A Facile Synthesis of 1-Chloro-2,2,2-trifluoroethyl Sulfides

Yuriy Pustovit,*[a] Anatoliy Alexeenko,[a] Sergii Trofymchuk,[a] Oleg Lukin,*[b,c] Andrey A. Tolmachev[b,c]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmans'ka St. 5, 02094 Kiev, Ukraine

[b] National Taras Shevchenko University, ChemBioCenter, Volodymyrska St. 62, 01033 Kiev, Ukraine

[c] Enamine Ltd., A. Matrosova St. 23, 01103 Kiev, Ukraine
Fax +380(44)5373253; E-mail: oleg.lukin@mail.univ.kiev.ua

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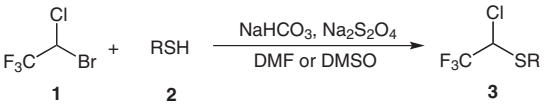
Abstract: A facile synthesis of structurally diverse 1-chloro-2,2,2-trifluoroethyl sulfides from readily available 1-bromo-1-chloro-2,2,2-trifluoroethane (Halothane®) and various aliphatic and aromatic thiols in the presence of sodium dithionite/sodium bicarbonate is described. The synthetic utility of the prepared sulfides is illustrated by the synthesis of biologically potent heterocycles and by their electrophilic reactions with thiophene.

Key words: thiols, radical reactions, alkylations, fluorinated compounds, sulfides

Compounds bearing fluoroalkyl groups exhibit a broad spectrum of biological activity.[1] In this context the development of reliable methods for the preparation of the fluoroalkyl derivatives is of great importance in drug discovery and agrochemistry. Trifluoroethylation is one of the most useful reactions leading to such biologically active species. Monochlorinated fluoroethyl sulfides are especially useful building blocks for fluoroalkylation[2] and the preparation of fluorinated olefins[3] and heterocycles. Monochlorinated trifluoroethyl sulfides are usually prepared by chlorination of the corresponding trifluoroethylated precursors with chlorine,[4] sulfuryl chloride,[5] and phosphorus pentachloride.[6] The 1-chlorotrifluoroethyl group can also be introduced directly by the reaction of aromatic thiols with 1-bromo-1-chloro-2,2,2-trifluoroethane (Halothane®) in the presence of sodium hydride.[7] However, the use of these aggressive reagents limits the available methods for the preparation of 1-chloro-2,2,2-trifluoroethyl sulfides to the preparation of nonfunctionalized compounds only, whereas for biomedical purposes methods for preparing diversely functionalized analogues of organofluorine compounds are highly desirable. There are reports on a mild perfluoroalkylation of aliphatic disulfides and aliphatic thiols in the presence of sodium hydroxymethanesulfinate resulting in the formation of the corresponding perfluoroalkyl sulfides in low yield.[8,9] However, no sulfides with functional groups were obtained by this method. In this connection the use of alternative reagents and the development of new synthetic routes to trifluoroethyl sulfides are necessary. In this contribution we report an easy and efficient method for the preparation of diversely functionalized 1-chloro-2,2,2-trifluoroethyl sulfides.

The reaction of Halothane® (**1**) with thiols **2** giving rise to the corresponding sulfides **3** is outlined in Scheme 1. Despite the apparent simplicity of the reaction, the proper selection of conditions tolerating a variety of functional groups on the thiol component turned out to be problematic. In the course of our research it was found that a combination of sodium dithionite and sodium bicarbonate in *N*,*N*-dimethylformamide or dimethyl sulfoxide promotes the alkylation of thiols under very mild conditions. The reaction proceeds at 40–45 °C, yielding 1-chloro-2,2,2-trifluoroethyl sulfides with hydroxy, amino, amide, and ester functional groups in 32–80% yield. Notably, similar conditions were used for a different purpose in the so-called sulfinatodehalogenation[10] reactions.



Scheme 1 The synthetic route developed for the preparation of functionalized 1-chloro-2,2,2-trifluoroethyl sulfides

Although S_N2 nucleophilic substitution of the bromide with a thiolate cannot be fully excluded in our case, most probably the reaction proceeds by a radical mechanism initiated by the sulfoxylate radical anion generated from the dithionite anion. The detection of byproducts including 1,1,1-trifluo-2-chlororoethane, sulfinate salt, and disulfides and a substantial reduction of the fluoroalkylation product yields, e.g., from 63% to about 3% for 2-(1-chloro-2,2,2-trifluoroethyl)ethanol in the presence of *p*-dinitrobenzene as a radical trap are supportive of the radical mechanism.

