Fluoroalkylthio Five-Membered Heteroaromatics

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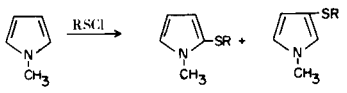
Received March 7, 1975

Fluoroalkylthio substituted five-membered ring aromatic heterocycles were prepared by direct substitution with fluoroalkylsulfenyl chlorides.

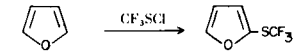
As recently as 1967, a review by Senning and Kraae (1) indicated that little was known about trihalomethylsulfur (also referred to as trihalomethylmercapto or thio) groups as substituents in heteroaromatic compounds. Electrophilic substitution on benzenoid aromatic compounds with trifluoromethylsulfenyl chloride has been described (2) but the literature suggested that this might not be feasible with heterocycles since thiophene was known to be unreactive toward trichloromethylsulfenyl chloride (3). However, heteroaromatic sulfides have been prepared from nitrobenzenesulfenyl chlorides (4-6) and trifluoromethylsulfenyl chloride substitution on uracil and 1,3-dimethyluracil has been recently reported (7a). Condensation of perhalomethylthio-substituted ketones with phenylhydrazines led to pyrazoles (7b). This paper reports on the preparation of fluoroalkylthio five-membered ring aromatic heterocycles by a direct substitution with fluoroalkylsulfenyl chlorides. Reactions were possible with both π-rich aromatic mono-heteroatom heterocycles and di-heteroatom containing heterocycles with electron-donating (*ortho-para* directing) substituents (8,9).

The reaction of *N*-methylpyrrole with trifluoromethylsulfenyl chloride, fluorodichloromethylsulfenyl chloride, trichloromethylsulfenyl chloride, and perfluoroheptylsulfenyl chloride led to 1-methyl-2-(trifluoromethylthio)-pyrrole (**1**) and 1-methyl-3-(trifluoromethylthio)pyrrole (**2**), 1-methyl-2-(fluorodichloromethylthio)pyrrole (**3**), 1-methyl-2-(trichloromethylthio)pyrrole (**4**), and 1-methyl-2-(perfluoroheptylthio)pyrrole (**5**), respectively. The magnitude of the proton nmr coupling constants was used to establish the position of substitution since the values of 3.4 to 3.8 Hz noted are indicative of coupling between C-3 and C-4 protons (10). A smaller coupling constant, $J_{2,5}$ of 2.5 Hz, was observed as expected with the 3-trifluoromethylthio substituted isomer, compound **2**, isolated as a minor product. The proton nmr data are summarized in Table I and the fluorine data in Table II.



1 (R = CF_3) **2** (R = CF_3)
3 (R = $CFCl_2$)
4 (R = CCl_3)
5 (R = C_7F_{15})

Analogous structural assignments were based upon known coupling constants (11) for the products of trifluoromethylsulfenyl chloride with furan as 2-(trifluoromethylthio)furan (**6**) and with thiophenes as 2-(trifluoromethylthio)thiophene (**7**) and 2-methyl-5-(trifluoromethylthio)thiophene (**8**). These results are consistent with normal electrophilic substitution, occuring largely at the 2-position in pyrrole, furan, and thiophene derivatives (8,9).



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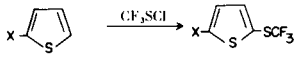


7 (X = H)
8 (X = CH_3)

The introduction of an electron-donating substituent in the 2-position of *N*-methylimidazole and thiazole enhances reactivity and reinforces electrophilic substitution at the 5-position (12). As expected, substitution took place readily with trifluoromethylsulfenyl chloride on 2-(methylsulfonamido)thiazole to yield 2-(methylsulfonamido)-4(5)-(trifluoromethylthio)thiazole (**9**). The nmr ^{13}C proton coupling constant has been used previously to establish the position of substituents in this system (13a) but examination of this signal was inconclusive in this case since the value ($J\ ^{13}CH$ = 196 Hz) was beyond the ranges suggested for isomer differentiation. The necessary presence of the 2-substituent precludes an examination of the aromatic

Table I

Proton (τ) Nmr Values (a)

