A new method for the synthesis of fluorinated vinyl sulfides and ketene dithioacetals

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A new method was developed for the synthesis of fluorine-containing functionally substituted vinyl sulfides and ketene dithioacetals from the corresponding derivatives of α-trifluoromethyl-substituted CH-acids and thiols in the presence of $BF_3 \cdot NEt_3$.

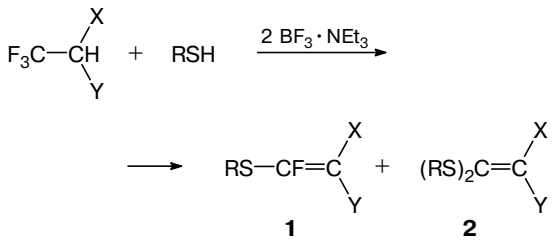
Key words: CH-acids, thiols, fluorinated vinyl sulfides, fluorinated ketene dithioacetals, dehydrofluorination, $BF_3 \cdot NEt_3$.

One of the main methods for the synthesis of fluorinated vinyl sulfides involves the reactions of thiols with fluoroalkenes followed by dihydrofluorination of the addition products.[1] Vinyl sulfides and ketene dithioacetals are formed in one stage by the reactions of fluoroalkenes with sodium thiolates, the direction of the reaction depending on the order in which the reagents are added and on the reagent ratio.[2] However, the starting fluoroalkenes, in particular, functionally substituted compounds, are difficultly accessible compounds, which is an essential limitation of these procedures.

We found that the reactions of thiols with derivatives of some α-trifluoromethyl-containing CH-acids in the presence of 2 equiv. of the $BF_3 \cdot NEt_3$ complex afforded vinyl sulfides **1** in one step in preparative yields (Scheme 1). In some cases, fluorine-containing ketenes **2** are formed as the major products or by-products (Table 1).

Functionally substituted fluorine-containing CH-acids, such as methyl ester and nitrile of 2-hydrohexafluoroisobutyric acid, dimethyl (trifluoromethyl)malonate, and 2-hydrotetrafluoropropiononitrile, enter into this reaction. The reaction conditions are determined by the strength of the CH-acid. Thus the reactions with derivatives of hexafluoroisobutyric and (trifluoromethyl)malonic acids occurred at 50 °C, the reaction with tetrafluoroproiononitrile, which is a weaker CH-acid, required heating to 90—100 °C, whereas methyl 2-hydrotetrafluoropropionate (the weakest CH-acid studied) did not give the target products even on heating in a sealed tube at 150 °C.

Scheme 1



Apparently, the first stage of the reaction (Scheme 2) involves dehydrofluorination of the CH-acid to form

Scheme 2

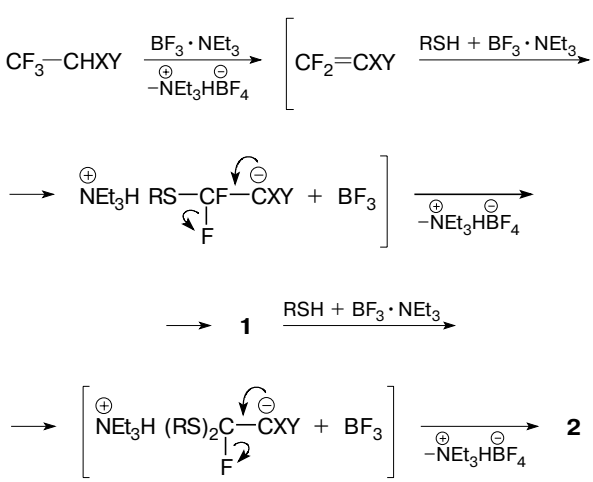


Table 1. Products of the reactions of CH-acids with RSH

Compound	X	Y	R	1	2
1a, **2a**	CF_3	COOMe	$PhCH_2$	3	2
1b, **2b**	CF_3	COOMe	CH_2COOMe	1	1
1c	CF_3	COOMe	Bu^t	1	0
1d, **2d***	COOMe	COOMe	$PhCH_2$	4	1
1e, **2e**	CF_3	CN	$PhCH_2$	7	3
1f, **2f**	CF_3	CN	CH_2COOMe	3	2
1g	CF_3	CN	Bu^t	1	0
1h, **2h**	F	CN	$PhCH_2$	1	4
1i	F	CN	Bu^t	1	0
1j, **2j**	F	CN	Me	1	9

* Compound **2d** was not isolated in individual form because it decomposed on fractionation; its formation was detected based on the data from GLC-mass spectrometry (*m/z* 388 $[M]^+$).

