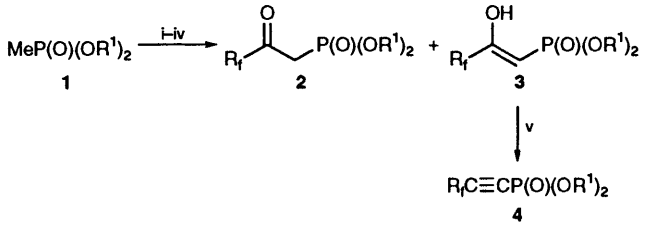
New Synthesis of Dialkyl Fluoroalkynylphosphonates

Yanchang Shen* and Ming Qi
Shanghai Institute of Organic Chemistry, Academia Sinica 345 Lingling Lu, Shanghai 200032, China

A new synthesis of dialkyl fluoroalkynylphosphonates involving trifluoromethanesulfonation and elimination starting from commercially available substances is described.

Many phosphonic acids and their derivatives have been shown to exhibit biological activities.[1] Vinylphosphonates have attracted much interest from synthetic organic chemists.[2,3] Considerable efforts have recently been made to develop methodologies for the synthesis of fluorinated organic compounds owning to their enhanced biological and physiological activities and fluorine-containing vinylphosphonates are regarded as useful intermediates in organic synthesis.[2] However, to the best of our knowledge, methods for the preparation of fluoroalkynylphosphonates are still limited. Diphenyl fluoroalkynylphosphonates have been prepared by intramolecular Wittig reaction,[4] however, the attempted preparation of dialkyl fluoroalkynylphosphonates by this methodology failed as it was not possible to prepare the corresponding dialkoxyphosphorylmethylene(triphenyl)phosphorane.[5] We now report a new synthetic method for the preparation of dialkyl fluoroalkynylphosphonates in 65–80% yields starting from commercially available substances *via* trifluoromethanesulfonation and elimination.

Lithium dialkyl methylphosphonate generated from **1** and butyllithium was treated with fluoroalkanoate **5**, to give, after distillation, a mixture of **2** and **3**,[6] which can be converted into the fluoroalkynylphosphonate by treatment with trifluoromethanesulfonic anhydride in the presence of *N*,*N*-diisopropylethylamine as shown in Scheme 1. The results are summarized in Table 1.



Scheme 1 *Reagents and conditions:* i, BuLi–THF, −78 °C; ii, $R_fCO_2R^2$ **5**, < −50 °C; iii, 6 mol dm^{-3} HCl, −20 °C; iv, distillation; v, $(CF_3SO_2)_2O$, Pr^i_2NEt, CH_2Cl_2, 0 °C

Experimental

The mixture of **2** and **3** was prepared according to the method reported by Nickson.[6]

General Procedure for the Preparation of Fluoroalkynylphosphonates **4**.—Into a solution of a mixture of **2** and **3** (3 mmol in 3 cm^3 of dry CH_2Cl_2), diisopropylethylamine (10.8 mmol) was added at 0 °C under nitrogen, followed by trifluoromethanesulfonic anhydride (3.6 mmol). After being stirred at 0 °C for 4 h, the reaction mixture was diluted with diethyl ether (30 cm^3) and filtered, the residue was washed with diethyl ether (2 × 10 cm^3). The filtrate was collected, washed with water (10 cm^3), HCl (1 mol dm^{-3}; 15 cm^3) and dried. Evaporation of the solvent gave a residue which was purified by flash column chromatography to give the product **4**.

Diethyl 3,3,3-*trifluoroprop*-1-*ynylphosphonate* **4a**. B.p. 53 °C/10 mmHg (Found: C, 36.35; H, 4.3. $C_7H_{10}F_3O_3P$ requires C, 36.55; H, 4.35%); ν(film, neat)/cm^{-1} 2986s, 2220w, 1253s and 1023s; δ_H($CDCl_3$/internal $SiMe_4$)† 4.27 (m, 4 H) and 1.42 (t, *J* 7.0, 6 H); δ_F($CDCl_3$/external trifluoroacetic acid, positive for downfield shifts 26.1 (s, 3 F); *m*/*z* 231 (M + 1), 185, 161 and 93.

