Fluorinated Ketene Dithioacetals; 1. Preparation and Application to the Synthesis of α-Trifluoromethylthiocarboxylic *S*-Esters and Aldehyde Derivatives

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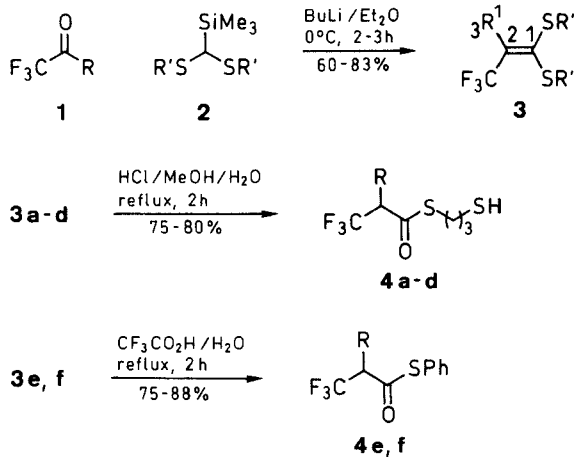
α-Trifluoromethylketene dithioacetals **3** were synthesized by Peterson reaction from trifluoromethyl ketones **1** and trimethylsilyl dithioacetals **2**. Acid hydrolysis and reduction yielded α-trifluoromethylthiocarboxylic *S*-esters **4** and α-trifluoromethyl dithioacetals **5**, respectively. Transacetalisation of the latter with ethanol gave the corresponding diethyl acetal. New procedures were developed to effect reduction and transacetalisation.

Ketene dithioacetals are versatile compounds in organic synthesis, because they have both ketene character and umpolung reactivity.[1] Owing to the growing interest in fluorinated intermediates for the synthesis of fluorinated bioactive molecules, we decided to undertake the study of ketene derivatives as precursors of various fluorinated acid or keto derivatives. At the very beginning of this study, only difluoroketene dithioacetals were known in the literature.[2] A recent paper dealt with 2-trifluoroethylidenedithiane.[3] We report here the synthesis of trifluoromethylketene dithioacetals **3** from trifluoromethyl ketones **1** and their use in the synthesis of α-trifluoromethylthiocarboxylic *S*-esters **4** and α-trifluoromethyl aldehyde equivalents **5** and **6**.

We adopted as a general methodology the Peterson reaction between trifluomethylketones **1** and bis(alkylthio or arylthio)(lithio)(trimethylsilyl) methanes (from **2**) (Scheme 1). Starting ketones are either commercially available or were prepared by Grignard condensation with ethyl trifluoroacetate.[4] Table 1 summarizes results obtained in the synthesis of 2-(α-trifluoromethylalkylidene)-1,3-dithianes and bis(phenylthio)methanes, which illustrate the generality and efficiency of the method. An exception has to be mentioned: no product could be isolated from trifluoroacetone, although the reaction worked well with other enolizable ketones, and trifluoroacetaldehyde gave a moderate yield (35%). The method recently reported for these two compounds,[3] using ethyl trifluoroacetate as starting material is more suitable. Otherwise, the straightforward strategy reported here is advantageous.



1–4	R	R′... R′
a	Et	$(CH_2)_3$
b	C_6H_{13}	$(CH_2)_3$
c	*c*-C_6H_{11}	$(CH_2)_3$
d	Ph	$(CH_2)_3$
e	*c*-C_6H_{11}	Ph, Ph
f	Ph	Ph, Ph

Scheme 1

The optimal hydrolysis conditions of **3** were different depending on the substituents at sulfur. The best conditions were found to be methanol/hydrochloric acid for dithiane derivatives and trifluoroacetic acid for bis(phenylthio) derivatives. The reaction yielded the corresponding thiolester **4** (Scheme 1, Table 2). These α-trifluoromethylthiocarboxylic *S*-esters proved to be very stable. Further solvolysis were not observed, even after several days of refluxing in strong acidic medium. Moreover, conditions known to favour the formation of carboxylic acids of esters with non-fluorinated analogs did not work