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the corresponding fluoroalkene. The latter is immediately attacked by the anion generated under the action of $BF_3 \cdot NEt_3$ on a thiol. The intermediate thus formed is stabilized by β-elimination of the fluoride ion, which is irreversibly incorporated into triethylammonium tetrafluoroborate. It is this fact that is responsible for the absence of the addition products. Products **2** are formed analogously.

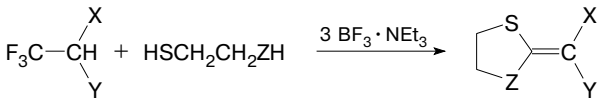
Mixtures of products **1** and **2** can readily be separated by fractionation or crystallization. The proportion of disubstitution products depends on the reaction conditions (the yield increases under more drastic conditions) and on the structure of the initial thiol. Thus the reaction of tetrafluoropropiononitrile with methanethiol afforded ketene dimethyl dithioacetal **2j** as the major product, whereas even no traces of the corresponding ketene dithioacetal were detected among the products of the reaction with sterically hindered Bu^tSH. Previously,[3] the role of steric effects in the reactions of fluoroalkenes with secondary amines has been noted.

The composition of the reaction products depends essentially on the reagent ratio. Thus the introduction of the third equivalent of $BF_3 \cdot NEt_3$ and the second equivalent of the thiol makes it possible to direct the synthesis toward double substitution products. In particular, bifunctional thiols, such as 1,2-ethanedithiol and mercaptoethanol, gave exclusively ethylene (di)thioacetals **3** (Scheme 3).

Table 2. Yields, properties, spectral characteristics, and the data from elemental analysis of compounds **1—3**

Compound	Yield (%)	B.p./°C (Torr) [m.p./°C]	Found / Calculated (%) C	Found / Calculated (%) H	Molecular formula	^{1}H NMR (DMSO-d_6), δ	MS (EI, 70eV), *m/z*, $[M]^+$
1a	52	112—114 (3)	48.76 / 48.98	3.43 / 3.40	$C_{12}H_{10}F_4O_2S$	7.75 (m, 5 H, Ph); 4.34 and 4.28 (both s, 2 H each, CH_2, ratio 1 : 9); 3.79 (s, 3 H, Me)	294
1b	43	103—104 (3)	34.95 / 34.78	2.92 / 2.90	$C_8H_8F_4O_4S$	4.02 and 3.97 (both s, 2 H, CH_2, ratio 1 : 7); 3.84 and 3.82 (both s, 3 H, Me, ratio 1 : 7); 3.68 (s, 3 H, Me)	276
1c[4]	71	55—57 (3)	41.40 / 41.54	4.58 / 4.62	$C_9H_{12}F_4O_2S$	3.83 and 3.81 (both s, 3 H, Me, ratio 1 : 4); 1.53 (s, 9 H, Bu^t)	260
1d	66	160—165 (3)	54.80 / 54.93	4.57 / 4.58	$C_{13}H_{13}FO_4S$	7.30 (m, 5 H, Ph); 4.27 (s, 2 H, CH_2); 3.74 (s, 3 H, Me); 3.70 (s, 3 H, Me)	284
1e	63	86—88 (3)	50.71 / 50.57	2.63 / 2.68	$C_{11}H_7F_4NS$	7.30 (m, 5 H, Ph); 5.50 (s, 2 H, CH_2)	261
1f	52	78—79 (3)	34.80 / 34.57	2.04 / 2.06	$C_7H_5F_4NO_2S$	4.11 (s, 2 H, CH_2); 3.78 (s, 3 H, Me)	243
1g	73	70—72 (12)	42.37 / 42.29	4.00 / 3.96	$C_8H_9F_4NS$	1.67 (s, Bu^t)	227
1h	18	76—78 (3)	56.92 / 56.87	3.33 / 3.32	$C_{10}H_7F_2NS$	7.35 (m, 5 H, Ph); 4.32 and 4.27 (both s, 2 H each, CH_2, ratio 1 : 1)	211
1i	73	57—60 (15)	47.65 / 47.46	5.05 / 5.08	$C_7H_9F_2NS$	1.50 (s, Bu^t)	177
1j	9	45—47 (15)	35.29 / 35.56	2.27 / 2.22	$C_4H_3F_2NS$	2.58 and 2.57 (both s, Me, ratio 3 : 1)	135
2a	34	185—190 (3)	57.34 / 57.29	4.23 / 4.27	$C_{19}H_{17}F_3O_2S_2$	7.30 (m, 10 H, 2 Ph); 4.26 and 4.18 (both s, 2 H each, 2 CH_2); 3.68 (s, 3 H, Me)	398
2b	46	160—163 (3)	36.52 / 36.46	3.61 / 3.59	$C_{11}H_{13}F_3O_6S_2$	3.86 (s, 2 H, CH_2); 3.83 (s, 3 H, Me); 3.77 (s, 2 H, CH_2); 3.69 (s, 6 H, 2 Me)	362
2e	24	[53—54]	59.27 / 59.18	3.85 / 3.84	$C_{18}H_{14}F_3NS_2$	7.35 (m, 10 H, 2 Ph); 4.46 and 4.42 (both s, 2 H each, 2 CH_2)	365
2f	32	145—147 (3)	36.63 / 36.47	3.08 / 3.04	$C_{10}H_{10}F_3NO_4S_2$	4.07 and 4.04 (both s, 2 H each, 2 CH_2); 3.75 and 3.74 (both s, 3 H each, 2 Me)	329
2h	59	177—180 (3)	64.91 / 64.76	4.40 / 4.44	$C_{17}H_{14}FNS_2$	7.30 (m, 10 H, 2 Ph); 4.25 and 4.08 (both s, 2 H each, 2 CH_2)	315
2j	69	109—111 (9)	36.68 / 36.81	3.71 / 3.68	$C_5H_6FNS_2$	2.55 and 2.48 (both s, 3 H each, 2 Me)	163
3a	82	[51—52]	34.52 / 34.43	2.90 / 2.87	$C_7H_7F_3O_2S_2$	3.75 (s, 3 H, Me); 3.57 and 3.46 (both m, 2 H each, 2 CH_2)	244
3b	76	[55—56]	34.20 / 34.12	1.87 / 1.90	$C_6H_4F_3NS_2$	3.86 and 3.74 (both m, 2 H each, 2 CH_2)	211
3c	72	[56—57]	37.36 / 37.27	2.50 / 2.48	$C_5H_4FNS_2$	3.68 (m, 2 CH_2)	161
3d	75	[30—31]	36.92 / 36.84	3.06 / 3.07	$C_7H_7O_3F_3S$	4.75 (t, 2 H, CH_2O, J = 8 Hz); 3.73 (s, 3 H, Me); 3.32 (t, 2 H, CH_2S, J = 8 Hz)	228

