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A novel one-pot synthesis of functionalized perfluoroalkylated 1,4-alkadienes

Yanchang Shen*, Shu Gao and Yuejun Xiang
Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai 200032 (People's Republic of China)

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Abstract

A novel one-pot synthesis of functionalized perfluoroalkylated 1,4-alkadienes via the Reformatsky reaction of unsaturated halo esters with fluorinated β-ketophosphonium salts is described. This new methodology provides a four-carbon homologation giving functionalized perfluoroalkylated 1,4-alkadienes exclusively in 37–55% yields (three steps).

Introduction

Functionalized 1,4-alkadienes are potentially useful intermediates in organic syntheses being an important class of natural products [1] and capable of undergoing useful transformations, such as cyclization to various six- or seven-membered carbo- or hetero-cycles [2]. However, only a few reports have appeared in the literature concerning the preparation of 1,4-alkadienes [2, 3] and the perfluoroalkylated analogues have not been reported previously although they would be expected to be useful intermediates for the synthesis of fluorinated biologically active compounds.

Results and discussion

The Reformatsky reaction is a useful method for the formation of carbon–carbon bonds [4] and the reaction involving unsaturated halo esters with carbonyl substrates provides a four-carbon homologation affording functionalized 1,3-dienes [5] which are thermodynamically stable regioisomers. Nevertheless, functionalized 1,4-dienes are not easy to obtain, because they are thermodynamically unstable with respect to 1,3-dienes. In our continuing studies to exploit the synthetic utility of fluorinated β-ketophosphonium salts in organic synthesis [6], we have found that the Reformatsky reaction of unsaturated halo esters with fluorinated β-ketophosphonium salts provides a four-carbon homologation giving functionalized perfluoroalkylated 1,4-

*Author to whom all correspondence should be addressed.

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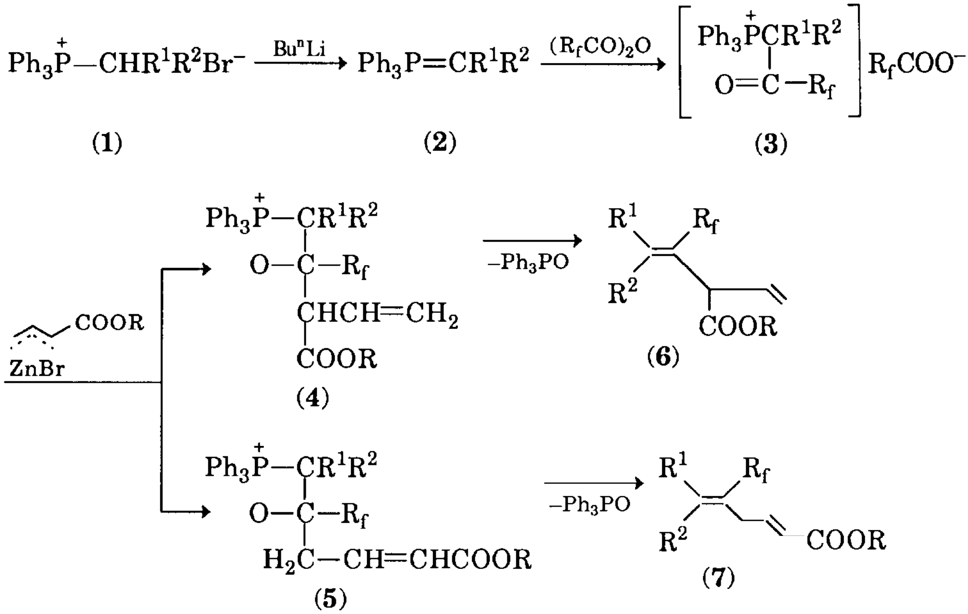
alkadienes exclusively. The reaction sequence is as follows:



The phosphoranes **2** generated from the corresponding phosphonium salts **1** and n-butyllithium in tetrahydrofuran were acylated by the addition of perfluoroalkanoic anhydrides to give the fluorinated β-ketophosphonium salts **3** which in the reaction medium employed were attacked by unsaturated organozinc compounds followed by elimination of triphenylphosphine oxide to give functionalized perfluoroalkylated 1,4-alkadienes **6** and **7**. The results are summarized in Table 1.

It is noteworthy that this one-pot reaction provides a new method for the synthesis of the title compounds which are not easy to access otherwise and would be useful for the synthesis of fluorine-containing biologically active compounds.

