBr_3 \rightarrow (i\text{-}PrO)_2P(O)CFBr_2 + i\text{-}PrBr$$

The boiling point of fluorotribromomethane at atmospheric pressure is 106–107 °C compared with 24 °C for fluorotrichloromethane, thus the reaction with the former is easier to carry out. We have found that the Arbusov reaction between fluorotrichloromethane and triisopropyl phosphite does not take place at all, and the Michaelis–Becker reaction between fluorotrichloromethane and sodium diisopropyl phosphite only takes place in low yield.

Treatment of diisopropyl dibromofluoromethylphosphonate with three equivalents of sodium diisopropyl phosphite in hexane followed by evaporation of the solvent after reaction had taken place and flash chromatography of the crude products on silica (elution with acetone/petroleum ether, 1/8, v/v) gave a fraction which contained tetraisopropyl monofluoromethylene bisphosphonate as the major product (65%) together with tetraisopropyl pyrophosphate (35%) as determined by ^{31}P NMR. The latter was identified by comparison authentic material. These two compounds could not be separated by chromatography on silica. However, deesterification of the mixture with bromotrimethylsilane followed by chromatography on DE52 cellulose (elution with triethylammonium bicarbonate) gave di(triethylammonium) monofluoromethylene bisphosphonate, which could be converted by further ion exchange chromatography into pure monofluoromethylene bisphosphonic acid (overall yield 42%). When less than three equivalents of sodium diisopropyl phosphite are used in this reaction the yield of tetraisopropyl monofluoromethylene

bisphosphonate is reduced.

$$(\text{i-PrO})_3\text{P} + \text{CFBr}_3 \rightarrow (\text{i-PrO})_2\text{P(O)CFBr}_2 + \text{RBr}$$

$$(\text{i-PrO})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{–CFBr}_2 + (\text{i-PrO})_2\text{PO}^-\text{Na}^+ \rightarrow (\text{i-PrO})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{–CFBr–}\overset{\overset{\text{O}}{\|}}{\text{P}}(\text{i-PrO})_2 + \text{NaBr}$$

$$(\text{i-PrO})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{–CFBr–}\overset{\overset{\text{O}}{\|}}{\text{P}}(\text{i-PrO})_2 + (\text{i-PrO})_2\text{PO}^-\text{Na}^+ \rightarrow$$

$$(\text{i-PrO})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{–}\underset{-}{\text{CF}}\text{–}\overset{\overset{\text{O}}{\|}}{\text{P}}(\text{i-PrO})_2\text{Na}^+ + (\text{i-PrO})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{–Br}$$

$$(\text{i-PrO})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{–}\underset{-}{\text{CF}}\text{–}\overset{\overset{\text{O}}{\|}}{\text{P}}(\text{i-PrO})_2\text{Na}^+ \xrightarrow{\text{HA}} (\text{i-PrO})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{–CHF–}\overset{\overset{\text{O}}{\|}}{\text{P}}(\text{i-PrO})_2$$

$$(\text{i-PrO})_2\text{P(O)Br} + (\text{i-PrO})_2\text{PO}^-\text{Na}^+ \rightarrow (\text{i-PrO})_2\text{P(O)OP(O)(i-PrO)}_2$$

The nucleophilic dehalogenation of phosphonates, particularly those which can form stable anions, is a well known process and the preparation of monobromo- and monochloromethylene bisphosphonates by this route has already been mentioned [7,8]. Furthermore, Burton and Flynn have observed that when diethyl bromodifluoromethylphosphonate is treated with sodium diethyl phosphite in diethyl phosphite as solvent, debromination can occur, to yield the diethyl difluoromethylphosphonate anion, which is protonated by the diethyl phosphite [12].