Although the mechanism of the transformation is not fully proven, the method provides the desired sulfides **3** in good to high yields with usually no need for chromatographic purification of the products. As can be discerned from Table 1, the major limitation of the method is its sensitivity to the steric load around the sulfur atom of the thiol, which can lead to a decreased or no yield of the sulfide, resulting in the formation of the corresponding disulfides. For example, aliphatic thiols with comparable steric loads around their sulfur atoms produce the corresponding sulfides under identical conditions in similar yields (42–65%) (entries 1–6). The only exception is the reaction

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with 2-furylmethanethiol yielding only 34% of the desired sulfide, due to the partial polymerization of the reagent under the reaction conditions (entry 7). Reaction with *tert*-butyl thiol gave rise to the disulfide as the only product (entry 22). No traces of the desired sulfide were detected by ^{19}F NMR in the latter case. Reactions of the aromatic thiols revealed a similar trend (entries 8–11); methyl-2-sulfanylbenzoate and 2-aminobenzenethiol resulted in reduced yields (44% and 38%, respectively; entries 10 and 11, respectively) compared with that of thiophenol (51%) (entry 8). In the case of the heteroaromatic thiols (entries 12–21), the steric load at the sulfur atom is relatively low, and the differences in the yields of the sulfides appear to result from electronic factors. Generally, the heteroaromatic units that can be easily oxidized resulted in lower yields (entries 12–14, 17, 18).

Table 1 Synthesis of Functionalized 1-Chloro-2,2,2-trifluoroethyl Sulfides **3**

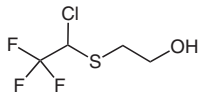
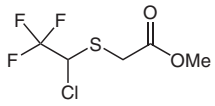
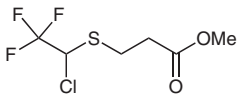
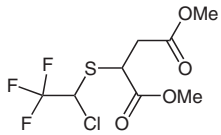
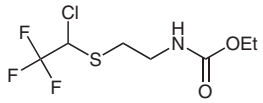
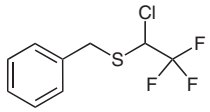
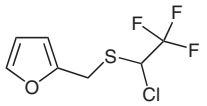
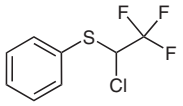
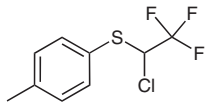
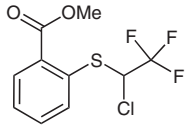
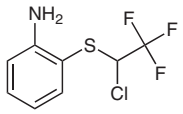
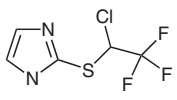
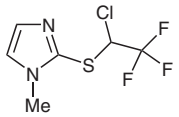
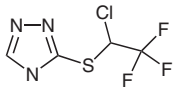
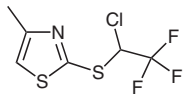
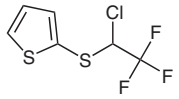
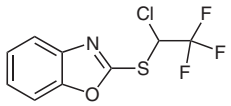
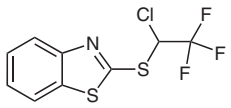
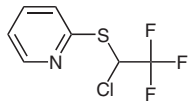
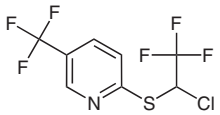
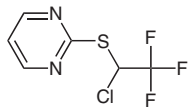
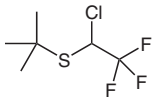
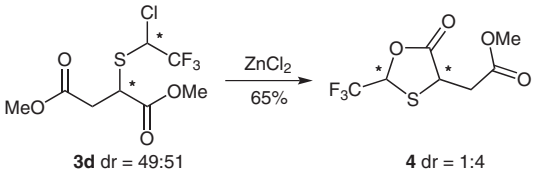
Entry	Product	**3**	Solvent	Yield (%)	Bp (°C)/pressure (Torr)
1		**3a**	DMF	63	105–108/20
2		**3b**	DMSO	63	80/15
3		**3c**	DMSO	63	98–100/15
4		**3d**[a]	DMF	65	103/0.8
5		**3e**[b]	DMSO	42	–
6		**3f**	DMF	62	103–104/12
7		**3g**	DMSO	34	98–100/25
8		**3h**	DMF	51	87–89/12
9		**3i**[c]	DMF	65	97–100/12
10		**3j**[d]	DMF	44	(55–57)[g]
11		**3k**	DMF	38	76/0.3
12		**3l**	DMF	32	(98–100)[g]

Table 1 Synthesis of Functionalized 1-Chloro-2,2,2-trifluoroethyl Sulfides **3** (continued)

