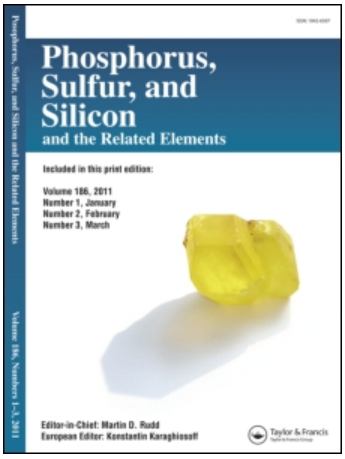

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FLUOROALKYLTHIO SUBSTITUTED AROMATIC DERIVATIVES

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FLUOROALKYLTHIO SUBSTITUTED AROMATIC DERIVATIVES

by

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ABSTRACT

Multiple fluoroalkyl substitution has been shown to occur with fluoroalkanesulfenyl chlorides on activated aromatics.

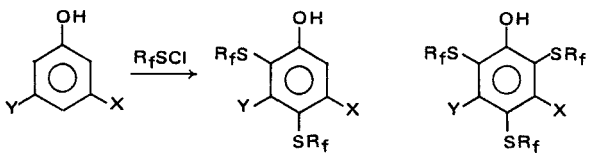
Results and Discussion

In the previous paper,[1] electrophilic substitution with fluoroalkanesulfenyl chlorides on appropriately activated acetophenones, benzophenones, benzaldehydes, and benzoates was described. As a further extension of the synthetic utility of these substitution reactions, this paper reports on the multiple fluoroalkylthio aromatic compounds which result from arrangement of electron-donating groups meta to one another on the ring systems so as to activate specific positions.

The pioneering work by Senning[2] concerning substitution on reactive aromatics with trichloromethanesulfenyl chloride was expanded later to include fluorine containing derivatives.[3, 4, 14] However, only one report has appeared concerning the introduction of multiple trifluoromethylthio units into aromatic structures. Here, chlorination occurred with trifluoromethanesulfenyl chloride with hydroquinone rather than the desired substitution. But with *p*-methoxyphenol, two trifluoromethylthio groups were introduced and further manipulation gave completely substituted *p*-methoxy and *p*-hydroxy phenols. On the other hand, catechol gave only a mono-trifluoromethylthio product.[4]

With this knowledge, the more reactive resorcinol was investigated and found to lead to multiple substitution when heated with trifluoromethanesulfenyl chloride in chloroform and pyridine as shown by Scheme I with 1,3-dihydroxy-4,6-bis(trifluromethylthio)benzene (**1**). These same reactants in a stainless steel Hoke pressure reactor at 25° led to even further substitution to yield compound **2**, 1,3-dihydroxy-2,4,6-tris(trifluoromethylthio)benzene. As might be expected, substitution occurred at all three available sites with 1,3,5-trihydroxybenzene with the formation of compound **3**. Depending on the conditions, either two or three trifluoromethylthio groups could be introduced into 3-methoxyphenol, as exemplified by compounds **4** and **5**. Even with perfluoroheptanesulfenyl chloride, a disubstituted product, compound **6** was obtained from 3-methoxyphenol through the use of iron powder to facilitate the reaction. These various synthetic techniques afforded 3,5-dimethoxy 2,4,6-tris(trifluoromethylthio)phenol (**7**) from 3,5-dimethoxyphenol, 3-methyl-2,4,6-tris(trifluoromethylthio)phenol (**8**) from 3-methylphenol,3,5-dimethyl-2,4-bis(trifluoromethylthio)phenol (**9**) and 3,5-dimethyl-2,4,6-tris(trifluoromethylthio)phenol (**10**) from 3,5-dimethylphenol, and 1,3-dihydroxy-5-methyl-2,4,6-tris(trifluoromethylthio)benzene (**11**) from 1,3,-dihydroxy-5-methylbenzene (see the Experimental Section for synthetic details).

