Journal of Fluorine Chemistry, 46 (1990) 423–431

Received: March 28, 1989; accepted: July 31, 1989

TRIFLUOROMETHYLATION OF AROMATIC COMPOUNDS WITH BIS(TRIFLUOROACETYL) PEROXIDE

Hideo SAWADA and Masaharu NAKAYAMA
Tsukuba Research Laboratory, Nippon Oil & Fats Co., Ltd., Tokodai, Tsukuba-city, Ibaraki 300-26 (Japan)

Masato YOSHIDA,* Tatsuro YOSHIDA, and Nobumasa KAMIGATA
Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Fukazawa, Setagaya-ku, Tokyo 158 (Japan)

SUMMARY

Bis(trifluoroacetyl) peroxide was found to be thermally stable, and trifluoromethylation of aromatic compounds was studied using this peroxide. Trifluoromethylation of electron-rich benzenes, furan, thiophene, or their benzo derivatives proceeded with the peroxide in moderate to high yields.

INTRODUCTION

We have been exploring the perfluoroalkylation of electron-rich substrates using bis(perfluoroalkanoyl) peroxides [1]. The studies were mainly performed using bis(heptafluorobutyryl) peroxide because its preparation and properties were well known. Although the synthesis of bis(trifluoroacetyl) peroxide has been reported [2], the properties and the reactivity are little known, and its synthesis was difficult. The trifluoromethyl group is a fundamental perfluoroalkyl group, and trifluoromethylated aromatic or heteroaromatic compounds are very important for medical and agricultural usage. Therefore, in the series of our studies it is important to examine the utility of bis(trifluoroacetyl) peroxide as a

0022-1139/90/$3.50

reagent for trifluoromethylation. In the present work, we synthesized bis(trifluoroacetyl) peroxide and examined the trifluoromethylation of typical aromatic or heteroaromatic compounds.

RESULTS AND DISCUSSION

Bis(trifluoroacetyl) peroxide (**1**) was synthesized from trifluoroacetic anhydride and hydrogen peroxide in Freon 113 ($CFCl_2CF_2Cl$) by the modified method described in the literature [3]. The solution of **1** in Freon 113 was used without further purification and the concentration of the peroxide was determined by iodometry. By the use of this method we could obtained 0.2 mol/l solution of **1** in Freon 113 in 30% yield.

The thermal stability of **1** has not yet been studied, so first of all we examined the thermal reaction of **1** in Freon 113. The decomposition of **1** followed a first-order equation at each temperature, and gave the coupling product of two perfluoroalkyl radicals as was observed in bis(perfluoroalkanoyl) peroxide ($\geq C_2$) [3,4].

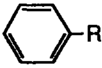
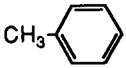
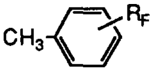
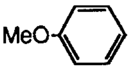
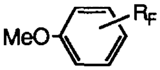
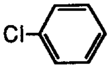
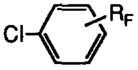
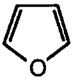
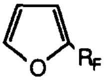
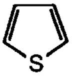
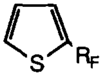
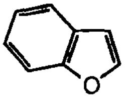
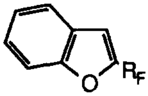
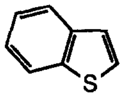
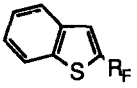
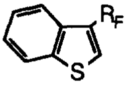
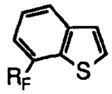
$$CF_3(CO)OO(CO)CF_3 \longrightarrow 2\,CF_3\bullet + 2\,CO_2 \longrightarrow C_2F_6 + 2\,CO_2$$

The rate of the decomposition of **1** was measured at 45 - 60 °C : $kd \times 10^5 = 1.59$ (45 °C), 3.08 (50 °C), 5.97 (55 °C), and 10.38 (60 °C) $\Delta H^{\ddagger} = 108.1$ KJ/mol, $\Delta S^{\ddagger} = 2.8$ J/Kmol. Unexpectedly, **1** was thermally stable compared with bis(heptafluorobutyryl) peroxide (**2**) or bis(pentadecafluorooctanoyl) peroxide (**3**); these peroxides were reported to decompose smoothly at 20 °C [3,4]. The half-life of **1** at 0 °C was calculated to be 498 days, so **1** is facile to handle and store.

