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Perfluoropropylation of Furans, Thiophenes, and Pyridines with Bis(heptafluorobutyryl) Peroxide

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Bis(heptafluorobutyryl) peroxide (**1**) smoothly reacted with furans and thiophenes under mild conditions to regioselectively give 2-perfluoropropylfurans and thiophenes in high yields. Mechanistically, reactions with furans or thiophenes are considered to be initiated by one-electron transfers from substrates to **1**. On the other hand, the perfluoropropylation of pyridine was proceeded by the usual free-radical substitution to a pyridinium salt by a heptafluoropropyl radical produced by the homolytic decomposition of **1**.

Recently, remarkable attention have been focused on fluoroalkyl-containing compounds due to their unique properties. However, the introduction of fluoroalkyl groups is not easy since the usual methods for alkylation can not be applied to perfluoroalkylation due to the high electronegativity of perfluoroalkyl groups. Especially, an exploration of electrophilic perfluoroalkylating agents is desired since reactions involving a perfluoroalkyl cation as an intermediate are very limited.[1] We have been studying the perfluoroalkylation of nucleophilic substrates with bis(heptafluorobutyryl) peroxide **1** via an electron-transfer process (shown in Scheme 1) and the heptafluoropropylation of electron-rich benzenes, naphthalene, anthracene, and electron-rich olefins has been achieved.[2,3]

$$\begin{aligned}\mathrm{Nu{:}} + (C_3F_7CO_2)_2 &\longrightarrow \mathrm{Nu}^{\dot{+}} + (C_3F_7CO_2)_2^{\dot{-}}\\ &\longrightarrow \mathrm{Nu}^{\dot{+}} + C_3F_7\cdot + C_3F_7CO_2^- + CO_2\\ &\longrightarrow \mathrm{Nu}^+C_3F_7 + C_3F_7CO_2^- + CO_2\end{aligned}$$

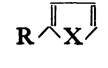
Scheme 1.

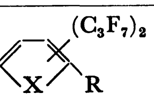
In this paper, we wish to report on reactions involving bis(heptafluorobutyryl) peroxide with such heteroaromatic compounds as furans, thiophenes, and pyridines.

Results and Discussion

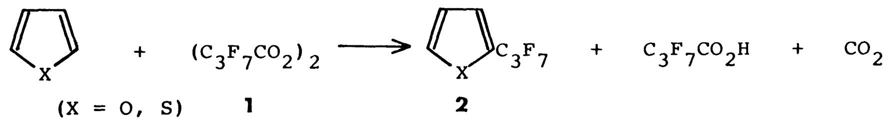
Two moles of furan or thiophene per mol of **1** were added to a solution of **1** in Freon-113. The mixture was degassed by a freeze-thaw cycle, sealed in an ampoule and kept at 40 °C for 3 h. Regioselectively 2-substituted furan or thiophene with a perfluoropropyl group was obtained in 98% yield and a substantial amount of perfluorobutyric acid was also formed. Several substituted furans and thiophenes

Table 1. Reactions of Furans, Thiophenes with Bis(heptafluorobutyryl) Peroxide in Freon-113 at 40 °C for 3 h

			Peroxide/mmol	Yield of the products/%[a)]		
X	R	mmol		**2**	**3**[b)]	$C_3F_7CO_2H$
O	H	2	4	Trace[c)]	8[d)]	52[c)]
O	H	2	2	32[c)]	2	88
O	H	4	2	98	0	98
O	CH_3	4	2	64	4[e)]	108
O	CH_3OCO	4	2	17	0	93
S	H	4	2	98	0	99
S	CH_3	4	2	92	4	98
S	Cl	4	2	78	0	102
S	Br	4	2	44	0	89

a) The yields of products are based on peroxide. b) Bis(perfluoropropyl)furans, thiophenes .

c) Considerable amounts of polymeric compounds were obtained. d) The yield of product is based on furan. e) Trace amount of 2-methyl-3,4,5-tris(perfluoropropyl)furan was also formed.



were also reacted with **1** and the results are summarized in Table 1. The production of perfluorobutyric acid, not heptafluoropropane (C_3F_7H), should be important from the viewpoint of synthetic chemistry; the produced perfluorobutyric acid could be recovered as a sodium salt and used again for the synthesis of peroxide **1**.