Experimental

All boiling points were uncorrected. Infrared spectra of products were obtained as films on a Shimadzu IR-440 spectrometer. ^{19}F and ^{1}H NMR spectra were obtained on a Varian EM-360 spectrometer at 60 MHz or of an XL-200 spectrometer using TFA as the external reference and TMS as the internal reference. Mass spectra were recorded on a Finnigan GC-MS 4021 mass spectrometer.

General procedure for the preparation of perfluoroalkylated 1,4-alkadienes

n-Butyllithium (4 mmol in 4 ml n-hexane) was added dropwise with stirring to a suspension of phosphonium bromide **1** (4 mmol) in absolute

TABLE 1

Preparation of perfluoroalkylated 1,4-alkadienes[a]

Compounds 6+7	R	R^1	R^2	R_f	Yield (%)[b]	7/6[c]
a	Me	Me	Me	C_2F_5	43	100:0
b	Me	$-(CH_2)_5-$		C_2F_5	42	100:0
c	Et	Me	Me	n-C_3F_7	37	100:0
d	Me	Me	Me	CF_3	42	73:27
e	Me	$-(CH_2)_5-$		CF_3	52	85:15
f	Me	$-(CH_2)_6-$		CF_3	42	95:5
g	Et	Me	Me	CF_3	41	83:17
h	Et	$-(CH_2)_5-$		CF_3	55	89:11
i	Et	$-(CH_2)_6-$		CF_3	47	94:4

[a]All compounds are new and were characterized by microanalyses, IR, NMR and mass spectroscopy.
[b]Isolated yields (three steps).
[c]Ratios of **7** to **6** were estimated on the basis of NMR spectra.

tetrahydrofuran (40 ml) under nitrogen. The reaction mixture was stirred at −20 °C for 30 min and perfluoroalkanoic anhydride (4 mmol) was added slowly at −78 °C. The mixture was stirred at −78 °C for 15 min, allowed to warm to room temperature and 4-bromocrotonic ester (4 mmol) and zinc (0.33 g, 5 mmol) were added. After stirring at room temperature for 4 h, the product was isolated by column chromatography on silica gel eluting with light petroleum ether (b.p. 60–90 °C)/ethyl acetate (10:1).

Compound **7a**: B.p. 44 °C/1 mmHg. IR (film) (cm^{-1}): 1730 (s); 1660 (s); 1280 (s). ^1H NMR ($CDCl_3$/TMS) δ: 6.91 (dt, 1H, J=15.9, 5.9 Hz); 5.80 (dt, 1H, J=15.9, 1.4 Hz); 3.73 (s, 3H); 3.04 (d, 2H, J=5.9 Hz); 1.92 (t, 3H, J=2.5 Hz); 1.81 (t, 3H, J=2.5 Hz) ppm. ^{19}F NMR (CCl_4/TFA) δ: 7.0 (s, 3F); 32.3 (s, 2F) ppm. MS (m/e): 273 (M^++1, 100); 272 (M^+, 28); 213 (44); 153 (13). Analysis: Calc. for $C_{11}H_{13}F_5O_2$: C, 48.53; H, 4.81%. Found: C, 48.55; H, 4.74%.

Compound **7b**: B.p. 54 °C/1 mmHg. IR (film) (cm^{-1}): 1730 (s); 1660 (s); 1280 (s). ^1H NMR ($CDCl_3$/TMS) δ: 6.77 (dt, 1H, J=15.4, 6.4 Hz); 5.79 (dt, 1H, J=15.4, 1.8 Hz); 3.68 (s, 3H); 3.17 (d, 2H, J=6.2 Hz); 2.66–2.22 (m, 4H); 1.74–1.57 (m, 4H) ppm. ^{19}F NMR (CCl_4/TFA) δ: 6.7 (s, 3F); 35.3 (s, 2F) ppm. MS (m/e): 299 (M^++1, 100); 298 (M^+, 38); 267 (41); 239 (43); 179 (25). Analysis: Calc. for $C_{13}H_{15}F_5O_2$: C, 52.35; H, 5.07%. Found: C, 52.31; H, 5.14%.