SCHEME I



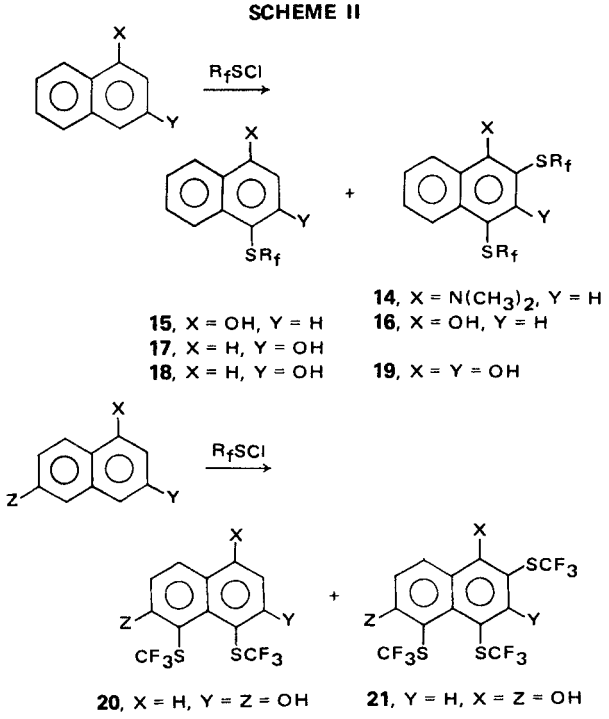
1, X = OH, Y = H
2, X = OH, Y = H
3, X = Y = OH
4, X = OCH_3, Y = H
5, X = OCH_3, Y = H
6, X = OCH_3, Y = H
7, X = Y = OCH_3
8, X = CH_3, Y = H
9, X = Y = CH_3
10, X = Y = CH_3
11, X = OH, Y = CH_3

Note: $R_f = CF_3$ except for **6** where $R_f = C_7F_{15}$

Even the less activated methoxybenzenes reacted with trifluoromethanesulfenyl chloride to form 1,3-dimethoxy-4-(trifluoromethylthio)benzene (**12**) and 2,4-bis(trifluoromethylthio)-1,3,5-trimethoxybenzene (**13**) from 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene, respectively. This contrasted to the radical chlorination reported previously with trichloromethylsulfenyl chloride and 1,3-dimethoxybenzene.[2]

Although *N,N*-dimethylnaphthylamine gave only a poorly defined product with trichloromethanesulfenyl chloride,[2] this same compound proved highly reactive to trifluoromethanesulfenyl chloride to yield *N,N*-dimethyl-2,4-bis(trifluoromethylthio)naphthalene (**14**) (see Scheme II). A similar reactivity was noted with 1-hydroxy-naphthalene except that 1-hydroxy-4-(trifluoromethylthio)naphthalene (**15**) was produced in an uncatalyzed reaction and 1-hydroxy-2,4-bis(trifluoromethylthio)naphthalene (**16**) in the presence of iron powder. Substitution occurred in the 1- position of 2-hydroxynaphthalene with formation of compound **17** with trifluoromethanesulfenyl chloride and compound **18** from the perfluoroheptanesulfenyl chloride. These results are consistent with the normal electrophilic pathway of naphthalene substitution.[6] Dihydroxynaphthalenes also led to multiple substitution with formation of 1,3-dihydroxy-2,4-bis(trifluoromethylthio)naphthalene (**19**), 2,7-dihydroxy-1,8-bis(trifluoromethylthio)naphthalene (**20**), and 1,6-dihydroxy-2,4,5-tris(trifluormethylthio)naphthalene (**21**).

