Preliminary Note

3-Trifluoromethylthiophens from hexafluoroacetone

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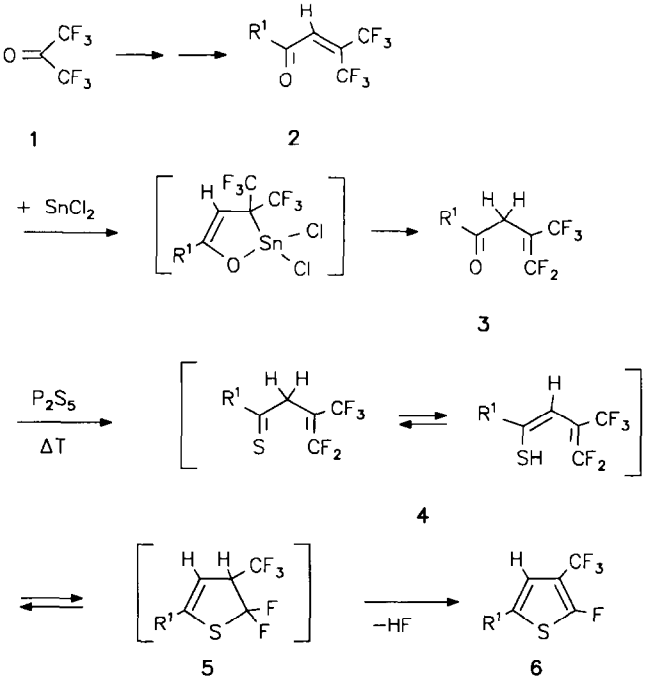
Abstract

A one-pot procedure for the synthesis of 2-fluoro-3-trifluoromethyl-substituted thiophens **6** from 1-aryl-4,4-difluoro-3-trifluoromethylbut-3-en-1-one (**3**) and phosphorus pentasulfide is described. The fluorine atom at C-2 of compounds **6** undergoes nucleophilic displacement reactions.

The development of synthetic methodology for the regioselective introduction of short-chain perfluoroalkyl groups into organic molecules is of current interest [1, 2]. From the biomedical viewpoint, fluoro substitution often confers unique properties on a molecule, e.g. in terms of increasing lipophilicity, which in turn changes *in vivo* absorption and transport rates. Hence, biological activity is often enhanced [3].

Although numerous synthetic routes to thiophens have been reported [4], only very few routes to fluorine- and/or perfluoroalkyl-substituted thiophens have been described [5]. Here we report on a versatile new route to 3-trifluoromethylthiophens starting from hexafluoroacetone (**1**).

α,β-Unsaturated ketones **2** can easily be prepared from hexafluoroacetone (**1**) via procedures reported in the literature [6]. Heterodienes **2** can be transformed into the β,γ-unsaturated ketones **3** by [4+1] cycloaddition of tin(II) chloride followed by thermally-induced fluoride elimination [7]. Treatment of **3** with phosphorus pentasulfide at 120–140 °C results in an oxygen/sulfur exchange reaction (**3**→**5**). The higher nucleophilicity of sulfur compared with that of oxygen facilitates an intramolecular 1,5-cyclization. Elimination of HF from **5** results in aromatization to give the 2-fluoro-3-trifluoromethylthiophens **6**.



R^1 = (a) phenyl, (b) 4-methoxyphenyl, (c) 4-chlorophenyl, (d) 4-fluorophenyl, (e) 2-fluorophenyl

Scheme 1.

Compounds **6** were characterized by ^1H, ^{13}C and ^{19}F NMR data as well as by mass spectrometry and elemental analyses.

General procedure for the preparation of compounds 6 — Compound **3** (10 mmol) and 2.22 g (10 mmol) phosphorus pentasulfide were heated for 2–6 h at 120–140 °C. After cooling to room temperature, 20 ml of hexane was added to the reaction mixture which was then stirred for an additional 2 h. The reaction mixture was filtered, concentrated under reduced pressure and purified via column chromatography (silica gel 0.2–0.063 mm; eluent, hexane).

Compound **6a**: Yield, 1.35 g, 55%, oil. Analysis: Calc. for $C_{11}H_6F_4S$: C, 53.66; H, 2.46%. Found: C, 53.52; H, 2.52%. ^{19}F NMR (Bruker AC 250, 235.3 MHz, $CDCl_3$) δ: −45.99 (dq, $J_{FH}=3$ Hz, $J_{FF}=12$ Hz, 1F, thiophen-*F*); 19.30 (d, $J_{FF}=12$ Hz, 3F, CF_3) ppm. ^1H NMR (Bruker AM 360, 360.1 MHz, $CDCl_3$) δ: 6.98 (d, $J_{HF}=3$ Hz, 1H, thiophen-*H*); 7.36 (m, 3H, phenyl-*H*); 7.44 (m, 2H, phenyl-*H*) ppm. ^{13}C NMR (Bruker 360, 90.6 MHz, $CDCl_3$) δ: 113.11 (dq, $J_{CF}=4$ Hz, $J_{CF}=36$ Hz, thiophen-*C3*); 116.40 (m, thiophen-*C4*); 120.94 (dq, $J_{CF}=3$ Hz, $J_{CF}=270$ Hz, CF_3); 125.52 (d, $J_{CF}=1$ Hz); 128.53, 129.16, 132.42 (phenyl-*C*); 132.65 (d, $J_{CF}=2$ Hz, thiophen-*C5*);

