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Heptafluoropropylation of Various Substituted Thiophenes with Bis(heptafluorobutyryl) Peroxide. Preparation of 3-Heptafluoropropylthiophene

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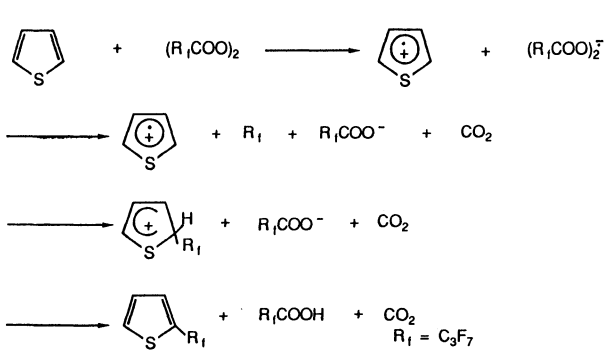
The heptafluoropropylations of several substituted thiophenes with bis(heptafluorobutyryl) peroxide were studied. The orientations of the heptafluoropropylation were examined and compared with those of usual electrophilic substitution. The method for the preparation of 3-heptafluoropropylthiophene was also explored.

The introduction of perfluoroalkyl groups has been the subject of much research in organofluorine chemistry, since the usual methods for alkylation cannot be applied to perfluoroalkylation. We have been studying perfluoroalkylation with bis(perfluoroalkanoyl) peroxide and have succeeded in introducing a heptafluoropropyl group into electron-rich compounds such as electron-rich benzenes, naphthalene, anthracene,[1] electron-rich olefins,[2] furan, and thiophene,[3] with bis(heptafluorobutyryl) peroxide (**1**). In this paper, we report on the orientation of the heptafluoropropylation in several substituted thiophenes with **1** as well as the method for the preparation of 3-heptafluoropropylthiophene.[4]

As described in our previous paper, a heptafluoropropyl group was introduced into the 2-position of thiophene regioselectively, with 98% yield.[3] The decomposition of bis(heptafluorobutyryl) peroxide **1** was accelerated in the presence of thiophene and the activation entropy for the decomposition of **1** in the presence of thiophene showed a negative value. From these results we propose the mechanism shown in Scheme 1.[3] The reaction is initiated by electron transfer from thiophene to the peroxide. The radical anion of the peroxide decomposes to the heptafluoropropyl radical, heptafluorobutyrate, and carbon dioxide. The heptafluoropropyl radical is coupled with the radical cation of thiophene to give heptafluoropropylthiophene. The reaction proceeds in a solvent cage, so the heptafluoropropyl group is introduced in good yield. Due to the high electronegativity of a perfluoroalkyl group, perfluoroalkylation involving a perfluoroalkyl cation as an intermediate are limited,[5] and the development of cationic perfluoroalkylation is very valuable. The method described in Scheme 1 is superficially equivalent to cationic perfluoroalkylation.



Scheme 1.

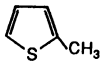
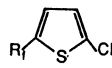
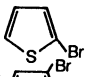
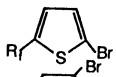
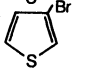
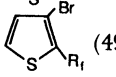
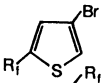
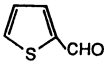
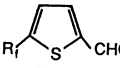
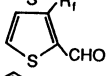
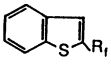
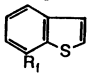
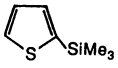
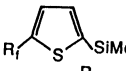
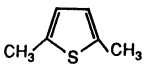
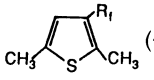
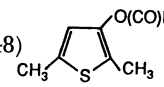
The factor for determining the orientation of the heptafluoropropylation with **1** should be the spin density distribution of a radical cation of thiophene[6] or the stability of cationic Wheland intermediates.[7] Thus, we were interested in examining the orientation of the heptafluoropropylation of various substituted thiophenes with peroxide **1** and compared with those of the usual electrophilic substitution.