SCHEME II



15, X = OH, Y = H
17, X = H, Y = OH
18, X = H, Y = OH

14, X = $N(CH_3)_2$, Y = H
16, X = OH, Y = H

19, X = Y = OH

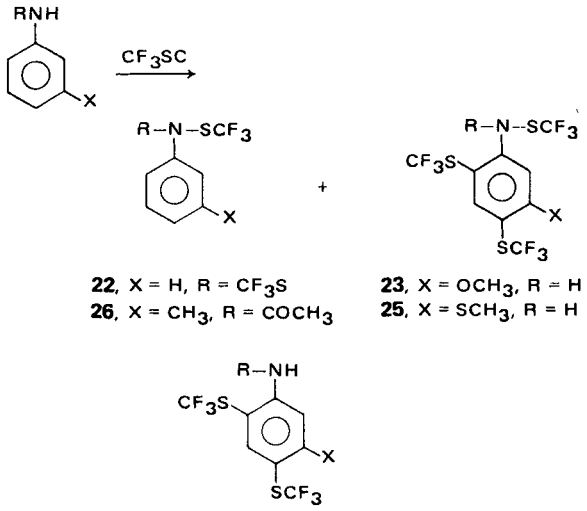
20, X = H, Y = Z = OH

21, Y = H, X = Z = OH

Note: $R_f = CF_3$ except for **18** where $R_f = C_7F_{15}$

Trichloro- and trifluoromethanesulfenyl chloride have been reported to replace an amine hydrogen with aniline, *N*-methylaniline and *N*-acetylaniline.[7] On the other hand, *N,N*-dimethylaniline yielded a para substituted trihalomethylthio group with either trichloro[2,8] or trifluoromethanesulfenyl chloride[3] without any ortho or multiple substitution. In an attempt to carry out ring substitution, both amine hydrogens in aniline were replaced to give compound **22** (see Scheme III) when a pressure reactor was utilized. However, placing a methoxy group or methylthio group in the meta position of aniline was sufficient to activate the ring. Thus, 3-methoxyaniline led to two products, *N*-(trifluoromethylthio)-4,6-bis(trifluoromethylthio)-3-methoxyaniline (**23**) and 4,6-bis(trifluoromethylthio)-3-methoxy aniline (**24**) whereas 3-methylthioaniline gave only *N*-(trifluoromethylthio)-4,6-bis(trifluoromethylthio)-3-methylthio aniline (**25**). From augmentation of the reactivity of *N*-acetylaniline with a 3-methyl group, only *N*-acetyl-*N*-(trifluoromethylthio)-3-methylaniline (**26**) resulted but with a 3-hydroxy substituent, a poor yield of *N*-acetyl-4,6-bis(trifluoromethylthio)-3-hydroxy aniline (**27**) was obtained.

SCHEME III



22, X = H, R = CF_3S
26, X = CH_3, R = $COCH_3$

23, X = OCH_3, R = H
25, X = SCH_3, R = H

24, X = OCH_3, R = H
27, X = OH, R = $COCH_3$

With *N*-methylaniline, *N*-methyl-*N*-(trifluoromethylthio)aniline (**28**), *N*-methyl-*N*-(trifluoromethylthio)-4-(trifluoromethylthio)aniline (**29**) and *N*-methyl-4(trifluoromethylthio)aniline (**30**) were characterized.

Alkylation reactions, using 2,2,2-trifluoroethyltrifluoromethanesulfonate,[9] led to three additional starting materials, *N*-(2,2,2-trifluoroethyl)-3-methoxyaniline (**31**), *N* (2,2,2-trifluoroethyl)-3-(2,2,2-trifluoroethoxy)aniline (**32**), and *N,N'*-(2,2,2-trifluoroethyl)-

1,3-diamino benzene (**33**). Each of these gave the expected disubstituted product with trifluoromethanesulfenyl chloride as indicated in Scheme IV; *N*-(2,2,2-trifluoroethyl)-4,6-bis(trifluoromethylthio)-3-methoxy aniline (**34**) from **31**, *N*-(2,2,2-trifluoroethyl)-4,6-bis(trifluoromethylthio)-3-(2,2,2-trifluoroethoxy)-aniline (**35**) from **32**, and *N,N'*-di(2,2,2-trifluoroethyl)-4,6-bis(trifluoromethylthio)-1,3-diamino benzene (**37**) from **33**. In addition to **35**, *N*-(2,2,2-trifluoroethyl)-*N*-(trifluoromethylthio)-3-hydroxy-2,4,6-tris(trifluoromethylthio)aniline (**36**) was also characterized from **32**.