Table 1. Trifluoromethylketene Dithioacetals **3** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	MS (70 eV) *m/z* (%)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)		^{13}C NMR ($CDCl_3$/TMS) δ, *J* (Hz)				^{19}F NMR δ, ($CDCl_3$/$CFCl_3$)
					R'... R'	CH_n-3	C-1	C-2	C-3	CF_3	
3a	60	oil	$C_8H_{11}F_3S_2$ (228.3)	228 (M^+, 35), 213 (100)	2.13 (quin, *J* = 7), 2.95, 3.00 (t, *J* = 7)	2.45 (q, *J* = 7)	142.0	125.7 (q, *J* = 29)	23.8	124.0 (q, *J* = 244)	−58.7
3b	83	oil	$C_{12}H_{19}F_3S_2$ (284.4)	284 (M^+, 18), 213 (100)	2.12 (quin, *J* = 7), 2.95, 3.01 (t, *J* = 7)	2.39 (t, *J* = 7)	142.4	124.6 (q, *J* = 28)	31.5	124.0 (q, *J* = 275)	−58.7
3c	85	oil	$C_{12}H_{17}F_3S_2$ (282.4)	282 (M^+, 100), 235 (68)	2.10 (quin, *J* = 7), 2.94, 3.01 (t, *J* = 7)	2.90 (m)	142.5	125.6 (q, *J* = 29)	42.8	124.5 (q, *J* = 277)	−54.6
3d	65	81	$C_{12}H_{11}F_3S_2$ (276.3)	276 (M^+, 100), 201 (80)	2.06 (quin, *J* = 7), 2.86, 3.00 (t, *J* = 7)	–	147.8	124.2 (q, *J* = 28)	134.7	123.0 (q, *J* = 275)	−56.6
3e	76	44	$C_{21}H_{21}F_3S_2$ (394.5)	394 (M^+, 70) 55 (100)	7.0–7.25 (m)	3.45 (m)	140.1	141.5 (q, *J* = 27)	45.2	126.6 (q, *J* = 279)	−54.1
3f	76	91	$C_{21}H_{15}F_3S_2$ (388.5)	388 (M^+, 30), 239 (100)	6.9–7.4 (m)		145.2	134.6 (q, *J* = 30.5)		122.6 (q, *J* = 275)	−55.1

[a] Yield of pure, isolated product.

[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.3.

Table 2. α-Trifluoromethyl Thiolesters **4** from Hydrolysis of Ketene Dithioacetals **3**

Product	Method[a]	Yield[b,c] (%)	Molecular Formula[d]	MS (70 eV) (*m/z*, %)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS), δ			^{19}F NMR δ, ($CDCl_3$/$CFCl_3$)
						C-1	C-2	CF_3	
4a	A	76	$C_8H_{13}F_3OS_2$ (246.3)	247 (M^+ + 1, 20), 107 (100)	1.02 (t, 3H, *J* = 7), 1.42 (t, 1H, *J* = 7, SH), 1.78–2.08 (m, 4H), 2.60 (m, 2H), 3.10 (t, 2H, *J* = 7), 3.20 (m, CF_3CH)	193.3	58.6 (q, *J* = 26)	124.1 (q, *J* = 281)	−68.0 (d, *J* = 8)
4b	A	80	$C_{12}H_{21}F_3OS_2$ (302.4)	303 (M^+ + 1, 15), 107 (100)	0.89 (t, 3H, *J* = 7), 1.22–1.44 (m, 9H), 1.82 (m, 1H, SH), 1.85–2.00 (m, 3H), 3.09 (t, 2H, *J* = 7), 3.26 (m, 1H, CF_3CH)	193.5	57.3 (q, *J* = 26)	124.2 (q, *J* = 281)	−68.1 (d, *J* = 8)
4c	A	75	$C_{12}H_{19}F_3OS_2$ (300.4)	301 (M^+ + 1, 20), 83 (100)	1.00–1.33 (m, 5H), 1.41 (t, 5H, *J* = 9), 1.60–1.81 (m, 5H), 1.83–1.95 (m, 2H), 1.96–2.11 (m, 1H), 2.60 (q, 2H, *J* = 9), 3.03–3.17 (m, 3H)	193.4	62.7 (q, *J* = 25)	124.2 (q, *J* = 281)	−63.5 (d, *J* = 9)
4d	A	81	$C_{12}H_{13}F_3OS_2$ (294.4)	295 (M^+ + 1, 30), 107 (100)	1.36 (t, 1H, *J* = 7, SH), 1.86 (quin, 2H, *J* = 7), 2.52 (q, 2H, *J* = 7), 3.63 (t, 2H, *J* = 7), 4.48 (q, 1H, *J* = 9, CF_3CH)	191.4	62.2 (q, *J* = 28)	123.3 (q, *J* = 282)	−66.9 (d, *J* = 9)
4e	B	87	$C_{15}H_{17}F_3OS$ (302.4)	303 (M^+ + 1, 100), 193 (75)	1.10–2.20 (m, 11H), 3.20 (quin, 1H, *J* = 9, CF_3CH), 7.40–7.47 (m, 5H)	191.8	63.3 (q, *J* = 25)	124.3 (q, *J* = 271)	−63.4 (d, *J* = 9)
4f	B	88	$C_{15}H_{11}F_3OS$ (296.3)		4.56 (q, 1H, *J* = 9, CF_3CH), 7.33–7.50 (m, 10H)	189.9	61.7 (q, *J* = 28)	123.3 (q, *J* = 281)	−66.9 (d, *J* = 9)

