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Regiospecific synthesis of (perfluoroalkyl vinyl)-furans and -thiazoles

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Abstract

Regiospecific synthesis of (perfluoroalkyl vinyl)-thiazoles and -furans by the reaction of fluorinated β-oxophosphonium salts with substituted furyl-lithiums or thiazolyl-lithiums is described.

Keywords: Regiospecific synthesis; (Perfluoroalkyl vinyl)furans; (Perfluoroalkyl vinyl)thiazoles; NMR spectroscopy; IR spectroscopy; Mass spectrometry

1. Introduction

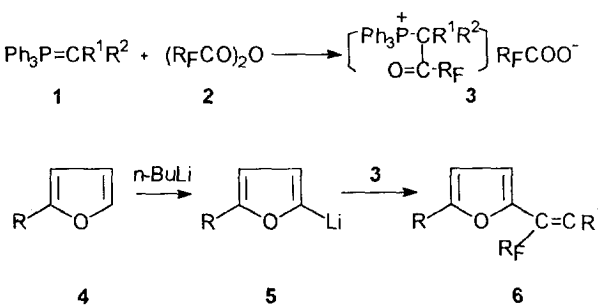
Introduction of a fluorine atom or perfluoroalkyl group into organic molecules often causes pronounced changes in their biological activities, and regiospecific introduction is very important [1]. Owing to their significant biologically active properties in the field of medicinal and agricultural chemistry, heterocyclic compounds, and particularly fluoro species, have received much attention [2]. For example, fluorinated pyrimidines which act as anti-cancer agents are particularly well known.

2. Results and discussion

In our previous papers [3] we reported that nucleophiles could attack fluorinated β-oxophosphonium salts leading to the formation of tetrasubstituted fluoroalkenes, fluoroenynes and α-fluoroalkylvinyl phosphonates. In our continuing investigation to exploit the synthetic utility of fluorinated β-oxophosphonium salts in organic synthesis, we now wish to report the regiospecific synthesis of (perfluoroalkyl vinyl)-furans and -thiazoles by the reaction of fluorinated β-oxophosphonium salts with substituted furyl-lithium and thiazoyl-lithium species.

Phosphoranes **1**, generated from the corresponding phosphonium salts and n-butyllithium in tetrahydrofuran, were acylated by the addition of a perfluoroalkanoic anhydride to give fluorinated β-oxophosphonium salts **3** which, in the reaction medium, were attacked by substituted furyl-lithiums **5**, followed by elimination of triphenylphosphine oxide, to give perfluoroalkyl vinylfurans **6**. The reaction was regiospecific, and *E*-isomers appeared to be obtained exclusively as judged on the basis of their NMR spectra. The reaction sequence is shown in Scheme 1 and the results are summarized in Table 1.

Similarly, fluorinated β-oxophosphonium salts **3** were attacked by thiazolyl-lithium, followed by elimination of tri-



Scheme 1.

Table 1
(Perfluoroalkyl vinyl) furans prepared

Compound	R^1	R^2	R	R_F	Yield (%) [a]
6a	Ph	Me	H	CF_3	57
6b	Ph	Me	Me	CF_3	56
6c	Ph	Me	Me_3Si	CF_3	51
6d	Me	Me	Me	C_2F_5	55
6e	Me	Me	Me_3Si	C_2f_5	50
6f	Me	Me	Me_3Si	CF_3	52
6g	$-(CH_2)_4-$		H	CF_3	65
6h	$-(CH_2)_4-$		Me	CF_3	65

[a] Isolated yields. All products were characterized by microanalysis and IR and NMR spectroscopy and mass spectrometry.

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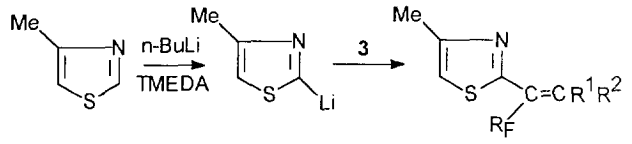

7 8 9

Scheme 2.