TABLE I

New Phenol Derivatives

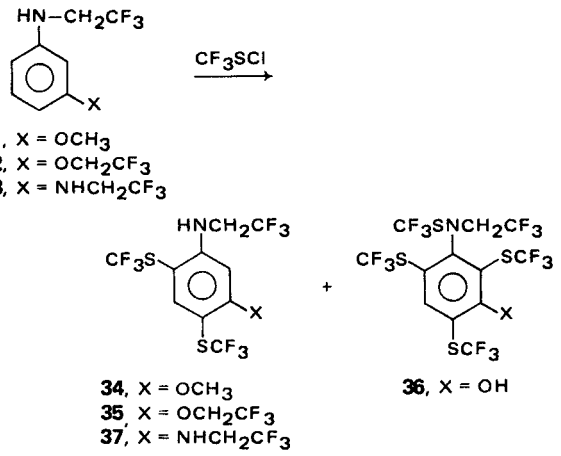
Cpn (Method-Yield %)	MP (°C) (bp*)	Analysis (%) Calculated C	Calculated F	Found C	Found F	ϕ‡	NMR† τ	Group
1 (A-80)	58-9	31.0	36.7	30.7	36.2	44.4	2.17, 3.25 3.43	ring CH OH
2 (C-50)	48-9	26.3	41.7	26.3	41.4	42.5, 44.1	1.94 2.74	ring CH OH
3 (A-63)	74-8	25.4	40.1	25.1	40.0	43.5	2.70	OH
4 (A-77)	(72-5)	33.3	35.2	33.4	35.2	44.1, 44.5	2.15, 3.36 3.43 6.11	ring CH OH CH_3
5 (C-35)	(75-8)	28.3	40.3	28.7	39.9	41.9, 43.3 43.4	1.89 2.81 5.90	ring CH OH CH_3
6 (B-15)	(155-160)	27.3	61.7	27.6	61.3	87.9, 88.2 (–CF_2S–)	2.14, 3.33 3.50 6.07	ring CH OH CH_3
7 (C-50)	–	29.1	37.7	29.1	37.4	42.3, 42.5	2.81 5.89	OH CH_3
8 (C-6)	29-31	29.4	41.9	29.6	41.8	42.1, 43.0 43.8	1.85 2.73 7.12	ring CH OH CH_3
9 (B-30)	34-6	37.3	35.4	37.1	35.0	42.9, 43.2	3.06 3.31 7.13, 7.43	ring CH OH CH_3
10 (C-26)	40-2	31.3	40.5	31.2	40.5	42.6, 43.2	2.62 7.03	OH CH_3
11 (C-60)	44-6	28.3	40.3	28.4	40.0	42.7, 43.2	2.51 7.10	OH CH_3
12 (A-44)	(67-9)	45.4	23.9	45.5	24.0	44.2	2.57, 3.58 6.20, 6.25	ring CH CH_3
13 (C-63)	73-5	35.9	30.9	35.9	30.8	42.9	3.62 6.03	ring CH CH_3

* at *ca.* 1 mm or less.

† In $CFCl_3$ except for cpns **2**, **6**, **8**, **11**, and **13** where $CDCl_3$ was added.

‡ CF_3S–.

SCHEME IV



From *N*-(trifluoromethylsulfonyl)-3-methoxyaniline,[10] compound **38**, *N*-(trifluoromethylsulfonyl)-4,6-bis(trifluoromethylthio)-3-methoxyaniline, was identified.

Although both Senning[2] and Andreades and coworkers[3] had not found ortho substitution with *N,N*-dialkylanilines and haloalkanesulfenyl chloride, the use of a Hoke reactor for the reaction of trifluoromethanesulfenyl chloride and *N,N*-diethylaniline led to *N,N*-diethyl-2,4-bis(trifluoromethylthio)aniline (**39**). Further enhancement of the aromatic reactivity as with *N,N*-dimethyl-3-hydroxyaniline produced both di- and trisubstitution, *N,N*-dimethyl-4,6-bis(trifluoromethylthio)-3-hydroxyaniline (**40**) and *N,N*-dimethyl-3-hydroxy-2,4,6-tris(trifluoromethylthio)aniline (**41**). Finally, *N,N*-dimethyl-3-(2,2,2-trifluoroethoxy)aniline (**42**), prepared as before utilizing 2,2,2-trifluoroethyl trifluoromethanesulfonate, reacted similarly to form *N,N*-dimethyl-4,6-bis(trifluoromethylthio)-3-(2,2,2-trifluoroethoxy)aniline (**43**).

