Organic Chemistry

Synthesis of esters of polyfluoro-substituted 2-methyl- and 3-methyl-2,4-alkadienoic acids by Horner—Emmons olefination of polyfluoroalkanals

V. N. Odinokov,[a] V. R. Akhmetova,[a] R. G. Savchenko,[a] A. A. Fatykhov,[a]*
K. I. Pachkevich,[b] and E. P. Serebryakov[c]

[a]*Institute of Petrochemistry and Catalysis, the Bashkortostan Republic Academy of Sciences,*
141 prosp. Oktyabrya, 450075 Ufa, Russian Federation.
Fax: +7 (347 2) 31 2750
[b]*Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences,*
20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation.
Fax: + 7 (343 2) 44 4133
[c]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,*
47 Leninsky prosp., 117913 Moscow, Russian Federation.
Fax: +7 (095) 135 5328

Ethyl 2- and 3-methyl-6,6,7,7-tetrafluoro-2,4-heptadienoates and ethyl 2-methyl-6,6,7,7,8,8,9,9-octafluoro-2,4-nonadienoate were synthesized by condensing 2,2,3,3-tetrafluoropropanal or 2,2,3,3,4,4,5,5-octafluoropentanal with ethyl 2-methyl-4-diisopropoxyphosphono- and ethyl 3-methyl-4-diethoxyphosphono-2-butenoates under the conditions of the Horner—Emmons reaction.

Key words: Horner—Emmons reaction, polyfluoroalkanal, polyfluoro-2,4-alkadienoate.

Introduction of fluorine atoms into a molecule of a natural compound can markedly affect its biological activity.[1—3] Interest in the synthesis of fluorine-containing analogs of insect pheromones and juvenoids has been steadily growing in recent years.[4—8]

With the aim of synthesizing polyfluorinated derivatives of 2,4-alkadienoates, whose hydrogen analogs exhibit high juvenoid potency,[9,10] we studied the Horner—Emmons olefination of 2,2,3,3-tetrafluoropropanal (**1**) and 2,2,3,3,4,4,5,5-octafluoropentanal (**2**). Under the conditions of phase-transfer catalysis (in the presence of KOH and dibenzo-18-crown-6)[9] aldehydes **1** and **2** were found to not react with phosphonate **3**. The olefination took place upon the action of the Et_3N—LiBr system[11] in THF; however, the yield of the product did not exceed 20 %. Ethyl 2-methyl-6,6,7,7-tetrafluoro-2,4-heptadienoate (**4**) and 2-methyl-6,6,7,7,8,8,9,9-octafluoro-2,4-nonadienoate (**5**) were obtained in higher yields (30 and 35 %, respectively) when the reaction was carried out in THF in the presence of lithium diisopropylamide[12] (Scheme 1).

It should be noted that the olefination of aldehyde **1** with sterically hindered phosphonate **3** affords the individual (*E*,*E*)-isomer of compound **4** (as indicated by

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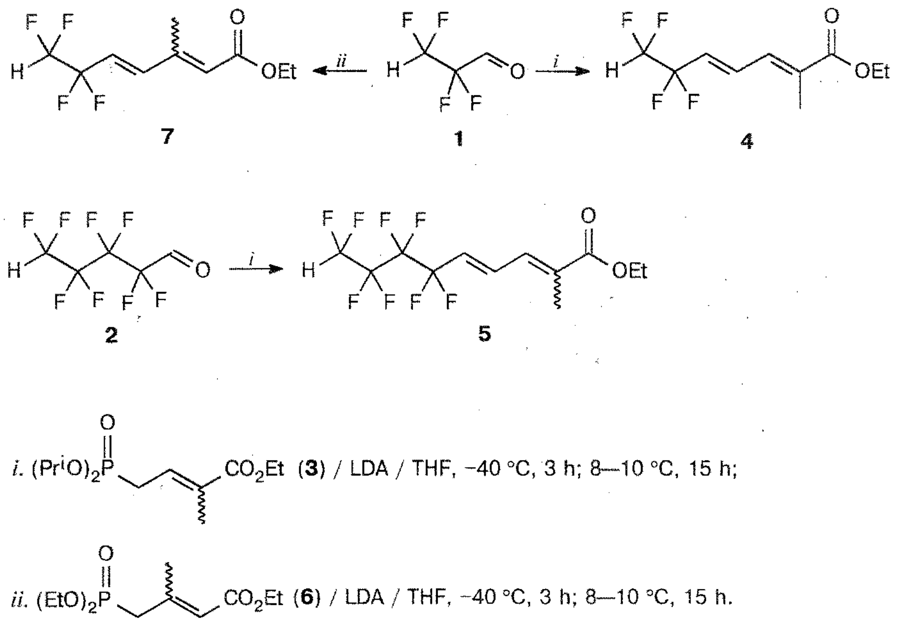
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2196—2198, November, 1995.

