Synthetic Uses of Thio- and Selenoesters of Trifluoromethylated Acids. 1. Preparation of Trifluoromethyl Sulfides and Selenides

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Trifluorothioacetates ($CF_3CO-S-R$, from $(CF_3CO)_2O$ and thiols) as well as trifluoromethanethio- or trifluoromethaneselenosulfonates (CF_3SO_2-Y-R; Y = S, Se; from CF_3SO_2Na, RYYR, and Br_2) can be formally decarbonylated or desulfonylated, respectively, provided that they are photolyzed at 40 °C in the presence of 1 equiv of the corresponding disulfide or diselenide. Trifluoromethyl sulfides or selenides are obtained, and the added disulfide (or diselenide) is recovered after reaction. In such a way, S-(trifluoromethyl)cysteine derivatives can be obtained.

Introduction

The direct introduction of a CF_3 group is now emerging as one of the major routes to trifluoromethylated compounds. Apart from the use of expensive trifluoromethyl trimethylsilane,[1] which behaves as a "$^-CF_3$" equivalent, radical trifluoromethylation constitutes the most versatile tool for this purpose.[2] Nevertheless, most of the $^\bullet CF_3$ precursors are either expensive (i.e., CF_3I, anhydrous CF_3COCF_3), hazardous (i.e., $(CF_3COO)_2$, $(CF_3)_2N_2$), toxic (i.e., $(CF_3)_2Hg$, $(CF_3)_2Te$), not readily available (i.e., Umemoto's reagents) or need to be treated under special conditions (i.e., electrochemical oxidation of trifluoroacetic acid).

Several years ago, we demonstrated that trifluoromethyl radicals can be easily generated by single-electron reduction of bromotrifluoromethane with cheap dithionite[3] or by single-electron oxidation of sodium trifluoromethanesulfinate (CF_3SO_2Na)[4] with aqueous *tert*-butyl hydroperoxide.[5] Through such processes, $^\bullet CF_3$ is produced either in reducing or oxidizing media. However, it would be useful to have in hands a technique in which the trifluoromethyl radical could be generated under "neutral" conditions (from a redox point of view), starting from easily available reagents.

For this purpose, we planned to homolyze, under irradiation, the thio- and selenoesters of triflic acid (CF_3SO_2-SR and CF_3SO_2SeR) that we recently described.[6] In such a way, we expected to form, along with sulfenyl and selenenyl radicals, triflyl radicals ($CF_3SO_2^\bullet$). In contrast with arylsulfonyl and alkylsulfonyl radicals, also generated by photolysis of thiosulfonates[7] or selenosulfonates,[8] triflyl radicals collapse very quickly into sulfur dioxide and trifluoromethyl radicals.[5,9] Thus, trifluoromethyl sulfides (or selenides) should result from recombination of $^\bullet CF_3$ and $RS^\bullet$ (or $RSe^\bullet$) during the photolysis of CF_3-SO_2SR (or CF_3SO_2SeR). Trifluoromethyl sulfides are very interesting because of the high hydrophobicity brought by the CF_3S moiety (Hansch parameter $\Pi_R = 1.44$)[10] which increases the bioavailability of these compounds.[11] Many of them (or their oxidized derivatives) exhibit important biological responses and some are used as pharmaceuticals,[12] veterinary drugs,[13] or agrochemicals.[12h,14] Though very few trifluoromethyl selenides have been described,[15] they can be suspected to exhibit interesting biological properties, too. Like trifluoromethanethiosulfonates, thioesters of trifluoroacetic acid were also expected to deliver trifluoromethyl sulfides by photolysis since trifluoroacetyl radicals are known to decompose into carbon monoxide and trifluoromethyl radicals.[16] Thus, their homolysis has also been studied.

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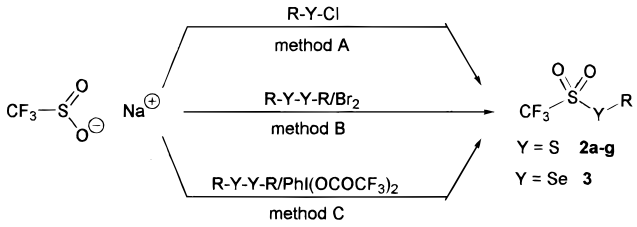
Scheme 1. Preparation of Trifluoromethanethiosulfonates



Results and Discussion

Alkyl and aryl trifluorothioacetates ($CF_3C(O)SR$) were readily prepared from trifluoroacetic anhydride and the corresponding thiols, in the presence of pyridine and catalytic amounts of 4-(dimethylamino)pyridine (DMAP). As already mentioned,[6a] alkyl and aryl trifluoromethanethiosulfonates cannot be obtained in the same way from triflic anhydride and thiols. According to the techniques we recently described,[6] they were prepared (as well as their seleno analogues) either from sodium trifluoromethanesulfinate and sulfenyl (or selenenyl) chlorides or from CF_3SO_2Na and disulfides (or diselenides) under oxidative conditions (Scheme 1, Table 1).

According to their UV spectra (Table 6), trifluorothioacetates exhibit a small absorption at 195−215 nm and a strong one at 220−255 nm, whereas trifluoromethanethiosulfonates show a strong absorption at 190−200 nm and a less intense one at 235−245 nm. Consequently, their photolysis was performed in quartz vessel with a high-pressure mercury lamp (HPK 125). Dichloromethane was chosen as solvent.

In preliminary experiments, **1d** (CF_3COSR, R = CH_2-CH_2CO_2Et) and **2d** (CF_3SO_2SR, same R) were submitted to photolysis in refluxing dichloromethane. As expected, they delivered ethyl 3-(trifluoromethylthio)propionate but in 32% and 22% yields, respectively. The almost quantitative side-formation of the corresponding disulfide **4d** (RSSR) and of some chloromethyl sulfides ($ClCH_2SR$ and Cl_2CHSR resulting from CH_2Cl_2) confirmed the radical nature of the reaction. Thus, recombination of $^{\bullet}CF_3$ and $RS^{\bullet}$ was not as efficient as expected. This result could be explained by the fact that these two transient radicals ($t_{1/2} = 10^{-3}$ s) were not produced in the same reaction. Moreover, dichloromethane was not viscous enough ($\eta^{30} = 0.393$ cP) to favor cage phenomena, and diffusion prevailed over recombination. In such a situation, two processes could be invoked to explain the formation of CF_3SR out of the solvent cage: either a chain reaction between $^{\bullet}CF_3$ and CF_3COSR or CF_3SO_2SR (Scheme 2), or a S_H2 process involving the reaction of $^{\bullet}CF_3$ with the disulfide resulting from the recombination of thiyl radicals (Scheme 3).

