Preparation and reaction of 3,3,3-trifluoropropiondithioacetals as trifluoromethyl-containing building blocks

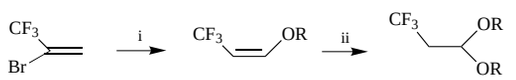
Hui-Ping Guan, Bing-Hao Luo, Quan-Fu Wang and Chang-Ming Hu *

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

The preparation and reaction of 3,3,3-trifluoropropiondithioacetals 5 as possible trifluoromethyl-containing synthons has been studied. The synthesis of alkyl 1-acetoxy-3,3,3-trifluoropropyl thioethers 6 from compounds 5 and the Lewis acid-mediated reactions of compounds 6 with enol silyl ethers are also described.

In recent years, direct introduction of the trifluoromethyl group into organic compounds has become a significant synthetic target,[1–4] since it avoids the many technical and economical difficulties often associated with selective fluorination or trifluoromethylation.[5] In this connection, although dithioacetals are valuable intermediates in organic synthesis, few fluorine-containing derivatives have been studied.

In a recent paper,[6] we reported a novel synthesis of alkyl 3,3,3-trifluoropropenyl ethers **2** and acetals **3** from the readily available 2-bromo-3,3,3-trifluoropropene[7] **1** (Scheme 1).



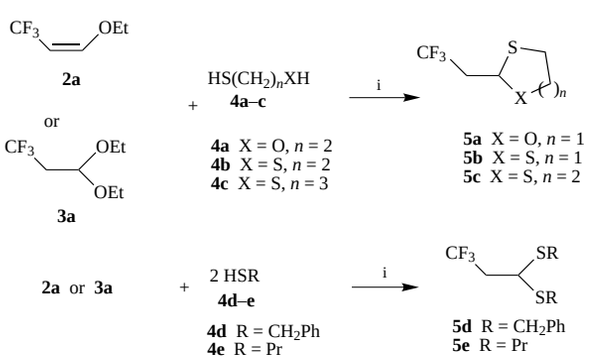
1 **2a** R = Et **3a** R = Et

Scheme 1 *Reagents:* i, ROH, KOH, cat. H_2O; ii, ROH, TsOH, CH_2Cl_2

Here, the synthesis of the corresponding trifluoromethylated thioacetal **5a** and dithioacetals **5b–e** from compounds **1**, **2** or **3** is reported. The synthesis of the trifluoromethylated α-acetoxy sulfides **6** from compounds **5** and the Lewis acid-mediated reactions of **6** with enol silyl ethers are also described.

Results and discussion

Treatment of 2-bromo-3,3,3-trifluoropropene **1** with 2-mercaptoethanol **4a** or ethane-1,2-dithiol **4b** under basic conditions furnished complex and inseparable products containing only a trace of 3,3,3-trifluoropropiondithioacetals. However, in the presence of Lewis acid at room temperature, compounds **2a** reacted with 2-mercaptoethanol **4a**, 1,2-ethanedithiols **4b**, propane-1,3-dithiols **4c**, toluene-α-thiol **4d** and 3-mercaptopropane **4e** to give the thioacetal **5a** and the dithioacetals **5b–e**, respectively in high yields (Scheme 2). Such products were obtained if the acetal **3a** was used instead of compound **2a**. The results are listed in Table 1.



2a

or

3a

4a X = O, *n* = 2
4b X = S, *n* = 2
4c X = S, *n* = 3

5a X = O, *n* = 1
5b X = S, *n* = 1
5c X = S, *n* = 2

2a or **3a** + 2 HSR **4d–e**

4d R = CH_2Ph
4e R = Pr

5d R = CH_2Ph
5e R = Pr

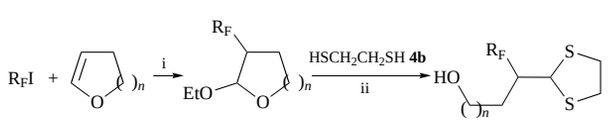
Scheme 2 *Reagents:* i, $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT 6 h

Table 1 Preparation of the fluoroalkylated thio- or dithio-acetals

Entry	Substrate	Reagent	Product	Yield (%)[a]
1	**2a**	**4a**	**5a**	89
2	**2a**	**4b**	**5b**	90
3	**2a**	**4c**	**5c**	91
4	**2a**	**4d**	**5d**	88
5	**2a**	**4e**	**5e**	85
6	**3a**	**4a**	**5a**	88
7	**3a**	**4b**	**5b**	90
8	**3a**	**4c**	**5c**	92
9	**3a**	**4d**	**5d**	89
10	**3a**	**4e**	**5e**	85
11	**3b**	**4a**	**5f**	90
12	**3c**	**4a**	**5g**	87

