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Highly stereoselective synthesis of perfluoroalkylated enynylphosphonates

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Abstract

Perfluoroalkylated enynylphosphonates have been synthesized via nucleophilic addition of lithium acetylides to perfluoroacylated bisphosphonates, followed by elimination of phosphonic acid anion, in 55–80% yields with *Z*-isomers exclusively or predominantly.

Keywords: Highly stereoselective synthesis; Perfluoroalkylated enynylphosphonates; Enynyl-phosphonates

1. Introduction

A large number of phosphonic acids and their derivatives has been shown to exhibit important biological properties, including antibiotic, antileukaemic and insecticidal activity, depending on the nature of the substituent on the phosphonate group [1–5]. Recently fluorinated phosphonates and bisphosphonates have attracted much interest since they are utilized as intermediates in the synthesis of biologically active compound [6–11]. However, to the best of our knowledge methods for the preparation of perfluoroalkylated enynylphosphonates have not been reported previously. Therefore it would be valuable to develop a convenient method for the synthesis of the title compounds, expected to be useful intermediates in the synthesis of fluorine-containing biological active compounds. They may also possess biological activity.

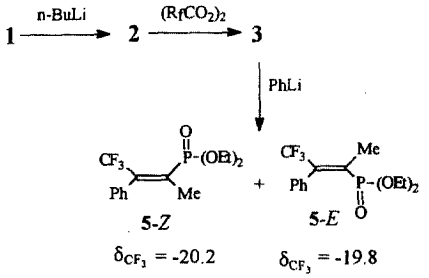
2. Results and discussion

In our continuing investigation to explore the new synthetic methods [12–15] for the preparation of perfluoroalkylated functionalized phosphonates, herein we report the stereoselective synthesis of perfluoroalkylated enynylphosphonates via nucleophilic addition of lithium acetylides to perfluoroacylated bisphosphonates, followed by elimination of phosphonic acid anion, in 55–80% yields with *Z*-isomer exclusively or predominantly.

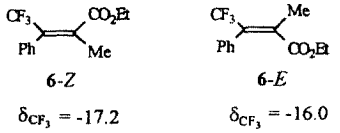
The reaction sequence is shown in Scheme 1.

When bisphosphonate **1** was treated with *n*-butyllithium in THF at −78°C and the resulting carbanion **2** reacted with perfluoroalkanoic anhydride, the perfluoroacylated bisphosphonate **3** was formed. Without isolation **3** was attacked by lithium acetylide to give perfluoroalkylated enynylphosphonates **4**. The results are shown in Table 1. All compounds are new and have been characterized by IR, NMR, mass spectroscopy and microanalyses, or high resolution mass spectroscopy.

For the assignment of the configurations of products we carried out the following reactions.



The ^{19}F NMR data of similar compounds **6-*Z*** and **6-*E*** have been reported [16].



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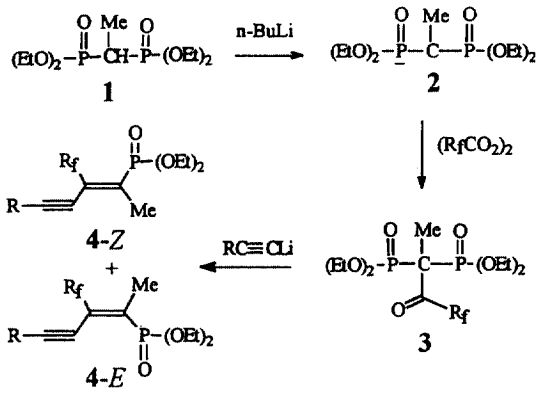

Scheme 1.

Table 1
The synthesis of perfluoroalkylated enynylphosphonates 4

Compound	R	R_f	Yield (%)[a]	Z:E[b]
4a	phenyl	CF_3	80	100:0
4b	phenyl	C_2F_5	72	100:0
4c	phenyl	n-C_3F_7	71	100:0
4d	n-butyl	CF_3	70	100:0
4e	n-butyl	C_2F_5	62	85:15
4f	n-butyl	n-C_3F_7	55	85:15

[a]Isolated yields.
[b]Ratios of *Z*- to *E*-isomers were estimated on the basis of NMR data.

The CF_3 signal in the ^{19}F NMR spectrum of compound **6-Z** is shifted downfield while that of compound **6-*E*** is shifted upfield. We assume that CF_3 signal of compound **5-*Z*** is shifted downfield while that of compound **5-*E*** is shifted upfield. Furthermore the NOESY spectra of 5 shows that the methyl group is *cis* with respect to the phenyl group in **5-*Z***. Hence the configuration of products **4e** and **4f** could be ascertained on the basis of their NMR data.