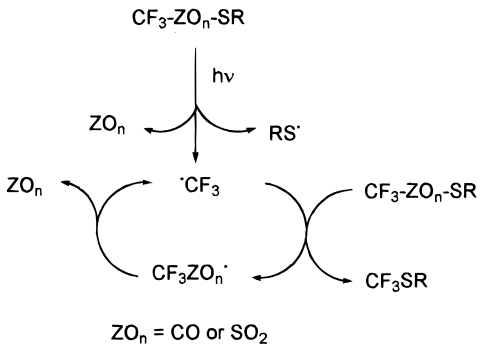
According to Scheme 2, the photon should act as a "catalyst" and the reaction rate should not be very sensitive to the light power. However, when using a less powerful lamp (NPK 12) or when moving the lamp away from the reaction vessel, conversion of **1d** or **2d** dropped significantly. Thus, the chain process can be ruled out all the more so since it implies the attack of an electrophilic trifluoromethyl radical[17] upon thioesters in which the S(II) atom is also an electrophilic site because of the

Table 1. Preparation of Thioesters of Trifluoroacetic and Triflic Acids

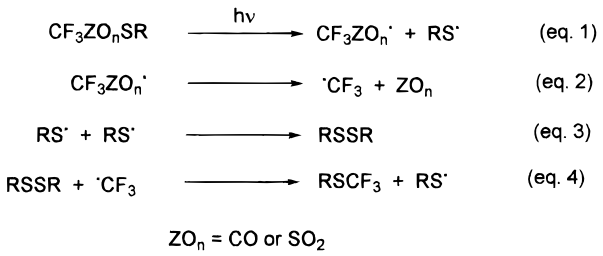
				CF_3SO_2YR (%)[6]			
		CF_3COYR			method		
Y	R		(%)	cpd	A	B	C
S	n-C_8H_{17}	**1a**	97	**2a**		88	70
S	c-C_6H_{11}	**1b**	80	**2b**		65	80
S	t-Bu	**1c**	63	**2c**		0	0
S	$CH_2CH_2CO_2Et$	**1d**	81	**2d**		88	
S	CH_2Ph	**1e**	84	**2e**		90	
S	Ph	**1f**	96	**2f**	85	67	87
S	4-Cl−C_6H_4	**1g**	87	**2g**		50	
S	CH_2CO_2Et	**1h**	81				
S	$CH_2CH(NHCOCF_3)CO_2Me$	**1i**	94[a]				
Se	Ph			**3**	95	55	80

[a] Reaction in AcOEt without pyridine and DMAP.

Scheme 2. Radical Chain Process



Scheme 3. S_H2 Process



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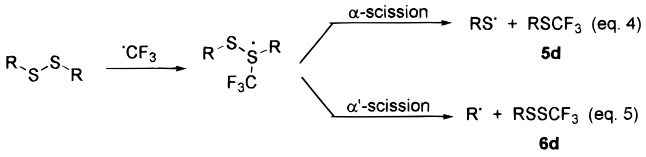
Scheme 4. Formation of Trifluoromethyl Sulfides and Disulfides

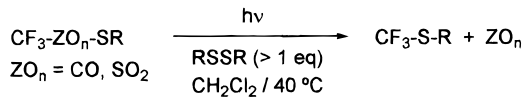


electron-withdrawing effect of CF_3CO and CF_3SO_2. Thus, the S_H2 mechanism (Scheme 3) looks more suitable. The detection of small quantities of CF_3SSR **6d** (R = $CH_2CH_2CO_2Et$) argues also for the reaction of a trifluoromethyl radical on the disulfide (Scheme 4).

Nevertheless, the S_H2 process should compete with side-reactions from the trifluoromethyl radical (dimerization or abstraction of an hydrogen atom). Traces of fluoroform were effectively detected.

According to eq 4, the formation rate of trifluoromethyl sulfide was dependent on the concentration of disulfide; this one increased as the reaction progressed, but was not high enough, especially at the beginning of the process, to compete efficiently with side-reactions. Consequently, we assumed that the formation of $RSCF_3$ should be favored by additional disulfide (with R of the same nature as in the starting thioester). Indeed, when illuminating a mixture of CF_3COSR or CF_3SO_2SR (R = $CH_2CH_2CO_2Et$) and increasing quantities of the corresponding disulfide RSSR (R = $CH_2CH_2CO_2Et$), the yield of the expected trifluoromethyl sulfide increased too (Table 2). Correlatively, chlorinated byproducts ($ClCH_2$-SR and Cl_2CHSR) decreased, and the balance between introduced and recovered fluorine and sulfur atoms became more satisfying.

Entries 5 to 7 in Table 2 show that, provided that at least 1 equiv of the corresponding disulfide was present, the photolysis of CF_3COSR and CF_3SO_2SR looked like a formal decarbonylation or desulfonylation process since the added disulfide was recovered in a high yield (or even quantitatively):



These observations were in accordance with a S_H2 mechanism (Scheme 5).

To bring further evidence of this mechanism, **1c** (CF_3-COS-*t*Bu) and **2a** ($CF_3SO_2SC_8H_{17}$) were photolyzed in the presence of **4d** (R = $CH_2CH_2CO_2Et$): as expected from Scheme 5, the two possible trifluoromethyl sulfides and the three possible disulfides were present at the end of the reaction (Table 3).

This formal decarbonylation or desulfonylation of trifluoromethylated thioesters has been applied to the preparation of other trifluoromethyl sulfides from the corresponding disulfides and trifluorothioacetates or trifluoromethanethiosulfonates. The first experiments were performed with aliphatic substrates (Table 4).

As shown from Table 4, trifluoromethanethiosulfonates were converted more rapidly and more extensively than trifluorothioacetates. This difference reflected the relative SO_2−S and CO−S bond energies. Nevertheless, the yields of trifluoromethyl sulfides (relative to converted thioesters) were comparable in the trifluoroacetic and triflic series. Good results were obtained with primary R groups, except benzylic ones (entry 8): **2e** was converted slower than other primary trifluoromethanesulfonates, probably because of the UV absorption of the aromatic ring (vide infra) which decreased the quantum yield, and the yield of **5e** (vs converted **2e**) decreased as the reaction progressed, indicating that this compound was either photosensitive or decomposed through radical processes. As far as primary aliphatic substrates are concerned, comparison between entries 6 and 9 shows that the yield of **5** was also dependent on the nucleophilicity of sulfur atoms in the corresponding disulfide, as already reported.[5a] When comparing secondary compounds (R = cyclohexyl, entries 3−5) with primary ones (R = octyl, entries 1 and 2), it must be noted that steric hindrance influenced the reaction in two ways. First, secondary thioesters (**1b**, **2b**) were converted slower than primary ones (**1a**, **2a**). Second, as already reported too,[5a] the condensation of $^{\bullet}CF_3$ was less efficient with the secondary disulfide **4b** than with the primary one **4a**, as shown from the respective yields of **5b** and **5a** (vs converted **1b** and **1a**); consequently, significant yields of fluoroform (6.4%) where also detected during irradiation of a mixture of **1b** and **4b**. Moreover, products resulting from α′-scission (cf. Scheme 4) were always present in a slight but detectable amount from **1b**. Extensive α′-scission processes could be also the reason a very poor yield of trifluoromethyl sulfide was observed from **1c** (CF_3COS-*t*-Bu) and *tert*-butyl disulfide.

This photochemical reaction has been extended to the preparation of long-chain perfluoroalkyl sulfides from the corresponding perfluoroacyl chlorides (Scheme 6).[18]

Aryl trifluoromethanethiosulfonates and trifluorothioacetates have been also photolyzed under the same conditions, in the presence of the corresponding disulfides. However, the expected aryl trifluoromethyl sulfides were obtained in poor yields along with noticeable amounts of trifluoromethylated byproducts and traces of aryl dichloromethyl sulfides (Table 5).