Scheme 3



3a—d

	a	b	c	d
X	CF_3	CF_3	F	CF_3
Y	COOMe	CN	CN	COOMe
Z	S	S	S	O

Thus, this type of reactions is a convenient one-stage procedure for the synthesis of fluorine-containing vinyl sulfides and ketene dithioacetals containing functional groups at the double bond based on the use of readily accessible fluorine-containing CH-acids.

Experimental

The ^{19}F NMR spectra were recorded on a Bruker AC-200F spectrometer operating at 188.31 MHz. The ^1H NMR spectra were measured on a Bruker AC-300SF instrument operating at 300.13 MHz. The chemical shifts (δ) are given relative to CF_3COOH (^{19}F, the external standard) and Me_4Si (^1H, the internal standard). The IR spectra were recorded on a Perkin—Elmer 1720X instrument. The ratios of the reaction products were determined by GLC on an HP5890 instrument equipped with an HP-5972 mass-selective detector. The yields, properties, spectral characteristics, and the data from elemental analysis of the resulting compounds are given in Table 2.

Reactions of CH-acids with thiols (general procedure). A mixture of a CH-acid (0.1 mol), a thiol (0.1 mol), and the $BF_3 \cdot NEt_3$ complex (0.21 mol) was heated in a flask equipped with a reflux condenser to 50 °C (the reactions of 2-hydrotetrafluoropropiononitrile were carried out in sealed glass tubes at 100 °C). The beginning of the reaction was evidenced by the appearance of traces of a white fume above the reaction mixture and substantial heat evolution. Once the reaction started, heating was terminated, and the reaction mixture was cooled with cold water, which was accompanied by formation of an abundant precipitate. The mixture was washed with water and 5% HCl. The reaction products were extracted with ether, dried with Na_2SO_4, and fractionated.