3. Experimental

The IR spectra of products were obtained as films on a Digilab FTS-20E spectrometer. ^1H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer (δ values in ppm from tetramethylsilane, in $CDCl_3$, J-values are given in Hz). ^{19}F NMR spectra were taken on a Varian EM-360 (60 MHz) spectrometer (δ in ppm from external trifluoroacetic acid, in $CDCl_3$, positive for upfield shifts). Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer. HRMS data were obtained on a Finnigan-Mat 8430 high resolution mass spectrometer.

3.1. General procedure for the preparation of perfluoroalkylated 1,4-diene (4)

Bisphosphonate **1** (0.9 g, 3 mmol) was treated with butyllithium (3 mmol) at −78°C in absolute THF (15 ml) giving the carbanion **2**. The reaction mixture was stirred at −78°C for 0.5 h under nitrogen and perfluoroalkanoic anhydride (3 mmol) was added to it in one portion. After stirring at −78°C for 1 h, the lithium acetylide (3 mmol) [prepared by the reaction of n-butyllithium (3 mmol) and terminal acetylenes (3 mmol) in THF (10 ml) for 15 min at 0°C] was added dropwise to the mixture which was stirred and allowed to warm to room temperature within 4 h. The reaction mixture was poured into water (30 ml) and the water layer was extracted with dichloromethane (3×20 ml). The combined organic layer was washed with water (3×10 ml), and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was purified by silica column chromatography eluting with petroleum ether (60–90°C)-ethyl acetate (8:2) to give the product **4**.

3.1.1. Diethyl 4-phenyl-2-trifluoromethyl-but-1-en-3-ynylphosphonate (4a)

Yield, 80%; oil; *Z*:*E* = 100:0. IR (film) (cm^{-1}) 2985, 2220, 1490, 1440, 1246, 1204, 760, 690. ^1H NMR δ: 7.60−7.50 (m, 2H), 7.42−7.30 (m, 3H), 4.30−4.10 (m, 4H), 2.26 (dq, 3H, J 16.0, 2.4 Hz), 1.35 (t, 6H, J 7.2 Hz). ^{19}F NMR δ: −18.4 (s, 3F). MS *m/z* (rel. int.) 347 (M^+ + 1, 41), 346 (97), 278 (25), 250 (100), 208 (14), 139 (64), 105 (49), 77 (23). HRMS *m/z*: 346.0931 (M^+), calculated $C_{16}H_{18}F_3O_3P$ = 346.0946.

3.1.2. Diethyl 4-phenyl-2-pentafluoroethyl-but-1-en-3-ynylphosphonate (4b)

Yield 72%; oil; *Z*:*E* = 100:0; IR (film) (cm^{-1}) 2980, 2220, 1490, 1440, 1257, 1211, 760, 690. ^1H NMR ($CDCl_3$/TMS) δ: 7.56−7.48 (m, 2H), 7.38−7.30 (m, 3H), 4.30−4.10 (m, 4H), 2.27 (dt, 3H, J 16.2, 3.2 Hz), 1.36 (t, 6H, J 7.1 Hz). ^{19}F NMR δ: 4.4 (s, 3F), 31.4 (s, 2F). MS *m/z* (rel. int.) 396 (M^+, 47), 328 (14), 300 (100), 258 (5), 189 (7), 155 (15), 139 (39), 105 (47), 77 (27). HRMS *m/z*: 396.0920 (M^+), calculated $C_{17}H_{18}F_5O_3P$ = 396.0914.

3.1.3. Diethyl 6,6,6,5,5,4,4-heptafluoro-2-phenylethenyl-1-methyl-pent-1-enyl-phosphonate (4c)

Yield, 71%; oil; *Z*:*E* = 100:0. IR (cm^{-1}) 2960, 2210, 1490, 1440, 1290, 1026, 760, 690. ^1H NMR δ: 7.58−7.48 (m, 2H), 7.42−7.30 (m, 3H), 4.30−4.10 (m, 4H), 2.26 (dt, 3H, J 16.0, 3.1 Hz), 1.36 (t, 6H, J 7.0 Hz). ^{19}F NMR δ: 3.8 (t, 3F, J 10 Hz), 28.4 (m, 2F), 48.6 (s, 2F). MS *m/z* (rel. int.) 447 (M^+ + 1, 96), 446 (97), 398 (3), 350 (30), 139 (11), 105 (5). HRMS *m/z*: 446.0848 (M^+), calculated $C_{18}H_{18}F_7O_3P$ = 446.0882.