[a] Overall isolated yield based on **2** or **3**

α-Fluoroalkyl substituted cyclic acetals **3b–c**, readily prepared from fluoroalkyl iodides, also reacted successfully with α,ω-dithiols to give the corresponding cyclic dithioacetals **5f**,**g** in excellent yields (Scheme 3). Such reactions proceeded

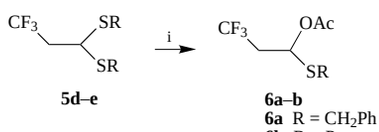


3b,**c** **5f**,**g**

Scheme 3 **3b**, **5f**: *n* = 2, $R_F = F(CF_2)_4$; **3c**, **5g**: *n* = 1, $R_F = Cl(CF_2)_4$ i, $Na_2S_2O_4$–$NaHCO_3$, EtOH, 50 °C; ii, $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT, 6 h

smoothly in many aprotic solvents such as CH_2Cl_2, THF and Et_2O. Lewis acids such as $BF_3{\cdot}EtO_2$, $TiCl_4$, $SnCl_4$ and strong protonic acid TsOH all facilitated the reaction.

Simple acetoxylated sulfides could be prepared from sulfoxides by a Pummerer reaction.[8] However, such a rearrangement is not regioselective in unsymmetrical sulfoxides.[9] It was reported that the reaction of mercuric acetate with thioacetals afforded an α-acetoxy sulfide instead of the normal hydrolysis product.[10] When compounds **5d**,**e** were treated with mercuric acetate in acetic acid at room temperature, alkyl 1-acetoxy-3,3,3-trifluoropropyl thioethers **6a**,**b** were obtained in 76 and 70% yields, respectively (Scheme 4).



5d–e **6a–b**
6a R = CH_2Ph
6b R = Pr

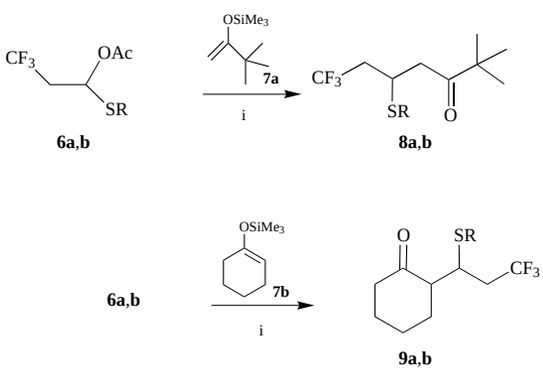
Scheme 4 *Reagents:* i, $(AcO)_2Hg$, AcOH, CH_2Cl_2, RT, 8 h

Table 2 Reaction of trifluoromethylated dithioacetals

Entry	Substrate	R	Reagent	Product	Yield (%)[a]
1	**5d**	$PhCH_2$	$(AcO)_2Hg$	**6a**	76
2	**5e**	Pr	$(AcO)_2Hg$	**6b**	80
3	**6a**	$PhCH_2$	**7a**	**8a**	86
4	**6b**	Pr	**7a**	**8b**	85
5	**6a**	$PhCH_2$	**7b**	**9a**	88
6	**6b**	Pr	**7b**	**9b**	82

[a] Overall isolated yield based on the corresponding starting material.

The reaction of dithioacetals with enol silyl ethers has been reported by Reetz,[11] Mukaiyama[12] and Kraus.[13] But to the best of our knowledge, the Lewis acid-mediated reactions of the fluorine-containing α-acetoxy sulfides have not been exploited yet. In the presence of $SnCl_4$, compounds **6a**,**b** reacted with 3,3-dimethylbut-1-en-2-yl trimethylsilyl ether **7a** and cyclohex-1-enyl trimethylsilyl ether **7b** to furnish the nucleophilic substitution products **8a**,**b** and **9a**,**b**, respectively, in high yield (Scheme 5). The results of the synthesis of compounds **6**, **8** and **9** from compounds **5** are listed in Table 2.