Trifluoromethylations of benzenes or heteroaromatic compounds with **1** were examined. To a solution of **1** (1.0 mmol) in Freon 113, substrate (1.5 - 2.0 mmol) was added, and the resulting solution was degassed and kept at an appropriate temperature until the peroxide was completely consumed. Trifluoromethylated compounds were obtained, although the yields were not so high compared with those of heptafluoropropylation with peroxide **2** and a higher reaction temperature was required [1]. The results are shown in Table 1.

TABLE 1

Perfluoroalkylation of aromatic or heteroaromatic compounds with bis(perfluoroalkanoyl) peroxide

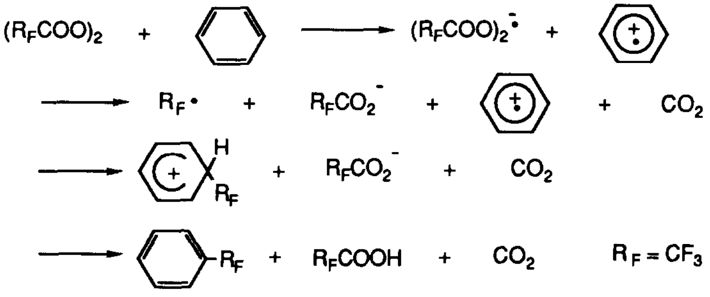
Substrate	R_F of peroxide	Temp. / °C	Products / %[a]	
	CF_3 CF_3 C_3F_7 C_7F_{15}	40 70 40 40		4 54 86[b] 97
	CF_3	70		71[c]
	CF_3	70		69 (o; 60, m; 15, p; 25)
	CF_3	70		18 (o; 44, m; 17, p; 39)
	CF_3	60		53
	CF_3	60		72
	CF_3	60		47
	CF_3	60	 10  9  9	

---

[a] GC yield. [b] Data from lit. [1].

[c] Trifluoromethyltoluenes were obtained as a mixture of three isomers, but each isomer could not be isolated and identified. The ratio of the isomers were determined by ^{19}F-NMR to be 19% (δ_F ppm from CF_3CO_2H 13.1), 24% (δ_F 12.7) and 56% (δ_F = 13.7).

The trifluoromethylation of these substrates must proceed via electron transfer from the substrates to the peroxide as was proposed in perfluoropropylation with **2** [1]. The proposed mechanism for trifluoromethylation of benzene is shown in Scheme 1.



Scheme 1.

In the electron-transfer reaction, the rate-determining step must be the electron-transfer process, which competes with unimolecular homolytic decomposition of **1**. Thus, the rate constants and activation parameters of the decay of **1** in the presence or absence of benzene in Freon 113 were measured, and these data were compared with those of peroxides **2** and **3**. The results are shown in Table 2.

TABLE 2

Rate constants and activation parameters in the decay of peroxide **1**, **2**, and **3** in Freon 113.

R_F of peroxide	kd x $10^5(s^{-1})$	Temp./ °C	$\Delta H^{\ddagger}$ (KJ/mol)	$\Delta S^{\ddagger}$(J/Kmol)
CF_3	10.38	60	108.1	2.8
CF_3[a]	27.86	60	105.1	-1.4
C_3F_7[b]	3.49	25	103.8	18.0
C_3F_7[a]	13.43	25	88.4	-21.8
C_7F_{15}	5.86	25	106.8	32.3
C_7F_{15}[a]	24.32	25	75.8	-59.8

[a] Five equivalents of benzene were added to a solution of **1** (0.02 mol/l) in Freon 113 . [b] Data from literature [1].