3-Substituted thiophenes are important for polymeric materials and the exploitation in the preparation of 3-substituted thiophenes is valuable.[8] From results concerning the orientation of the heptafluoropropylation with **1**, we also explored the method for the preparation of 3-heptafluoropropylthiophene.

Results and Discussion

The reactions of **1** and several thiophenes were performed in Freon-113; results are summarized in Table 1. Generally, in electrophilic substitution reactions with thiophenes, an orienting effect is common for both substituents; +I and +M effect such as a methyl group and −I and +M effect such as a bromine group. Thus, for 2-substituted thiophenes further substitution occurs at position 5; for the 3-substituted type, substitution occurs preferentially at 2, unless a steric requirement forces an incoming substituent at position 5.[7] In the heptafluoropropylation of both 2-methylthiophene and 2-bromothiophene with peroxide **1**, heptafluoropropyl group was introduced into the 5-position. In a reaction of 3-bromothiophene and **1**, a heptafluoropropyl group was introduced into both the 2 and 5 positions in yields of 49% and 30%, respectively. When a substituent, such as a formyl group with −I and −M effect, are present at position 2, a further substitution occurs at the 4- or 5-position;[7] sulfur of thiophene activates the 5-position, while the 4-position is the least deactivated by an electron-withdrawing 2-substituent. However, in a reaction of 2-formylthiophene and **1**, a heptafluoropropyl group

Table 1. Heptafluoropropylation of Thiophenes with Bis(heptafluorobutyryl) Peroxide

Run	Substrate	Products (Yields/%)[a]
1		 (98)[b] $R_f=C_3F_7$
2		 (92)[b]
3		 (44)[b]
4		 (49)  (30)
5		 (25)  (24)
6		 (54)  (20)
7		 (68)
8		 (48)  (9)[c]

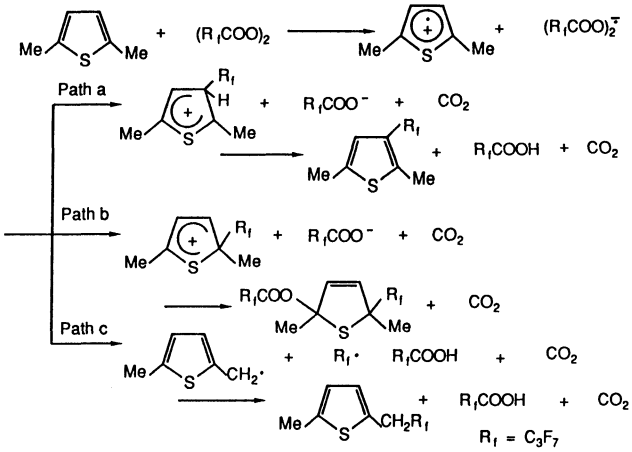
a) The yields were determined by GC based on peroxide. b) The data from Ref. 3. c) This product was not isolated and its structure was estimated by GC-MS.

was introduced into the 3- and 5-position in a ratio of about 1 : 1; heptafluoropropylation at the 4-position did not occur. An electron-withdrawing formyl group decreases the electron-transfer tendency; thus, on the whole, the yield of the heptafluoropropylation was low in 2-formylthiophene. An electrophilic attack on benzothiophene occurs at the β-position of the thiophene ring prior to the α-position.[7] However, in a reaction of benzothiophene and **1**, 2-heptafluoropropylbenzothiophene and 7-heptafluoropropylbenzothiophene were formed, with no 3-heptafluoropropylbenzothiophene.

As described in our previous paper, heptafluoropropylations of benzenes, especially electron-rich benzenes, were achieved with **1**; the orientations and partial rate factors were much different from those for the usual free radical substitutions, but similar to those for electrophilic aromatic substitutions. We therefore proposed an electron-transfer mechanism for the heptafluoropropylation, but not a free radical aromatic substitution mechanism by a heptafluoropropyl radical produced by a homolytic cleavage of **1**.[1] In this study, we found that a heptafluoropropyl group was introduced into substituted thiophenes with **1** regioselectively. The orientations were similar to those expected from the usual electrophilic substitutions in 2-methylthiophene, 2- or 3-bromothiophenes. However, some differences were found in the orientations for the heptafluoropropylation of 2-formylthiophene and benzothiophene with **1** from those for the usual electrophilic substitutions; the orientations for the heptafluoropropylation cannot be explained in terms of the stabilities of cationic intermediates, and may be characteristic for an electron-transfer reaction.

