ELSEVIER

Journal of Fluorine Chemistry 71 (1995) 51–54

JOURNAL OF FLUORINE CHEMISTRY

The reaction of perfluoroalkanesulfinates. IX. Perfluoroalkylation of pyridine and its derivatives with sodium perfluoroalkanesulfinates

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Received 24 December 1993; accepted 6 May 1994

Abstract

The reaction of pyridine and its derivatives with sodium perfluoroalkanesulfinates (R_FSO_2Na) in the presence of $Mn(OAc)_3$ is reported. Pyridines react with this reagent system readily to give the corresponding perfluoroalkylated products as a mixture of isomers with moderate yield. However, reaction of quinoline and isoquinoline under similar conditions gives the C(5)- and C(8)-substituted products regioselectively.

Keywords: Perfluoroalkanesulfinates; Perfluoroalkylation; Pyridine; Quinoline; Isoquinoline

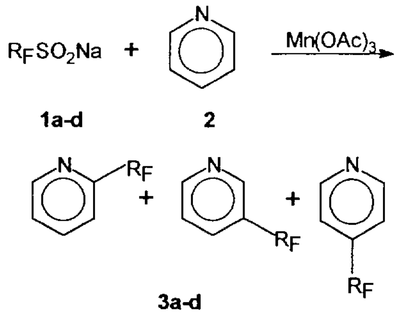
1. Introduction

Perfluoroalkylation of aromatic compounds by means of perfluoroalkyl free radicals has been studied extensively and various methods developed to generate R_F radicals [1–5]. However, many reagent systems are suitable only for the perfluoroalkylation of electron-rich aromatic compounds due to the electrophilic nature of R_F radicals; electron-deficient heteroaromatic compounds such as pyridine and quinoline have been perfluoroalkylated only with difficulty. Pyridine is stable to many perfluoroalkylating reagents and its perfluoroalkylation has only been achieved in a few cases, e.g. through thermolysis with perfluoroalkyl iodides [2] or by means of the $R_FI/HOCH_2SO_2Na$ system [6].

Recently, sodium perfluoroalkanesulfinates were found in our laboratory to be efficient perfluoroalkylating reagents. They produce perfluoroalkyl radicals through oxidation under suitable conditions and have thus been used for the perfluoroalkylation of olefins and some aromatic compounds [7–10]. In this paper we report the perfluoroalkylation of pyridine and related compounds with the $R_FSO_2Na/Mn(OAc)_3$ reagent system.

2. Results and discussion

Sodium perfluoroalkanesulfinates (**1**) were readily available from perfluoroalkyl iodides through sulfinatodehalogenation [11]. In the presence of $Mn(OAc)_3$, they reacted with pyridine smoothly in MeCN:AcOH:Ac_2O (5:5:1) at 80–85 °C, giving the corresponding perfluoroalkylated products as a mixture of 2-, 3- and a small amount of 4-substituted isomers. The results are listed in Table 1.



R_F: **a**, $F(CF_2)_6$; **b**, $Cl(CF_2)_4$; **c**, $Cl(CF_2)_6$; **d**, $Cl(CF_2)_8$

Under similar conditions, 4-picoline (**4**), 3-picoline (**5**) and 3,5-lutidine (**6**) also reacted to form the corresponding perfluoroalkylated products (**7**–**9**).

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0022-1139/95/$09.50
SSDI 0022-1139(94)03151-7

Table 1
The reaction of pyridine and its derivatives with $R_FSO_2Na/Mn(OAc)_3$

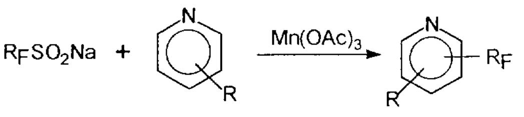
R_FSO_2Na	ArH	Products	Total yield (%) [a]	Product distribution (%) [b]		
				2-Isomer	3-Isomer	4-Isomer
1a	**2**	**3a**	58	46	47	7
1b	**2**	**3b**	62	47	44	9
1c	**2**	**3c**	50	47	45	8
1d	**2**	**3d**	60	46	45	8
1a	**4**	**7a**	58	44	56	
1b	**4**	**7b**	55	48	52	
1c	**4**	**7c**	50	45	55	
1b	**5**	**8b**	52	60 [c]	27 [d]	13
1b	**6**	**9b**	48	93		7
1c	**6**	**9c**	51	95		5

[a] Isolated yield based on R_FSO_2Na.
[b] Determined by ^{19}F NMR spectroscopy.
[c] A mixture of 2- and 6-isomers (2-/6- = 42:58).
[d] 5-R_F compound.