For all peroxides the decay rates were accelerated in the presence of benzene, but the acceleration of **1** was not so marked compared with those of **2** or **3**. For efficient electron transfer to occur, the approach of benzene to the O-O bond of the peroxide is necessary. Peroxide **3**, having a long fluoroalkyl chain, may be sterically unfavourable for this, inhibiting electron transfer. In fact, activation entropies for the electron-transfer reactions of these peroxides with benzene increased negatively in the order of **1** < **2** < **3**. However, the rate of the reaction of the peroxide with benzene was largest in peroxide **3**, that is, activation enthalpy compensated the disadvantage of activation entropy as shown in Table 2. This suggests that the energy level of O-O antibonding orbitals of these peroxides heighten in the order of **3** < **2** < **1**.

Thus, electron transfer to peroxide **1** is energetically unfavourable compared to peroxide **2** or **3**, and this may be the reason why the trifluoromethylation of aromatic compounds with **1** required a higher temperature or the yields were not as high compared to heptafluoropropylation or pentadecafluoroheptylation with **2** or **3**. However, trifluoromethylation with **1** could be applied to electron-rich substrates. Due to the high electronegativity of fluorine, trifluoromethylations of aromatic compounds via trifluoromethyl cation intermediates, such as the Friedel-Crafts reaction, are very limited, so a trifluoromethyl radical should play an important role for trifluoromethylation. Controls of chemo- and regioselectivities in radical reactions are very difficult due to the high reactivity of the trifluoromethyl radical. In trifluoromethylation with **1** the trifluoromethyl radical is produced as a radical pair in close proximity with the radical cation of the substrates in a solvent cage, so that the trifluoromethyl radical is selectively paired with the radical cation. Further, as the trifluoromethylation is initiated by electron transfer and proceeds via a cation intermediate, it is superficially equivalent to cationic trifluoromethylation into electron-rich substrates. Although the Ullman type coupling reactions of iodoarenes with copper and trifluoromethyl iodide have been used for a long time as the methods for perfluoroalkylations of aromatic rings [5], substitutions by trifluoromethyl group on hydrogens of aromatic rings are very few [6]. The generation of trifluoromethyl radicals by photoirradiation of trifluoromethyl iodide has been well known, but the yields of trifluoromethylation of aromatic rings using the method were poor [7]. Recently, novel method to produce trifluoromethyl radicals from trifluoroacetic acid mediated by xenon difluoride [8] was reported, though the method could not be applied to the electron-rich aromatic rings. Peroxide **1** therefore could have high potential as an effective and novel type of trifluoromethylating agent for electron-rich substrates.

EXPERIMENTAL

GC analysis was performed on a Shimadzu GC-8A gas chromatograph with a 2 m glass column (SE-30, 20%) or Hitachi G-3000 gas chromatograph with a 1 m stainless steel column (SE-30 10%) or a capillary column (0.32 mm ID x 25 m, df = 0.2 μm SE-30). IR spectra were recorded on a Hitachi 260-10 spectrometer. Mass spectra were taken with a JEOL JMS-DX300 spectrometer by an electron-impact (EI) ionization technique at 70 ev. NMR spectra were taken with a JEOL JNM Fx90Q FT-NMR (90 MHz) spectrometer or JNM PMX 60SI (60 MHz) spectrometer.

Synthesis of Peroxide **1**

To a solution of sodium carbonate (8.42 g) and sodium chloride (4.58 g) in 75.7 g of water, 30%-hydrogen peroxide (8.1 ml) and then Freon 113 (74 ml) was added at 10 °C. The two phase solution was cooled to -3 °C, stirred vigorously, and 100 mmol of trifluoroacetic anhydride was added drop by drop. The Freon layer was separated and the concentration of the peroxide was determined by iodometry (yield; 30%). IR; ν 1860, 1840 cm^{-1} (C=O).