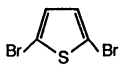
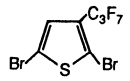
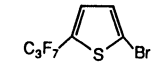
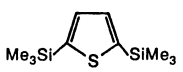
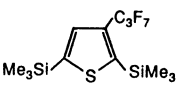
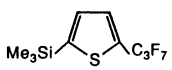
Electrophilic ipso-substitutions of arylsilanes are well known.[9] Thus, it is interesting to examine whether ipso-substitution occurs in a reaction of 2-trimethylsilylthiophene and **1**. Regarding this reaction, however, the heptafluoropropyl group was found to enter into a 5-position (Table 1, run 7).

There are three expected products in the reaction of **1** and 2,5-dimethylthiophene, as shown in Scheme 2. It is known that the radical cation of 2,5-dimethylthiophene electrochemically produced gives those three types of compounds.[10] As a result, a heptafluoropropyl group was solely introduced into the 3-position of the thiophene to give 2,5-dimethyl-3-heptafluoropropylthiophene (Table 1, run 8), although the spin density of the radical cation of 2,5-dimethylthiophene is higher at the α-position than at the β-position.[6] These results suggested that we should use 2,5-disubstituted thiophene in order to prepare 3-heptafluoropropylthiophene: 2,5-disubstituted thiophenes are fluoroalkylated with **1**; then, substituents at the 2 and 5 positions are removed to give



Scheme 2.

Table 2. Heptafluoropropylation of 2,5-Disubstituted Thiophenes with Bis(heptafluorobutyryl) Peroxide[a]

Substrate (mmol)	Products (Yields/%)[b]	
		
1.5	37	6
5.0	35	13
		
1.5	15	35
5.0	27	30
1.5[c]	47	5
5.0[c]	55	13

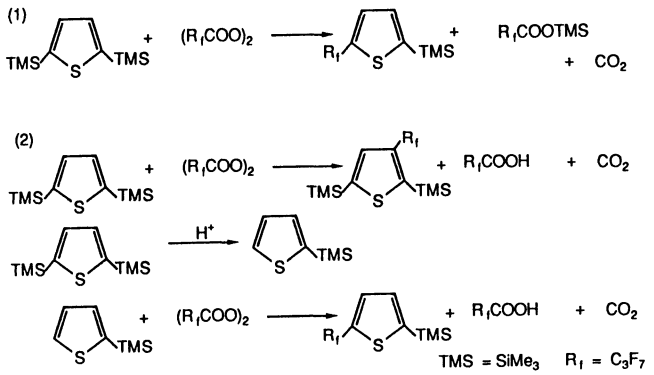
a) One mmol of the peroxide was used. b) The yields were determined by GC based on the peroxide. c) Ten mmol of MgO was added.

3-heptafluoropropylthiophene. At first, the reaction of commercially available 2,5-dibromothiophene was examined. The yield of 2,5-dibromo-3-heptafluoropropylthiophene was less than 40% (Table 2). Regarding electron transfer, it may not be adequate to use a bromine group as a protecting group of the 2,5-position. We also examined a reaction of 2,5-bis(trimethylsilyl)thiophene and peroxide **1**. In this reaction, the main product was 2-trimethylsilyl-5-heptafluoropropylthiophene; the yield of the desired 2,5-bis(trimethysilyl)-3-heptafluoropropylthiophene was low. There are two plausible reaction mechanisms for the formation of 2-trimethylsilyl-3-heptafluoropropylthiophene. One is an ipso-substitution of trimethylsilyl group, as shown in Scheme 3 (1). The other is shown in Scheme 3 (2). The acid-promoted desilylation of 2,5-bis(trimethylsilyl)thiophene occurred first. Since 2-trimethylsilylthiophene is more reactive than 2,5-bis(trimethylsilyl)thiophene in a reaction with **1**, 2-trimethylsilyl-5-heptafluoropropylthiophene is formed preferentially.