Diisopropyl 3,3,3-*trifluoroprop*-1-*ynylphosphonate* **4b**. B.p. 56 °C/6 mmHg (Found: C, 41.7; H, 5.6. $C_9H_{14}F_3O_3P$ requires C, 41.9; H, 5.4%); ν/cm^{-1} 2982s, 2220w and 1254s; δ_H 1.40 (d, *J* 7.0, 12 H) and 4.60–5.10 (m, 2 H); δ_F 25.8 (s, 3 F); *m*/*z* 259 (M + 1), 201 and 189.

Diethyl 3-*chloro*-3,3-*difluoroprop*-1-*ynylphosphonate* **4c**. B.p. 68 °C/7 mmHg (Found: C, 33.8; H, 3.9. $C_7H_{10}ClF_2O_3P$ requires C, 34.1; H, 4.0%). ν/cm^{-1} 2985s, 2220w, 1279s and 1023s; δ_H 1.28 (t, *J*, 7.0, 6.H) and 3.92–4.40 (m, 4 H); δ_F 37.5 (s, 2 F); *m*/*z* 247 (M + 1), 211, 202 and 183.

Diisopropyl 3-*chloro*-3,3-*difluoroprop*-1-*ynylphosphonate* **4d**. B.p. 75 °C/7 mmHg (Found: C, 39.05; H, 5.15. $C_9H_{14}ClF_2O_3P$ requires C, 39.3; H, 5.1%); ν/cm^{-1} 2982s, 2220w, 1278s and 1001s; δ_H 1.40 (d, *J* 7.0, 12 H) and 4.55–5.10 (m, 2-H); δ_F 37.5 (s, 2 F); *m*/*z* 275 (M + 1), 256, 232 and 189.

Dimethyl 3-*chloro*-3,3-*difluoroprop*-1-*ynylphosphonate* **4e**. B.p. 55 °/10 mmHg (Found: C, 27.1; H, 2.8. $C_5H_6ClF_2O_3P$ requires C, 27.4; H, 2.7%). ν/cm^{-1} 2982s, 2220w, 1278s and 1021s; δ_H 3.88 (d, *J* 12.5, 6 H); δ_F 36.7 (s, 2 F); *m*/*z* 219 (M + 1), 217, 188 and 133.

Diethyl 3,3,4,4,5,5,5-*heptafluoropent*-1-*ynylphosphonate* **4f**. B.p. 70 °C/9 mmHg (Found: C, 32.4; H, 3.0. $C_9H_{10}F_7O_3P$ requires C, 32.7; H, 3.0%). ν/cm^{-1} 2987s, 2220w, 1234s and

† *J* Values are given in Hz.

Table 1 Preparation of dialkyl fluoroalkynylphosphonates **4**

	Compound	R_f	R^1	R^2	Yields of **2** + **3** (%)[a]	**2**:**3**[b]	Yields of **4**[c] (%)[a]
a		CF_3	Et	Et	92	86:14	80
b		CF_3	Pr^i	Et	81	82:18	75
c		$ClCF_2$	Et	Me	83	78:22	70
d		$ClCF_2$	Pr^i	Et	88	75:25	65
e		$ClCF_2$	Me	Me	85	75:25	65
f		n-C_3F_7	Et	Et	92	80:20	75

[a] Isolated yields. [b] The mixture of **2** and **3** was characterized by ^1H NMR, ^{19}F NMR and IR spectroscopy. The ratios of **2**:**3** were estimated on the basis of ^{19}F NMR spectroscopy. [c] All compounds **4** are new and characterized on the basis of microanalysis, IR and NMR spectroscopy and mass spectrometry.

1024s; δ_H 1.40 (t, J 7.0, 6 H), 4.02–4.50 (m, 4 H); δ_F −2.2 (s, 3 F), −24.1 (s, 2 F), −49.1 (s, 2 F); m/z 331 (M + 1), 285 and 261.

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