Hitherto, the direct perfluoroalkylation of heteroaromatic compounds has been carried out thermally or photochemically using perfluoroalkyl iodides.[4,5] However, these processes require high temperatures or irradiation for long periods of time. Recently, Umemoto et al. reported the perfluoroalkylation of various aromatic compounds with perfluoroalkylphenyliodonium trifluoromethanesulfonate(FITS) under mild conditions.[6] Now, peroxide **1** has also been shown to be an excellent reagent for the perfluoropropylation of furans and thiophenes under very mild conditions.

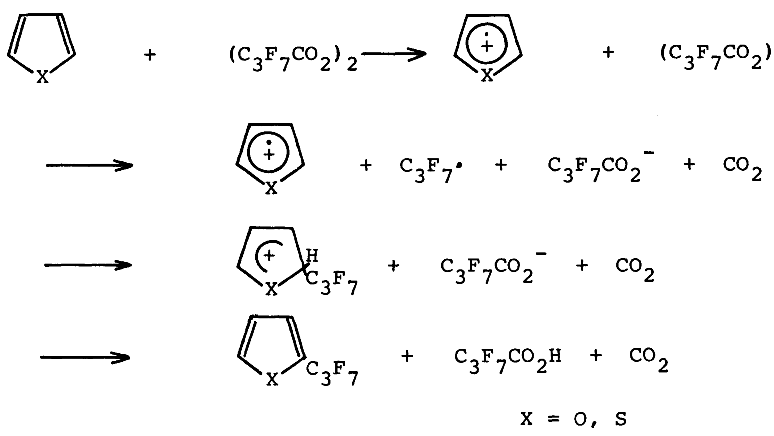
A plausible reaction mechanism for perfluoroalkylation with **1** is shown in Scheme 2; the reaction is initiated by one-electron transfers from substrates to peroxide **1**. The reactions of benzoyl peroxide with thiophene or furan via an electron-transfer process have been reported.[7,8] In an MO calculation for the substituted benzoyl peroxides, an electron-withdrawing substituent lowers the O–O antibonding energy level.[9] Thus, the energy level of the O–O antibonding of peroxide **1** should be lower than that of benzoyl peroxide due to the high electronegativity of perfluoroalkyl group. Thus, the mechanism shown in Scheme 2 involving an electron-transfer process is reasonable.[10]

The rate of decomposition of **1** should be accelerated in the presence of furans and thiophenes if the reaction is initiated by one-electron transfers from furans or thiophenes to **1**. The decomposition of **1** was followed by iodometry in the presence or absence of 5 mol of thiophenes or furan per mol of **1** and shown to be markedly accelerated by adding thiophenes or furan. The rate of decomposition of **1** was not affected by $C_3F_7CO_2H$. The results are summarized in Table 2.

When pyridine was added to a solution of **1** in

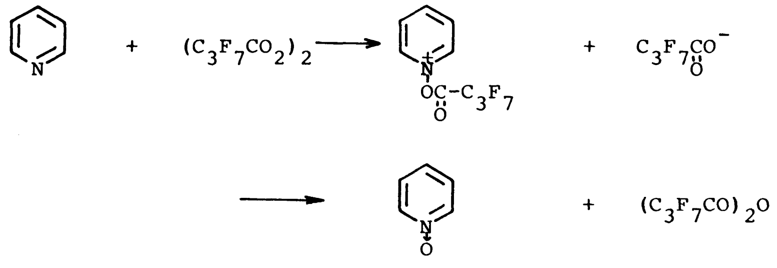
Table 2. Apparent First-Order Rate Constants for the Thermal Decomposition of 0.02 mol/l $(C_3F_7CO_2)_2$ in the Presence of 0.10 mol/l 2-Substituted Thiophenes or Furan in Freon-113

2-Substituted thiophene, furan	Temp °C	$k_d/10^{-4}\ s^{-1}$	ΔH^{*} kJ mol^{-1}	ΔS^{*} JK^{-1} mol^{-1}
Thiophene	5.0	0.74±0.03	87.70	−8.03
	10.0	1.47±0.02		
	15.0	2.57±0.05		
	20.0	5.61±0.11		
Methyl-thiophene	5.0	4.24±0.17	73.93	−42.55
	7.5	6.27±0.18		
	10.0	7.57±0.18		
	15.0	13.79±0.49		
Chloro-thiophene	5.0	1.25±0.08	77.57	−40.12
	10.0	2.18±0.02		
	15.0	3.84±0.05		
	20.0	7.40±0.14		
Furan	15.0	9.84±0.34		
None	15.0	0.08±0.00	100.71	7.57
	20.0	0.16±0.00		
	25.0	0.33±0.00		
	30.0	0.66±0.01		
$C_3F_7CO_2H$ (0.02 mol/l^{-1})	15.0	0.10±0.00	94.64	−11.51
	20.0	0.20±0.00		
	25.0	0.37±0.01		
	30.0	0.77±0.02		