TABLE II

New Naphthalene Derivatives

Cpn (Method-Yield %)	MP (°C) (bp[a])	Analysis (%) Calculated C	Calculated F	Found C	Found F	ϕ[c]	NMR[b] τ	Group
14 (A-80)	(110–113)	45.3	30.7	45.9	30.8	42.4, 43.0	1.59, 1.8, 1.83, 2.45	ring CH
							6.90	CH_3
15 (A-20)	–	54.1	23.4	53.8	23.0	43.9	*ca.* 1.5 to 2.9	ring CH
							3.29	OH
16 (B-52)	77–78	41.9	33.1	42.0	32.8	43.3, 43.6	1.55, 1.91	ring CH
							2.28	
							2.73	OH
17 (A-80)	90–92	54.1	23.4	54.2	23.0	42.3	1.65, 2.07	ring CH
							2.20, 2.38	
							2.52, 2.7	
							3.10	OH
18 (B-56)	70–73	37.5	52.4	37.9	52.0	85.9 ($-CF_2S-$)	*ca.* 1.7 to 2.7	ring CH
							3.16	OH
19 (A-50)	130–131	40.0	31.6	40.0	31.5	42.7, 43.1	1.73, 2.24	ring CH
							2.52	
							2.45, 2.70	OH
20 (A-64)	80–86	40.0	34.7	40.1	34.4	43.6	1.92	OH
							2.14, 2.74	ring CH
21 (A-15)	65–68	33.9	37.1	34.0	36.9	43.2, 43.3	1.37, 1.75	ring CH
						44.6	2.55	
							2.6	OH

[a] At *ca.* 1 mm or less.
[b] In $CDCl_3/CFCl_3$.
[c] CF_3S-.

TABLE III

New Aniline Derivatives

Cpn (Method-Yield %)	MP (°C) (bp*)	Analysis (%) Calculated C	Calculated F	Found C	Found F	φ‡	NMR† τ	Group
22 (C-55)	–	32.8	38.9	33.1	39.1	52.3	*ca.* 2.5 to 3.0	ring CH
23 (A-10)	–	28.4	40.4	28.9	39.9	43.9, 44.3	2.17, 2.83	ring CH
						52.9	3.43	NH
							6.03	CH_3
24 (A-60)	(106–7)	33.4	35.3	33.7	35.0	44.3, 44.8	2.38, 3.41	ring CH
							4.13	NH_2
							6.14	CH_3
25 (A-48)	56–60	27.3	38.9	27.1	38.9	43.3, 43.8	2.18, 2.62	ring CH
						52.5	3.42	NH
							7.48	CH_3
26 (A-70)	(93–6)	48.2	22.9	48.8	22.8	50.5	*ca.* 2.90	ring CH
							7.69	ring CH_3
							7.88	CH_3
27 (B-10)	–	34.2	32.4	34.5	31.9	43.5, 44.5	−0.18, 1.15	OH, NH
							1.65, 2.13	ring CH
							7.72	CH_3
28 (A-30)	–	46.4	27.5	46.4	27.9	51.0	*ca.* 2.7, 3.3	ring CH
							6.60	CH_3
29 (A-7)	–	35.2	37.1	35.4	37.4	44.4, 51.0	2.45, 2.80	ring CH
							6.49	CH_3
30 (A-7)	–	46.4	27.5	46.1	27.7	45.4	2.62, 3.53	ring CH
							6.22	NH
							7.18	CH_3
31 (65)	(93–5)	52.7	27.8	52.6	27.6	72.9	3.00, 3.67, 3.88	ring CH
						(CF_3)	6.39	CH_3
							6.53	CH_2
							6.5	NH
32 (38)	(80–2)	44.0	41.8	44.0	41.4	73.2, 74.8	1.93, 3.72, 2.80	ring CH
						(CF_3)	6.3	NH
							5.81, 6.38	CH_2
33 (40)	(75–76)	44.1	41.9	44.1	41.3	72.1	3.08, 3.78, 3.86	ring CH
						(CF_3)	4.83	NH
							6.17	CH_2
34 (A-60)	–	32.6	42.2	32.5	41.9	44.5	2.20, 3.72	ring CH
						72.8 (CF_3)	4.35	NH
							6.10	CH_3
							6.15	CH_2
35 (C-50)	–	30.5	48.2	30.2	48.4	44.1, 44.4	2.12, 3.69	ring CH
						72.7 (CF_3)	4.24	NH
						74.5 (CF_3)	5.61, 6.15	CH_2
36 (C-16)	–	24.4	48.2	24.9	48.3	38.6, 41.9	1.83	ring CH
						42.9, 52.1	3.04	OH
						71.1 (CF_3)	5.73	CH_2