$$(\text{EtO})_2\text{P(O)CFBr}_2 + \text{Na}^+(\text{EtO})_2\text{P–O}^- \rightarrow (\text{EtO})_2\text{P(O)Br} + (\text{EtO})_2\text{P(O)CF}_2^-$$

$$\downarrow \text{(EtO)}_2\text{P(O)H}$$

$$(\text{EtO})_2\text{P–O}^- + (\text{EtO})_2\text{P(O)CF}_2\text{H}$$

The formation of tetraisopropyl pyrophosphate in our reaction was unexpected, and we believe that it arises from the reaction between diisopropyl phosphorobromidate and the sodium salt of diisopropyl phosphite. Similar reactions have been reported by Steinberg [13], and in our hands treatment of diisopropyl phosphorobromidate with sodium diisopropyl phosphite in dry hexane at $-78\,^\circ\text{C}$ gave a variety of products, including tetraisopropyl pyrophosphate (40% by ^{31}P NMR). We believe that an early step in our reaction sequence may be the debromination of diisopropyl dibromofluoromethylphosphonate by the diisopropyl phosphite anion. Confirmatory evidence for this reaction is the detection of small amounts of diisopropyl bromofluoromethylphosphonate in our crude reaction mixtures.

$$(\text{i-PrO})_2\text{P(O)CFBr}_2 + \text{Na}^+(\text{i-PrO})_2\text{P–O}^- \rightarrow (\text{i-PrO})_2\text{P(O)CFBr}^-\text{Na}^+$$

$$+ (\text{i-PrO})_2\text{P(O)Br}$$

$$\downarrow$$

$$(\text{i-PrO})_2\text{P(O)CBrFH}$$

Table 1

NMR data for phosphonates and related compounds (in solution in $CDCl_3$) [a]

Compound	Chemical shifts δ (ppm) and spin–spin coupling constants J (Hz)			
	^1H	^{13}C	^{31}P	^{19}F
$(i\text{-PrO})_2P(O)CBr_2F$ (a)	1.45 (dd, J(HH) 6.7); 4.52 (m, J(HH) 6.7, J(HP) 6.7)	23.1 (d, J(CP) 5.9), 23.3 (d, J(CP) 2.7) 75.6 (d, J(CP) 7.4), 88.9 (dd, J(CP) 333, J(CP) 203)	0.60 (d, J(PF) 77)	−77.2 (d, J(PF) 77)
$(i\text{-PrO})_2P(O)CF_2P(O)(i\text{-PrO})_2$ (b)	1.42 (dd, J(HH) 7.2); 4.95 (m)	23.3 (s), 23.9 (s), 74.2 (t, J(CP) 3.7) 115.3 (tt, J(CF) 279, J(CP) 199)	2.05 (t, J(PF) 88)	−122.5 (t, J(PF) 88)
tricyclohexylammonium $(HO)_2P(O)CF_2P(O)(OH)_2$ (c)	1.1–1.5 (m), 1.62 (m), 1.78 (m) 1.96 (m), 3.12 (m) in D_2O	n.d.	5.2 (t, J(PF) 80) in D_2O	n.d.
$(HO)_2P(O)CHFP(O)(OH)_2$ (d)	5.02 (dt, J(HF) 47, J(HP) 13) in D_2O 5.45 (dt, J(HF) 46, J(HP) 14) in DCl (20%)	35.3 (dt, J(CF) 181, J(CP) 150) in D_2O	9.65 (d, J(PF) 66.8) in D_2O	−149.5 (td, J(PF) 65 J(FH) 46) in D_2O
$(i\text{-PrO})_2P(O)CFBrP(O)(i\text{-PrO})_2$ (e)	1.35 (dd, J 6.0, J(HH) 7.2), 5.0 (m)	23.7 (d, J 75), 74.7 (d, J 28) 95.2 (dt, J(CF) 227, J(CP) 166)	5.45 (d, J(PF) 74)	−155 (t, J(PF) 74
$(i\text{-PrO})_2P(O)OP(O)(i\text{-PrO})_2$ (f)	1.38 (d, J(HH) 6.2), 4.80 (m)	23.4 (q, J(CP) 2.9), 73.9 (t, J(CP) 2.9)	−15.1 (s)	No resonance

[a] n.d. not determined.

The diisopropyl phosphorobromidate then can react with the anion derived from diisopropyl bromofluoromethylphosphonate to yield tetraisopropyl bromofluoromethylene bisphosphonate.