[a] Method A: HCl/MeOH/H_2O; Method B: CF_3CO_2H/H_2O.

[b] Pure isolated compounds.

[c] All products are obtained as oils, except **4e** (mp 69 °C) and **4f** (mp 73 °C)

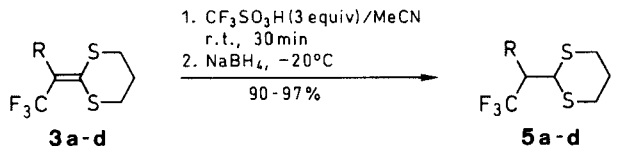
[d] Satisfactory microanalyses obtained: C ±0.3, H ±0.3.

with compounds **4**. For example, no reaction took place when **4c** was treated with mercuric acetate or mercuric trifluoroacetate and ethanol, whereas reduction to disulfide was observed with cupric trifluoroacetate.[5]

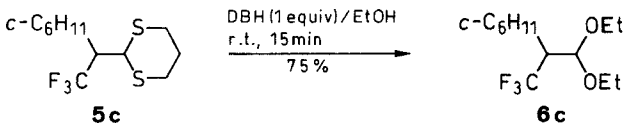
The reduction of ketene dithioacetals was usually performed by an ionic hydrogenation procedure, using trifluoroacetic acid and triethylsilane.[6] This method, very efficient with non-fluorinated analogs, gave poor yields with our trifluoromethyl derivatives. For example, treatment of compound **3c** according to these conditions led to the corresponding dithioacetal **5c** in only 16% yield, confirming previously reported results.[3]

We assumed that the electron-withdrawing effect of CF_3 group was responsible for the inefficiency of this reaction by lowering the basicity of the substrate, and we have found that using trifluoromethanesulfonic (triflic) acid as a "super" proton source, quantitative reduction took place. Furthermore, cheap and convenient sodium borohydride is now effective as hydride donor. Thus, treatment of ketene dithioacetals **3a–e** with triflic acid in acetonitrile, then with excess of sodium borohydride gave dithioacetals **5a–d** in high yields (Scheme 2, Table 3). Only dithianes derivatives are suitable, if aldehyde equivalents are the desired products, because reduction of **3e** gave poorer yield.

Although the classical mercury(II) chloride/mercuric oxide treatment[7] worked well to effect the transacetalisation (64% of the diethyl acetal from **5c**), we tried various



Scheme 2



Scheme 3

methods to avoid or limit the use of mercuric salts. Some reported procedures were completely inefficient, e.g. mercuric oxide/tetrafluoroboric acid/water in dichloromethane,[8] Amberlyst 15/acetone/formaldehyde/water.[9] Others led to complete conversion of the starting dithioacetal, but we could not isolate any product, probably because of the acidic character of the medium [trifluoroacetic acid/*m*-chloroperbenzoic acid,[10] hydrogen peroxide/methanol/hydrochloric acid,[11] [bis(trifluoroacetoxy)iodo]benzene/methanol/water,[12] chloramine T trihydrate/methanol/water,[13] *N*-bromosuccinimide/acetonitrile/water,[14] and methyl iodide/methanol.[15] Only 15% yield of the corresponding dimethyl acetal could be isolated from reaction of **5c** with chloramine T trihydrate in methanol without adding water to the medium. Finally, we obtained excellent results by using 1,3-dibromo-5,5-dimethylhydantoin (DBH). The use of this cheap brominating reagent for the transformation of dithioketal functions into difluoromethylene groups[16] and for α-fluorination of sulfide[17] prompted us to explore its behavior in solvolytic conditions. Indeed, we have found conditions to effect the S/O-transacetalization in high yields, as exemplified in Scheme 3. The procedure is simple and convenient and undoubtedly DBH is a promising reagent for such reactions.