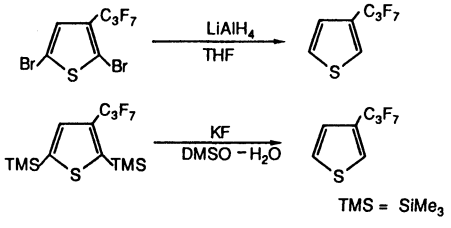
In order to trap the produced heptafluorobutyric acid, MgO was added. The yield of 2,5-bis(trimethylsilyl)-3-heptafluoropropylthiophene was improved in the presence of MgO, as shown in Table 2. This may imply the acid-promoted desilylation.

Bromine atoms of 2,5-dibromo-3-heptafluoropropylthiophene were reduced by $LiAlH_4$ in THF and 3-heptafluoropropylthiophene was obtained in 60% yield. Trimethylsilyl groups were removed from 2,5-bis(trimethylsilyl)-3-heptafluoropropylthiophene with KF in DMSO in the presence of water almost quantitatively.

It is known that, in a direct heptafluoroalkylation of thiophenes, 2-isomers are obtained as the main products.[11] Only one example is known for the preparation of 3-perfluoroalkylthiophene; the reaction of 3-halogenothiophene, perfluoroalkyl iodide and copper-bronze in DMF gave 3-perfluoroalkylthiophene in the yield of 17—50%.[12] We have so far explored novel methods for the introduction of a heptafluoropropyl group into the 3-position of thiophene.



Scheme 3.



Scheme 4.

Experimental

^1H NMR spectra were taken with a JEOL JNM PMX 60Si (60MHz) spectrometer. ^{13}C NMR and ^{19}F NMR spectra were taken with a JEOL JNM FX90Q FTNMR spectrometer. IR spectra were recorded on a Hitachi 260-10 spectrometer. Gas chromatography was performed by using a Hitachi 163 or 263-30 gas chromatograph with SE-30 (10%) 1- or 2-m stainless columns. Gel permeation chromatography was performed by means of a JAI Model LC-08 liquid chromatograph equipped with two JAIGEL-1H columns and using chloroform as an eluent. MS spectra were obtained with JEOL JMS D-300 spectrometer by an electron-impact (EI) ionizing technique at 70 eV.

Materials. Thiophenes, except for 2-trimethylsilylthiophene and 2,5-bis(trimethylsilyl)thiophene, were commercially available and used after purification. 2-Trimethylsilylthiophene and 2,5-bis(trimethylsilyl)thiophene were synthesized from 2-lithiothiophene and 2,5-dilithiothiophene with trimethylsilyl chloride. The lithiothiophenes were synthesized according to methods described in the literature.[13] Bis(heptafluorobutyryl) peroxide was prepared from heptafluorobutyryl chloride and hydrogen peroxide in Freon-113 and water according to the literature.[14] The peroxide was not isolated and used as a solution of Freon-113.

General Procedure for Reactions of 1 and Thiophenes. A solution of **1** (1.0 mmol) and thiophenes (1.5 mmol) in 10 ml Freon-113 was degassed by a freeze-thaw cycle, sealed in an ampoule and kept at 40 °C for adequate time (until the peroxide was consumed). The reaction mixture was washed two times with 5% aq NaOH or $NaHCO_3$ and then with water. An organic layer was separated and dried over $MgSO_4$. The yields of the products were determined by GC using chlorobenzene as an internal standard. The products were isolated from the reaction mixture by the use of gel permeation chromatography and/or column chromatography over silica gel (Wakogel C-60), and identified by IR, NMR, and MS.

2-Heptafluoropropyl-3-bromothiophene: ^1H NMR ($CDCl_3$) δ=7.03, 7.42 (ABq, J=6.3 Hz); ^{13}C NMR ($CDCl_3$) δ=113.9 (C_3, t, J_{CCCF}=4.3 Hz), 129.1 (C_5), 133.2 (C_4); IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); MS m/z 332 (M^++2), 330 (M^+); Exact MS: m/z 329.8928. Calcd for $C_7H_2F_7SBr$: M, 329.8949.