Entry	Product	3	Solvent	Yield (%)	Bp (°C)/pressure (Torr)
13		**3m**	DMF	41	88/1
14		**3n**	DMF	33	170/18 (108–110)[g]
15		**3o**	DMF	67	98/14
16		**3p**	DMF	47	70–71/12
17		**3q**	DMF	35	101/1 (42–44)[g]
18		**3r**	DMSO	76	123/0.7
19		**3s**	DMSO	74	103–107/23
20		**3t**	DMF	81	89/13
21		**3u**[e]	DMF	45	–
22		**3v**[f]	DMF	0	–

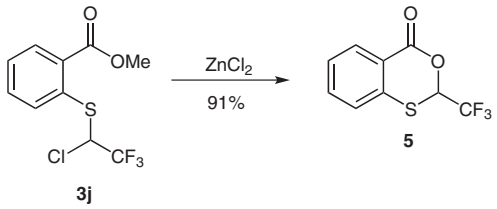
[a] Mixture of two diastereomers (51:49).
[b] The compound was purified by chromatography (EtOAc–hexane, 1:5).
[c] An alternative route to the compound is reported in ref. 7.
[d] The compound was purified by chromatography (EtOAc–hexane, 1:4).
[e] The isolated liquid product was of high purity; no distillation needed.
[f] The only product was di(*tert*-butyl) disulfide, isolated in 85% yield.
[g] Mp (°C).

To illustrate the synthetic utility of the obtained sulfides, compounds **3d**, **3c**, **3j**, and **6** were employed in a series of Lewis acid mediated reactions. As shown in Scheme 2, heating of **3d** (mixture of two diastereomers) with zinc(II) chloride gave rise to the corresponding five-membered 1,3-oxathiolanone **4**. It is noteworthy that the reaction proceeds regiospecifically, because no six-membered ring byproducts were detected. An attempt to carry out the intramolecular cyclization of methyl 3-[(1-chloro-2,2,2-trifluoroethyl)sulfanyl]propanoate (**3c**) under similar conditions gave only a tar, instead of the expected six-membered oxathianone. On the other hand, methyl 2-[(1-chloro-2,2,2-trifluoroethyl)sulfanyl]benzoate (**3j**) gave rise to a benzoxathianone **5** (Scheme 3).



3d dr = 49:51 **4** dr = 1:4

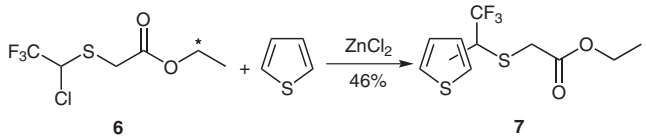
Scheme 2



Scheme 3

Only a few reports on the synthesis of fluorinated oxathiolanones with potential applications as enzyme inhibitors[11,12] and plant growth regulators[13,14] have appeared so far.

The 2,2,2-trifluoro-1-sulfanylethyl cation intermediates formed in the presence of zinc(II) chloride can also be applied in intermolecular electrophilic reactions, e.g., with electron-rich aromatic compounds. Scheme 4 shows that the zinc(II) chloride mediated reaction of **6** with thiophene yields a mixture of two regioisomers.



Scheme 4

To summarize, the method for the preparation of 1-chloro-2,2,2-trifluoroethyl sulfides described in this work tolerates a wide variety of functional groups on the thiol fragment, and is thus far the most straightforward procedure for the synthesis of these compounds, with potential use in the parallel synthesis of combinatorial libraries of these biologically potent compounds. The sulfides thus obtained can also be used as versatile synthetic building blocks. The latter was demonstrated in this work by the syntheses of heterocyclic compounds and thiophene derivatives.

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer; samples were prepared as $CDCl_3$ solns with TMS as an internal standard. ^{19}F (188 MHz) NMR spectra were recorded on a Varian Gemini 200 spectrometer; samples were prepared as $CDCl_3$ solns (unless stated otherwise) with CCl_3F as an internal standard. Melting points were determined on a Büchi melting point apparatus and are uncorrected. All chemicals were purchased from commercial sources and were used without further purification. Chromatographic purification of products was performed on Merck silica gel 60 (0.040–0.063 mm).

1-Chloro-2,2,2-trifluoroethyl Sulfides 3; General Procedure

2-Bromo-2-chloro-1,1,1-trifluoroethane (**1**; 44.33 g, 0.225 mol) was added dropwise to a stirred suspension of the appropriate thiol **2** (0.18 mol), 85% $Na_2S_2O_4$ (38.69 g, 0.189 mol), and $NaHCO_3$ (15.88 g, 0.189 mol) in the appropriate solvent (DMSO or DMF, 150 mL; see Table 1) at 35–40 °C. The reaction mixture was stirred at 40–45 °C for 4 h, then poured into H_2O (500 mL), and extracted with Et_2O (4 × 70 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and dried (Na_2SO_4). The Et_2O was removed under reduced pressure and the residue was distilled under reduced pressure or chromatographed (silica gel) (see Table 1).