The isolation of tetraisopropyl monofluoromethylene bisphosphonate rather than the expected bromofluoromethylene bisphosphonate can be ascribed to the ready debromination of the latter by the remaining diisopropyl phosphite anion, and the anion derived from monofluoromethylene bisphosphonate would be extremely stable. We prepared an authentic sample of tetraisopropyl bromofluoromethylene bisphosphonate [10] and added it to our reaction: the bromofluoromethylene bisphosphonate underwent rapid debromination and tetraisopropyl monofluoromethylene bisphosphonate could be detected by ^{31}P NMR as the major product. Furthermore, when fluorotrichloromethane was treated with sodium diisopropyl phosphite under similar conditions some tetraisopropyl chlorofluoromethylenebisphosphonate could be detected in the crude reaction mixture. The slower nucleophilic dehalogenation of chloro- rather than bromo-methylene bisphosphonates has already been observed [7].

It should be noted that attempts to prepare tetraalkyl monofluoromethylene bisphosphonates from the corresponding difluoromethylene bisphosphonates by conventional methods involving nucleophilic dehalogenation were unsuccessful [7,8]. In all cases where reaction took place P–C bond cleavage occurred resulting in the formation of dialkyl difluoromethylphosphonates.

The procedure outlined above for the synthesis of monofluoromethylene bisphosphonic acid is simple and should be easy to adapt for the large scale synthesis of this compound. Although the tetraisopropyl ester of monofluoromethylene bisphosphonic acid cannot readily be separated from tetraisopropyl pyrophosphate, deesterification of the mixture of both compounds with bromotrimethylsilane allowed isolation of monofluoromethylene bisphosphonic acid in good yield. This procedure is also superior to a synthetic route starting from dibromofluoromethane, as in the latter case the yield in the initial reaction is very low. Furthermore, dibromofluoromethane is considerably more expensive than tribromofluoromethane.

Experimental

All ^{1}H NMR spectra were recorded at either 220 MHz with tetramethylsilane (TMS) as internal reference or at 400 MHz with TMS as external reference standard. ^{31}P NMR spectra were recorded at either 36.43 or at 162.0 MHz with 85% H_3PO_4 as external reference standard in both cases, and shifts to higher frequency are given positive values. ^{19}F NMR spectra were recorded in dilute solution at either 84.67 or 75.39 MHz with trifluoroacetic acid, hexafluorobenzene, 1,2-difluorotetrachloroethane or fluorotrichloromethane as internal standards where appropriate. All ^{19}F NMR chemical shifts are expressed relative to fluorotrichloromethane, with shifts to higher frequency given positive values. ^{13}C NMR spectra were recorded at 100.62 MHz with TMS as external reference standard. Broad band decoupling was employed for all ^{31}P and ^{13}C NMR spectra and all coupling constants are expressed in Hz. ^{19}F NMR spectra were not proton decoupled. Data from the NMR spectra of individual compounds are given in Table 1.

Synthesis of phosphonates

Diisopropyl dibromofluoromethylphosphonate (a). This was prepared in 78% yield by the method of Burton and Flynn [15] and purified by flash chromatography on silica with acetone/petroleum ether (1/20, v/v) as eluant. Analysis. Found: C, 24.10; H, 4.12; P, 8.55; F, 4.86. $C_7H_{14}Br_2FO_3P$ calc: C, 23.62; H, 3.96; P, 8.70; F, 5.34%. Mass spectrum (NH_3/CI) $(M + H)^+$ *m/z* 355, 357, 359.

Tetraisopropyl difluoromethylene bisphosphonate (b). A solution of dibromodifluoromethane (5.05 g, 24 mmol) in dry hexane (10 ml) was added dropwise during 30 min to a solution of sodium diisopropyl phosphite (48 mmol) in dry hexane under N_2 at −78°C. The solution was stirred at −78°C for 3 h then filtered through Celite 545. Evaporation of the hexane in vacuo left a colourless oil, which was vacuum distilled to yield a fraction distilling above 75°C at 0.8 mbar. Flash chromatography of this fraction on silica with elution by acetone/petroleum ether (1/15, v/v) yielded the title compound (3.66 g, 40%). Analysis. Found: C, 40.15; H, 7.51; P, 16.25; F, 7.95. $C_{13}H_{28}F_2O_6P_2$ calc: C, 41.06; H, 7.42; P, 16.29; F, 9.99%. Mass spectrum (NH_3/CI) $(M + H)^+$ 381.1427 (calculated for $C_{13}H_{28}F_2O_6P_2$ 381.1425).