Two reasons could explain these disappointing results. First, light absorption by aromatic nuclei lowered the quantum yield of the photolytic process (and consequently the conversion of **1f,g** or **2f,g**). Second, **5f,g** were also photosensitive, as already reported[19] and confirmed by our determinations (Table 7). In fact, when illuminated in refluxing dichloromethane for 3.5 h, **5g** was quite completely converted (up to 90%) into the corresponding disulfide **4g**, 4-chlorophenyl dichloromethyl sulfide, and fluoroform (16% from ^{19}F NMR analysis). Such a high conversion of **5g** was probably favored by the tetrahedral configuration of the sulfur atom which lowered the conjugative stabilization.[20] Table 5 also indicates the formation of ring-trifluoromethylated disufides as byproducts. They can be explained according to our previous studies on trifluoromethylation of aromatic disulfides[5a] (Scheme 7).

In contrast with aryl trifluorothioacetates and trifluoromethanethiosulfonates, phenyl trifluoromethanesele-

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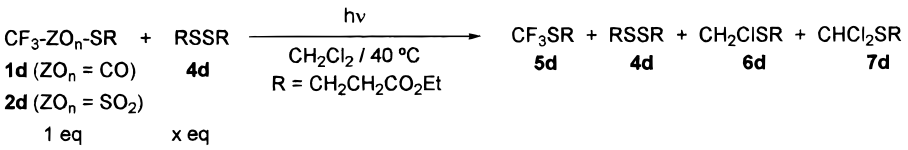
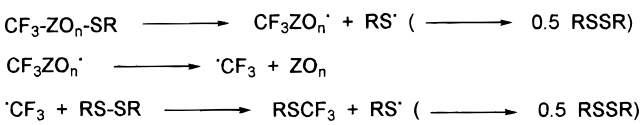
Table 2. Photolysis of 1d or 2d in the Presence of 4d



entry	reagent	*x* (equiv)	time (min)	conv **1d** or **2d** (%)	**5d** (%)	recovered **4d** (equiv)	**6d** (%)	**7d** (%)	recovered CF_3 (%)	recovered RS (%)
1	**1d**	0	75	93	32	0.2	4	12	39	81
2	**2d**	0	40	100	22					
3	**1d**	0.2	80	97	44	0.2	trace	trace	47	70
4	**1d**	0.4	75	90	50	0.4	trace	trace	60	77
5	**1d**	1.0	105	79	64	0.8	trace	trace	85	81
6	**1d**	2.0	75	80	64	1.9	trace	trace	87	91
7	**2d**	1.0	40	100	78	1.0	0	0	78	93

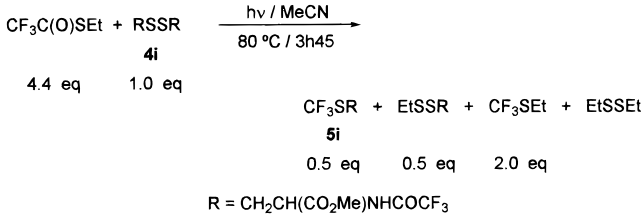
Scheme 5. S_H2 Mechanism



nosulfonate **3** delivered a fair yield of phenyl trifluoromethyl selenide **10** when irradiated in the presence of 1 equiv of diphenyl diselenide **11** (Scheme 8). This is due to the fact that the main absorption of **10** lies at 191 nm, rather far from the wavelength needed to cleave **3** (244 nm). In this case too, **11** was recovered quite unchanged after reaction.

Finally, the decarbonylations of trifluorothioacetates have been illustrated by the preparation of methyl *N*-(trifluoroacetyl)-*S*-(trifluoromethyl)-(L)-cysteinate **5i** from suitable derivatives of (L)-cysteine **1i** and (L)-cystine **4i**[21] (Scheme 9). Like *ω*,*ω*,*ω*-trifluoromethionine[12e−g] (which could be also prepared by our technique from homocysteine and homocystine), this unatural amino acid could exhibit original biological properties.

5i has been also prepared by photolysis of a mixture of **4i** and commercially available CF_3COSEt in excess. In this case, however, only one thiyl moiety of **4i** was consumed to deliver **5i**.



Conclusion

Formal photolytic desulfonylation of trifluoromethanethiosulfonates and formal photolytic decarbonylation of trifluorothioacetates offer an easy access to valuable trifluoromethyl sulfides, especially aliphatic ones, provided that 1 equiv of disulfide is present during irradiation to act as a "collisioner". Such techniques, performed under "neutral" conditions (from a redox point of view), constitute an alternative route to the trifluoromethylation of disulfides with bromotrifluoromethane under reducing conditions[3] or with sodium trifluoromethanesulfinate under oxidative conditions, a process in which one thiyl moiety only delivers the expected compound.[5a,d] It must be noted that the decarbonylation of trifluorothioacetates avoid the use of CF_3Br, which is banned now because of its deleterious effect upon stratospheric ozone. S-Trifluoromethylated derivatives of cysteine have been prepared in this way, which probably allows the access to analogous compounds from homocyteine and penicillamine. Moreover, the desulfonylation technique can be applied to the preparation of rather unknown trifluoromethyl selenides, the properties of which are under study in our laboratory.

Experimental Section

Solvents were distilled prior use and stored over 3 Å molecular sieves. Other reagents were used as received. Unless stated otherwise, ^1H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200, 188, and 50 MHz, respectively. Chemical shifts are given in ppm relative to TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) used as internal references. Coupling constants are given in hertz. UV absorptions were determined in acetonitrile in a 1 cm long cell, concentrations of the studied compounds lying between 0.4 and 6.7×10^{-4} mol l^{-1}. Mass spectrometry, using electron impact at 70 eV, was coupled with gas chromatography. Trifluoromethanethiosulfonates (**2a**−**g**) and phenyl trifluoromethaneselenosulfonate (**3**) were prepared according to our previous reports.[6] Dimethyl bis(*N*-trifluoroacetyl)-(L)-cystinate **4i** was obtained according to literature procedure.[21] Common spectroscopic features (UV, ^{19}F NMR, ^{13}C NMR) of thio- and selenoesters of trifluoroacetic and triflic acids are given in Table 6 and those of trifluoromethyl sulfides and selenides are given in Table 7.

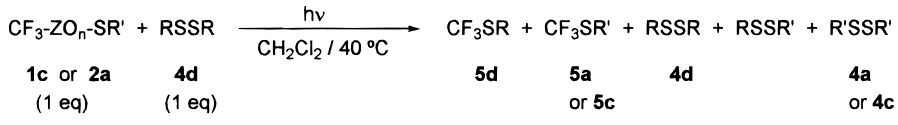
General Procedure for the Preparation of Trifluorothioacetates (1a−h). Trifluoroacetic anhydride (8 mL, 56.5 mmol), dissolved in anhydrous dichloromethane (50 mL), was dropped, over approximately 15 min, on a solution, kept at 0 °C under nitrogen, of pyridine (4 mL, 49.5 mmol), thiol (49.5 mmol), and a few milligrams of 4-(dimethylamino)pyridine (DMAP) in anhydrous dichloromethane (150 mL). After addition, the reaction mixture was kept at room temperature for 1 h and then brought to reflux (40 °C) for about 1 h (the reaction was monitored by GC). After cooling, it was poured in water (150 mL) and decanted. The aqueous phase was extracted with dichloromethane (2 × 200 mL), and then combined organic phases were dried over $MgSO_4$ and evaporated under vacuum at room temperature. **1a**−**h** were obtained by distillation of the crude residue. Yields are reported in Table 1.