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]ethanol (3a)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.23 (s, 1 H), 3.04 (m, 1 H), 3.09 (m, 1 H), 3.94 (m, 2 H), 5.41 (q, $^3J_{HF}$ = 6.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.0, 61.5, 62.2 (q, $^2J_{CF}$ = 36 Hz), 123.0 (q, $^1J_{CF}$ = 279 Hz).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.95 (d, $^3J_{FH}$ = 6.5 Hz).

Anal. Calcd for $C_4H_6ClF_3OS$: C, 24.69; H, 3.11; Cl, 18.22; F, 29.29; S, 16.48. Found: C, 24.83; H, 3.19; Cl, 18.00; F, 29.07; S, 16.14.

Methyl [(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]acetate (3b)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.55 (d, $^2J_{HH}$ = 15.7 Hz, 1 H), 3.63 (d, $^2J_{HH}$ = 15.7 Hz, 1 H), 3.79 (s, 3 H), 5.50 (q, $^3J_{HF}$ = 6.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.1, 52.9, 61.2 (q, $^2J_{CF}$ = 36 Hz), 122.9 (q, $^1J_{CF}$ = 279 Hz), 169.0.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.77 (d, $^3J_{FH}$ = 6.5 Hz).

Anal. Calcd for $C_5H_6ClF_3O_2S$: C, 26.98; H, 2.72; Cl, 15.93; F, 25.60; S, 14.40. Found: C, 27.23; H, 2.88; Cl, 15.77; F, 25.29; S, 14.25.

Methyl 3-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]propanoate (3c)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.73 (t, $^3J_{HH}$ = 7.0 Hz, 2 H), 3.12 (m, 2 H), 3.73 (s, 3 H), 5.28 (q, $^3J_{HF}$ = 6.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.1, 34.1, 52.0, 62.1 (q, $^2J_{CF}$ = 36 Hz), 123.0 (q, $^1J_{CF}$ = 279 Hz), 171.6.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.76 (d, $^3J_{FH}$ = 6.5 Hz).

Anal. Calcd for $C_6H_8ClF_3O_2S$: C, 30.45; H, 3.41; Cl, 14.98; F, 24.09; S, 13.55. Found: C, 30.74; H, 3.53; Cl, 15.17; F, 23.76; S, 13.32.

Dimethyl 2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]succinate (3d)

Minor Diastereomer (49%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.81 (dd, $^2J_{HH}$ = 32.7 Hz, $^3J_{HH}$ = 5.2 Hz, 1 H), 3.09 (dd, $^2J_{HH}$ = 32.7 Hz, $^3J_{HH}$ = 9.5 Hz, 1 H), 3.73 (s, 3 H), 4.02 (m, 1 H), 5.61 (q, $^3J_{HF}$ = 6.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.6, 41.4, 52.3, 53.16, 60.6 (q, $^2J_{CF}$ = 37 Hz), 122.6 (q, $^1J_{CF}$ = 279 Hz), 170.17, 170.55.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.85 (d, $^3J_{FH}$ = 6.6 Hz).

Major Diastereomer (51%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.84 (dd, $^2J_{HH}$ = 32.7 Hz, J_{HH} = 5.4 Hz, 1 H), 3.06 (dd, $^2J_{HH}$ = 32.7 Hz, $^3J_{HH}$ = 9.5 Hz, 1 H), 3.82 (s, 3 H), 4.02 (m, 1 H), 5.52 (q, $^3J_{HF}$ = 6.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.1, 42.4, 52.3, 53.20, 62.0 (q, $^2J_{CF}$ = 37 Hz), 122.8 (q, $^1J_{CF}$ = 279 Hz), 170.23, 170.64.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.65 (d, $^3J_{FH}$ = 6.6 Hz).

Anal. Calcd for $C_8H_{10}ClF_3O_4S$: C, 32.61; H, 3.42; Cl, 12.03; F, 19.34; S, 10.88. Found: C, 32.90; H, 3.48; Cl, 11.86; F, 19.09; S, 10.61.

Ethyl *N*-{2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]ethyl}carbamate (3e)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3 H), 3.01 (m, 2 H), 3.46 (m, 2 H), 4.13 (q, $^3J_{HH}$ = 7.1 Hz, 2 H), 5.06 (br s, 1 H), 5.26 (q, $^3J_{HF}$ = 6.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5, 31.6, 39.8, 61.2, 61.8 (q, $^2J_{CF}$ = 37 Hz), 123.0 (q, $^1J_{CF}$ = 279 Hz), 156.6.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.73 (d, $^3J_{FH}$ = 6.6 Hz).

Anal. Calcd for $C_7H_{11}ClF_3NO_2S$: C, 31.65; H, 4.17; Cl, 13.34; F, 21.45; S, 12.07. Found: C, 31.77; H, 4.26; Cl, 13.06; F, 21.36; S, 12.01.