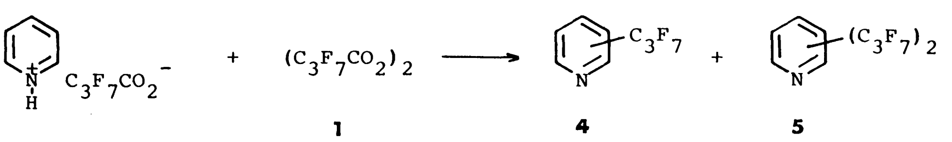
Scheme 2.

Freon-113, the solution turned to reddish-brown at once; the solution was maintained at 40 °C for 6 h under N_2, and the products were analyzed. Perfluoropropylpyridines were not detected and pyridinium heptafluorobutyrate and pyridine *N*-oxide heptafluorobutyrate were obtained. The reaction proceeded even at −20 °C to give pyridine heptafluorobutyrate and pyridine *N*-oxide heptafluorobutyrate. This means that the nucleophilic attack of an *N*-lone pair of pyridine on an O–O bond of **1** may be more preferential than an electron-transfer reaction from the π-orbital of pyridine to **1** observed in reactions with furan or thiophene. A similar nucleophilic attack of an *N*-lone pair on an O–O bond of benzoyl peroxides has been reported.[11]



The thermal decomposition of benzoyl peroxide in pyridine gives a mixture of 2-, 3-, and 4-phenylpyridine due to the substitution of a phenyl radical to pyridine;[12] however similar reactions with *m*-nitrobenzoyl peroxides gave an abnormally high yield of the nitrobenzoic acid and pyridine *N*-oxide.[11] The nucleophilic attack should compete more effectively with homolytic substitution when the peroxide contains powerful electron-withdrawing substituents.[11]

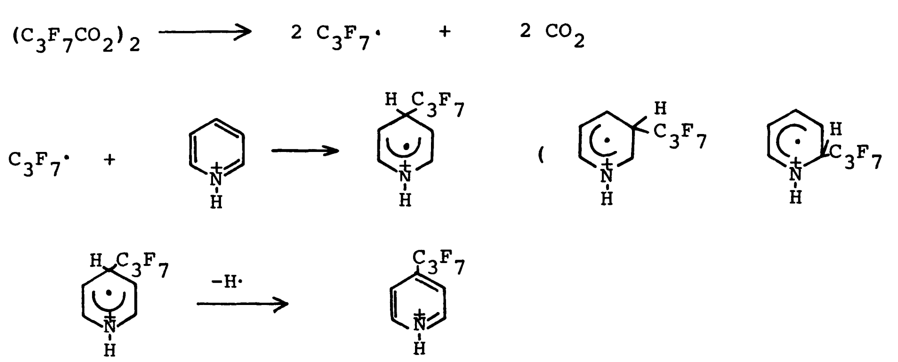
We have attempted a reaction with pyridinium heptafluorobutyrate which has no lone pair on the nitrogen atom with **1** in Freon-113. The results are summarized in Table 3. In the reaction of pyridinium heptafluorobutyrate with **1**, perfluoropropylpyridines were obtained. Almost the same regioselectivities (α:β:γ=21:18:22) were observed in the perfluoropropylation of pyridinium salt, suggesting a free-radical character of this reaction as shown in Scheme 3.[13]



Experimental

Measurement. ^{1}H-NMR spectra were taken with a JEOL JNM-MH-100 (100 MHz) spectrometer. ^{13}C-NMR spectra were taken with a JEOL FX-60 FT-NMR spectrometer. A GC analysis was performed on Shimadzu GC-4APTF gas chromatograph. IR spectra were recorded on a JASCO A-3 spectrophotometer. GC-IR spectra were taken with a Shimadzu GC-IR-VGS-1 spectrophotometer. The Mass spectra were taken with a JEOL JMS-D300 spectrometer and a JEOL DX-500 spectrometer.