6a, **8a**, **9a**: R = CH_2Ph, **6b**, **8b**, **9b**: R = Pr,
Scheme 5 *Reagents:* i, $SnCl_2$, CH_2Cl_2, −78 °C, 1 h

In conclusion, the trifluoromethyl-containing thioacetal **5a** and the dithioacetals **5b**–**e** have been synthesized from simple derivatives of 2-bromo-3,3,3-trifluoropropene **1**. A study of carbon chain extension in compounds **5** has shown that such compounds may be used as versatile trifluoromethyl-containing synthons in organic synthesis.

Experimental

The ^1H NMR spectra were measured with $CDCl_3$ as the solvent and internal TMS as the standard on a FX-90Q spectrometer. The ^{19}F NMR were measured with external CF_3CO_2H as the standard and with upfield shifts positive using a Varian EM-360L spectrometer at 56.4 MHz. *J* Values given in Hz. The IR spectra were recorded pure as a film on a Shimadzu IR-440 spectrometer. The mass spectra were recorded on a HP5989A mass spectrometer.

General method for the preparation of compounds 5 from compounds 2 or 3

To a well stirred mixture of either compound **2** or **3** (5 mmol) and the mercaptans **4** (6 mmol for **4a**, **4b** and **4c**; 12 mmol for **4d** and **4e**) in anhydrous CH_2Cl_2 (10 ml) was added $BF_3{\cdot}Et_2O$ (5 mmol) dropwise. The mixture was stirred at room temperature for 6 h after which it was poured into the ice–water (50 ml) and extracted with diethyl ether (3 × 30 ml). The combined extracts were washed successively with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The resulting residue was purified by flash chromatography on silica gel using light petroleum (bp 60–90)–EtOAc (100:0–100:3) as eluent to give the pure compounds **5** in high yields.

2-(2,2,2-Trifluoroethyl)-1,3-oxothiolane 5a. ν_{max}/cm^{-1} 2900, 1400, 1385, 1250 and 1140; δ_H 5.30 (1H, t, *J* 5), 4.33–3.90 (2H, m), 3.06 (2H, m) and 2.63 (2H, dq, *J* 5, 11); δ_F −11.0 (3F, t, *J* 11); *m*/*z* 172 (M^+, 100), 155 (12.01) and 89 ($CSCH_2CH_2O$, 67.18) (Found: C, 34.65; H, 4.04; F, 33.12. Calc. for $C_5H_7F_3OS$: C, 34.88; H, 4.07; F, 33.14%).

2-(2,2,2-Trifluoroethyl)-1,3-dithiolane 5b. ν_{max}/cm^{-1} 2910, 1420, 1385, 1250 and 1140; δ_H 4.66 (1H, t, *J* 7), 3.30 (4H, s) and 2.70 (2H, dq, *J* 7, 10); δ_F −11.0 (3F, m); *m*/*z* 188 (M^+, 86.13), 160 ($M^+ - CH_2CH_2$, 3.18), 140 ($M^+ - CH_2CH_2 - HF$, 34.63), 127 ($M^+ - CH_2CH_2SH$, 15.07) and 105 [$^+C(SCH_2)_2$, 100] (Found: C, 29.66; H, 3.52; F, 29.93; S, 34.90. Calc. for $C_5H_7F_3S_2$: C, 31.91; H, 3.72; F, 30.3; S: 34.04%).

2-(2,2,2-Trifluoroethyl)-1,3-dithiane 5c. ν_{max}/cm^{-1} 2900, 1420, 1380, 1260 and 1140; δ_H 4.27 (1H, t, *J* 7), 2.93 (4H, t), 2.60 (2H, dq, *J* 7, 11) and 2.01 (2H, m); δ_F −14.5 (3F, t, *J* 11); *m*/*z* 202 (M^+, 100), 160 [$M^+ - (CH_2)_3$, 1.60], 155 ($M^+ - SCH_3$, 7.51), 148 (11.77) and 119 [$C(SCH_2)_2CH_2$, 67.18] (Found: C, 35.54; H, 4.59; F, 28.25. Calc. for $C_6H_9F_3S_2$: C, 35.64; H, 4.46; F, 28.20%).

1,1-Bisbenzylthio-3,3,3-trifluoropropane 5d. ν_{max}/cm^{-1} 3100 (ArH), 2910, 1600, 1500, 1460 (C=C), 1260, 1130 and 700; δ_H 7.26 (10H, s), 3.76 (4H, s), 3.72 (1H, t, *J* 7) and 2.46 (2H, dq, *J* 7, 11); δ_F −14.0 (3F, t, *J* 11); *m*/*z* 342 (M^+, 3.09), 259 ($M^+ - CF_3CH_2$, 1.08), 251 ($M^+ - CH_2Ph$, 8.08), 218 ($M^+ - PhCH_2SH$, 100) and 91 ($PhCH_2$, 85.59) (Found: C, 59.21; H, 4.66; F, 17.38; S, 19.16. Calc. for $C_{17}H_{17}F_3S_2$: C, 59.65; H, 4.97; F, 16.67; S, 18.71%).