Common Spectroscopic Features of CF_3COSR (1a−h). See Table 6.

Additional Data for CF_3COSR (1a−h). *n*-Octyl Trifluorothioacetate (1a). Oil. Bp_{20}: 120 °C. ^1H NMR: δ 3.05 (t, J = 7.0, 2H), 1.67 (m, 2H), 1.27 (m, 10H), 0.88 (t, J = 6.6, 3H). ^{13}C NMR: δ 31.86, 29.38, 29.18, 29.07, 28.81, 28.74, 28.73, 14.10. MS: *m*/*z* 242 ($M^{\bullet+}$), 185, 173, 145, 143, 112, 97, 69, 45.

(21) Harpp, D. N.; Gleason, J. G. *J. Org. Chem.* **1971**, *36*, 73.

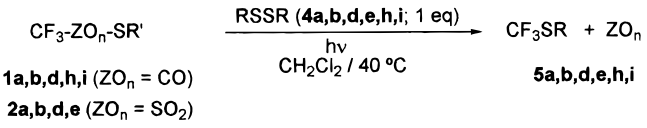
Table 3. Cross-Coupling Trifluoromethylation



ZO_n	R′	CF_3SR (equiv)[a]	CF_3SR' (equiv)	recov RSSR (equiv)[a]	RSSR′ (equiv)[a]	R′SSR′ (equiv)	others (equiv)
CO	*t*-Bu	0.31 (**5d**)	0.01[b] (**5c**)	0.55 (**4d**)	0.41	0[c] (**4c**)	CF_3SSR (0.02)[a] CF_3SSR' (0.13)[b] CF_3 on C_{sp2} (0.06)
SO_2	*n*-C_8H_{17}	0.44 (**5d**)	0.25 (**5a**)	>0[d] (**4d**)	>0[d]	>0[d] (**4a**)	

[a] R = $CH_2CH_2CO_2Et$. [b] α′-Scission of the intermediate radical favored over α-scission when R′ = *t*-Bu (Scheme 4). [c] Formation of **4c** disfavored because of steric factors. [d] Comparable amounts of RSSR, RSSR′, and R′SSR′ from gas-phase chromatography.

Table 4. Preparation of Aliphatic Trifluoromethyl Sulfides from Aliphatic Trifluoromethylated Thioesters



entry	R	substrate	time (min)	conv (%)	$RSCF_3$ **5** (%)[a] vs conv **1** or **2**	$RSSCF_3$ (%)[a]	recov CF_3 (%)
1	*n*-C_8H_{17}	**1a**	105	92	76	(5)	83
2	*n*-C_8H_{17}	**2a**	40	100	74 (80)	0	80
3	*c*-C_6H_{11}	**1b**	90	72	29 (42)	(2)	67
4	*c*-C_6H_{11}	**2b**	80	88	38	(7)	45
5	*c*-C_6H_{11}	**2b**	150	94	32 (39)	(11)	43
6	$CH_2CH_2CO_2Et$	**1d**	105	79	81	0	85
7	$CH_2CH_2CO_2Et$	**2d**	40	100	74 (78)	0	78
8	CH_2Ph	**2e**	40	41	27	(6)	70
	CH_2Ph	**2e**	80	78	17	(9)	35
9	CH_2CO_2Et	**1h**	125	87	53	(4)	61
10	$CH_2CH(E)NHCOCF_3$ (E = CO_2Me)	**1i**	110	100	60		60

[a] Isolated yields. In parentheses:crude yields from ^{19}F NMR.

Scheme 6. Synthesis of Long-Chain Perfluoroalkanoic Thioesters

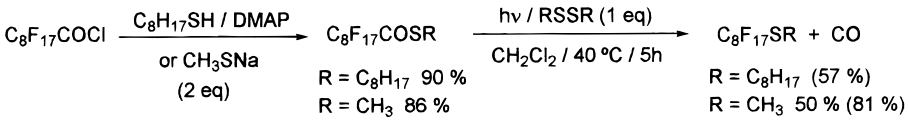
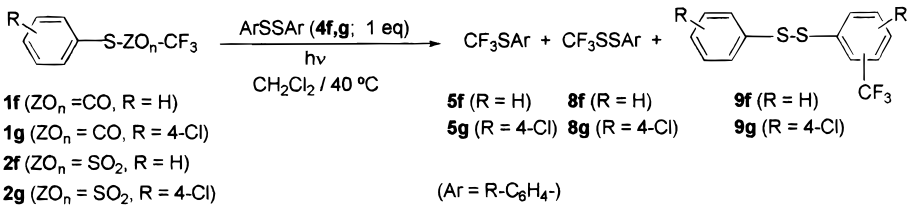


Table 5. Formation of Aryl Trifluoromethyl Sulfides from Aryl Trifluoromethylated Thioesters



entry	R	CF_3ZO_nSAr	time (min)	conv **1** or **2** (%)	$ArSCF_3$ **5** vs conv **1** or **2** (%)[a]	$ArSSCF_3$ **8** (%)[a]	$ArCF_3$ **9** (%)[a]	recov CF_3 (%)
1	H	**1f**	180	77	34	>0	(10)	59
2	H	**2f**	80	100	20 (25)	(2)	(10)	37
3	4-Cl	**1g**	210	68	40	>0	(3)	62
4	4-Cl	**2g**	80	94	27 (31)	(7)	0	42

[a] Isolated yields. In parentheses:crude yields from ^{19}F NMR.

c-Hexyl Trifluorothioacetate (1b). Oil. Bp_{20}: 94 °C. ^1H NMR: δ 3.70 (m, 1H), 1.97 (m, 2H), 1.50 (m, 8H). ^{13}C NMR: δ 43.73, 32.51, 25.78, 25.41. MS: *m*/*z* 212 ($M^{\bullet+}$), 143, 115, 97, 83, 45.

***tert*-Butyl Trifluorothioacetate (1c).** Oil. Bp_{760}: 99 °C. ^1H NMR: δ 1.56 (s, 3H). ^{13}C NMR: δ 50.50, 29.43. MS: *m*/*z* 186 ($M^{\bullet+}$), 171, 97, 74, 69, 57, 59, 56.

Ethyl 3-(Trifluoroacetylthio)propionate (1d). Oil. Bp_{20}: 101−102 °C. ^1H NMR: δ 4.20 (q, *J* = 7.2, 2H), 3.31 (t, *J* = 6.8, 2H), 2.71 (t, *J* = 6.8, 2H), 1.28 (t, *J* = 7.2, 3H). ^{13}C NMR: δ 171.01, 61.15, 33.30, 24.25, 14.04. MS: *m*/*z* 230 ($M^{\bullet+}$), 185, 157, 133, 101, 97, 87, 73, 69, 45.