Materials. Bis(heptafluorobutyryl) peroxide was prepared from heptafluorobutyryl chloride and hydrogen peroxide in the presence of aqueous sodium hydroxide in



Scheme 3.

Table 3. Reaction Products for the Perfluoropropylation of Pyridinium Compounds with Bis(heptafluorobutyryl) Peroxide in Freon-113

	Reagent/mmol		Temp/Time	Yield of the products/%[a]	
	$PyH^+RCO_2^-$	Peroxide	°C/h	**4**	**5**
$R=C_3F_7$	2[b]	2	40/ 3	18	6
$=C_3F_7$	2[b]	4	40/ 6	59[c]	14
$=CH_3$	20	20	40/20	0	0
$=C_3F_7$	2[d]	5	40/ 8	29	6

a) The yields of products are based on the pyridine consumption. b) Pyridinium heptafluorobutyrate. c) Isomer composition: $\alpha:\beta:\gamma=42:36:22$. d) 2,6-Lutidinium heptafluorobutyrate.

Freon-113 by a method described in the literature.[14)]

Reaction with Furans and Thiophenes. A solution containing 2 mmol of bis(heptafluorobutyryl) peroxide and 4 mmol of furans or thiophenes in 30 g of Freon-113 was degassed and kept at 40 °C for 3 h in a sealed tube. The solution was washed with 20 mL of water. The organic layer was analyzed by GLC using internal standards and $C_3F_7CO_2H$ in aqueous layer was determined by titration.

The 2-perfluoropropylfurans and thiophenes were isolated by distillation of the reaction mixture, which was obtained by scaled-up reactions under similar conditions, and identified by IR, ^1H-NMR, ^{13}C-NMR, and GC–MS.

2-Perfluoropropylfuran: ^1H-NMR ($CDCl_3$) δ=6.60 (1H, m), 6.93 (1H, m), 7.74 (1H, m); IR (cm^{-1}) 1355 (CF_3), 1230 (CF_2); ^{13}C-NMR ($CDCl_3$) δ=111.0, 113.9, 145.9; MS *m/z* 236 (M^+), 217, 167, 148, 117, 69, 39. Exact MS: *m/z* 236.0062. Calcd for $C_7H_3F_7O$: 236.0072.

2-Perfluoropropylthiohene: ^1H-NMR ($CDCl_3$) δ=7.08 (1H, m), 7.34 (1H, m), 7.57 (1H, m); IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); ^{13}C-NMR ($CDCl_3$) δ=127.5, 130.2, 130.3 (t, J_{CCCF}=6.1 Hz); MS *m/z* 252 (M^+), 233, 133. Exact MS: *m/z* 251.9811. Calcd for $C_7H_3F_7S$: 251.9844.

2-Methyl-5-perfluoropropylfuran: ^1H-NMR ($CDCl_3$) δ= 2.24 (3H, s), 5.86 (1H), 6.42 (1H); IR (cm^{-1}) 1350 (CF_3), 1255 (CF_2); ^{13}C-NMR ($CDCl_3$) δ=13.4, 107.4, 115.0 (t, J_{CCCF}=3.7 Hz), 156.7; MS *m/z* 250 (M^+), 231, 131. Exact MS: *m/z* 250.0186. Calcd for $C_8H_5OF_7$: 250.0229.

2-Methyl-3,4,5-tris(perfluoropropyl)furan: MS *m/z* 586 (M^+).

2-Methyl-5-perfluoropropylthiophene: ^1H-NMR ($CDCl_3$) δ=2.54 (3H, s), 6.80 (1H), 7.26 (1H); IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); ^{13}C-NMR ($CDCl_3$) δ=15.0, 125.7, 130.3 (t, J_{CCCF}=6.1 Hz), 145.5; MS *m/z* 266 (M^+), 147, 96. Exact MS: *m/z* 265.9989. Calcd for 266.0000.

2-Methyl-bis(perfluoropropyl)thiophene: MS *m/z* 434 (M^+), 415, 315, 265, 144.

2-Methyl-bis(perfluoropropyl)furan: MS *m/z* 418 (M^+), 130.