Table 2
(Perfluoroalkyl vinyl)thiazoles prepared

Compound	R^1	R^2	R_F	Yield (%) [a]	Z/E [b]
9a	Ph	Me	CF_3	86	100:0
9b	^{n}Bu	Me	CF_3	62	52:48
9c	Me	Me	CF_3	71	
9d	Me	Me	C_2F_5	50	
9e	$-(CH_2)_4-$		CF_3	68	
9f	$-(CH_2)_4-$		C_2F_5	53	
9g	$-(CH_2)_5-$		CF_3	63	

[a] Isolated yields. All products were characterized by microanalysis and IR and NMR spectroscopy and mass spectrometry.
[b] Z/E Ratio estimated from NMR data.

phenylphosphine oxide, to give perfluoroalkyl vinyl thiazoles **9** regiospecifically. The reaction sequence is shown in Scheme 2 and the results are summarized in Table 2.

The configurations of compounds **9a** and **9b** were ascertained on the basis of their ^{19}F NMR data [4].

3. Experimental details

All melting points and boiling points are reported uncorrected. The IR spectra of solid products were obtained as KCl disks and of liquid products as films on a Shimadazu IR-440 spectrometer. NMR spectra (chemical shifts in ppm from internal TMS for ^1H NMR and from external TFA for ^{19}F NMR, positive for upfield shifts) were obtained on a Varian EM-360 (60 MHz) or XL-200 (200 MHz) spectrometer. Mass spectra were measured on a Finnigan GC–MS 4021 spectrometer.

3.1. General procedure for the preparation of (perfluoroalkyl vinyl)-furans and -thiazoles

Phosphoranes **1** were generated from the corresponding phosphonium salts (3 mmol) and n-butyllithium (3 mmol) in tetrahydrofuran (30 ml) at 0 °C under nitrogen. The reaction mixture was cooled to −78 °C and a perfluoroalkanoic anhydride (2.5 mmol) was slowly added until the ylidic color (orange) had disappeared. After the mixture had been stirred at −78 °C for 5 min, a substituted furyl-lithium or thiazolyl-lithium [prepared by the reaction of a substituted furan (3 mmol) or thiazole (3 mmol) with n-butyllithium (3 mmol) in THF (10 ml) for 10 min at 0 °C; in the case of thiazole 3.0 mmol of *N,N,N′,N′*-tetramethylethylenediamine was also added] was added. The mixture was allowed to warm to room temperature, stirred for a further 2 h and then diluted with petroleum ether (b.p. 30–60 °C, 100 ml). The mixture was filtered. The filtrate was collected and evaporation of the solvents gave a residue which was purified by column chromatography on silica gel (200–300 mesh) eluting with petroleum ether (b.p. 30–60 °C)/diethyl ether (2:1) to afford the following products (**6** or **9**).

(*E*)-2-[(2-Phenyl-1-trifluoromethyl)prop-1-enyl]furan (**6a**): Yield, 57%; b.p. 65–76 °C/0.3 Torr. Analysis: Calc. for $C_{14}H_{11}F_3O$ (252.2): C, 66.67; H, 4.40%. Found: C, 66.68; H, 4.30%. MS *m/z*: 252 (M^+); 233; 183; 155; 77; 43. IR(film) (cm^{-1}): 1650; 1600; 1490. ^1H NMR ($CDCl_3$/TMS) δ: 2.10 (q, 3H, J=2.1 Hz); 6.48 (br.s, 2H); 7.20–7.50 (m, 6H) ppm. ^{19}F NMR ($CDCl_3$/TFA)/δ: −21.2 (s, 3F) ppm.