Benzyl Trifluorothioacetate (1e). Oil. Bp_{20}: 115−117 °C. ^1H NMR: δ 7.80 (s, 5H), 4.24 (s, 2H). ^{13}C NMR: δ 134.88,

Table 6. Spectroscopic Features of CF_3ZO_nYR:CF_3COSR (1a−j), CF_3SO_2SR (2a−g), and CF_3SO_2SePh (3)

				^{13}C NMR				
no.	R	ZO_nY	^{19}F NMR δ (ppm) J_{C-F} (Hz)	CF_3 (q) δ (ppm) J_{C-F} (Hz)	CF_3CO δ (ppm) J_{C-F} (Hz)	CF_3ZO_nYC δ (ppm)	λ_{max} (nm)	ϵ (L mol^{-1} cm^{-1})
	Et (commercial)	COS					243	7500
1a	*n*-C_8H_{17}	COS	−75.98	115.75 290.0	184.95 40.0	31.86	244	5200
1b	c-C_6H_{11}	COS	−76.04	115.74 291.0	184.45 36.7	43.73	245	5010
1c	*t*-Bu	COS	−76.29	115.38 292.0	189.55 38.6	50.50	243	4300
1d	$CH_2CH_2CO_2Et$	COS	−76.00	118.62 290.4	185.29 40.2	24.25	242	2600
1e	CH_2Ph	COS	−76.47	115.79 290.6	184.39 40.3	33.66	218 246	4750 4750
1f	Ph	COS	−75.50	116.02 291.8	183.34 39.9	123.17	219 246	4400 2600
1g	4-Cl-C_6H_4	COS	−75.28	115.93 291.5	183.04 40.4	121.55	228 254	20000 6900
1h	CH_2CO_2Et	COS	−75.69	115.60 290.3	183.77 41.0	31.64		
1i	$CH_2CH(CO_2Me)$ $NHCOCF_3$	COS	−75.67	115.50 289.0	184.37 39.0	30.60		
2a	*n*-C_8H_{17}	SO_2S	−78.96	119.65 327.7		37.97	193 239	2105 105
2b	c-C_6H_{11}	SO_2S	−79.20	119.52 327.7		53.72	192 239	1917 94
2d	$CH_2CH_2CO_2Et$	SO_2S	−78.95	119.58 327.6		34.49	195 237	2812 625
2e	CH_2Ph	SO_2S	−78.64	119.68 327.9		41.99		
2f	Ph	SO_2S	−77.60	120.11 330.0		124.57	200 238	22325 10930
2g	4-Cl-C_6H_4	SO_2S	−75.46	120.06 330.0		122.94		
3	Ph	SO_2Se	−77.60	118.63 332.0		125.41	200 244	12217 7195

Table 7. Spectroscopic Features of CF_3YR:CF_3SR (5a−j) and CF_3SePh (10)

				^{13}C NMR			
no.	R	Y	^{19}F NMR δ (ppm) J_{C-F} (Hz)	CF_3 (q) δ (ppm) J_{C-F} (Hz)	CF_3YC δ (ppm) J_{C-F} (Hz)	λ_{max} (nm)	ϵ (L mol^{-1} cm^{-1})
5a	*n*-C_8H_{17}	S	−41.73	131.32 305.6	29.94 2.0		
5b	c-C_6H_{11}	S	−39.60	122.73 306.0	43.98 1.5		
5c	*t*-Bu	S	−36.64				
5d	$CH_2CH_2CO_2Et$	S	−41.87	130.93 306.0	24.68 2.3		
5e	CH_2Ph	S	−42.15	130.70 306.8	34.28 2.3		
5f	Ph	S	−43.37	129.73 307.8	124.45 2.1	193 238	13375 1812
5g	4-Cl-C_6H_4	S	−43.35	129.35 308.2	122.80 2.2	220 239	8500 3900
5h	CH_2CO_2Et	S	−42.82	130.21 307.0	31.91 3.0		
5i	$CH_2CH(CO_2Me)$ $NHCOCF_3$	S	−41.33	130.27 307.0	30.75		
10	Ph	Se	−36.60	122.75 332.6	122.62 1.5	191 213 260	20555 7407 741

129.09, 129.07, 128.28, 33.66. MS: *m*/*z* 220 ($M^{\bullet+}$), 151, 121, 91, 77, 69, 45.

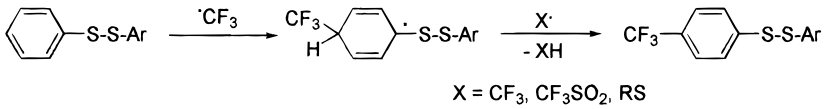
Phenyl Trifluorothioacetate (1f). Oil. Bp_{20}: 85−95 °C. ^{1}H NMR: δ 7.45 (m 5H). ^{13}C NMR: δ 134.61, 130.90, 129.91, 123.17. MS: *m*/*z* 206 ($M^{\bullet+}$), 137, 109, 77, 69.

4-Chlorophenyl Trifluorothioacetate (1g). Oil. Bp_{20}: 123−124 °C. ^{1}H NMR: δ 7.46−7.33 (m, 5H). ^{13}C NMR: δ 137.66, 135.87, 130.27, 121.55. MS: *m*/*z* 242 ($M^{\bullet+}$ + 2), 240 ($M^{\bullet+}$), 171, 145, 143, 108, 99, 45.

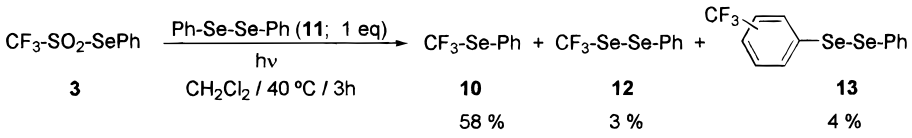
Ethyl 2-(Trifluoroacetylthio)acetate (1h). Oil. Bp_{20}: 90 °C. ^{1}H NMR: δ 4.24 (q, J = 7.1, 2H), 3.86 (s, 2H), 1.30 (t, J = 7.1, 3H). ^{13}C NMR: δ 166.69, 62.64, 31.46, 14.05. MS: *m*/*z* 216 ($M^{\bullet+}$), 171, 147, 144, 143, 119, 97, 75, 69, 45.

