O- and *C*-Perfluoroalkylations of Phenol System with (Perfluoroalkyl)phenyliodonium Triflates

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Synopsis. The reaction of FITS reagents with the phenols bearing bulky substituents at *C*-positions yielded *O*- and *C*-perfluoroalkylation products whose ratios were dependent on the steric bulkiness of the substituents or the perfluoroalkyl groups and the reaction temperature.

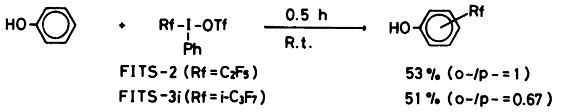
It is well known that both *O*- and *C*-alkylations occur when phenoxide anions are allowed to react with electrophilic agents such as alkyl halides.[1] However, similar alkylations utilizing perfluoroalkyl halides have never been reported. This may be because the perfluoroalkyl halides would not be effective electrophilic reagents, since the perfluoroalkyl (Rf) group has an extraordinary high electronegativity (3.45).[2]

In 1977, Shreeve and Kitazume reported that phenol reacted with bis(trifluoromethyl)bis(trifluoromethoxy)sulfurane to give trifluoromethoxybenzene.[3] They, however, proposed a mechanism involving the intramolecular displacement of the phenolic hydroxyl group with the trifluoromethoxyl group *via* an electrocyclic process. Accordingly, their reaction may not be the electrophilic perfluoroalkylation of phenol. Such perfluoroalkylations would be realized only when very efficient electrophilic perfluoroalkylating agents have been developed.

In recent years,[4] we have developed an effective perfluoroalkylating agents, *i.e.* (perfluoroalkyl)phenyliodonium triflates (FITS reagents). In the previous paper,[5] it was demonstrated that the FITS reagent reacts with phenol at its aromatic ring to afford perfluoroalkylphenols. In the present paper, it is shown that both *C*- and *O*-alkylations take place when alkylphenols are allowed to react with FITS reagents.

Results and Discussion

Phenol reacted with FITS-2 or 3*i* in acetonitrile in the presence of pyridine at room temperature to produce a mixture of *C*-Rf phenols without occurrence of *O*-perfluoroalkylation (Eq. 1). The use of FITS-3*i* diminished the formation of the *o*-isomer, suggesting that steric repulsion between the bulky perfluoroisopropyl and the hydroxyl groups influenced the proportions of the products formed.



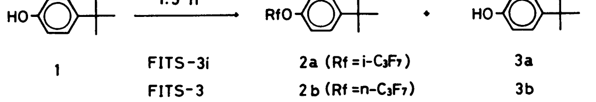
(1)

Table 1. *O*/*C*-Perfluoroalkylations of **1** with FITS-3*i* or -3

Run	FITS	Solvent	Temp/°C	Yield/% **2**	Yield/% **3**	Yield/% **1** (Recovered)	Ratio **2/3**
1	-3*i*	CH_2Cl_2	−78→R.t.[a)]	11	48	24	0.23
2	-3*i*	CH_3CN	R.t.	26	24	22	1.1
3	-3*i*	CH_2Cl_2	R.t.	27	21	30	1.3
4	-3*i*	CH_2Cl_2	Reflux	28	17	29	1.6
5	-3*i*	CH_3CN	Reflux	30	14	26	2.1
6	-3*i*	$ClCH_2CH_2Cl$	Reflux	31	15	34	2.1
7	-3	CH_2Cl_2	R.t.	9	41	23	0.22
8	-3	$ClCH_2CH_2Cl$	Reflux	14	29	31	0.48

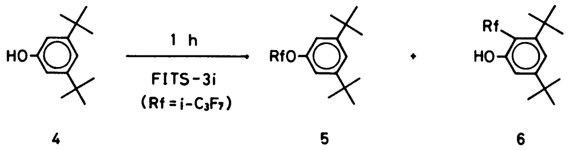
a) Addition of FITS was carried out at −78 °C and the reaction mixture was gradually warmed to room temperature overnight.