(*E*)-2-[(2-Phenyl-1-trifluoromethyl)prop-1-enyl]-5-methylfuran (**6b**): Yield, 56%; b.p. 73–75 °C/0.3 Torr. Analysis: Calc. for $C_{15}H_{13}F_3O$ (266.3): C, 67.67; H, 4.92%. Found: C, 67.65; H, 4.85%. MS *m/z*: 266 (M^+); 247; 246; 183; 77; 43. IR(film) (cm^{-1}): 1650; 1600; 1550; 1490. ^1H NMR ($CDCl_3$/TMS) δ: 2.13 (q, 3H, J=2.1 Hz); 2.35 (s, 3H); 6.06 (d, 1H, J=3.3 Hz); 6.34 (d, 1H, J=3.3 Hz); 7.24–7.37 (m, 5H) ppm. ^{19}F NMR ($CDCl_3$/TFA)/δ: −21.2 (s, 3F) ppm.

(*E*)-2-[(2-Phenyl-1-trifluoromethyl)prop-1-enyl]-5-trimethylsilylfuran (**6c**): Yield, 51%; b.p. 76–78 °C/0.3 Torr. Analysis: Calc. for $C_{17}H_{19}F_3OSi$ (324.4): C, 62.94; H, 5.90%. Found: C, 63.06; H, 5.61%. MS *m/z*: 324 (M^+); 305; 255; 77; 73. IR(film) (cm^{-1}): 1640; 1600; 1580; 1490; 840. ^1H NMR ($CDCl_3$/TMS) δ: 0.30 (s, 9H): 2.13 (s, 3H); 6.45 (br.s, 1H); 6.63 (d, 1H, J=3.0 Hz); 7.30 (br.s, 5H) ppm. ^{19}F NMR ($CDCl_3$/TFA)/δ: −21.2 (s, 3F) ppm.

2-[(2-Methyl-1-pentafluoroethyl)prop-1-enyl]-5-methylfuran (**6d**): Yield, 55%; b.p. 35–37 °C/0.2 Torr. Analysis: Calc. for $C_{11}H_{11}F_5O$ (254.2): C, 51.98; H, 4.36%. Found: C, 51.94; H, 4.26%. MS *m/z*: 254 (M^+); 135, 43. IR(film) (cm^{-1}): 1655; 1605; 1555; 1490. ^1H NMR ($CDCl_3$/TMS) δ: 1.78 (br.s, 3H); 2.03 (br.s, 3H); 2.28 (s, 3H); 5.96 (d, 1H, J=3.1 Hz); 6.11 (d, 1H, J=3.1 Hz) ppm. ^{19}F NMR ($CDCl_3$/TFA)/δ: 6.3 (s, 3F); 30.2 (s, 2F) ppm.

2-[(2-Methyl-1-pentafluoroethyl)prop-1-enyl]-5-trimethylsilylfuran (**6e**): Yield, 50%; b.p. 56–58 °C/0.3 Torr. Analysis: Calc. for $C_{13}H_{17}F_5OSi$ (312.4): C, 49.99; H, 5.49%. Found: C, 50.21; H, 5.60%. MS *m/z*: 312 (M^+); 293, 201, 133, 73. IR(film (cm^{-1}): 1650; 1580; 1490; 840. ^1H NMR ($CDCl_3$/TMS) δ: 0.25 (s, 9H); 1.75 (br.s, 3H); 2.06 (br.s, 3H); 6.22 (d, 1H, J=3.2 Hz); 6.58 (d, 1H, J=3.2 Hz) ppm. ^{19}F NMR ($CDCl_3$/TFA)/δ: 7.0 (s, 3F); 30.7 (s, 2F) ppm.

2-[(2-Methyl-1-trifluoromethyl)prop-1-enyl]-5-trimethylsilylfuran (**6f**): Yield, 52%; b.p. 50–52 °C/0.3 Torr. Analysis: Calc. for $C_{12}H_{17}F_3OSi$ (262.4): C, 54.94; H, 6.53%. Found: C, 54.62; H, 6.52%. MS *m/z*: 262 (M^+); 243, 73. IR(film) (cm^{-1}): 1660; 1580; 1490; 840. ^1H NMR ($CDCl_3$/TMS) δ: 0.15 (s, 9H); 1.70 (q, 3H, J=2 Hz); 1.96 (q, 3H, J=2 Hz); 6.10 (d, 1H, J=3.0 Hz); 6.45 (d, 1H,

J=2.0 Hz) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −19.6 (s, 3F) ppm.