{[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]methyl}benzene (3f)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.03 (s, 2 H), 4.96 (q, $^3J_{HF}$ = 6.4 Hz, 1 H), 7.34 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.4, 61.6 (q, $^2J_{CF}$ = 36 Hz), 123.1 (q, $^1J_{CF}$ = 279 Hz), 128.1, 129.0, 129.2, 134.9.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.31 (d, $^3J_{FH}$ = 6.4 Hz).

Anal. Calcd for $C_9H_8ClF_3S$: C, 44.92; H, 3.35; Cl, 14.73; F, 23.68; S, 13.32. Found: C, 45.21; H, 3.46; Cl, 14.96; F, 23.49; S, 13.01.

2-{[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]methyl}furan (3g)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.01 (d, $^2J_{HH}$ = 14.4 Hz, 1 H), 4.09 (d, $^2J_{HH}$ = 14.4 Hz, 1 H), 5.15 (q, $^3J_{HF}$ = 6.5 Hz, 1 H), 6.32 (s, 1 H), 6.35 (s, 1 H), 7.41 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.9, 61.7 (q, $^2J_{CF}$ = 36 Hz), 109.3, 110.7, 123.1 (q, $^1J_{CF}$ = 279 Hz), 143.3, 148.4.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.38 (d, $^3J_{FH}$ = 6.5 Hz).

Anal. Calcd for $C_7H_6ClF_3OS$: C, 36.45; H, 2.62; Cl, 15.37; F, 24.71; S, 13.90. Found: C, 36.69; H, 2.73; Cl, 15.56; F, 24.67; S, 13.81.

[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]benzene (3h)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.26 (q, $^3J_{HF}$ = 6.5 Hz, 1 H), 7.40 (m, 3 H), 7.62 (m, 2 H).

^{13}C NMR (125 MHz, benzene-d_6): δ = 65.5 (q, $^2J_{CF}$ = 35 Hz), 123.4 (q, $^1J_{CF}$ = 279 Hz), 129.5, 129.6, 129.9, 135.0.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.58 (d, $^3J_{FH}$ = 6.5 Hz).

Anal. Calcd for $C_8H_6ClF_3S$: C, 42.39; H, 2.67; Cl, 15.64; F, 25.15; S, 14.15. Found: C, 42.52; H, 2.72; Cl, 15.41; F, 24.91; S, 13.84.

1-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-4-methylbenzene (3i)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 5.20 (q, $^3J_{HF}$ = 6.6 Hz, 1 H), 7.21 (d, $^3J_{HH}$ = 7.7 Hz, 2 H), 7.51 (d, $^3J_{HH}$ = 7.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 65.8 (q, $^2J_{CF}$ = 35 Hz), 122.9 (q, $^1J_{CF}$ = 279 Hz), 125.9, 130.3, 135.2, 140.6.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.25 (d, $^3J_{FH}$ = 6.6 Hz).

Anal. Calcd for $C_9H_8ClF_3S$: C, 44.92; H, 3.35; Cl, 14.73; F, 23.68; S, 13.32. Found: C, 45.11; H, 3.44; Cl, 15.02; F, 23.41; S, 13.06.

Methyl 2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]benzoate (3j)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.95 (s, 3 H), 5.64 (q, $^3J_{HF}$ = 6.3 Hz 1 H), 7.43 (t, $^3J_{HH}$ = 7.5 Hz, 1 H), 7.56 (t, $^3J_{HH}$ = 7.5 Hz, 1 H), 7.65 (d, $^3J_{HH}$ = 7.9 Hz, 1 H), 7.94 (d, $^3J_{HH}$ = 7.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.6, 64.1 (q, $^2J_{CF}$ = 35 Hz), 123.0 (q, $^1J_{CF}$ = 279 Hz), 128.3, 131.2, 131.9, 132.5, 132.6, 132.7, 166.9.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.15 (d, $^3J_{FH}$ = 6.3 Hz).

Anal. Calcd for $C_{10}H_8ClF_3O_2S$: C, 42.19; H, 2.83; Cl, 12.45; F, 20.02; S, 11.26. Found: C, 42.44; H, 2.88; Cl, 12.60; F, 19.79; S, 11.02.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]aniline (3k)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.44 (br s, 2 H), 5.21 (q, $^3J_{HF}$ = 6.6 Hz, 1 H), 6.76 (m, 2 H), 7.25 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 7.47 (d, $^3J_{HH}$ = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.1 (q, $^2J_{CF}$ = 35 Hz), 111.9, 115.6, 118.9, 123.0 (q, $^1J_{CF}$ = 280Hz), 132.4, 137.8, 149.1.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.25 (d, $^3J_{FH}$ = 6.6 Hz).