Compound **7c**: B.p. 55 °C/1 mmHg. IR (film) (cm^{-1}) 1730 (s); 1660 (s); 1280 (s). ^1H NMR ($CDCl_3$/TMS) δ: 6.92 (dt, 1H, J=15.7, 5.7 Hz); 5.80 (dt, 1H, J=15.7, 2.4 Hz); 4.03 (q, 2H, J=6.9 Hz); 3.06 (d, 2H, J=5.7 Hz); 1.94 (t, 3H, J=2.5 Hz); 1.83 (t, 3H, J=2.5 Hz); 1.28 (t, 3H, J=6.9 Hz) ppm. ^{19}F NMR (CCl_4/TFA) δ: 3.0 (s, 3F); 28.8 (s, 2F) ppm. MS (m/e): 337 (M^++1, 93); 336 (M^+, 28); 291 (68); 263 (100). Analysis: Calc. for $C_{13}H_{15}F_7O_2$: C, 46.43; H, 4.50%. Found: C, 46.70; H, 4.65%.

Compounds **6d** + **7d**: B.p. 70 °C/5 mmHg. Ratio **6d/7d** = 27:73. IR (film) (cm^{-1}): 1730 (s); 1660 (s); 1280 (s). ^{1}H NMR ($CDCl_3$/TMS) δ: **6d**: 6.39–6.02 (m, 1H); 5.24–4.90 (m, 2H); 4.20 (d, 1H, *J* = 6.5 Hz); 3.73 (s, 3H); 1.78 (q, 3H, *J* = 1.6 Hz); 1.94 (q, 3H, *J* = 1.6 Hz); **7d**: 6.88 (dt, 1H, *J* = 16.0, 6.4 Hz); 5.77 (dt, 1H, *J* = 16.0, 1.5 Hz); 3.73 (s, 3H); 3.08 (d, 2H, *J* = 6.4 Hz); 1.94 (q, 3H, *J* = 1.6 Hz); 1.78 (q, 3H, *J* = 1.6 Hz) ppm. ^{19}F NMR (CCl_4/TFA) δ: **6d**: −21.4 (s); **7d**: −19.5 (s) ppm. MS (*m/e*): 222 (M^+, 34); 191 (44); 163 (100); 153 (13). Analysis: Calc. for $C_{10}H_{13}F_3O_2$: C, 54.04; H, 5.90%. Found: C, 54.25; H, 6.12%.

Compounds **6e** + **7e**: B.p. 76 °C/2 mmHg. Ratio **6e/7e** = 15:85. IR (film) (cm^{-1}): 1730 (s); 1660 (s); 1280 (s). ^{1}H NMR ($CDCl_3$/TMS) δ: **6e**: 6.20–5.97 (m, 1H); 5.25–4.94 (m, 2H); 4.06 (d, 1H, *J* = 6.4 Hz); 3.74 (s, 3H); 2.69–2.05 (m, 4H); 1.83–1.57 (m, 4H); **7e**: 6.89 (dt, 1H, *J* = 15.9, 6.2 Hz); 5.83 (dt, 1H, *J* = 15.9, 1.6 Hz); 3.74 (s, 3H); 3.19 (d, 2H, *J* = 6.2 Hz); 2.69–2.05 (m, 4H); 1.83–1.57 (m, 4H) ppm. ^{19}F NMR (CCl_4/TFA) δ: **6e**: −18.2 (s); **7e**: −16.2 (s) ppm. MS (*m/e*): 249 ($M^+ + 1$, 19); 248 (M^+, 55); 217 (57); 169 (100). Analysis: Calc. for $C_{12}H_{15}F_3O_2$: C, 58.06; H, 6.09%. Found: C, 58.37; H, 6.08%.

Compounds **6f** + **7f**: B.p. 85 °C/2 mmHg. Ratio **6f/7f** = 5:95. IR (film) (cm^{-1}): 1730 (s); 1660 (s); 1280 (s). ^{1}H NMR ($CDCl_3$/TMS) δ: **7f**: 6.93 (dt, 1H, *J* = 15.9, 6.0 Hz); 5.80 (dt, 1H, *J* = 15.9, 1.8 Hz); 3.74 (s, 3H); 3.10 (d, 2H, *J* = 6.0 Hz); 2.48–2.06 (m, 4H); 1.51–1.72 (m, 6H) ppm. ^{19}F NMR (CCl_4/TFA) δ: **6f**: −22.3 (s); **7f**: −20.9 (s) ppm. MS (*m/e*): 263 ($M^+ + 1$, 58); 262 (M^+, 61); 231 (51); 203 (63); 100 (100). Analysis: Calc. for $C_{13}H_{17}F_3O_2$: C, 59.03; H, 6.53%. Found: C, 59.93; H, 6.61%.