2-[(1-Cyclopentylidene-1-trifluoromethyl)methyl]furan (**6g**): Yield, 65%; b.p. 45–47 °C/0.2 Torr. Analysis: Calc. for $C_{11}H_{11}F_3O$ (216.2): C, 61.11; H, 5.13%. Found: C, 61.25; H, 5.11% MS m/z: 216 (M^+); 197, 175, 67. IR(film) (cm^{-1}): 1660; 1505. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.55–1.75 (m, 4H); 2.40–2.70 (m, 4H); 6.23 (br.s, 2H); 7.30 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −18.0 (s, 3F) ppm.

2-[(1-Cyclopentylidene-1-trifluoromethyl) methyl]-5-methylfuran (**6h**): Yield, 65%; b.p. 48–50 °C/0.2 Torr. Analysis: Calc. for $C_{12}H_{13}F_3O$ (230.2): C, 62.60; H, 5.69%. Found: C, 62.67; H, 5.83%. MS m/z: 230 (M^+), 189, 161, 43. IR(film) (cm^{-1}): 1660; 1600; 1550. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.62–1.79 (m, 4H); 2.30 (s, 3H); 2.53–2.68 (m, 4H); 5.99 (d, 1H, J=3.2 Hz); 6.20 (d, 1H, J=3.2 Hz) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −18.3 (s, 3F) ppm.

(*Z*)-2-[(2-Phenyl-1-trifluoromethyl) prop-1-enyl]-4-methylthiaozole (**9a**): Yield, 86%; b.p. 98 °C/0.3 Torr. Analysis: Calc. for $C_{14}H_{12}F_3NS$ (283.3): C, 59.35; H, 4.27; N, 4.94%. Found: C, 59.18; H, 4.03; N, 5.14%. MS m/z: 283 (M^+); 268; 262; 244; 214. IR(film) (cm^{-1}): 1645; 1600; 1520; 1490; 1320. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.06 (q, 3H, J=2 Hz); 2.50 (s, 3H); 6.96 (s, 1H); 7.30 (br.s, 5H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −21.3 (s, 3F) ppm.

(*Z*)-2-[(2-Phenyl-1-trifluoromethyl) hex-1-enyl]-4-methylthiazole [(*Z*)-**9b**]: Yield, 32%; b.p. 80 °C/0.3 Torr. Analysis: Calc. for $C_{12}H_{16}F_3NS$ (263.3): C, 54.74; H, 6.12; N, 5.32%. Found: C, 54.66; H, 6.12; N, 5.46%. MS m/z: 263 (M^+); 248; 244; 183; 71. IR(film) (cm^{-1}): 1650; 1600; 1520; 1320. ^{1}H NMR ($CDCl_3$/TMS) δ: 0.80 (t, 3H, J=7.3 Hz); 1.10–1.60 (m, 4H); 1.80–2.00 (m, 2H); 2.03 (q, 3H, J=2 Hz); 2.36 (s, 3H); 6.80 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −20.5 (s, 3F) ppm.

(*E*)-2-[(2-Phenyl-1-trifluoromethyl) hex-1-enyl]-4-methylthiazole [(*E*)-**9b**]: Yield, 30%; b.p. 80 °C/0.3 Torr. Analysis: Calc. for $C_{12}H_{16}F_3NS$ (263.3): C, 54.74; H, 6.12; N, 5.32%. Found: C, 54.57; H, 6.16; N, 5.36%. MS m/z: 264 (M^++1); 248; 244; 194; 71. IR(film) (cm^{-1}): 1650; 1600; 1520; 1320. ^{1}H NMR ($CDCl_3$/TMS) δ: 0.85 (t, 3H, J=7.3 Hz); 1.10–1.60 (m, 4H); 1.62 (q, 3H, J=2 Hz); 2.15–2.45 (m, 3H); 2.35 (s, 3H); 6.78 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −21.2 (s, 3F) ppm.