TABLE III (*continued*)

Cpn (Method-Yield %)	MP (°C) (bp*)	Analysis (%) Calculated C	Calculated F	Found C	Found F	φ‡	NMR† τ	Group
37 (A-41)	67-68	30.5	48.3	30.4	48.6	44.8 72.7 (CF_3)	2.24, 3.93 4.38 6.20	ring CH NH CH_2
38 (A-85)	58-60	26.4	37.6	26.3	37.7	43.1, 44.1 76.7 (CF_3)	2.0, 2.51 2.12 6.03	ring CH NH CH_3
39 (C-51)	(76-78)	41.2	32.7	41.3	32.9	42.6, 44.0	2.22, 2.45, 2.92 6.83 8.92	ring CH CH_2 CH_3
40 (A-55)	104-107	35.6	33.8	35.9	33.2	44.3, 44.4	2.23, 3.32 7.07	ring CH CH_3
41 (A-25)	40-1	30.2	39.1	30.3	39.2	43.3, 43.8 44.3	2.01 6.94	ring CH CH_3
42 (27)	(82-84)	54.8	26.0	54.7	25.9	–	2.97, 3.78 5.83 7.15	ring CH CH_2 CH_3
43 (A-52)	72-3	34.4	40.8	34.4	41.0	44.1 74.5 (CF_3)	2.11, 3.50 5.61 7.0	ring CH CH_2 CH_3

* At *ca.* 1 mm or less.

† In $CFCl_3$, except for cpns **24**, **40**, and **41** where CD_3COCD_3 was added.

‡ CF_3S–.

Experimental Section

Where possible, analytical samples were purified with a F and M Model 700 gas chromatograph employing a 16 ft by 1/4 in column packed with 15% OV-17 on ABS. The nmr spectra were obtained using a Varian XL-100 spectrometer. Perfluoroheptanesulfenyl chloride was prepared as previously described[11] and trifluoromethanesulfenyl chloride by the method of Tullock and Coffman.[12] The sulfenyl chlorides should be treated as hazardous materials and suitable precautions taken to prevent contact.[13] All other reagents were from chemical sources, mainly Aldrich Chemical Co., except where noted.

In general, the following method, designated as Method A, was used to prepare the compounds described. A solution of the appropriate aromatic compound was dissolved in chloroform and a slight excess of pyridine and cooled to –40°. With the low-boiling trifluoromethanesulfenyl chloride, bp –2°, an excess of this reagent was bubbled into the solution using a dry-ice condenser to retain the sulfenyl chloride. With the higher boiling perfluoroheptanesulfenyl chloride, a dropping funnel and water condenser was used. The temperature was raised slowly by external heating to 60° and maintained for three or more hours. The resulting mixture was then washed three times with dilute (about five percent) hydrochloric acid, dried with $MgSO_4$, and the products purified by distillation or recrystallization. The addition of 100 mg of iron powder (reduced by hydrogen–Baker Chem. Co.) to facilitate the reaction will be indicated as Method B. Finally, Method C consisted of placing the reactants in a stainless steel Hoke reactor after cooling and evacuating, with reaction taking place at 25° overnight. The analytical, physical, and nmr data for the new phenols are listed in Table I, for new naphthalenes in Table II, and for the new anilines in Table III.

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