1,1-Dipropylthio-3,3,3-trifluoropropane 5e. ν_{max}/cm^{-1} 2950, 1450, 1360, 1260 and 1140; δ_H 4.05 (1H, t, *J* 8), 2.80 (6H, m), 1.75 (4H, m) and 1.20 (6H, t); δ_F −13.5 (3F, t); *m*/*z* 246 (M^+, 16.53), 218 ($M^+ - CH_2CH_2$, 9.86), 189 (218 − CH_2CH_3, 9.28), 171 [$M^+ - (CH_2CH_3)_2 - CH_2 - H$, 87.76], 163 ($M^+ - CF_3CH_2$, 4.92), 129 (30.98) and 43 ($CH_2CH_2CH_3$, 100).

2-[1-(3′-Hydroxypropyl)-2,2,2,3,3,4,4,5,5-nonafluoropentyl]-1,3-dithiolane 5f. ν_{max}/cm^{-1} 3350, 2920, 1390, 1250 and 1160; δ_H 4.83 (1H, d, *J* 3), 3.66 (2H, m), 3.30 (4H, s), 2.53 (1H, s, OH) and 1.99 (5H, m); δ_F 3.60 (3F, s), 35.4 (2F, s), 43.5 (2F, s) and 47.8 (2F, s); *m*/*z* 397 ($M^+ + 1$, 2.31), 397 ($M^+ - OH$, 8.47), 319 (4.58), 303 [$M^+ + 1 - (SCH_2)_2$, 64.37], 283 (5.16) and 105 [$^+C(SCH_2)_2$, 100] (Found: C, 32.87; H, 3.20; F, 43.54; S, 16.77. Calc. for $C_{11}H_{13}F_9S_2O$: C, 33.33; H, 3.28; F, 43.18; S, 16.16%).

2-[5-Chloro-1-(2′-hydroxyethyl)-2,2,3,3,4,4,5,5-octafluoropentyl]-1,3-dithiolane 5g. δ_H 4.70 (1H, d, *J* 3.0), 4.0 (2H, m), 3.0 (5H, m), 2.20 (2H, m) and 1.80 (1H, m); δ_F −9.6 (2F, s), 37.0 (2F, s), 44.2 (2F, s) and 47.0 (2F, s); *m*/*z* 398 (M^+, 0.66), 381 ($M^+ - OH$, 1.77), 325 ($M^+ - OHCH_2CH_2$, 0.7), 337 ($M^+ - SCH_2CH_2$, 3.71), 305 [$M^+ - (SCH_2)_2$, 100] and 257 (38.21).

General method for the preparation of compounds 6a,b from compounds 5d–e

To a well stirred solution of the dithioacetals **5d**,**e** (6 mmol) in glacial acetic acid (20 ml) was added mercuric acetate (6.2 mmol). The mixture was stirred at room temperature for 8 h after which it was poured into saturated aqueous Na_2CO_3 and filtered. The filtrate was extracted with diethyl ether (3 × 30 ml). The combined extracts were washed successively with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The resulting residue was purified by flash chromatography on silica gel using light petroleum (bp 60–90)–AcOEt (10:1, v/v) as eluent to give the pure compounds **6**.

1-Benzylthio-3,3,3-trifluoropropyl acetate 6a. ν_{max}/cm^{-1} 3050, 2970, 1758, 1610, 1590, 1500, 1380, 1275, 1220 and 1150; δ_H 7.20 (5H, s), 6.15 (1H, m), 3.88 (2H, s), 2.55 (2H, m) and 1.93 (3H, s); δ_F −13.2 (t, *J* 16); *m*/*z* 277 ($M^+ - 1$, 1.01), 259 ($M^+ - 18$, 1.10), 219 (70.09), 218 ($M^+ - CH_3CO_2$, 75.06) and 91 ($PhCH_2$, 100).