Preparation of Methyl Bis(*N*,*S*-trifluoroacetyl)-(L)-cysteinate (1i). Trifluoroacetic anhydride (17 mL, 120 mmol) was dropped, over approximately 35 min, on a suspension of methyl (L)-cysteinate hydrochloride (5.13 g, 30 mmol) in ethyl acetate (30 mL), kept at 0 °C under nitrogen. The suspension dissolved during dropping, after which stirring was continued at room temperature for 1 h 30 min. Ethyl acetate was then evaporated under vacuum at 50 °C, and the white solid residue was added to water (50 mL). The resulting aqueous phase was extracted with dichloromethane (3 × 70 mL). The combined organic phases were washed with a 5% aqueous solution of $NaHCO_3$ until pH = 8 and then with water until neutral and dried over $MgSO_4$. Dichloromethane was evaporated under

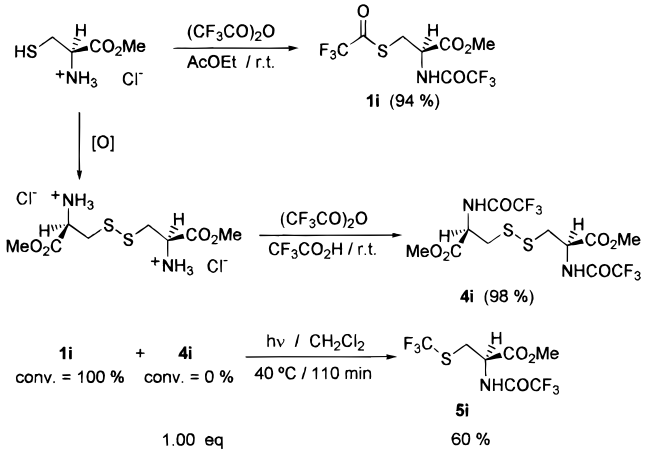
Scheme 7. Formation of Ring-Trifluoromethylated Products



Scheme 8. Photolysis of Phenyl Trifluoromethaneselenosulfonate 3



Scheme 9. Preparation of Methyl *N*-(Trifluoroacetyl)-*S*-(trifluoromethyl)-(L)-Cysteinate



vacuum at room temperature. After recrystallization in petroleum ether, the solid residue affored **1i** in a 94% yield (white needles). Mp: 77−78 °C. $[\alpha]^{25}_D = +67.8°$ ($c = 1.2$, $CHCl_3$). ^1H NMR: δ 7.24 (m, 1H), 4.92 (m, $J_{AX} + J_{BX} + J_{XNH} = 18.1$, 1H), 3.85 (s, 3H), 3.74 (dd, $J = 4.9$ and 14.4, 1H), 3.56 (dd, $J = 5.9$ and 14.4, 1H). ^{13}C NMR δ 168.00, 157.17 (q, $J = 38.5$), 115.44 (q, $J = 289$), 63.35, 51.81, 29.99, 13.91. ^{19}F NMR (not reported in Table 7) δ − 76.40. *m/z* 327 ($M^{\bullet+}$), 296, 268, 230, 214, 198, 184, 170, 156, 155, 143, 138, 129, 124, 117, 97, 69. Anal. Calcd for $C_8H_7F_6NO_4S$: C, 29.37; H, 2.16; N, 4.28; S, 9.80. Found: C, 29.45; H, 2.12; N, 4.24; S, 9.86.

Preparation of *n*-Octyl Pentadecafluorothiooctanoate ($C_7F_{15}C(O)S(CH_2)_7CH_3$). A solution of *n*-octanethiol (0.86 mL, 5 mmol) and DMAP (0.90 g, 7.5 mmol) in anhydrous dichloromethane (12 mL) was cooled at 0 °C. Then, a solution of pentadecafluorooctanoyl chloride (1.6 mL, 6.5 mmol) in anhydrous dichloromethane (10 mL) was dropped on it over 20 min. After addition, the reaction mixture was kept at room temperature under stirring for 2 h 30 min and then brought to reflux for 1 h. After cooling, the crude mixture was treated with trifluoroacetic acid (0.135 mL, 2.5 mmol) and then separated by flash chromatography on silica gel (10 g) with dichloromethane as eluent. This chromatography was monitored by GC. The interesting fractions were combined, dried over $MgSO_4$, and evaporated under vacuum at room temperature to afford 2.29 g of $C_7F_{15}C(O)S(CH_2)_7CH_3$ were obtained (yield = 90%). Colorless oil. ^1H NMR: δ 3.1 (t, $J = 7.3$, 2H), 1.6 (m, 2H), 1.3 (m, 10H), 0.9 (m, 3H). ^{13}C NMR δ 186.52, 108.96−120.79 (m), 22.63−31.81, 13.78. ^{19}F NMR δ −81.52 (t, $J = 9.5$, 3F), −116.89 (t, $J = 13.2$, 2F), −121.81 (broad, 2F), −122.42 (broad, 4F), −123.20 (broad, 2F), −126.69 (broad, 2F).

Preparation of Methyl Pentadecafluorothiooctanoate ($C_7F_{15}C(O)SCH_3$). A suspension of sodium methanethiolate (0.14 g, 2 mmol) in anhydrous dichloromethane (5 mL) was cooled at 0 °C. Then, a solution of pentadecafluorooctanoyl chloride (0.24 mL, 1.0 mmol) in anhydrous dichloromethane (5 mL) was dropped on it over 20 min. After addition, the reaction mixture was kept at room temperature under stirring for 1 h and then brought to reflux for 2 h. After cooling, the crude mixture was treated with trifluoroacetic acid (0.1 mL, 1 mmol) and then filtered on silica gel (10 g) with dichloromethane as eluent. The filtrate was dried over $MgSO_4$, filtered, and evaporated under vacuum at room temperature to afford 0.38 g of $C_7F_{15}C(O)SCH_3$ (yield = 86%). Colorless oil. ^1H NMR: δ 2.49 (s, 3H). ^{13}C NMR: δ 187.13, 107.67−120.96, 11.86. ^{19}F NMR: δ −81.43 (t, $J = 9.9$, 3F), −116.97 (t, $J = 13.2$, 2F), −121.87 (broad, 2F), −122.51 (broad, 4F), −123.22 (broad, 2F), −126.67 (broad, 2F). *m/z* 444 ($M^{\bullet+}$), 397, 75, 69, 47.

General Procedure for the Photolysis of Thioesters of Trifluoroacetic (1a,b,d−i), Triflic (2a,b,d−g), and Pentadecafluoroheptanoic Acids as well as for Phenyl Trifluoromethaneselenosulfonate (3). The photolysis was performed in a cylindrical flask ($\Phi = 50$ mm, $l = 15$ mm), the vertical flat walls of which were made out of quartz. It was fitted with a vertical reflux condenser. The mercury vapor lamp (Phillips HPK125, 125 W) was placed at 50 mm from one of the quartz walls, leaning at 45° from the vertical axis. A 1 mmol amount of the desired thioester and 1 mmol of the corresponding disulfide, dissolved in 20 mL of dichloromethane, were introduced in the reaction vessel. Before irradiation, air was blown off from this solution with nitrogen, under magnetic stirring. Then, the reaction mixture was illuminated under stirring, and heat from the lamp brought it to reflux. The reaction was monitored by GC. At the end of the reaction, the crude mixture was concentrated under vacuum (without heating), analyzed by GC, MS, and ^{19}F NMR, and then separated by chromatography on silica gel (with petroleum ether or cyclohexane as eluent, unless stated otherwise). Yields of the resulting compounds are given in Results and Discussion. Their common UV, ^{19}F NMR, and ^{13}C NMR data are given in Table 7, and their specific analytical data are described below.

Common Spectroscopic Features of CF_3SR (5a−i) and CF_3SePh (10). See Table 7.