Scheme 1



a singlet at 2.05 ppm due to 2-Me in the ^{1}H NMR spectrum and a quartet at 13.5 ppm due to C(2) in the ^{13}C NMR spectrum), whereas the starting phosphonate **3** is a mixture of (*E*)- and (*Z*)-isomers in a ratio of 1 : 1.4 (based on the intensities of the MeC=C signals at δ 2.03 and 2.3 ppm). On the other hand, in the case of aldehyde **2**, the process was less stereoselective: according to ^{1}H NMR data, the product of its olefination prepared under the same conditions is a 2 : 1 mixture of (2*E*,4*E*)- and (2*Z*,4*E*)-isomers of **5**. The conclusion that the Δ^4 bond in compounds **4** and **5** has a transoid configuration was based on the value of $^3J_{H-H}$ (15 Hz). The existence of the 2,4-diene system in compounds **4** and **5** was confirmed by the presence of the cross-peaks of protons at C(3) (7.2 ppm) and C(4) (7.03 ppm) as well as of the protons at C(4) and C(5) (6.0 ppm) in the two-dimensional H—H-correlation spectrum (COSY). Mass spectra of compounds **4** and **5** exhibit the corresponding molecular ions (M^+ 240 and 340). Their fragmentation involves a characteristic cleavage of the C(5)—C(6) bond, yielding the 2-methylpentadienoate ion (*m/z* 139), which subsequently undergoes McLafferty rearrangement[13] to give ethylene and an ion corresponding to the most abundant peak of the spectrum (*m/z* 111).

The Horner—Emmons reaction of compound **1** with sterically less hindered phosphonate **6** was not stereospecific, but still selective. Olefination of aldehyde **1** by phosphonate **6** (according to the ratio between the intensities of the singlets at 2.05 and 2.3 ppm in its ^{1}H NMR spectrum the latter was a 1 : 1.3 mixture of (*E*)- and (*Z*)-isomers) afforded a mixture of (2*E*,4*E*)- and (2*Z*,4*E*)-isomers of ethyl 3-methyl-6,6,7,7-tetrafluoro-2,4-heptadienoate (**7**) in which the (*E*,*E*)-isomer slightly predominated (1.4 : 1, as indicated by the ratio between the intensities of the singlets due to C(2)H at 5.95 ppm (*E*-Δ^2) and 6.00 ppm (*Z*-Δ^2)). The (*E*)-configuration of the Δ^4 bond in ester **7** was confirmed by the value of $^3J_{H-H}$ for C(4)H and C(5)H (16 Hz).

It should be noted that the ^{1}H NMR spectra of compounds **4**, **5**, and **7** exhibit typical signals in the region of 5.8—6.0 ppm (triplet of triplets) corresponding to the H atom of the terminal difluoromethyl group. The substantial difference between the chemical shifts of the signals of the vinylic protons at the C(4) atom in the ^{1}H NMR spectra of (2*E*,4*E*)- and (2*Z*,4*E*)-isomers of ester **7** which appear as the doublets of triplets at 8.25 and 6.75 ppm, respectively, is also notable. The foregoing assignment of these signals was confirmed by the fact that the COSY spectrum of compound **7** exhibits two cross-peaks attesting to interaction of C(4) (8.25 and 6.75 ppm) with the vinylic protons at the C(5) atom (6.0 ppm for both geometric isomers of compound **7**).