Anal. Calcd for $C_8H_7ClF_3NS$: C, 39.76; H, 2.92; Cl, 14.67; F, 23.58; S, 13.27. Found: C, 39.84; H, 2.99; Cl, 14.51; F, 23.39; S, 13.10.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-1*H*-imidazole (3l)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.47 (q, $^3J_{HF}$ = 6.4 Hz, 1 H), 7.34 (s, 2 H), 11.51 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 62.9 (q, $^2J_{CF}$ = 36 Hz), 122.6 (q, $^1J_{CF}$ = 277 Hz), 126.0, 132.3.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.28 (d, $^3J_{FH}$ = 6.4 Hz).

Anal. Calcd for $C_5H_4ClF_3N_2S$: C, 27.72; H, 1.86; Cl, 16.37; F, 26.31; S, 14.80. Found: C, 27.98; H, 1.96; Cl, 16.43; F, 26.09; S, 14.61.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-1-methyl-1*H*-imidazole (3m)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 5.66 (q, $^3J_{HF}$ = 6.4 Hz, 1 H), 7.07 (d, $^3J_{HH}$ = 1 Hz, 1 H), 7.21 (d, $^3J_{HH}$ = 1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.8, 63.6 (q, $^2J_{CF}$ = 36 Hz), 122.6 (q, $^1J_{CF}$ = 279 Hz), 124.3, 131.0, 135.0.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.52 (d, $^3J_{FH}$ = 6.4 Hz).

Anal. Calcd for $C_6H_6ClF_3N_2S$: C, 31.25; H, 2.62; Cl, 15.37; F, 24.71; S, 13.90. Found: C, 31.37; H, 2.69; Cl, 15.19; F, 24.49; S, 13.75.

3-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-4*H*-1,2,4-triazole (3n)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.18 (q, $^3J_{HF}$ = 6.6 Hz, 1 H), 8.35 (s, 1 H), 9.08 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 61.6 (q, $^2J_{CF}$ = 37 Hz), 122.7 (q, $^1J_{CF}$ = 280 Hz), 145.4, 154.7.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.42 (d, $^3J_{FH}$ = 6.6 Hz).

Anal. Calcd for $C_4H_3ClF_3N_3S$: C, 22.08; H, 1.39; Cl, 16.29; F, 26.19; S, 14.74. Found: C, 22.30; H, 1.48; Cl, 16.48; F, 26.08; S, 14.61.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-4-methyl-1,3-thiazole (3o)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 6.17 (q, $^3J_{HF}$ = 6.6 Hz, 1 H), 6.96 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.1, 62.7 (q, $^2J_{CF}$ = 37 Hz), 117.0, 122.7 (q, $^1J_{CF}$ = 279 Hz), 154.3, 155.1.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.13 (d, $^3J_{FH}$ = 6.6 Hz).

Anal. Calcd for $C_6H_5ClF_3NS_2$: C, 29.10; H, 2.03; Cl, 14.31; F, 23.01; S, 25.89. Found: C, 29.26; H, 2.11; Cl, 14.43; F, 22.73; S, 25.67.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]thiophene (3p)

^{1}H NMR (500 MHz): 5.10 (q, $^3J_{HF}$ = 6.4 Hz, 1 H), 7.08 (t, $^3J_{HH}$ = 4.4 Hz, 1 H), 7.38 (d, $^3J_{HH}$ = 3.6 Hz, 1 H), 7.56 (d, $^3J_{HH}$ = 5.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 65.4 (q, $^2J_{CF}$ = 35 Hz), 122.7 (q, $^1J_{CF}$ = 280 Hz), 125.9, 128.1, 133.3, 138.4.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.40 (d, $^3J_{FH}$ = 6.4 Hz).

Anal. Calcd for $C_6H_4ClF_3S_2$: C, 30.97; H, 1.73; Cl, 15.24; F, 24.50; S, 27.56. Found: C, 31.23; H, 1.76; Cl, 15.01; F, 24.12; S, 27. 34.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-1,3-benzoxazole (3q)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.51 (q, $^3J_{HF}$ = 6.6 Hz, 1 H), 7.33 (m, 2 H), 7.49 (d, $^3J_{HH}$ = 7.5 Hz, 1 H), 7.66 (d, $^3J_{HH}$ = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 60.8 (q, $^2J_{CF}$ = 38 Hz), 110.4, 119.2, 122.4 (q, $^1J_{CF}$ = 279 Hz), 125.0, 125.1, 141.1, 152.4, 159.0.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.56 (d, $^3J_{FH}$ = 6.6 Hz).