Additional Data for CF_3SR (1a−i) and $C_7F_{15}SR$ (R = C_8H_{17}, CH_3).

Octyl Trifluoromethyl Sulfide (5a). Oil. ^1H NMR: δ 2.87 (t, $J = 7.4$, 2H), 1.69 (quint, $J = 7.3$, 2H), 1.28 (m, 10H), 0.89 (t, $J = 6.7$, 3H). ^{13}C NMR: δ 31.85, 29.50, 29.18, 29.02, 28.62, 22.71, 14.09. MS: *m/z* 214 ($M^{\bullet+}$), 195, 145, 129, 115, 83, 69. Anal. Calcd for $C_9H_{17}F_3S$: C, 50.48; H, 7.94; S, 14.95. Found: C, 50.56; H, 8.12; S, 14.97.

Cyclohexyl Trifluoromethyl Sulfide (5b). Oil. ^1H NMR: δ 3.25 (m, 1H), 2.06 (m, 2H), 1.75 (m, 2H), 1.7 to 1.2 (m, 1/2 width = 28 Hz, 6H). ^{13}C NMR: δ. 33.89, 25.74, 25.33. MS: *m/z* 184 ($M^{\bullet+}$), 141, 115, 101, 83, 45.

Ethyl 3-(Trifluoromethylthio)propionate (5d). Oil (eluent: petroleum ether/ethyl ether 19:1). ^1H NMR: δ 4.18 (q, $J = 7.3$, 2H), 3.13 (t, $J = 7.0$, 2H), 2.74 (t, $J = 7.0$, 2H), 1.28 (t, $J = 7.3$, 3H). ^{13}C NMR: δ 170.85, 61.02, 34.78, 24.74, 14.08. MS: *m/z* 202 ($M^{\bullet+}$), 157, 133, 129, 115, 105, 87, 69, 45.

Benzyl Trifluoromethyl Sulfide (5e). Oil. ^1H NMR: δ 7.34 to 7.25 (m, 5H), 4.09 (s, 2H). ^{13}C NMR: δ 135.04, 128.95, 128.89, 128.04. MS: *m/z* 192 ($M^{\bullet+}$), 91, 65.

Phenyl Trifluoromethyl Sulfide (5f). Oil. Bp_{760}: 140 °C. ^1H NMR: δ 7.66 (dd, $J = 7.9$ and 1.6, 2H), 7.47 to 7.34 (m, 3H). ^{13}C NMR: δ 136.54 (q, $J = 0.9$), 130.82, 129.48. MS: *m/z* 178 ($M^{\bullet+}$), 159, 109, 108, 77, 69.

4-Chlorophenyl Trifluoromethyl Sulfide (5g). Oil. ^{1}H NMR: δ 7.59 (d, J = 8.5, 2H), 7.39 (d, J = 8.5, 2H). ^{13}C NMR: δ 137.76, 137.63 (q, J = 1.0), 129.85. MS: m/z 214 ($M^{\bullet+}$), 212, 193, 145, 143, 108, 99, 69, 45.

Ethyl 2-(Trifluoromethylthio)acetate (5h). Oil (eluent: petroleum ether/diethyl ether 95:5, then 80:20). ^{1}H NMR: δ 4.24 (q, J = 7.1, 2H), 3.66 (s, 2H), 1.27 (t, J = 7.1, 3H). ^{13}C NMR: δ 167.65, 62.36, 14.00. MS: m/z 188 ($M^{\bullet+}$), 143, 115, 75, 69, 46, 45, 42, 29.

Methyl *N*-(Trifluoroacetyl)-*S*-(trifluoromethyl)-(L)-cysteinate (5i). Mp: 53 °C. $[\alpha]_D25$ = +58.5 ° (C = 0.8, $CHCl_3$). ^{1}H NMR: δ 7.36 (m, 1H), 4.91 (m, ΣJ = 16.8, 1H), 3.85 (s, 3H), 3.57 (dd, J = 14.9 and 4.6, 1H), 3.37 (dd, J = 14.9 and 5.1, 1H). ^{13}C NMR: δ 168.62, 157.26, 109.85, 53.64, 52.40. ^{19}F NMR: δ −76.41 (CF_3CONH). MS: m/z 299 ($M^{\bullet+}$), 280, 268, 240, 202, 198, 186, 184, 170, 138, 124, 117, 115, 97, 69, 59, 45.

Octyl Pentadecafluoroheptyl Sulfide. Oil. ^{19}F NMR: δ −126.37 (broad, 2F), −122.96 (broad, 2F), −122.22 (broad, 2F), −121.46 (broad, 2F), −120.08 (broad, 2F), −87.68 (t, J = 12, 2F), −81.09 (t, J = 9, 3F).

Methyl Pentadecafluoroheptyl Sulfide. Oil. ^{1}H NMR: δ 2.4 (s). ^{19}F NMR: δ −126.87 (broad, 2F), −123.46 (broad, 2F), −122.73 (broad, 2F), −122.05 (broad, 2F), −120.35 (broad, 2F), −90.92 (t, J = 14, 2F), −81.29 (t, J = 8.5, 3F).

Additional Data for CF_3SePh (10). Phenyl Trifluoromethyl Selenide (10). Oil. ^{13}C NMR: δ 137.09 (q, J = 0.7), 130.33, 129.59. MS: m/z 226 ($M^{\bullet+}$), 157, 127, 77, 69, 65, 50. Anal. Calcd for $C_7H_5F_3Se$: C, 37.36; H, 2.24; Se, 35.08. Found: C, 36.99; H, 2.21; Se, 35.13.

Spectroscopic Data for Byproducts Formed during Photolysis Experiments. Chloromethyl Octyl Sulfide (6a). MS: m/z 196 ($M^{\bullet+}$ + 2), 194 ($M^{\bullet+}$), 159, 145, 97, 95, 83, 49, 45.

Chloromethyl c-Hexyl Sulfide (6b). MS: m/z 166 ($M^{\bullet+}$ + 2), 164 ($M^{\bullet+}$), 129, 115, 83, 82, 45.

Ethyl 3-(Chloromethylthio)propionate (6d). MS: m/z 184 ($M^{\bullet+}$ + 2), 182 ($M^{\bullet+}$), 147, 139, 137, 133, 111, 109, 102, 101, 97, 95, 87, 74, 73, 59, 45.

Dichloromethyl Octyl Sulfide (7a). MS: m/z 230 ($M^{\bullet+}$ + 2), 228 ($M^{\bullet+}$), 195, 193, 145, 87, 85, 83, 45.

Dichloromethyl c-Hexyl Sulfide (7b). MS: m/z 200 ($M^{\bullet+}$ + 2), 198 ($M^{\bullet+}$), 165, 163, 115, 83, 82, 45.

Ethyl 3-(Dichloromethylthio)propionate (7d). MS: m/z 220 ($M^{\bullet+}$ + 4), 218 ($M^{\bullet+}$ +2), 216 ($M^{\bullet+}$), 183, 181, 175, 173, 171, 147, 145, 143, 117, 95, 93, 87, 73, 59, 45.