1-Propylthio-3,3,3-trifluoropropyl acetate 6b. ν_{max}/cm^{-1} 2950, 2800, 1758, 1430, 1370, 1270, 1220 and 1140; δ_H 6.20 (1H, t, *J* 9), 2.70 (4H, m), 1.97 (3H, s), 1.55 (2H, m) and 0.95 (3H,

t, J 7); δ_F −13.2 (t, J 16); m/z 230 (M^+, 2.40), 170 ($M^+ - CH-CO_2H$, 31.42), 155 ($M^+ - SCH_2CH_2CH_3$, 2.30) and 43 (100) [Found: m/z (HRMS), 230.0564. Calc. for $C_8H_{13}F_3O_2S$: 230.0589].

General method for the synthesis of compounds 8 and 9 from compounds 6a,b

To a well stirred solution of **6** (5 mmol) and enol silyl ethers (6 mmol) in anhydrous methylene dichloride (20 ml) at −78 °C was added stannic chloride (5.5 mmol). After 1 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ to the mixture which was then extracted with CH_2Cl_2 (3 × 30 ml). Work-up followed by flash chromatography [light petroleum (bp 60–90)–AcOEt, 10:1, v/v] gave the pure products **8a**,**b** or **9a**,**b**.

2,2-Dimethyl-6-benzylthio-8,8,8-trifluorooctan-2-one 8a. ν_{max}/cm^{-1} 3010, 2980, 1720, 1610, 1590, 1500, 1480, 1430, 1370, 1270 and 1130; δ_H 7.23 (5H, s), 3.80 (2H, s), 2.70 (3H, m), 2.00 (2H, m) and 1.10 (9H, s); δ_F −14.3 (t, J 16); m/z 318 (M^+, 5.39), 319 (2.89), 261 [$M^+ - (CH_3)_3C$, 0.77], 227 ($M^+ - PhCH_2$, 3.22), 185 (25.79), 171 (25.05), 123 (44.35) and 91 ($PhCH_2$, 100) [Found: m/z (HRMS), 318.1233. Calc. for $C_{16}H_{21}F_3OS$: 318.1266].

2,2-Dimethyl-6-propylthio-3,3,3-trifluorooctan-2-one 8b. ν_{max}/cm^{-1} 2980, 1720, 1485, 1380, 1270 and 1140; δ_H 2.88 (2H, m), 2.63 (3H, m), 1.83 (2H, m), 1.45 (2H, m), 1.25 (9H, s) and 1.08 (3H, t, J 6); δ_F −14.1 (t, J 16); m/z 270 (M^+, 39.55), 271 (52.11), 253 ($M^+ - 17$, 2.66), 195 ($M^+ - CH_3CH_2CH_2S$, 10.80), 185 [$M^+ - (CH_3)_3C$ CO, 72.60], 171 [$M^+ - (CH_3)_3C$ $COCH_2$, 76.37] and 57 (100); [Found: m/z (HRMS), 270.1267. Calc. for $C_{12}H_{21}F_3OS$: 270.1266].

2-(1-Benzylthio-3,3,3-trifluoropropyl)cyclohexanone 9a. ν_{max}/cm^{-1} 3010, 2950, 2900, 1720, 1610, 1500, 1460, 1270 and 1140; δ_H 7.20 (5H, s), 3.80 (2H, s), 2.12–2.60 (6H, m) and 1.40–2.10 (6H, m); δ_F −14.0 (t, J 16); m/z 316 (M^+, 6.26), 317 (7.79), 298 ($M^+ - 18$, 2.94), 225 ($M^+ - PhCH_2$, 16.18), 123 ($PhCH_2S$, 62.68) and 91 ($PhCH_2$, 100) [Found: m/z (HRMS), 316.1156. Calc. for $C_{16}H_{19}F_3OS$: 316.1110].

2-(1-Propylthio-3,3,3-trifluoropropyl)cyclohexanone 9b. ν_{max}/cm^{-1} 2980, 2800, 1725, 1460, 1385, 1270 and 1150; δ_H 2.60 (5H, m), 2.05 (3H, m), 1.65 (8H, m) and 0.97 (3H, t, J 7); δ_F −13.3 (t, J 16); m/z 268 (M^+, 14.77), 250 ($M^+ - 18$, 7.12), 225 ($M^+ - CH_3CH_2CH_2$, 12.03), 193 ($M^+ - CH_3CH_2CH_2S$, 23.26), 171 ($M^+ - C_6H_9O$, 42.33), 165 (52.72), 97 (C_6H_9O, 24.32), 91 (68.87) and 43 (100); [Found: m/z (HRMS), 268.1120. Calc. for $C_{12}H_{19}F_3OS$: 268.1110].

Acknowledgements

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