Anal. Calcd for $C_9H_5ClF_3NOS$: C, 40.39; H, 1.88; Cl, 13.25; F, 21.29; S, 11.98. Found: C, 40.52; H, 1.92; Cl, 13.21; F, 21.04; S, 11.81.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-1,3-benzothiazole (3r)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.74 (q, $^3J_{HF}$ = 6.9 Hz, 1 H), 7.37 (t, $^3J_{HH}$ = 7.6 Hz, 1 H), 7.48 (t, $^3J_{HH}$ = 7.6 Hz, 1 H), 7.79 (d, $^3J_{HH}$ = 8.2 Hz, 1 H), 7.95 (d, $^3J_{HH}$ = 8.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 60.8 (q, $^2J_{CF}$ = 37 Hz), 121.4, 122.5, 122.8 (q, $^1J_{CF}$ = 279 Hz), 125.5, 126.7, 135.8, 152.3, 159.5.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.09 (d, $^3J_{FH}$ = 6.9 Hz).

Anal. Calcd for $C_9H_5ClF_3NS_2$: C, 38.10; H, 1.78; Cl, 12.50; F, 20.09; S, 22.60. Found: C, 38.35; H, 1.98; Cl, 12.29; F, 19.81; S, 22.52.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]pyridine (3s)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.90 (q, $^3J_{HF}$ = 7.5 Hz, 1H), 7.15 (t, $^3J_{HH}$ = 4.1 Hz, 1 H), 7.23 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 7.62 (t, $^3J_{HH}$ = 7.8 Hz, 1 H), 8.52 (d, $^3J_{HH}$ = 4.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 59.3 (q, $^2J_{CF}$ = 37 Hz), 121.5, 122.5, 123.3 (q, $^1J_{CF}$ = 278 Hz), 137.2, 149.8, 152.3.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.71 (d, $^3J_{FH}$ = 7.5 Hz).

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-5-(trifluoromethyl)pyridine (3t)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.88 (q, $^3J_{HF}$ = 7.1 Hz, 1 H), 7.34 (d, $^3J_{HH}$ = 8.4 Hz, 1 H), 7.83 (d, $^3J_{HH}$ = 8.4 Hz, 1 H), 8.77 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 58.4 (q, $^2J_{CF}$ = 37 Hz), 122.0, 123.1 (q, $^1J_{CF}$ = 278 Hz), 123.3 (q, $^1J_{CF}$ = 272 Hz), 124.6 (q, $^2J_{CF}$ = 34 Hz), 134.1, 146.6, 157.2.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –62.87 (s, 3 F), –72.73 (d, $^3J_{FH}$ = 7.1 Hz, 3 F).

Anal. Calcd for $C_8H_4ClF_6NS$: C, 32.50; H, 1.36; Cl, 11.99; F, 38.56; S, 10.85. Found: C, 32.69; H, 1.44; Cl, 11.79; F, 38.42; S, 10.71.

2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]pyrimidine (3u)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.70 (q, $^3J_{HF}$ = 7.2 Hz, 1 H), 7.15 (t, $^3J_{HH}$ = 4.9 Hz, 1 H), 8.63 (d, $^3J_{HH}$ = 4.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 59.7 (q, $^2J_{CF}$ = 37 Hz), 118.2, 123.1 (q, $^1J_{CF}$ = 278 Hz), 158.0, 167.0.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.86 (d, $^3J_{FH}$ = 7.2 Hz).

Anal. Calcd for $C_6H_4ClF_3N_2S$: C, 31.52; H, 1.76; Cl, 15.51; F, 24.93; S, 14.02. Found: C, 31.64; H, 1.89; Cl, 15.70; F, 24.75; S, 13.90.

Methyl [5-Oxo-2-(trifluoromethyl)-1,3-oxathiolan-4-yl]acetate (4)

A mixture of anhyd $ZnCl_2$ (0.91 g, 6.7 mmol) and **3d** (0.99 g, 3.4 mmol) was heated for 2 h at 100 °C. After cooling to r.t., the reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with H_2O (3 × 25 mL) and dried ($MgSO_4$). After evaporation of the solvent under vacuum, the crude product was purified by thick-layer chromatography (silica gel, EtOAc–hexane, 1:2); this gave **4**.

Yield: 0.54 g (65%); R_f = 0.7 (EtOAc–hexane, 1:2).

Minor Diastereomer (20%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.92 (dd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 8.3 Hz, 1 H), 3.18 (dd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 3.7 Hz, 1 H), 3.76 (s, 3 H), 4.35 (dd, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 3.7 Hz, 1 H), 5.61 (q, $^3J_{HF}$ = 5.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.2, 39.9, 52.5, 74.6 (q, $^2J_{CF}$ = 37 Hz), 122.6 (q, $^1J_{CF}$ = 280 Hz), 170.0, 172.3.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –79.61 (d, $^3J_{FH}$ = 5.2 Hz).