Experimental

The IR spectrum of compound **7** was recorded on a Specord 75 IR spectrometer, and the spectra of other compounds were obtained on a UR-20 instrument (from films). GLC analysis was carried out on a Chrom-5 instrument with SE-30 (5 %) on Chromaton N-AW-DMCS (0.16—0.20 mm) as the stationary phase and helium as the carrier gas. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer (300 MHz). Mass spectra (EI, 70 eV) were obtained on an MKh-1320 instrument with a direct inlet into the ionization chamber (60 °C). The R_f values refer to a fixed SiO_2 (Silufol) layer with a heptane—ether mixture (7 : 3).

Ethyl 2-methyl-6,6,7,7-tetrafluoro-2*E*,4*E*-heptadienoate (4). A solution of ethyl 2-methyl-4-diisopropoxyphosphono-

2-butenoate (**3**) (2.84 g, 9.73 mmol) in THF (5 mL) was added with stirring (−40 °C, Ar) to a solution of Pr^i_2NLi (prepared from 10 mmol of Pr^i_2NH (5.5 mL) and 10 mmol (8.3 mL) of a 1.2 *N* solution of *n*-BuLi) in 7.5 mL of THF over a period of 1 h. Then a solution of aldehyde **1** (1.3 g, 10 mmol) in 5 mL of THF was added, and the mixture was stirred for 3 h at −40 °C, allowed to stand for 15 h at 8—10 °C, diluted with water (~20 °C), stirred again for 0.5 h, and extracted with ether. The extract was dried with $MgSO_4$ and evaporated. The residue (4.1 g) was chromatographed on SiO_2 using a pentane—ether mixture (9 : 1) as the eluent to give 0.69 g (30 %) of ester **4**, R_f 0.5. IR, ν/cm^{-1}: 1720 (C=O), 1645 and 1607 (C=C), 1400—1000 (C—F), 988, 840. ^{1}H NMR ($CDCl_3$), δ: 1.32 (t, 3 H, Me, *J* = 7.1 Hz); 2.05 (s, 3 H, 2-Me); 4.23 (q, 2 H, OCH_2, *J* = 7.1 Hz); 5.81 (tt, 1 H, CHF_2, $^2J_{HF}$ = 53.8 Hz, $^3J_{HF}$ = 1.9 Hz); 6.0 (dt, 1 H, C(5)H, $^3J_{HH}$ = 15.2 Hz, $^3J_{HF}$ = 12.4 Hz); 7.03 (ddt, 1 H, C(4)H, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 12.5 Hz, $^4J_{HF}$ = 2.2 Hz); 7.2 (d, 1 H, C(3)H, $^3J_{HH}$ = 12.5 Hz). ^{13}C NMR (C_6D_6), δ: 13.5 (q, 2-Me); 14.9 (q, Me); 61.6 (t, CH_2O); 167.7 (s, C-1); 135.2 (s, C-2); 134.7 (d, C-3); 134.0 (dt, C-4); 124.7 (dt, C-5); 111.3 (tt, C-6); 115.0 (ddt, C-7). MS, *m/z* (I_{rel} (%)): 240 $[M]^+$ (2.77), 225 $[M-Me]^+$ (0.62), 212 $[M-C_2H_4]^+$ (1.23), 195 $[M-OEt]^+$ (2.54), 167 $[M-CO_2Et]^+$ (1.23), 139 $[M-CF_2CF_2H]^+$ (2.07), 115 (0.62), 111 (100), 101 $[M-CF_2HCF_2]^+$ (0.38).