Decomposition Products of **1** in Freon 113

A solution of **1** (0.02 mol / l) in Freon 113 was degassed and kept at 50 °C for 72 h in a sealed tube. The resulting solution was analyzed by GC-MS with a Porapak-N (80 - 100 mesh) 2 m glass column, and the product was identified as hexafluoroethane by comparison with an authentic sample: MS; 119 (M^+-19), 69, 50, 44.

Kinetic Studies on the Decomposition of Bis(perfluoroalkanoyl) Peroxide in the Presence or Absence of Benzene

A solution of **1** (0.02 mol / l) in the absence or presence of benzene (0.10 mol / l) was degassed by freeze-pump-thaw cycles and sealed in a pyrex tube. Five tubes were then placed simultaneously in a regulated temperature bath. Each sample was removed after appropriate time intervals and immediately immersed into a Dry Ice-acetone bath to quench the reaction; the amount of the residual **1** was determined by iodometric titration. First-order rate constants were obtained from the initial slopes of the plots of the logarithm of the peroxide concentration against time.

Perfluoroalkylations of Arenes and Heteroarenes

A solution of **1** (1.0 mmol) and benzene (1.5 mmol) in Freon 113 (10 ml) was degassed and kept at 70 °C for 5 h in a sealed tube (until the peroxide was completely consumed). The resulting solution was washed with water (10 ml) and the organic layer was analysed by GC-MS. Trifluoromethylbenzene was identified by comparison with an authentic sample and the yield was determined by GC using chlorobenzene as an internal standard.

Similarly, the reactions of substituted benzenes or heteroaromatic compounds with **1** were performed. Trifluoromethylanisoles and chlorotrifluoromethylbenzenes were identified by the comparison with authentic samples of their GC retention times and their MS spectra. Trifluoromethylated furan [9], thiophene [10], benzofuran [11], or benzothiophenes [12] were identified by the comparison of their spectral data reported in the literatures. 2-Trifluoromethylfuran: δ_H (CCl_4) = 6.53, 6.83, and 7.58; δ_F (CCl_4; ppm from external CF_3COOH) = 12.1; m/z 136 (M^+). 2-Trifluoromethylthiophene: δ_H ($CDCl_3$) = 7.06, 7.41, and 7.48; δ_C = 127.0 (C-4), 128.6 (q, J_{CCCF} = 3.7 Hz, C-3), and 128.9 (C-5); δ_F ($CDCl_3$) = 20.8; m/z 152 (M^+) (Found: M^+, 151.9926. $C_5H_3F_3S$ requires M 151.9907). 2-Trifluoromethylbenzofuran: δ_H ($CDCl_3$) = 6.97 - 7.54 (m); δ_C ($CDCl_3$) = 108.2 (q, J_{CCCF} = 3.7 Hz, C-3), 112.1 (C-7), 122.5 (C-4), 124.1 (C-5), 126.2 (C-4a), 127.0 (C-6), and 155.3 (C-7a); δ_F ($CDCl_3$) = 11.0; m/z 186 (M^+). 2-Trifluoromethyl-benzothiophene: mp 46 - 47.5 °C δ_H ($CDCl_3$) = 7.30 - 7.45 (2H, m), 7.63 (1H, m), and 7.73 - 7.88 (2H, m); δ_C ($CDCl_3$) = 122.7 (C-7), 125.1 (C-4), 125.3 (C-5), 125.6 (q,