Major Diastereomer (80%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.87 (dd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 11 Hz, 1 H), 3.26 (dd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 3.2 Hz, 1 H), 3.76 (s, 3 H), 4.39 (dd, $^3J_{HH}$ = 11 Hz, $^3J_{HH}$ = 3.2 Hz, 1 H), 5.65 (q, $^3J_{HF}$ = 5.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.9, 40.7, 52.6, 74.7 (q, $^2J_{CF}$ = 37 Hz), 122.6 (q, $^1J_{CF}$ = 280 Hz), 170.4, 172.1.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –79.90 (d, $^3J_{FH}$ = 5.4 Hz).

Anal. Calcd for $C_7H_7F_3O_4S$: C, 34.43; H, 2.89; F, 23.34; S, 13.13. Found: C, 34.06; H, 2.98; F, 22.96; S, 12.88.

2-(Trifluoromethyl)-4*H*-3,1-benzoxathian-4-one (5)

A mixture of anhyd $ZnCl_2$ (1.9 g, 14 mmol) and **3j** (2 g, 7 mmol) was heated for 0.5 h at 110–115 °C. Upon cooling to r.t., the reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O (3 × 25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure; this gave **5**.

Yield: 1.5 g (91%); mp 60–62 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.88 (q, $^3J_{HF}$ = 5.2 Hz, 1 H), 7.39 (t, $^3J_{HH}$ = 7.4 Hz, 2 H), 7.57 (t, $^3J_{HH}$ = 7.4 Hz, 1 H), 8.18 (d, $^3J_{HH}$ = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 77.7 (q, $^2J_{CF}$ = 37 Hz), 121.5 (q, $^1J_{CF}$ = 281 Hz), 123.3, 127.7, 127.9, 132.8, 134.1, 134.6, 160.5.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –75.76 (d, $^3J_{FH}$ = 5.2 Hz).

Anal. Calcd for $C_9H_5F_3O_2S$: C, 46.16; H, 2.15; F, 24.34; S, 13.69. Found: C, 46.37; H, 2.33; F, 24.02; S, 13.50.

Ethyl {[2,2,2-Trifluoro-1-(2-thienyl)ethyl]sulfanyl}acetate and Ethyl {[2,2,2-Trifluoro-1-(3-thienyl)ethyl]sulfanyl}acetate (7)

Anhyd $ZnCl_2$ (0.29 g, 2.1 mmol) was added to a soln of **6**[14] (0.24 g, 1.0 mmol) and thiophene (0.15 g, 1.8 mmol) in $MeNO_2$ (2 mL), and the mixture was heated at reflux for 20 min. Upon cooling to r.t., the reaction mixture was treated with aq K_2CO_3 and extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were dried ($MgSO_4$). After evaporation of the solvent under vacuum, the crude product was purified by thick-layer chromatography (silica gel, EtOAc–hexane, 1:9); this gave **7**.

Yield: 0.13 g (46%); R_f = 0.5 (EtOAc–hexane, 1:9).

Ethyl {[2,2,2-Trifluoro-1-(2-thienyl)ethyl]sulfanyl}acetate

Major isomer (70%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3 H), 3.19 (d, $^2J_{HH}$ = 15.9 Hz, 1 H), 3.45 (d, $^2J_{HH}$ = 15.9 Hz, 1 H), 4.2 (q, $^3J_{HH}$ = 7.2 Hz, 2 H), 5.04 (q, $^3J_{HF}$ = 8.1 Hz, 1 H), 7.00 (m, 1 H), 7.15 (m, 1 H), 7.35 (d, $^3J_{HH}$ = 5.1 Hz, 1 H).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –69.34 (d, $^3J_{FH}$ = 8.1 Hz).

Ethyl {[2,2,2-Trifluoro-1-(3-thienyl)ethyl]sulfanyl}acetate

Minor isomer (30%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3 H), 3.14 (d, $^2J_{HH}$ = 15.6 Hz, 1 H), 3.42 (d, $^2J_{HH}$ = 15.6 Hz, 1 H), 4.2 (q,

$^3J_{HH}$ = 7.2 Hz, 2 H), 4.84 (q, $^3J_{HF}$ = 7.8 Hz, 1 H), 7.00 (m, 1 H), 7.15 (m, 1 H), 7.31 (d, $^3J_{HH}$ = 5.4 Hz, 1 H).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –68.91 (d, $^3J_{FH}$ = 7.8 Hz).

Anal. Calcd for $C_{10}H_{11}F_3O_2S_2$: C, 42.24; H, 3.90; F, 20.05; S, 22.56. Found: C, 42.45; H, 3.95; F, 19.71; S, 22.29.

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