Compd.	5-H (b)	3-H (b)	4-H (b)	CH_3 (c)	Coupling (Hz)
1	3.25	3.43	3.90	6.36	J_{34} = 3.8, J_{35} = 1.8, J_{45} = 2.9
2	3.53	3.27 (2-H)	3.77	6.47	J_{24} = 1.8, J_{25} = 2.5, J_{45} = 2.5
3	3.18	3.37	3.87	6.32	J_{34} = 3.9, J_{35} = 1.6, J_{45} = 2.7
4	3.14	3.28	3.83	6.28	J_{34} = 4.0, J_{35} = 1.8, J_{45} = 2.6
5	3.07	3.33	3.77	6.28	J_{34} = 3.8, J_{35} = 1.7, J_{45} = 2.8
6	2.45	3.18	3.59	--	J_{34} = 3.4, J_{35} = 0.8, J_{45} = 2.0
7	2.53	2.67	3.00	--	J_{34} = 3.8, J_{35} = 1.4, J_{45} = 5.4
8	--	3.32 (d)	2.83 (e)	7.53 (e)	J_{34} = 3.5, J_{3CH_3} = 1.0

(a) Samples at 10-25% dilution in trichlorofluoromethane (compound **5** in deuteriochloroform). (b) Doublet, doublet (except for compound **8**). (c) Singlet. (d) Doublet, quartet. (e) Doublet.

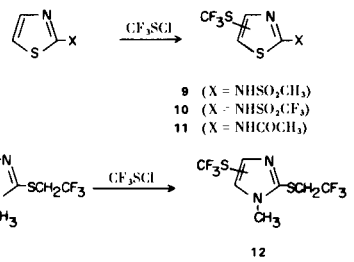
Table II

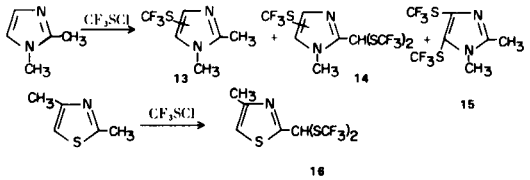
^{19}F Nmr Values

Compd.	Group	ϕ*
1	$-SCF_3$	46.2
2	$-SCF_3$	46.2
3	$-SCFCl_2$	22.3
5	$-SCF_2CF_2CF_2CF_2CF_2CF_2CF_3$ a b c d e f g	89.3 (a)
		120.2 (b)
		121.7 (c)
		122.4 (d)
		123.1 (e)
		126.6 (f)
		81.4 (g)
6	$-SCF_3$	44.5
7	$-SCF_3$	46.0
8	$-SCF_3$	46.3

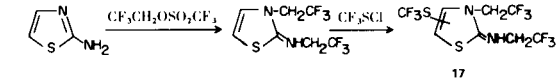
proton coupling constants also previously used to distinquish isomeric imidazoles. Other spectroscopic techniques, including mass spectrometry, have been suggested to be of doubtful diagnostic value (13b). However, substitution into the 5-position would be most likely here. Similarly, 2-(trifluoromethylsulfonamido)-4-(5)(trifluoromethylthio)-thiazole (**10**), 2-acetamido-4-(5)(trifluoromethylthio)thiazole (**11**), and 1-methyl-2-(2,2,2-trifluoroethylthio)-4(5)-(trifluoromethylthio)imidazole (**12**) were obtained with 2-(trifluoromethylsulfonamido)thiazole, 2-acetamidothiazole and 1-methyl-2-(2,2,2-trifluoroethylthio)imidazole respectively. Nmr data are presented in Tables III and IV.

1,2-Dimethylimidazole yielded 1,2-dimethyl-4-(5)(trifluoromethylthio)imidazole (**13**) with trifluoromethylsulfenyl chloride but, in addition, when a pressure reactor was used, trace amounts of 1-methyl-2-[di(trifluoromethylthio)methyl]-4(5)(trifluoromethylthio)imidazole (**14**) and 1,2-dimethyl-4,5-di(trifluoromethylthio)imidazole (**15**) were characterized by nmr spectroscopy. Replacement of methyl hydrogen atoms occupying certain positions in nitrogen-containing heterocycles is well known but largely restricted to 2-methylthiazoles or benzothiazoles (14). Thus, 2,4-dimethylthiazole with trifluoromethylsulfenyl chloride in a pressure reactor led only to methyl hydrogen replacement to give 2-[di(trifluoromethylthio)methyl]-4-methylthiazole (**16**). These are the first reported examples of methyl heterocycles with the hydrogen atoms of the methyl group replaced by trifluoromethylthio moieties. Benzyl, benzylidine, and benzotrifluoromethylthio derivatives have been reported from displacement with trifluoromethylthio salts on the corresponding halide (15,16).