In summary, we have reported a rather general and straightforward methodology for the synthesis of α-trifluoromethylketene dithioacetals and have illustrated the usefulness of these intermediates in giving access to trifluoromethyl derivatives. New methodologies were developed for highly efficient reduction to the corresponding dithioacetal and their further transacetalisation to diethyl acetals. Other kinds of fluorinated ketene dithioacetals and applications are under investigation and will be reported in a forthcoming paper.

^1H and ^{13}C spectra were recorded on a Bruker AC 300 spectrometer with $CDCl_3$ and TMS as solvent and reference, respectively. ^{19}F NMR spectra were recorded on a Brucker AC 250 or AM 400 spectrometer with $CDCl_3$ and $CFCl_3$ as solvent and reference respectively. IR spectra were recorded on a Philips SP3-300 spectrophotometer with $CHCl_3$ as solvent. All reactions with organometallic reagents were carried out under Argon, using syringe-cap techniques. Et_2O was distilled over benzophenone sodium. GC analysis were performed on a HP 5890 II chromatograph equipped with FID and a 25 m methylsilicon chemically bonded capillary column (HP ultra 1). Analytical TLC were performed on silica gel Merck 5554. Product separation was performed on silicagel 60, Merck, 40–63 μm.

Starting trifluoromethyl ketones were prepared according to a reported procedure[4] by condensation of a Grignard reagent with

Table 3. α-Trifluoromethyl Dithioacetals **5** from Reduction of Ketene Dithioacetals **3**

Product	Yield[a,b] (%)	Molecular[c] Formula	MS (70 eV) (*m/z*, %)	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS), δ			^{19}F NMR δ, ($CDCl_3$/$CFCl_3$)
					C-1	C-2	CF_3	
5a	92	$C_8H_{13}F_3S_2$ (230.3)	230 (M^+, 37), 119 (100)	1.11 (t, 3H, *J* = 8), 1.72–2.18 (m, 4H), 2.37 (m, 1H, CF_3CH), 2.80–3.10 (m, 4H), 4.48 (d, 1H, *J* = 2.8, CHS_2)	47.6	50.2 (q, *J* = 25)	126.8 (q, *J* = 282)	−66.7 (d, *J* = 8)
5b	90	$C_{12}H_{21}F_3S_2$ (286.4)	286 (M^+, 10), 119 (100)	0.90 (t, 3H, *J* = 7), 1.23–1.40 (m, 6H), 1.49 (m, 2H), 1.66–2.17 (m, 4H), 2.43 (m, 1H, CF_3CH), 2.80–3.08 (m, 4H), 4.49 (d, 1H, *J* = 2.3, CHS_2)	47.9	48.3 (q, *J* = 26)	126.8 (q, *J* = 282)	−67.0 (d, *J* = 8)
5c	97	$C_{12}H_{19}F_3S_2$ (284.4)	284 (M^+, 20), 119 (100)	1.08–2.20 (m, 13H), 2.10 (m, 1H, CF_3CH), 2.80–3.09 (m, 4H), 4.47 (d, 1H, *J* = 2.8, CHS_2)	47.7	53.9 (q, *J* = 25)	130.6 (q, *J* = 284)	−62.0 (d, *J* = 10)
5d	94	$C_{12}H_{13}F_3S_2$ (278.4)	278 (M^+, 32), 121 (100)	1.85 (m, 2H), 2.70–3.00 (m, 4H), 3.67 (dq, 1H, *J* = 9, 7, CF_3CH), 4.62 (d, 1H, *J* = 7, CHS_2), 7.30–7.45 (m, 5H)	46.9	54.8 (q, *J* = 27)	125.5 (q, *J* = 281)	−64.4 (d, *J* = 9)
5e	25	$C_{21}H_{23}F_3S_2$ (396.5)	396 (M^+, 2), 83 (100)	1.10–2.20 (m, 11H), 2.51 (m, 1H, CF_3CH), 4.71 (d, 1H, *J* = 2.3, CHS_2), 7.23–7.50 (m, 10H)	59.2	53.1 (q, *J* = 25)	127.0 (q, *J* = 284)	−62.3 (d, *J* = 8)