When 4-*t*-butylphenol **1** having a bulky substituent at the *p*-position was allowed to react with FITS-3*i* or -3, *O*-perfluoroalkylation was found to take place in addition to *C*-perfluoroalkylation. The reaction was carried out under several conditions and the results are shown in Table 1. The formation of the *O*-isomer **2a** exceeded that of *C*-isomer **3a** in the reaction of FITS-3*i* at room temperature, while the proportion of the *O*-isomer **2b** by FITS-3 was very low (Run 2 or 3, and 7). It may be attributed to the lesser bulk of the perfluoropropyl group of FITS-3 compared with that of the perfluoroisopropyl group of FITS-3*i*. The ratios of *O*/*C*-Rf phenols were also dependent on the reaction temperature. In the case of FITS-3*i*, **3a** was produced as a major component at low temperature, whereas elevated temperature gave predominantly **2a**. However, the amount of **2b** formed by FITS-3 was less than half of that of **3b** even at the elevated temperature (Run 8). On the other hand, the change in polarity of solvents brought about no significant difference in the ratios of **2**/**3**. From the above results, the appearance of *O*-perfluoroalkylation in the case of the phenol **1** would be mainly ascribed to the steric factor between the bulky substituent at an aromatic ring of **1** and the other bulky FITS reagents.



(2)

As expected, 3,5-di-*t*-butylphenol **4** where the *C*-positions are more hindered by two bulky substituents provided the higher proportion of *O*-perfluoroalkylation, but the *O*/*C* ratios were little affected by change in the reaction temperature (Eq. 3, Table 2).



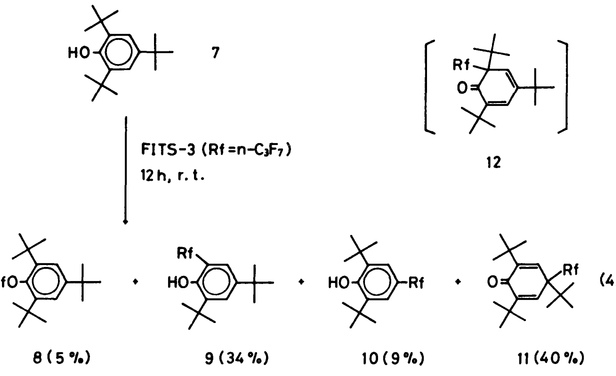
(3)

Furthermore, 2,4,6-tri-*t*-butylphenol **7** where all the reactive *C*- and *O*-positions are blocked gave three *C*-Rf compounds **9**—**11** and a small amount of *O*-Rf

Table 2. *O*/*C*-Perfluoroalkylations of **4** with FITS-3*i*

Run	Solvent	Temp	Yield/% **5**	Yield/% **6**	Yield/% **4** (Recovered)	Ratio **5/6**
1	CH_2Cl_2	R.t.	50	15	10	3.3
2	$ClCH_2CH_2Cl$	Reflux	56	16	18	3.5

phenol **8** (Eq. 4). The reaction proceeded smoothly at room temperature with change of color. Addition of FITS-3 to a solution of **7** in dichloromethane in the presence of an equivalent amount of pyridine produced a blue color, which soon faded. No color developed in the reactions with phenol, **1**, and **4**. From this fact, it appears that the reaction mechanism of the hindered phenol **7** with FITS is different from that of phenol, **1**, and **4**. The appearance of the color may suggest that the reaction of **7** proceeds *via* a radical cation generated by a one electron transfer from **7** to FITS. It is reasonable that **9** and **10** are formed through cyclohexadienone **12** and **11** with loss of *t*-butyl groups, respectively. The former **12** was not isolated.



Experimental

NMR spectra were measured in $CDCl_3$ and ^{19}F chemical shifts were given in ppm upfield from $CFCl_3$ as an internal standard. A gas chromatograph with a column of 20% Apiezon grease L on Uniport B or 2% Silicone OV-1 on Chromosorb WAW DMCS was used for analysis of the products. All the reactions were done under argon atmosphere. FITS-2, -3, and -3*i* were prepared by the method described in our first paper.[4] Reaction solvents were purified and dried by the usual methods.