Methyl 3-benzylthio-3-fluoro-2-trifluoromethylacrylate (1a), ^{19}F NMR (DMSO-d_6), δ: *E*-isomer, 20.4 (d, 3 F, CF_3, J = 22.0 Hz); 15.3 (q, 1 F, CF, J = 22.0 Hz); *Z*-isomer, 21.2 (d, 3 F, CF_3, J = 13.5 Hz); 17.1 (q, 1 F, CF, J = 13.5 Hz), E/Z = 9 : 1. **Methyl 3-fluoro-3-(methoxycarbonylmethyl)thio-2-trifluoromethylacrylate (1b)**, IR, ν/cm^{-1}: 1740, 1730 (C=O); 1600 (C=C). **Methyl 3-*tert*-butylthio-3-fluoro-2-trifluoromethylacrylate (1c)** (*cf.* lit.[4]) **Dimethyl benzylthio(fluoro)methylidenemalonate (1d)**, ^{19}F NMR (DMSO-d_6), δ: 17.3 (s, CF). **3-Benzylthio-3-fluoro-2-trifluoromethylacrylonitrile (1e)**, ^{19}F NMR (CD_3CN), δ: *E*-isomer, 22.5 (q, 1 F, CF, J = 18.0 Hz); 19.7 (m, 3 F, CF_3); *Z*-isomer, 24.0 (q, 1 F, CF, J = 10.9 Hz); 19.7 (m, 3 F, CF_3); E/Z = 4 : 1. **Methyl (2-cyanotetrafluoroprop-1-enyl)thioacetate (1f)**, IR, ν/cm^{-1}: 2235 and 2230 (CN); 1710 (C=O); 1590 (C=C). **3-*tert*-Butylthio-3-fluoro-2-trifluoromethylacrylonitrile (1g)**, IR, ν/cm^{-1}: 2241 and 2223 (CN); 1592 (C=C). **3-Benzylthio-2,3-difluoroacrylonitrile (1h)**, ^{19}F NMR (DMSO-d_6), δ: *E*-isomer, −4.4 and −50.7 (both d, 1 F each, CF, J = 12 Hz); *Z*-isomer, −30.2 and −76.6 (both d, 1 F each, CF, J = 144 Hz), Z/E = 1 : 1. **3-*tert*-Butylthio-2,3-difluoroacrylonitrile (1i)**, IR, ν/cm^{-1}: 2225 (CN); 1595 (C=C). **2,3-Difluoro-3-methylthioacrylonitrile (1j)**, ^{19}F NMR (DMSO-d_6), δ: *E*-isomer, −4.6 and −50.3 (both d, 1 F each, CF, J = 12 Hz); *Z*-isomer, −30.5 and −75.2 (both d, 1 F each, CF, J = 144 Hz), Z/E = 1 : 1. **Methyl 3,3-bis(benzylthio)-2-trifluoromethylacrylate (2a)**, ^{19}F NMR (DMSO-d_6), δ: 24.5 (s, CF_3). **Methyl 3,3-bis(methoxycarbonylmethylthio)-2-trifluoromethylacrylate (2b)**, ^{19}F NMR (DMSO-d_6), δ: 24.1 (s, CF_3). **Bis(benzylthio)-2-trifluoromethylacrylonitrile (2e)**, ^{19}F NMR (DMSO-d_6), δ: 26.5 (s, CF_3). **3,3-Bis(methoxycarbonylmethylthio)-2-trifluoromethylacrylonitrile (2f)**, ^{19}F NMR (DMSO-d_6), δ: 26.7 (s, CF_3). **3,3-Bis(benzylthio)-2-fluoroacrylonitrile (2h)**, ^{19}F NMR (DMSO-d_6), δ: −20.5 (s, CF). **2-Fluoro-3,3-bis(methylthio)acrylonitrile (2j)**, IR, ν/cm^{-1}: 2225 (CN); 1600 (C=C).

Reactions of CH-acids with bifunctional thiols. The reactions were carried out with the use of 3 equiv. of the $BF_3 \cdot NEt_3$ complex as described above. After removal of the solvent, the compounds were recrystallized from hexane. This procedure was used for the preparation of **2-(1-methoxycarbonyl)trifluoroethylidene-1,3-dithiolane (3a)**; **2-(1-cyano)trifluoroethylidene-1,3-dithiolane (3b)**; **2-(cyano)fluoromethylidene-1,3-dithiolane (3c)**, IR, ν/cm^{-1}: 2218 (CN), 1599 (C=C); and **2-(1-methoxycarbonyl)trifloroethylidene-1,3-oxathiolane (3d)**.

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