[a] Pure isolated compound.
[b] All products are obtained as oils, except for **5d** (mp 50°C).
[c] Satisfactory microanalyses obtained: C ±0.3, H ±0.3.

ethyl trifluoroacetate, except for commercial 2,2,2-trifluoroacetophenone and trifluoroacetaldehyde hydrate. Petroleum ether used refers to bp 40–60 °C.

Trifluoromethylketene Dithioacetals 3; General Procedure:
A solution of the trimethylsilyl dithioacetal **2** (0.01 mol) in Et_2O (30 mL) was cooled to 0 °C. A 1.6 M hexane solution of BuLi (0.01 mol) was added dropwise and the mixture was kept at 0 °C for 45 min. Then a solution of the appropriate trifluoromethyl ketone **1** (0.01 mol) in Et_2O (10 mL) was added dropwise. The mixture was stirred at 0 °C for 2–3 h and was neutralized with sat. NH_4Cl (15 mL). The organic layer was decanted and dried ($MgSO_4$). Et_2O was evaporated under vacuum and the crude product was purified by column chromatography on silica gel [eluent: petroleum ether/CH_2Cl_2, 80:20) (Table 1).

α-Trifluoromethylthiocarboxylic *S*-Esters 4; General Procedure:
Method A, *from dithiane derivatives:* To a solution of the ketene dithioacetal **3** (1 mmol) in MeOH (10 mL) was added conc. HCl (1 mL) and water (10 equiv). The mixture was warmed to reflux for 2 h, diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was dried ($MgSO_4$), the solvent evaporated under vacuum and the thio ester was purified by column chromatography on silica gel (eluent: petroleum ether/CH_2Cl_2, 85:15) (Table 2).

Method B, *from bis(phenylthio) derivatives:* The same procedure as above, was applied, except that CF_3CO_2H (5 mL) was used instead of methanolic HCl (Table 2).

α-Trifluoromethyl Dithioacetals 5; General Procedure:
To a solution of the ketene dithioacetal **3** (5 mmol) in anhydrous MeCN (20 mL) was added dropwise CF_3SO_3H (15 mmol). The formation of the protonated species was accompanied by an orange coloration. After stirring 30 min at r.t., the mixture was cooled to −20 °C and $NaBH_4$ (50 mmol) was added. At the same time the reaction mixture was discolored in a highly exothermic reaction. Water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was decanted and dried ($MgSO_4$). The product was purified by column chromatography over silica gel (eluent: petroleum ether/CH_2Cl_2, 85:15) (Table 3).

2-Cyclohexyl-3,3,3-trifluoropropionaldehyde Diethyl Acetal (6c):
Compound **5c** (0.5 g, 1.7 mmol) was dissolved in EtOH (5 mL). DBH (0.5 g, 1.7 mmol) was added at r.t. After 15 min, a GC control with dodecane as internal standard indicated a quantitative conversion of the starting material into **6c**. Saturated aqueous $NaHCO_3$ (5 mL) and Et_2O (10 mL) were added. The organic layer was decanted and dried (Na_2SO_4). After removal of the solvent, a rapid filtration over silica gel (petroleum ether/CH_2Cl_2, 75:25) gave the pure diethyl acetal **6c**; yield: 0.345 g (75%).

$C_{13}H_{23}F_3O_2$	calc.	C 58.19	H 8.64
(268.3)	found	57.92	8.93

^1H NMR ($CDCl_3$/TMS): δ = 1.21 and 1.22 (2 t, 3 H each, J = 7 Hz), 1.29–1.78 (m, 10 H), 2.20–2.35 (m, 1 H), 3.52 (m, 2 H), 3.68 (m, 2 H), 4.68 (d, 1 H, J = 7 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 51.7 (q, J = 22 Hz, $\underline{C}HCF_3$), 100.6 [$\underline{C}(OEt)_2$], 127.0 (q, J = 283 Hz, CF_3).

^{19}F NMR ($CDCl_3$/$CFCl_3$): δ = −62.5 (d, J = 11 Hz).

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