3.1.4. Diethyl 2-trifluoromethyl-1-methyl-oct-1-en-3-ynylphosphonate (4d)

Yield, 70%; oil; *Z*:*E* = 100:0. IR (cm^{-1}) 2962, 2220, 1253, 1211, 1169, 1053, 972. ^1H NMR δ: 4.30−4.10 (m, 4H), 2.40 (t, 2H, J 7.0 Hz), 2.14 (dq, 3H, J 16.0, 2.3 Hz), 1.62−1.46 (m, 2H), 1.46−1.35 (m, 2H), 1.34 (t, 6H, J 7.1 Hz); 0.92 (t, 3H, J 7.2 Hz). ^{19}F NMR δ: −18.3 (s, 3F). MS

m/z (rel. int.) 327 ($M^+ + 1$, 100), 299 (6), 284 (15), 256 (8), 228 (20), 187 (5), 105 (5). Analysis: calculated for $C_{14}H_{22}F_3O_3P$ (326.30): C, 51.53; H, 6.80%; found: C, 51.69; H, 6.83%.

*3.1.5. Diethyl 2-pentafluoroethyl-1-methyl-oct-1-en-3-ynylphosphonate (**4e**)*

Yield, 62%; oil; *Z*:*E*=85:15. IR (cm^{-1}) 2966, 2220, 1215, 1172, 1026, 976. ^1H NMR δ: 4.30−4.10 (m, 4H), 2.42 (t, 2H, *J* 7.1 Hz), 2.32 (dt, 0.15×3H, *J* 15.0, 2.6 Hz, *E*), 2.14 (dt, 0.85×3H, *J* 16.0, 3.2 Hz, *Z*), 1.64−1.48 (m, 2H), 1.48−1.35 (m, 2H), 1.36 (t, 6H, *J* 7.0 Hz), 0.93 (t, 3H, *J* 7.2 Hz). ^{19}F NMR δ: 4.6 (s, 3F), 29.6 (s, 0.15×2F, *E*), 31.3 (s, 0.85×2F, *Z*). MS *m/z* (rel. int.) 377 ($M^+ + 1$, 100), 376 (11), 349 (9), 334 (32), 306 (16), 278 (51), 237 (9), 155(6), 109 (5). HRMS *m/z*: 376.1230 (M^+), calculated $C_{15}H_{22}F_5O_3P$=376.1227.

*3.1.6. Diethyl 2-heptafluoropropyl-1-methyl-oct-1-en-3-ynylphosphonate (**4f**)*

Yield 55%; oil; *Z*:*E*=85:15. IR (film) (cm^{-1}) 2966, 2220, 1230, 1026, 976. ^1H NMR δ: 4.30−4.10 (m, 4H), 2.42 (t, 2H, *J* 7.1 Hz), 2.34 (dt, 0.15×3H, *J* 15.0, 2.7 Hz, *E*), 2.18 (dt, 0.85×3H, *J* 16.2, 3.2 Hz, *Z*), 1.64−1.48 (m, 2H), 1.48−1.36 (m, 2H), 1.37 (t, 6H, *J* 7.2 Hz), 0.91 (t, 3H, J 7.2 Hz). ^{19}F NMR δ: 2.8 (s, 3F), 26.6 (s, 0.15×2F, *E*), 28.1 (s, 0.85×2F, *Z*), 48.2 (s, 2F). MS *m/z* (rel. int.) 427 ($M^+ + 1$, 18), 398 (7), 384 (31), 356 (25), 328 (100), 287 (16). Analysis: calculated for $C_{16}H_{22}F_7O_3P$ (426.31): C, 45.07; H, 5.16%; found: C, 44.96; H, 5.09%.

*3.1.7. Diethyl 1-methyl-2-phenyl-3,3,3-trifluoro-prop-1-enylphosphonate (**5**)*

Yield, 40%; oil; *Z*:*E*=75:25. IR (cm^{-1}) 2985, 1490, 1442, 1249, 1211, 717, 702. ^1H NMR δ: 7.50−7.15 (m, 5H), 4.32−4.24 (m, 0.75×4H, *Z*), 3.46−3.14 (m, 0.25×4H, *E*), 2.31 (dq, 0.25×3H, *J* 15.1, 2.6 Hz, *E*), 1.81 (dq, 0.75×3H, *J* 16.0, 2.2 Hz, *Z*), 1.40 (t, 0.75×6H, *J* 7.1 Hz, *Z*), 1.14 (t, 0.25×3H, *J* 7.1 Hz, *E*). ^{19}F NMR δ: −20.2 (s, 0.75×3F, *Z*), −19.8 (s, 0.25×3F, *E*). MS *m/z* (rel. int.) 323 ($M^+ + 1$, 100), 322 (M^+ 23), 302 (13), 274 (6), 253 (5), 249 (9), 226 (18), 115 (25). HRMS *m/z*: 322.0949 (M^+), calculated $C_{14}H_{18}F_3O_3P$=322.0945.

Acknowledgements

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