Alkylation of 2-aminothiazoles was carried out using 2,2,2-trifluoroethyltrifluoromethylsulfonate (17). Differentiation between the two possible products, either an alkylamino or alkyl imino form, was based upon the presence of upfield ring proton signals and two methylene quartets which indicated imino thiazoline structures (18). Tables III and IV detail the nmr signals of the trifluoromethylsulfenyl chloride reaction products which on this basis are assigned as 2-(2,2,2-trifluoroethylimino)-3(2,2,2-trifluoroethyl)-4(5)trifluoromethylthio-4-thiazoline, compound **17**, and 4-methyl-2-(2,2,2-trifluoroethylimino)-3-(2,2,2-trifluoroethyl)-5-(trifluoromethylthio)-4-thiazoline, compound **18**.



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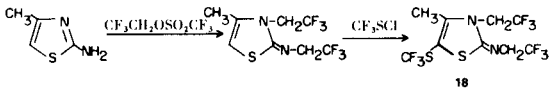

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Table III

Proton (τ) Nmr Values (a)

Compd.	ring-H	N-H	CH_3	CH	CH_2
9	2.09	broad	7.04	--	--
10	2.19	3.65	--	--	--
11	2.10	-2.65 (h)	7.77	--	--
12	2.49	--	6.32	--	6.12 (b)
13	2.61	--	7.56	--	--
			6.38 (c)	--	--
14	2.47	--	6.20	4.08	--
15	--	--	7.47	--	--
			6.29 (c)		
16	3.00	--	7.53	3.92	--
17	2.95	--	--	--	6.41 (d)
					5.51 (e)
18	--	--	7.63	--	6.41 (f)
					5.45 (g)

(a) Samples at 10-25% dilution in deuteriochloroform (Compounds **9** and **11** in d_6-DMSO and **10** in d_6-acetone). (b) Quartet, J = 9.2 Hz. (c) *N*-methyl. (d) Quartet, J = 9.0 Hz. (e) Quartet, J = 8.5 Hz. (f) Quartet, J = 9.1 Hz. (g) Quartet, J = 8.3 Hz. (h) A second NH peak at + 1.00 τ suggests an equilibrium with a thiazoline structure.

EXPERIMENTAL

The nmr spectra were obtained using Varian XL-100 and A-60 spectrometers, utilizing internal standards of fluorotrichloromethane and tetramethylsilane, with chemical shifts reported as ϕ^* (19) and τ values (20). A Hewlett-Packard Model 5752B gas chromatograph employing 6 ft by ¼ in columns packed with either 15% OV-17 on ABS or 33% FS-1265 on Chrom P were used to trap

Table IV

^{19}F Nmr Values

Compd.	Group	ϕ^*	Coupling (Hz)
9	$-SCF_3$	44.7	--
10	$-SCF_3$	44.7	--
	$-SO_2CF_3$	78.9	--
11	$-SCF_3$	45.1	--
12	$-SCF_3$	45.4	--
	$-CF_3$	67.8 (t)	9.2
13	$-SCF_3$	45.8	--
14	ring $-SCF_3$	46.6	--
	$-CH(SCF_3)_2$	41.2	--
15	$-SCF_3$	42.0 (q)	1.9
	$-SCF_3$	43.4 (q)	1.9
16	$-CH(SCF_3)_2$	41.6	--
17	$-SCF_3$	45.5	--
	CF_3	72.4 (t)	9.0
	CF_3	71.5 (t)	8.5
18	$-SCF_3$	45.2	--
	CF_3	72.4 (t)	9.1
	CF_3	69.7 (t)	8.3

analytical samples. The aromatic heterocycles and trichloromethylsulfenyl chloride were obtained from commercial sources, mainly Aldrich Chemical Co. The preparation of 2-(trifluoromethylsulfonamido)thiazole has been disclosed in the patent literature (21).

Trifluoromethylsulfenyl chloride was prepared by the method of Tullock and Coffman (22) and fluorodichloromethylsulfenyl chloride by that of Seel, Gombler, and Budenz (23). The sulfenyl chlorides should be treated as hazardous materials and suitable precautions taken to prevent contact (24).