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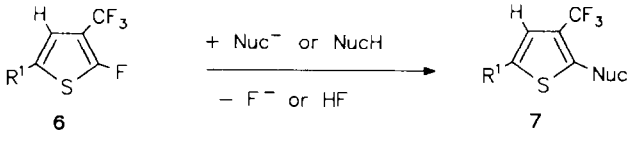
163.39 (dq, J_{CF} = 301 Hz, J_{CF} = 3 Hz, thiophen-*C2*) ppm. MS (*m/z*): 246 $[M]^+$; 227 $[M-F]^+$; 226 $[M-HF]^+$; 207 $[227-HF]^+$; 182 $[226-CS]^+$; 133 $[M-CF_3, -CS]^+$. IR (film) (cm^{-1}): 1600; 1520; 1490; 1450; 1410.

Because of the electron-withdrawing properties of the trifluoromethyl group, the fluorine atom at C-2 of compounds **6** is susceptible to nucleophilic displacement reactions with a broad range of nucleophiles [7]. Hence, the reaction sequence **1** → **3** → **6** → **7** offers a convenient method for the synthesis of 3-trifluoromethylthiophens with a variety of substitution patterns at C-2 and C-5. In particular, the possibility of introducing various side-chains with additional functional groups into ring position 2 in the final step of the reaction sequence (**6** → **7**), in order to enhance and/or modify biological activity [8], makes this strategy versatile and valuable from a preparative viewpoint.

A typical example of the nucleophilic substitution process involves the reaction of **6a** with sodium 2-propoxide. The alkoxide was generated *in situ* from 0.08 ml (1 mmol) 2-propanol and 0.02 g (1 mmol) sodium in 10 ml dioxane. Compound **6a** (0.25 g, 1 mmol) was added and the mixture stirred at room temperature for 1 h. The mixture was then washed with 10 ml water and extracted three times with 10 ml ether. The residue obtained on evaporation of the solvent was purified by column chromatography [eluent, hexane/trichloromethane (1:1)].

Compound **7a** ($R^1 = C_6H_5$, Nuc = $OCH(CH_3)_2$): Yield, 0.27 g, 93%, m.p. 57 °C. Analysis: Calc. for $C_{14}H_{13}F_3OS$: C, 58.73; H, 4.58%. Found: C, 58.81; H, 4.58%. ^{19}F NMR (Bruker AC 250, 235.3 MHz, $CDCl_3$) δ: 19.73 (s, 3F, CF_3) ppm. ^1H NMR (Bruker WP 200, 200.1 MHz, $CDCl_3$) δ: 1.43 (d, J_{HH} = 6 Hz, 6H, $CH(CH_3)_2$); 4.44 (sept., J_{HH} = 6 Hz, 1H, $OCH(CH_3)_2$); 7.05 (s, 1H, thiophen-*H*); 7.32 (m, 3H, phenyl-*H*); 7.47 (m, 2H, phenyl-*H*) ppm. ^{13}C NMR (Bruker AC 250, 50.3 MHz, $CDCl_3$) δ: 21.97 ($CH(CH_3)_2$); 80.59 ($OCH(CH_3)_2$); 113.79 (q, J_{CF} = 34 Hz, thiophen-*C3*); 117.95 (q, J_{CF} = 3 Hz, thiophen-*C4*); 122.13 (q, J_{CF} = 270 Hz, CF_3); 125.04, 127.49, 128.96 (phenyl-*C*); 130.51 (thiophen-*C5*); 133.52 (phenyl-*C*); 163.36 (q, J_{CF} = 3 Hz, thiophen-*C2*) ppm. MS (*m/z*): 286 $[M]^+$; 244 $[M-C_3H_6]^+$; 243 $[M-C_3H_7]^+$; 225 $[244-F]^+$; 224 $[243-F]^+$; 196 $[224-CO]^+$; 121 $[C_6H_5CS]^+$; 77 $[C_6H_5]^+$; 43 $[C_3H_7]^+$; 42 $[C_3H_6]^+$. IR (KBr) (cm^{-1}): 1590; 1525; 1500; 1460; 1420; 1400.



$Nuc^- = R^2O^-$, R^2S^-, CN^-, H^-, Ph^- $NucH = R^2_2NH$

Scheme 2.

The scope of the concept of transforming bis(trifluoromethyl)-substituted hetero-1,3-dienes into partially fluorinated five-membered heteroaromatic systems, and the synthetic potential of compounds **6**, will be described elsewhere.

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