Reaction of Phenol with FITS-2 or -3i. *Typical Procedure*: Into a solution of 376 mg (4 mmol) of phenol and 162 μl (2 mmol) of pyridine in 8 ml of acetonitrile, 944 mg (2 mmol) of FITS-2 was added in several portions at room temperature. The mixture was stirred for 0.5 h at room temperature. After evaporation of the solvent, the residue was column chromatographed on silica gel using dichloromethane as an eluent to give 120 mg (28%) of the *o*-isomer and 107 mg (25%) of the *p*-isomer. The *m*-isomer could not be isolated. The gas chromatography showed the corresponding small peak. *o*-C_2F_5-phenol: Slightly yellow oil. NMR: δ=5.68 (1H, bs, OH), 6.91—7.52 (4H, m). ^{19}F NMR: 85.0 (3F, s), 112.0 (2F, s). *p*-C_2F_5-phenol: Colorless crystals, mp 94—96 °C. NMR: δ=5.09 (1H, s, OH), 6.88 (2H, d, J=8.6 Hz), 7.44 (2H, d, J=8.6 Hz). ^{19}F NMR: 85.35 (3F, s), 114.3 (2F, bs). IR (KBr): 3280 (OH) cm^{-1}. MS: 212 (M$^+$). Found: C, 45.14; H, 2.46%. Calcd for $C_8H_5F_5O$: C, 45.30; H, 2.38%. *o*-*i*-C_3F_7-phenol: Slightly yellow oil. NMR: δ=5.73 (1H, bd, OH, J=14 Hz), 6.87—7.44 (4H, m). ^{19}F NMR: 75.32 (6F, d, J=7 Hz), 179.0 (1F, m). IR (neat): 3650 (OH), 3450 (OH) cm^{-1}. MS: 262 (M$^+$). *p*-*i*-C_3F_7-phenol: Slightly yellow crystals, mp 75—79 °C. NMR: δ=5.25 (1H, bs, OH), 6.88 (2H, d, J=8.6 Hz), 7.44 (2H, bd, J=8.6 Hz). ^{19}F NMR: 76.62 (6F, d, J=8 Hz), 182.2 (1F, heptet, J=8 Hz). IR (KBr): 3300 (OH) cm^{-1}. MS: 262 (M$^+$). Found: C, 41.18; H, 1.94%. Calcd for $C_9H_5F_7O$: C, 41.24; H, 1.92%.

Reaction of 1 or 4 with FITS-3i or -3. *Typical Procedure*: Into a solution of 206 mg (1 mmol) of **4** and 89 μl (1 mmol) of pyridine in 10 ml of dichloromethane, 522 mg (1 mmol) of FITS-3*i* was added in several portions at the temperature shown in Table 2. The mixture was stirred for 1 h at that temperature. Yields were determined by GC. The results are shown in Tables 1 and 2. For the isolation of the products, a similar post-treatment as described above was carried out. **2a**: Colorless oil. NMR: δ=1.31 (9H, s), 7.06 (2H, d, J=9.0 Hz), 7.33 (2H, d, J=9.0 Hz). ^{19}F NMR: 79.04 (6F, d, J=3.4 Hz), 135.6 (1F, m). MS: 318 (M$^+$). Found: C, 48.94; H, 4.12%. Calcd for $C_{13}H_{13}F_7O$: C, 49.06; H, 4.09%. **3a**: Colorless oil. NMR: δ=1.28 (9H, s), 5.57 (1H, d, OH, J=14 Hz), 6.84 (1H, dd, J=9.1, 1.0 Hz), 7.39 (1H, dd, J=9.1, 2.4 Hz), 7.38 (1H, m). ^{19}F NMR: 75.36 (6F, d, J=7.0 Hz), 178.9 (1F, m). IR (neat): 3660 (OH) cm^{-1} MS: 318 (M$^+$). Found: C, 48.92; H, 4.22%. Calcd for $C_{13}H_{13}F_7O$: C, 49.06; H, 4.09%. **2b**: Colorless oil. NMR: δ=1.31 (9H, s), 7.08 (1H, d, J=9.0 Hz), 7.36 (1H, d, J=9.0 Hz). ^{19}F NMR: 81.72 (3F, t, J=5.0 Hz), 83.92 (2F, m, OCF_2), 129.9 (2F, t, J=2.0 Hz). MS: 318 (M$^+$). **3b**: Colorless oil. NMR: δ= 1.29 (9H, s), 5.45 (1H, t, OH, J=5.0 Hz), 6.87 (1H, d, J=8.7 Hz), 7.33 (1H, d, J=2.2 Hz), 7.43 (1H, dd, J=8.7, 2.2 Hz). ^{19}F NMR: 70.02 (3F, t, J=10.0 Hz), 98.79 (2F, m, OCF_2), 127.0 (2F, s). IR (neat): 3660 (OH), 3500 (OH) cm^{-1}. MS: 318 (M$^+$). Found: C, 48.87; H, 4.19%. Calcd for $C_{13}H_{13}F_7O$: C, 49.06; H, 4.09%. **5**: Colorless oil. NMR: δ=1.31 (18H, s), 7.02 (2H, m), 7.34 (1H, d, J=1.6 Hz). ^{19}F NMR: 78.87 (6F, d, J=3 Hz), 134.7 (1F, m). MS: 374 (M$^+$). Found: C, 54.72; H, 5.47%. Calcd for $C_{17}H_{21}F_7O$: C, 54.55; H, 5.61%. **6**: Slightly yellow crystals, mp 118—120 °C. NMR: δ=1.30 (9H, s), 1.44 (9H, d, J=4.0 Hz), 5.08 (1H, bs, OH), 6.69 (1H, t, J=2.0 Hz), 7.37 (1H, d, J=2.0 Hz). ^{19}F NMR: 71.88 (6F, d, J=2.2 Hz), 164.8 (1F, m). IR (KBr): 3475 (OH) cm^{-1}. MS: 374 (M$^+$). Found: C, 54.98; H, 5.69%. Calcd for $C_{17}H_{21}F_7O$: C, 54.55; H, 5.61%.