Perfluoroheptylsulfenyl Chloride (25a).

A mixture of 26 g. of bis(perfluoroheptyl) disulfide (26), 50 ml. of Freon 113 and 7 g. of chlorine was shaken at 115° for 15 hours in a 180 ml. stainless steel pressure reactor. Distillation gave 24 g. of the yellow title compound, b.p. 88-90° (95 mm).

1-Methyl-2-(trifluoromethylthio)pyrrole (**1**) and 1-Methyl-3-(trifluoromethylthio)pyrrole (**2**).

While cooling at -40°, 41 g. of trifluoromethylsulfenyl chloride was bubbled into a solution of 19 g. of *N*-methylpyrrole in 19 g. of pyridine and 100 ml. of chloroform. A dry-ice condenser was used to retain the low boiling sulfenyl chloride until reaction was complete. The temperature was slowly brought up to 60° by external heating and held at 60° for three hours. Distillation after washing three times with dilute (about five percent) hydrochloric acid and drying (magnesium sulfate), led to the isolation of 21 g. of **1**, b.p. 152-156° (730 mm). Also separated by glpc techniques was 0.5 g. of **2**.

Similar methods were used to prepare 1-methyl-2-(fluorodichloromethylthio)pyrrole (**3**), 1-methyl-2-(trichloromethylthio)-pyrrole (**4**), 1-methyl-2-(perfluoroheptythio)pyrrole (**5**), 2-methyl-4-(trifluoromethylthio)thiophene (**8**), 2-(*N*-methylsulfonamido)-4(5)(trifluoromethylthio)thiazole (**9**), 2-(*N*-trifluoromethylsulfonamido)-4(5)(trifluoromethylthio)thiazole (**10**), 2-acetamido-4(5)(trifluoromethylthio)thiazole (**11**), 1-methyl-2-(2,2,2-trifluoroethylthio)-4(5)(trifluoromethylthio)imidazole (**12**), 2-(2,2,2-trifluoroethylimino)-3-(2,2,2-trifluoroethyl)-4(5)(trifluoromethylthio)-4-thiazoline (**17**), and 4-methyl-2-(2,2,2-trifluoroethylimino)-3-(2,2,2-trifluoroethyl)-5-(trifluoromethylthio)-4-thiazoline

Table V

Elemental Analyses

Compd.	Yield %	%C Calcd.	%C Found	%F (Cl) Calcd.	%F (Cl) Found	%H (N) Calcd.	%H (N) Found
1	50	39.8	39.9	31.5	31.3	3.3	3.1
2	1	39.8	39.7	31.5	31.0	3.3	3.3
3	42	33.6	33.6	8.9	9.4	2.8	2.8
4	41	31.2	31.4	(46.1)	(46.3)	2.6	2.7
5	92	30.0	29.9	59.2	59.1	1.3	1.3
6	1	35.7	35.6	33.9	33.4	1.8	2.0
7	50	32.6	32.6	31.0	30.8	1.6	1.7
8	50	36.4	36.7	28.8	28.5	2.5	2.8
9	15	21.6	21.5	20.5	21.1	1.8	1.8
10	28	18.1	18.1	34.3	34.5	0.6	0.6
11	60	29.7	30.0	--	--	(11.6)	(11.6)
12	24	28.4	28.1	38.5	38.7	2.0	2.0
13	35	36.7	36.6	29.2	29.7	(14.3)	(14.1)
16	14	26.8	27.1	36.4	36.2	(4.5)	(4.5)
17	83	26.4	26.6	46.9	46.6	(7.7)	(7.8)
18	74	28.6	28.6	45.2	45.0	1.9	2.0

(**18**). In those cases where fluorodichloromethylsulfenyl chloride, trichloromethylsulfenyl chloride and perfluoroheptylsulfenyl chloride was used a water condenser could be substituted for the dry-ice condenser and a dropping funnel for the gas inlet tube. The analytical verifications and yields (calculated from the glpc integration) for the new compounds are presented in Table V. No effort was made to optimize the yields and normally only one reaction was carried out.

2-(Methylsulfonamido)thiazole (25b).