2-[(2-Methyl-1-trifluoromethyl)prop-1-enyl]-4-methylthiazole (**9c**): Yield, 71%; b.p. 66 °C/0.3 Torr. Analysis: Calc. for $C_9H_{10}F_3NS$ (221.2): C, 48.86; H, 4.56; N, 6.33%. Found: C, 48.36; H, 4.51; N, 6.09%. MS m/z: 221 (M^+); 202, 113, 71. IR(film) (cm^{-1}): 1655; 1600; 1520; 1315. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.77 (q, 3H, J=2.1 Hz); 2.10 (q, 3H, J=2.3 Hz); 2.48 (s, 3H); 6.98 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −20.6 (s, 3F) ppm.

2-[(2-Methyl-1-pentafluoroethyl)prop-1-enyl]-4-methylthiazole (**9d**): Yield, 50%; b.p. 70 °C/0.3 Torr. Analysis: Calc. for $C_{10}H_{10}F_5NS$ (271.3): C, 44.28; H, 3.72; N. 5.16%. Found: C, 44.22; H, 3.69; N, 5.30%. MS m/z: 271 (M^+); 252; 202; 182; 113; 71. IR(film) (cm^{-1}): 1650; 1600; 1530; 1450; 1380. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.65 (br.s, 3H); 2.03 (br.s, 3H); 2.35 (s, 3H); 6.82 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: 6.0 (s, 3F); 29.3 (s, 2F) ppm.

2-[(1-Cyclopentylidene-1-trifluoromethyl) methyl]-4-methylthiazole (**9e**): Yield, 68%; b.p. 80 °C/0.3 Torr. Analysis: Calc. for $C_{11}H_{12}F_3NS$ (247.3): C, 53.43; H, 4.89; N, 5.67%. Found: C, 53.07; H, 4.91; N, 5.65%. MS m/z: 247 (M^+); 227; 206; 199. IR(film) (cm^{-1}): 1655; 1600; 1525; 1330. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.45–1.75 (m, 4H); 2.33 (s, 3H); 2.40–2.70 (m, 4H); 6.72 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −18.2 (s, 3F) ppm.

2-[(1-Cyclopentylidene-1-pentafluoroethyl) methyl]-4-methylthiazole (**9f**): Yield, 53%; b.p. 82 °C/0.3 Torr. Analysis: Calc. for $C_{12}H_{12}F_5NS$ (297.3): C, 48.48; H, 4.07; N, 4.71%. Found: C, 48.48; H, 4.02; N, 4.81%. MS m/z: 297 (M^+); 278; 208; 71. IR(film) (cm^{-1}): 1650; 1600; 1520; 1330. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.50–1.80 (m, 4H); 2.38 (s, 3H); 2.40–2.75 (m, 4H); 6.82 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: 6.3 (s, 3F); 32.7 (s, 2F) ppm.

2-[(1-Cyclohexylidene-1-trifluoromethyl) methyl]-4-methylthiazole (**9g**): Yield, 6%; m.p. 37–38 °C. Analysis: Calc. for $C_{12}H_{14}F_3NS$ (261.3): C, 55.16; H, 5.40; N, 5.36%. Found: C, 55.10; H, 5.34; N, 5.36%. MS m/z: 261 (M^+); 241; 232; 220; 71. IR(film) (cm^{-1}): 1650; 1600; 1525; 1340. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.60–1.90 (m, 6H); 2.00–2.20 (m, 2H); 2.48 (s, 3H); 2.50–2.70 (m, 2H); 6.95 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$/TFA) / δ: −22.0 (s, 3F) ppm.

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