J_{CCCF} = 3.7 Hz, C-3), and 126.6 (C-6); δ_F ($CDCl_3$) = 19.4 ; m/z 202 (M^+) (Found M^+, 202.0027. $C_9H_5F_3S$ requires M, 202.0064). 3-Trifluoromethylbenzothiophene: δ_H ($CDCl_3$) = 7.2 - 7.6 (3H, m), and 7.8 - 7.9 (2H, m); δ_C ($CDCl_3$) =122.6 (C-4 or C-7), 122.8 (C-7 or C-4), 125.3 (C-5 or C-6), 125.4 (C-6 or C-5), 128.8 (q, J_{CCCF} = 6.1 Hz, C-2), and 140.4 (C-7a); δ_F ($CDCl_3$) = 15.5; m/z 202 (M^+) (Found M^+ 202.0062). 7-Trifluoromethylbenzothiophene: δ_H ($CDCl_3$) = 7.43 and 8.03 (2H, ABq, J = 7.8 Hz), and 7.58 (3H, m); δ_C ($CDCl_3$) = 121.7 (q, J_{CCCF} = 4.9 Hz, C-6), 122.1 (C-5), 123.3 (C-3), 126.2 (C-2), 128.8 (C-4), and 141.4 (C-4a); δ_F ($CDCl_3$) = 14.3; m/z 202(M^+) (Found: M^+, 202.0065).

Perfluorohepthylation of benzene with bis(perfluorooctanoyl) peroxide, which was synthesized by the method described in the literature [3], was also performed at 40 °C. Perfluoroheptylbenzene: bp 65 - 67 °C / 3 mmHg. δ_H ($CDCl_3$) = 7.5 (3H, m) and 7.6 (2H, m); δ_C ($CDCl_3$) = 127.8 (C-2, t, J_{CCCF} = 7.3 Hz), 129.0 (C-3), and 132.5 (C-4); m/z 446(M^+)(Found M^+, 446.0128. $C_{13}H_5F_{15}$ requires M, 446.0152).

REFERENCES

1 M. Yoshida, H. Amemiya, M. Kobayshi, H. Sawada, H. Hagii, and K. Aoshima, J. Chem. Soc., Chem. Commun., (1985) 234; M. Yoshida, K. Moriya, H. Sawada, and M. Kobayashi, Chem. Lett., (1985) 755; H. Sawada, M. Yoshida, H. Hagii, K. Aoshima, and M. Kobayashi, Bull. Chem. Soc. Jpn., 59 (1986) 215.

2 W. H. Gumprecht and R. H. Dettre, J. Fluorine Chem., 5 (1975) 245.

3 C. Zhao, R. Zhou, H. Pan, X. Jin, Y. Qu, C. Wu, and X. Jiang, J. Org. Chem., 45 (1982) 2009.

4 M. Yoshida, M. Kobayashi, H. Sawada, H. Hagii, and K. Aoshima, Nippon Kagaku Kaishi, (1985) 1958 (Chem. Abstr., 105 (1986) 42128q).

5 Y. Kobayashi and I. Kumadaki, Tetrahedron Lett., (1969) 4095.

6 T. Umemoto and A. Ando, Bull. Chem. Soc. Jpn., 59 (1986) 447.

7 Y. Kobayashi, I. Kumadaki, A. Ohsawa, S. Murakami, and T. Nakano, Chem. Pharm. Bull. Jpn., 26 (1978) 1247.

8 Y. Tanabe, N. Matsuo, and N. Ohno, J. Org. Chem., 53 (1988) 4582.

9 J. Jullien, J. M. Pechine, F. Perz, and J. J. Piade, Tetrahedron, 38 (1982) 1413.

10 B. Verkoczy, A. G. Sherwood, I. Sofarik, and O. P. Strausz, Can. J. Chem., 61 (1983) 2268.

11 Y. Kobayashi, I. Kumadaki, and Y. Hasegawa, Chem. Pham. Bull. Jpn., 25 (1977) 3009.

12 T. Akiyama, K. Kato, M. Kajitani, Y. Sakaguchi, J. Nakamura, H. Hayashi, and A. Sugimori, Bull. Chem. Soc. Jpn., 61 (1988) 3531.