Into a mixture of 100 g. of 2-aminothiazole and 600 ml. of pyridine cooled in ice, 126 g. of methanesulfonyl chloride was added dropwise and the resulting solution stirred for 18 hours at 25°. After heating for one hour at 60° and pouring the products into ice water, the filtered solid was dried and recrystallized from absolute ethanol to yield 31 g. of the title compound, m.p. 220-222°; nmr (d_6-DMSO): -2.4 τ (broad, N*H*), 2.76 τ (d, J = 4.7 Hz, C*H*), 3.20 τ (d, J = 4.7 Hz, C*H*), 7.08 τ (s, CH_3).

Anal. Calcd. for $C_4H_6N_2O_2S_2$: C, 27.0; H, 3.4; N, 15.7. Found: C, 26.8; H, 3.4; N, 15.5.

2-(2,2,2-Trifluoroethylimino)-3-(2,2,2-trifluoroethyl)-4-thiazoline.

A mixture of 10 g. of 2-aminothiazole, 35 ml. of triethylamine and 58 g. of 2,2,2-trifluoroethyltrifluoromethanesulfonate in 100 ml. of dimethoxyethane was heated overnight at 85°. After 16 hours, most of the solvent was removed by distillation and chloroform used to wash the products into a separatory funnel where three water extractions were carried out. Distillation after drying (magnesium sulfate), led to the isolation of 7.5 g. of the title compound, b.p. 55° (*ca.* 1 mm); nmr (deuteriochloroform): 3.40 τ (d, J = 4.8 Hz, ring H), 4.02 τ (d, J = 4.8 Hz, ring H), 5.60 τ (q, J = 8.6 Hz, CH_2), 6.47 τ (q, J = 9.2 Hz, CH_2).

Anal. Calcd. for $C_7H_6F_6N_2S$: C, 31.8; H, 2.3. Found: C, 31.9; H, 2.3.

Prepared in a similar fashion was 4-methyl-2-(2,2,2-trifluoroethylimino)-3-(2,2,2-trifluoroethyl)-4-thiazoline, b.p. 79° (*ca.* 1 mm); nmr (deuteriochloroform): 4.38 τ (q, J = 1.2 Hz, ring C*H*), 5.58 τ (q, J = 8.4 Hz, CH_2), 6.42 τ (q, J = 9.3 Hz, CH_2), 7.87 τ (d, J = 1.2 Hz, CH_3).

Anal. Calcd. for $C_8H_8F_6N_2S$: C, 34.5; H, 2.9. Found: C, 34.6. H, 2.9.

Also prepared similarly was 1-methyl-2-(2,2,2-trifluoroethylthio)imidazole, b.p. 65 (*ca.* 1 mm); nmr (deuteriochloroform): 2.90 τ (d, J = 1.2 Hz, ring C*H*), 3.04 τ (d, J = 1.2 Hz, ring C*H*), 6.31 τ (s, CH_3), 6.43 τ (q, J = 9.6 Hz, CH_2).

Anal. Calcd. for $C_6H_7F_3N_2S$: C, 36.7; H, 3.6. Found: C, 36.5; H, 3.7.

2-(Trifluoromethylthio)thiophene (**7**).

A 150 ml. stainless steel Hoke cylinder was evacuated, cooled, and charged with 10 g. of thiophene, 4.7 g. of pyridine, 50 ml. of chloroform, and 20.5 g. of trifluoromethylsulfenyl chloride. After heating at 60° for 20 hours, the reaction products were collected, washed three times with dilute hydrochloric acid, dried, and distilled to give 11 g. of **7**, b.p. 141-146° (730 mm).

Isolated in a similar fashion were 2-(trifluoromethylthio)furan (**6**), 1,2-dimethyl-4(5)(trifluoromethylthio)imidazole (**13**), 1-methyl-2-[di(trifluoromethylthio)methyl]-4(5)(trifluoromethylthio)imidazole (**14**), and 2-[di(trifluoromethylthio)methyl]-4-methylthiazole (**16**) and 1,2-dimethyl-4,5-di(trifluoromethylthio)-imidazole (**15**).

Acknowledgments.

The authors wish to express their gratitude to Mr. G. B. Jefson for experimental assistance, to Mr. P. Olson and Mr. J. G. Gagnon for conducting the elemental analyses and Mr. J. R. Hill for operation of the nmr spectrometers.

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