Difluoromethylene bisphosphonic acid (tris[cyclohexylammonium] salt) (c). Tetraisopropyl difluoromethylene bisphosphonate (0.50 g, 1.32 mmol) was treated with bromotrimethylsilane (2.90 g, 19.0 mmol) and the solution stirred for 48 h. The mixture was freeze dried, shaken with water (10 ml) and again freeze dried to yield crude difluoromethylene bisphosphonic acid. This was dissolved in methanol (5 ml) and cyclohexylamine (0.62 g, 62 mmol) added dropwise with cooling. The resulting white precipitate was recrystallised twice from methanol to yield the title compound (0.44 g, 66%). Analysis, Found: C, 44.76; H, 8.46; N, 7.97. $C_{30}H_{63}F_2N_3O_6P_2$ calc: C, 44.79; H, 8.51; N, 8.25%.

Monofluoromethylene bisphosphonic acid (d). A solution in hexane of diisopropyl dibromofluoromethylphosphonate (1.08 g, 3.03 mmol) was added at −78°C to a solution in hexane under nitrogen of sodium diisopropyl phosphite prepared from diisopropyl phosphite (1.51 g, 9 mmol) and sodium (0.27 g, 12 mmol). The mixture was stirred at −78°C for 2 h then allowed to warm to room temperature, when hexane (20 ml) was added and the mixture filtered through Celite 545. Evaporation of the solvent in vacuo left a pale yellow oil, which was subjected to flash chromatography on silica (elution with acetone/petroleum ether, 1/10, v/v) to give a major fraction as an oil which contained tetraisopropyl monofluoromethylene bisphosphonate (65%) and tetraisopropyl pyrophosphate (35%) as indicated by its ^{31}P NMR spectrum. This fraction was treated with bromotrimethylsilane (6.96 g, 45.5 mmol) under nitrogen for 48 h and then lyophilised. Water was added and the mixture stirred, then lyophilised to yield a colourless oil. Chromatography of this oil on a DE52 cellulose column (3 × 33 cm, HCO_3^- form) with elution by a linear gradient of 0.1–0.5 *M* triethylammonium bicarbonate pH 7.5 followed by freeze drying gave di(triethylammonium) monofluoromethylene bisphosphonate as a white solid. Cation exchange chromatography on Dowex 50 (H^+-form) resin gave the free acid (0.25 g, 42%). Analysis. Found: C, 6.17; H, 2.76; P, 30.67. $CH_5FO_6P_2$ calc: C, 6.19; H, 2.58; P, 31.93%.

Tetraisopropyl bromofluoromethylene bisphosphonate (e). This was prepared by the method of Quimby [4] from a 1/1 mixture (by ^{31}P NMR) of tetraisopropyl monofluoromethylene bisphosphonate and tetraisopropyl pyrophosphate obtained

during the synthesis of monofluoromethylene bisphosphonate described above, and bromine in the presence of aqueous potassium carbonate. The title compound was readily purified by flash chromatography on silica with elution by acetone/petroleum ether (1/3, v/v) to yield 0.55 g (90% conversion) of the tetraester as a colourless oil. Analysis, Found: C, 35.12; H, 6.42; P, 14.20; F, 3.98. $C_{13}H_{28}BrFO_6P_2$ calc: C, 35.39; H, 6.40; P, 14.04; F, 4.31%. Mass spectrum (NH_3/CI) $(M + H)^+$ m/z 441, 443.

Tetraisopropyl pyrophosphate (f). This was prepared in 71% yield b.p. 101–102°C (0.1 mbar) from diisopropyl phosphite by the method of Steinberg [13]. Analysis, Found: C, 41.92; H, 8.34; P, 16.88. $C_{12}H_{28}O_7P_2$ calc: C, 41.2; H, 8.15; P, 17.89%. Mass spectrum (NH_3/CI) $(M + H)^+$ m/z 347.

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