Compounds **6g** + **7g**: B.P. 75 °C/5 mmHg. Ratio **6g/7g** = 17:83. IR (film) (cm^{-1}): 1730 (s); 1660 (s); 1280 (s). ^{1}H NMR ($CDCl_3$/TMS) δ: **6g**: 6.40–6.00 (m, 1H); 5.25–4.91 (m, 2H); 4.21 (d, 1H, *J* = 6.4 Hz); 4.18 (q, 2H, *J* = 7.2 Hz); 1.94 (q, 3H, *J* = 1.6 Hz); 1.78 (q, 3H, *J* = 1.6 Hz); 1.24 (t, 3H, *J* = 7.2 Hz); **7g**: 6.89 (dt, 1H, *J* = 19.5, 6.4 Hz); 5.78 (dt, 1H, *J* = 19.5, 1.5 Hz); 4.18 (q, 2H, *J* = 7.2 Hz); 3.08 (d, 2H, *J* = 6.4 Hz); 1.94 (q, 3H, *J* = 1.6 Hz); 1.78 (q, 3H, *J* = 1.6 Hz); 1.29 (t, 3H, *J* = 7.2 Hz) ppm. ^{19}F NMR (CCl_4/TFA) δ: **6g**: −21.5 (s); **7g**: −19.2 (s) ppm. MS (*m/e*): 237 ($M^+ + 1$, 37); 236 (M^+, 66); 191 (81); 143 (100). Analysis: Calc. for $C_{11}H_{15}F_3O_2$: C, 55.92; H, 6.40%. Found: C, 56.35; H, 6.35%.

Compounds **6h** + **7h**: B.p. 81 °C/2 mmHg. Ratio **6h/7h** = 11:89. IR (film) (cm^{-1}): 1730 (s); 1660 (s); 1280 (s). ^{1}H NMR ($CDCl_3$/TMS) δ: **6h**: 6.22–6.06 (m, 1H); 5.26–5.06 (m, 2H); 4.18 (q, 2H, *J* = 7.1 Hz); 4.06 (d, 1H, *J* = 6.0 Hz); 2.64–2.24 (m, 4H); 1.75–1.64 (m, 4H); 1.29 (t, 3H, *J* = 7.1 Hz); **7h**: 6.86 (dt, 1H, *J* = 15.6, 6.2 Hz); 5.82 (dt, 1H, *J* = 15.6, 1.7 Hz); 4.18 (q, 2H, *J* = 7.1 Hz); 3.04 (d, 2H, *J* = 6.2 Hz); 2.64–2.24 (m, 4H); 1.75–1.64 (m, 4H); 1.29 (t, 3H, *J* = 7.1 Hz) ppm. ^{19}F NMR (CCl_4/TFA) δ: **6h**: −18.3 (s); **7h**: −16.4 (s) ppm. MS (*m/e*): 262 (M^+, 25); 217 (35); 189 (30); 67 (100). Analysis: Calc. for $C_{13}H_{17}F_3O_2$: C, 59.53; H, 6.53%. Found: C, 59.66; H, 6.45%.

Compounds **6i** + **7i**: B.p. 92 °C/2 mmHg. Ratio **6i**/**7i** = 4:96. IR (film) (cm^{-1}): 1730 (s); 1660 (s); 1280 (s). ^1H NMR ($CDCl_3$/TMS) δ:**7i**: 6.91 (dt, 1H, J = 15.4, 5.9 Hz); 5.77 (dt, 1H, J = 15.4, 1.5 Hz); 4.33 (q, 2H, J = 6.7 Hz); 3.09 (d, 2H, J = 5.9 Hz); 2.51–2.03 (m, 4H); 1.51–1.72 (m, 6H); 1.28 (t, 3H, J = 6.7 Hz) ppm. ^{19}F NMR (CCl_4/TFA) δ: **6i**: −22.4 (s); **7i**: −20.8 ppm. MS (*m/e*): 277 (M^+ + 1, 100); 276 (M^+, 56); 257 (72); 231 (56). Analysis: Calc. for $C_{14}H_{19}F_3O_2$: C, 60.85; H, 6.93%. Found: C, 61.16; H, 6.95%.

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