2-Methoxycarbonyl-5-perfluoropropylfuran: ^1H-NMR ($CDCl_3$) 3.72 (3H, s), 6.65 (1H), 6.93 (1H); ^{13}C-NMR ($CDCl_3$) δ=50.8, 115.3, 118.0, 158.1; IR (cm^{-1}) 1740 (C=O), 1355 (CF_3), 1230 (CF_2); MS *m/z* 294 (M^+), 263, 175. Exact MS: *m/z* 294.0128. Calcd for $C_9H_5O_3F_7$: 294.0127.

2-Chloro-5-perfluoropropylthiophene: ^1H-NMR ($CDCl_3$) δ=7.20 (1H), 7.46 (1H); IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); ^{13}C-NMR ($CDCl_3$) δ=126.6, 129.9 (t, J_{CCCF}=6.1 Hz), 135.9. MS *m/z* 288, 286 (M^+), 169, 167, 69. Exact MS: *m/z* 285.9447. Calcd for $C_7H_2F_7SCl$: 285.9453.

2-Bromo-5-perfluoropropylthiophene: ^{13}C-NMR ($CDCl_3$) δ=118.2, 130.3, 130.7; IR (cm^{-1}) 1345 (CF_3), 1230 (CF_2). Exact MS: *m/z* 329.8952. Calcd for $C_7H_2F_7SBr$: 329.8949.

Kinetics of the Reaction with Thiophenes or Furan. Solutions of 0.02 mol/l $(C_3F_7CO_2)_2$ and 0.10 mol/l thiophenes or furan in degassed sealed tubes were immersed in a constant-temperature bath. Each sample tube was removed after appropriate time intervals and immediately immersed in the Dry Ice-acetone bath to quench the reaction; the amount of the residual $(C_3F_7CO_2)_2$ was estimated by iodometric titration. Apparent first-order rate constants were obtained from the initial slopes of the plot of the logarithm of the peroxide concentration against time.

Reaction Products with Pyridine. A solution containing 100 mmol of pyridine and 20 mmol of $(C_3F_7CO_2)_2$ in 400 g of Freon-113 in a 500-mL flask was deaerated with N_2. The flask was immersed in a bath at −20 °C for 3 d. The solution was then concentrated by evaporating the solvent under reduced pressure. A white solid (4.61 g) was obtained by the recrystallization of the residue from 2-propanol and identified as pyridinium heptafluorobutyrate on the basis of the following data; mp 54—56 °C (lit,[15)] 56—58 °C), IR (cm^{-1}) 1660 (C=O), 1350 (CF_3), 1220 (CF_2); ^1H-NMR ($CDCl_3$) δ=8.11 (2H, m), 8.58 (1H, m), 9.14 (2H, m), 16.76 (1H, s). NaOH was added to the alcohol solution and the solution was stirred at room temperature for 3 h. After removing the alcohol, diethyl ether was added and the precipitated solid was removed. From the ether solution pyridine *N*-oxide was obtained and identified by IR, ^1H-, and ^{13}C-NMR.

Reaction Products with Pyridinium Heptafluorobutyrate. A solution containing 2 mmol of pyridinium heptafluorobutyrate and 4 mmol of $(C_3F_7CO_2)_2$ in 30 g of Freon-113 was stirred under N_2 at 40 °C for 6 h. The solution was then diluted with 20 mL of 5% aqueous NaOH and 20 mL of water. The organic layer was analyzed by GLC using the internal standard. The products were identified by GC–MS and isomer composition of perfluoropropylpyridines were determined by GC–IR.

Perfluoropropylpyridine: IR (cm^{-1}) 1350 (CF_3), 1230 (CF_2); MS *m/z* 247 (M^+), 228, 128, 78, 69; CI-MS *m/z* 248 (M^++1).

Bis(perfluoropropyl)pyridine. MS *m/z* 396 (M^+-19), 296, 177, 69; CI-MS *m/z* 416 (M^++1).

GC-IR (aromatic C–H bend). 2-Perfluoropropyl pyridine 750 cm^{-1} (745 cm^{-1}), 3-Perfluoropropylpyridine 780, 710 cm^{-1} (779, 714 cm^{-1}), 4-Perfluoropropylpyridine 818, 740 cm^{-1} (818, 737 cm^{-1}). Values in parenthese are perfluorodecylpyridines.[4a)]

2,6-Dimethylperfluoropropylpyridine. MS *m/z* 275 (M^+) 256, 156.

2,6-Dimethylbis(perfluoropropyl)pyridine. MS *m/z* 324 ($M^+-C_2F_5$), 205, 69; CI-MS *m/z* 444 (M^++1).

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