2-Heptafluoropropyl-4-bromothiophene: ^1H NMR ($CDCl_3$) δ=7.21 (1H, s), 7.33 (1H, s); ^{13}C NMR ($CDCl_3$) δ=110.6 (C_4), 127.5 (C_5), 132.9 (C_3, t, J_{CCCF}=6.1 Hz); IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); MS m/z 332 (M^++2), 330 (M^+); Exact MS: m/z 329.8897. Calcd for $C_7H_2F_7SBr$: M, 329.8949.

2-Formyl-3-heptafluoropropylthiophene: ^1H NMR ($CDCl_3$) δ=7.22, 7.69 (ABq, J=5.4 Hz), 9.94 (1H, br); ^{13}C NMR ($CDCl_3$) δ=128.6 (C_4, t, J_{CCCF}=5.5 Hz), 134.1 (C_5), 181.8 (CHO, t, $J_{C\text{-}F}$=3.7 Hz);[15] ^{19}F NMR ($CDCl_3$, ppm from ext. CF_3COOH) −4.0, −27.6, −50.2; IR (cm^{-1}) 1340 (CF_3), 1230

(CF_2); MS m/z 280 (M^+); Exact MS: m/z 279.9830. Calcd for $C_8H_3F_7OS$: M, 279.9792.

2-Formyl-5-heptafluoropropylthiophene: ^1H NMR ($CDCl_3$) δ=7.44, 7.67 (ABq, J=4.2 Hz), 9.85 (1H, s); ^{13}C NMR ($CDCl_3$) δ=130.7 (C_4, t, J_{CCCF}=5.5 Hz), 134.6 (C_3), 147.4 (C_2), 182.5 (CHO); ^{19}F NMR ($CDCl_3$) −4.1, −27.7, −50.2; IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); MS m/z 280 (M^+); Exact MS: m/z, 279.9832. Calcd for $C_8H_3F_7OS$: M, 279.9792.

2-Heptafluoropropylbenzothiophene: ^1H NMR ($CDCl_3$) δ=7.2—7.9 (5H, m), ^{13}C NMR ($CDCl_3$) δ=122.5 (C_7), 125.2 (C_4), 125.3 (C_5), 126.7 (C_6), 127.6 (C_3, t, J_{CCCF}=6.1 Hz), 138.3 (C_8), 141.0 (C_9); IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); MS m/z 302 (M^+); Exact MS: m/z 301.9992. Calcd for $C_{11}H_5F_7S$: M, 302.0000.

7-Heptafluoropropylbenzothiophene: One of the possible isomers heptafluoropropylated at the benzene ring of benzothiophene was isolated and tentatively identified as 7-heptafluoropropylbenzothiophene, the possibility of 4-heptafluoropropylbenzothiophene cannot be denied. ^1H NMR ($CDCl_3$) δ=7.4—8.2 (5H, m); ^{13}C NMR ($CDCl_3$) δ=122.9 (C_5), 123.4 (C_3), 124.4 (C_6, t, J_{CCCF}=8.5 Hz), 126.5 (C_2), 128.7 (C_4), 141.7 (C_8); IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); MS: m/z 302 (M^+); Exact MS: m/z 301.9971. Calcd for $C_{11}H_5F_7S$: M, 302.0000.

2-Heptafluoropropyl-5-trimethylsilylthiophene: ^1H NMR ($CDCl_3$) δ=0.39 (9H, s), 7.17,* 7.41 (ABq, J=3.6 Hz, *J_{HF}=1.2 Hz); ^{13}C NMR ($CDCl_3$) δ=−0.4 ($SiCH_3$), 131.2 (C_3, t, J_{CCCF}= 4.9 Hz), 133.9 (C_4), 140.8 (C_5); IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); MS m/z 324 (M^+); Exact MS: m/z 324.0278. Calcd for $C_{10}H_{11}F_7SiS$: M, 324.0239.