Ethyl 2-methyl-6,6,7,7,8,8,9,9-octafluoro-2*E*/*Z*,4*E*-nonadienoate (5) was prepared from aldehyde **2** (1.5 g, 6.5 mmol) similarly to compound **4**; yield 0.77 g (35 %), R_f 0.49. IR, ν/cm^{-1}: 1700 (C=O), 1650 and 1625 (C=C), 1400—1000 (C—F), 960, 940, 900, 790, 750. ^{1}H NMR ($CDCl_3$), δ: 1.30 (t, 3 H, Me, *J* = 7.0 Hz); 2.00 (*E*) and 2.12 (*Z*) (s, 3 H, 2-Me); 4.2 (q, 2 H, OCH_2, *J* = 7.0 Hz); 6.05 (tt, 1 H, CHF_2, $^2J_{HF}$ = 53.8 Hz, $^3J_{HF}$ = 1.9 Hz); 6.08 (dt, 1 H, C(5)H, $^3J_{HH}$ = 15.4 Hz, $^3J_{HF}$ = 11.25 Hz); 7.08 (ddt, 1 H, C(4)H, $^3J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 12.8 Hz, $^4J_{HF}$ = 2.4 Hz); 7.2 (d, 1 H, C(3)H, $^3J_{HH}$ = 12.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 13.4 (q, 2-Me); 14.0 (q, Me); 61.7 (t, CH_2O); 168.3 (s, C-1); 135.1 (s, C-2); 134.4 and 133.8 (dt, *E*/*Z*, C-3); 134.0 (dt, C-4); 123.5 (dt, C-5); 110.0—120.5 (m, C(6)-C(8)); 107.9 (ddt, C-9). MS, *m/z* (I_{rel} (%)): 340 $[M]^+$ (11.76), 312 $[M-C_2H_4]^+$ (4.12), 295 $[M-OEt]^+$ (18.62), 267 $[M-CO_2Et]^+$ (7.45), 247 (2.55), 229 (3.14), 189 (8.82), 163 (23.52), 139 $[M-(CF_2)_3CF_2H]^+$ (37.25), 113 (76.47), 111 (100), 101 $[M-CF_2CF_2H]^+$ (47.05), 100 (60.78), 97 (56.86), 69 (9.41), 83 (49.01), 82 (54.90).

Ethyl 3-methyl-6,6,7,7-tetrafluoro-2*E*/*Z*,4*E*-heptadienoate (7) was prepared from aldehyde **1** (0.78 g, 6.0 mmol) and ethyl 3-methyl-4-diethoxyphosphono-2-butenoate (**6**) (1.6 g, 6.06 mmol) as described above for compound **4**; yield 0.36 g (25 %), R_f 0.55. IR, ν/cm^{-1}: 1680 (C=O), 1630 and 1595 (C=C), 1420—1030 (C—F), 945, 820. ^{1}H NMR ($CDCl_3$), δ: 1.35 (t, 3 H, Me, *J* = 7.0 Hz); 2.05 (*E*) and 2.30 (*Z*) (s, 3 H, 3-Me); 4.25 (q, 2 H, OCH_2, *J* = 7.0 Hz); 5.80 (tt, 1 H, CHF_2, $^2J_{HF}$ = 53.8 Hz, $^3J_{HF}$ = 1.9 Hz); 5.95 (*E*) and 6.00 (*Z*) (s, 1 H, C(2)H); 6.00 (m, 1 H, C(5)H); 6.75 (*Z*) and 8.25 (*E*) (d, 1 H, C(4)H, *J* = 16.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 13.5 (q, 3-Me); 14.9 (q, Me); 61.0 (t, CH_2O); 167.0 (s, C-1); 134.0 (d, C-2); 134.0 (s, C-3); 135.0 (dt, C-4); 124.5 (dt, C-5); 111.0 (tt, C-6); 115.0 (ddt, C-7).

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Received March 13, 1995