Reaction of 7 with FITS-3. Phenol **7** (535 mg, 2 mmol) was treated with 1.04 g (2 mmol) of FITS-3 and 178 μl (2 mmol) of pyridine in 8 ml of dichloromethane at room temperature in a similar manner as described above. After stirring for 12 h at room temperature, a similar post-treatment as above gave **8**, **9**, **10**, and **11** in 5, 34, 9, and 40% isolated yields, respectively. **8**: Colorless oil. NMR: δ=1.30 (9H, s), 1.36 (18H, s), 7.26 (2H, bs). ^{19}F NMR: 77.72 (2F, q, OCF_2 J=10.0 Hz), 81.74 (3F, t, J=10.0 Hz), 126.3 (2F, s). **9**: Slightly yellow oil. NMR: δ=1.29 (9H, s), 1.41 (9H, s), 582 (1H, t, OH, J=10.0 Hz), 7.18 (1H, m), 7.49 (1H, bd, J=2.0 Hz). ^{19}F NMR: 80.60 (3F, t, J=10.0 Hz), 108.1 (2F, dq, J=10.0, 10.0 Hz), 126.9 (2F, s). IR (neat): 3700 (OH) cm^{-1}. MS: 374 (M$^+$). Found: C, 54.50; H, 5.80%. Calcd for $C_{17}H_{21}F_7O$: C, 54.55; H, 5.61%. **10**: Colorless crystals, mp 58—60 °C. NMR: δ=1.44 (18H, s), 5.54 (1H, s, OH), 7.33 (1H, s). ^{19}F NMR: 80.56 (3F, t, J=10.0 Hz), 110.8 (2F, q, J=10.0 Hz), 126.8 (2F, s). IR (KBr): 3670 (OH) cm^{-1}. MS: 374 (M$^+$). Found: C, 54.56; H, 5.66%. Calcd for $C_{17}H_{21}F_7O$: C, 54.55; H, 5.61%. **11**: Pale yellow oil. NMR: δ=1.07 (9H, m), 1.25 (18H, s), 6.62 (2H, t, J=1.5 Hz). ^{19}F NMR: 80.25 (3F, t, J=13 Hz), 109.9 (2F, m), 121.1 (2F, bs). IR (neat): 1670 (C=O) 1645 (C=C), cm^{-1}. MS: 430 (M$^+$).

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