Octyl Trifluoromethyl Disulfide (8a). ^{19}F NMR: δ −46.68 (s). MS: m/z 246 ($M^{\bullet+}$), 145, 133, 101, 71, 69, 45.

c-Hexyl Trifluoromethyl Disulfide (8b). ^{19}F NMR: δ −46.61 (s). ^{13}C NMR: δ 129.40 (q, J = 314), 50.19, 32.37, 25.89, 25.49. MS: m/z 216 ($M^{\bullet+}$), 133, 115, 83, 69, 45.

***tert*-Butyl Trifluoromethyl Disulfide (8c).** ^{19}F NMR: δ −45.57 (s).

Ethyl 3-(Trifluoromethyldithio)propionate (8d). ^{19}F NMR: δ −46.61 (s). MS: m/z 234 ($M^{\bullet+}$), 189, 161, 147, 133, 105, 87, 73, 69, 59.

Benzyl Trifluoromethyl Disulfide (8e). ^{19}F NMR: δ −47.01.

Phenyl Trifluoromethyl Disulfide (8f). ^{19}F NMR: δ −46.40 (s,). MS: m/z 210 ($M^{\bullet+}$), 141, 109, 77, 69, 65.

4-Chlorophenyl Trifluoromethyl Disulfide (8g). ^{19}F NMR: δ −46.27 (s). MS: m/z 246 ($M^{\bullet+}$), 244 ($M^{\bullet+}$), 175, 143, 108, 69.

Ethyl 2-(Trifluoromethyldithio)acetate (8h). ^{19}F NMR: δ −46.56 (s).

Phenyl (Trifluoromethyl)phenyl Disulfide (9f; three isomers). ^{19}F NMR: δ −60.50 (s) and −63.00 (s). MS: first isomer m/z 286 ($M^{\bullet+}$), 267, 222, 177, 157, 109, 77, 69; second isomer m/z 286 ($M^{\bullet+}$), 267, 222, 177, 157, 109, 77, 69; third isomer m/z 286 ($M^{\bullet+}$), 218, 185, 154, 141, 109, 77, 69.

Cross-Coupling Trifluoromethylations. Trifluoromethylation of Diethyl 3,3′-Dithiodipropionate (4d) with *tert*-Butyl Trifluorothioacetate (1c). Following the general photolysis procedure, a mixture of **1c** (0.21 g, 1.1 mmol), **4d** (0.26 g, 0.98 mmol), and dichloromethane (20 mL) was irradiated at 40 °C for 1.5 h. After illumination, (trifluoromethoxy)-benzene (0.037 g, 0.23 mmol), used as internal standard for ^{19}F NMR analysis, was added to the cooled reaction mixture, in which the corresponding spectrum revealed the presence of **1c** (0.100 mmol), **5c** (0.143 mmol), **5d** (0.335 mmol), **8c** (0.013 mmol), **8d** (0.026 mmol), and a vinylic trifluoromethylated product (0.067 mmol). The crude mixture was evaporated at room temperature under vacuum to deliver an orange oil (0.400 g) which was submitted to flash chromatography over silica gel (14 g) with, first, 200 mL of petroleum ether/diethyl ether (95:5) and then 200 mL of petroleum ether/diethyl ether (80:20). The pale yellow oil, resulting from the first elution, contained **5d** (0.20 mmol), **8d** (0.02 mol), and ethyl 3-(*tert*-butyldithio)propionate (0.45 mmol), as indicated from ^{19}F and ^{1}H NMR with $PhOCF_3$ as internal standard. The second fraction was quite almost constituted of **4d**.

Ethyl 3-(*tert*-Butylthio)propionate. ^{1}H NMR: δ 4.14 (q, J = 7.5, 2H), 2.92 (t (broad), 2H), 2.69 (t (broad), 2H), 1.33 (s, 9H), 1.25 (t, J = 7.5, 3H). ^{13}C NMR: δ 171.84, 60.73, 47.95, 35.13, 34.45, 29.99, 14.23. MS: m/z 222 ($M^{\bullet+}$), 177, 166, 165, 121, 120, 101, 87, 73, 57, 45.

Trifluoromethylation of Diethyl 3,3′-Dithiodipropionate (4d) with Octyl Trifluoromethanethiosulfonate (2a). As above, a mixture of **2a** (0.278 g, 1 mmol), **4d** (0.266 g, 1 mmol), and dichloromethane (20 mL) was irradiated at 40 °C for 40 min. Analysis of the resulting crude mixture by GC coupled with MS indicated the presence of **4a**, **4d**, and ethyl 3-(octyldithio)propionate in similar amounts.

Ethyl 3-(Octyldithio)propionate. MS: m/z 278 ($M^{\bullet+}$), 233, 132, 120, 101, 29.

Trifluoromethylation of Dimethyl *N,N′*-Bis(trifluoroacetyl)-(L)-cystinate (4i) with Ethyl Trifluorothioacetate. A mixture of anhydrous acetonitrile (20 mL), ethyl trifluorothioacetate (0.086 g, 0.55 mmol) and **4i** (0.23 g, 0.50 mmol) was introduced in the reaction vessel, purged for 10 min with dry nitrogen at room temperature, and then illuminated under stirring at 40 °C for 45 min. After addition of more ethyl trifluoroacetate (0.086 g), illumination at 40 °C was continued for 1 h. This latter procedure was repeated twice. Reaction progress was monitored by GC. After irradiation (3 h 45 min), cooling, and addition of $PhOCF_3$ (0.037 g, 0.23 mmol) as internal standard, ethyl trifluoromethyl sulfide (δ −41.13 (s), 1.01 mmol) and **5i** (0.29 mmol) were detected by ^{19}F NMR in the crude reaction mixture, as well as some other trifluoroacetylated compounds. This crude mixture was concentrated at room temperature under vacuum. Then, the resulting brown oil (0.32 g) was purified by flash chromatography on silica gel with, first, petroleum ether/ethyl acetate (95:5), second, petroleum ether/ethyl acetate (80:20), and, finally, ethyl acetate. Though **5i** was the major component of the first fraction and methyl *S*-(ethylthio)-*N*-trifluoroacetyl-(L)-cysteinate the major component of the second fraction, these two compounds could not be clearly separated. The combined two fractions contained **5i** (65 mg, 0.22 mmol) and methyl *S*-(ethylthio)-*N*-(trifluoroacetyl)-(L)-cysteinate (85 mg, 0.30 mmol). The third fraction contained unreacted **4i**.

Methyl *S*-(Ethylthio)-*N*-(trifluoroacetyl)-(L)-cysteinate. ^{1}H NMR: δ 7.41 (m, broad, 1H), 4.92 (m, 1/2 width = 20.7, 1H), 3.32 (s, 3H), 3.32 to 3.12 (m, $\Delta\nu/J$ < 2, 2H), 2.73 (q, J = 7.3, 2H), 1.32 (t, J = 7.3, 3H). ^{13}C NMR: δ 169.41, 156.90 (q, J = 38), 115.59 (q, J = 288), 53.20, 52.27, 39.27, 32.72, 14.21. ^{19}F NMR: δ −76.41. MS: m/z 291 ($M^{\bullet+}$), 232, 198, 184, 178, 170, 138, 117, 107, 93, 79, 69, 61, 59, 45, 43, 29.

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