2,5-Dimethyl-3-heptafluoropropylthiophene: ^1H NMR ($CDCl_3$) δ=2.36 (3H, s), 2.44 (3H, t, J_{HF}=2.4 Hz),[15] 6.58 (1H, s); ^{13}C NMR ($CDCl_3$) δ=13.7 (2-CH_3), 14.9 (5-CH_3), 124.7 (C_2, t, J_{CCCF}=3.0 Hz), 127.3 (C_5), 137.0 (C_4); ^{19}F NMR ($CDCl_3$) −4.3, −30.8 (J_{HF}=2.4 Hz), −50.8; IR (cm^{-1}) 1340 (CF_3), 1230 (CF_2); MS m/z 280 (M^+); Exact MS: m/z 280.0119 Calcd for $C_9H_7F_7S$: M, 280.0156.

2,5-Dibromo-3-heptafluoropropylthiophene: ^1H NMR ($CDCl_3$) δ=6.97 (s); ^{13}C NMR ($CDCl_3$) δ=113.0 (C_5), 115.1 (C_2, t, J_{CCCF}=4.9 Hz), 130.1 (C_4); IR (cm^{-1}), 1360 (CF_3), 1230 (CF_2); MS m/z 408 (M^+); Exact MS: m/z 407.8067. Calcd for $C_7HF_7SBr_2$: M, 407.8055.

2,5-Bis(trimethylsilyl)-3-heptafluoropropylthiophene: ^1H NMR ($CDCl_3$) δ=0.3 (18H, br), 7.31 (1H, t, J_{HF}=1.5 Hz); ^{13}C NMR ($CDCl_3$) δ=−0.2 (5-$SiCH_3$), 0.4 (2-$SiCH_3$, t),[15] 135.1 (C_4, m for CF coupling), 147.3 (C_5), 150.1 (C_2, t, J_{CCCF}=4.3 Hz); IR (cm^{-1}) 1370 (CF_3), 1230 (CF_2); MS m/z 396 (M^+); Exact MS: m/z 396.0642. Calcd for $C_{13}H_{19}F_7Si_2S$: M, 396.0635.

The Removal of Trimethylsilyl Group from 2,5-Bis-(trimethylsilyl)-3-heptafluoropropylthiophene. 2,5-Bis-(trimethylsilyl)-3-heptafluoropropylthiophene (120 mg), KF (175 mg), and water (0.1 ml) were dissolved in 5 ml DMSO, and the solution was heated at 100 °C for 24 h. From the DMSO solution the resulting 3-heptafluoropropylthiophene was extracted with Freon-113; the Freon-113 solution was washed with 20 ml of water two times in order to completely remove any DMSO. Freon-113 was carefully removed and almost pure 3-heptafluoropropylthiophene was obtained.

3-Heptafluoropropylthiophene: ^1H NMR ($CDCl_3$) δ= 7.1—7.2 (2H, m), 7.6 (1H); ^{13}C NMR ($CDCl_3$) δ=125.5 (C_4, t, J_{CCCF}=3.7 Hz), 127.4 (C_5), 128.1 (C_2, t, J_{CCCF}=6.7 Hz); IR (cm^{-1}), 1350 (CF_3), 1230 (CF_2); MS m/z 252 (M^+); Exact MS: m/z 251.9871. Calcd for $C_7H_3F_7S$: M, 251.9844.

The Removal of a Bromo Group from 2,5-Dibromo-3-heptafluoropropylthiophene. A standard solution of lithium aluminum hydride in THF (1.5 mol l^{-1}) was prepared according to a method described in the literature.[16] A standard solution (0.77 ml) and then 2,5-dibromo-3-heptafluoropropylthiophene were added to THF; the resulting solution was refluxed for 24 h. The reaction flask was cooled in an ice bath; then a 1 : 1 mixture of water and THF 20 ml was added slowly, drop by drop. Then, a 0.1 g NaOH pellet was added. The aqueous phase was extracted five times with 20 ml portions of ether. The formation of 3-heptafluoropropylthiophene was confirmed by GC-MS.

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