Table 2
The reaction of quinoline and isoquinoline with $R_FSO_2Na/Mn(OAc)_3$

R_FSO_2Na	ArH	Products (% yield) [a]
1b	**10**	**13b** (32) + **15b** (23)
1c	**10**	**13c** (35) + **15c** (26)
1b	**11**	**14b** (27) + **16b** (18)
1b	**12**	**17b** (33) + **18b** (26)
1c	**12**	**17c** (31) + **18c** (25)

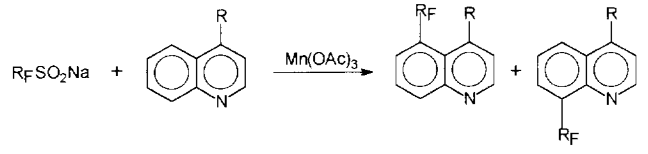
[a] Isolated yield based on R_FSO_2Na.



4-6 **7-9**

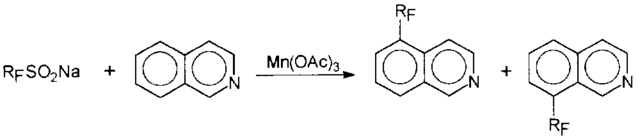
4,7: R=4-CH3; **5,8**: R=3-CH3; **6,9**: R=3,5-(CH3)2

As shown in Table 1, the reaction of R_FSO_2Na with pyridine and its methyl derivatives gave a mixture of isomers with the R_F group substituted in all positions in the aromatic ring. However, when quinoline (**10**) was used as the substrate, only two major products with R_F at the C(5) and C(8) positions were obtained. The same results were obtained in the case of 4-methylquinoline (**11**) and isoquinoline (**12**); they all reacted readily with $R_FSO_2Na/Mn(OAc)_3$ to give the C(5)- and C(8)-substituted products. The presence of methyl at C(4) had little influence on the reaction products, indicating a satisfactory regioselectivity of this reaction. The results are summarized in Table 2.



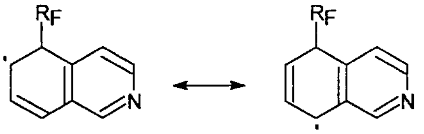
10, 11 **13, 14** **15, 16**

10, 13, 15: R=H; **11, 14, 16**: R=CH3



12 **17** **18**

The results obtained may be explained in terms of the stability of the radical intermediates formed during the course of the reaction. It has been confirmed by ESR spectroscopy that the reaction of R_FSO_2Na with oxidants resulted in the formation of perfluoroalkyl radicals [8]. Being more electron-rich than the heterocyclic ring, the carbocyclic ring of quinoline is attacked preferentially by the electrophilic R_F radicals to give the more stable radical intermediates. In this case, positions 5 and 8 are favored kinetically as the corresponding intermediates (**19**) can be represented by two canonical structures which still preserve the aromatic character of the heteroaromatic ring, whereas intermediates **20** resulting from the attack of an R_F group at positions 6 or 7 have only one canonical structure.



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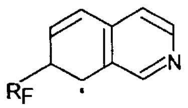

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3. Experimental details

Temperatures are uncorrected. IR spectra were obtained using a Shimadzu IR-440 spectrometer. ^1H NMR spectra were recorded on Varian EM-360A (60 MHz) and XL-200 (200 MHz) spectrometers using TMS as internal standard. ^{19}F NMR spectra were recorded on a Varian EM-360L spectrometer at 56.4 MHz, chemical shifts in ppm being positive upfield using TFA as external standard. The values reported were $\delta_F = \delta_{TFA} + 76.8$ ppm. Mass spectra were recorded on a Finnigan GC-MS 4201 spectrometer. $Mn(OAc)_3 \cdot 2H_2O$ was prepared from $Mn(OAc)_2 \cdot 4H_2O$ according to the literature method [12].

All known compounds were characterized by comparison with authentic specimens [2,6]. New compounds were characterized via elemental analyses, IR, MS, ^{1}H NMR and ^{19}F NMR spectra.

A typical procedure was as follows. To a solution of 25 ml MeCN, 5 ml AcOH and 5 ml Ac_2O was added 3.22 g (10 mmol) of **1b**, 1.6 g (20 mmol) of **2** and 6.75 g (25 mmol) of $Mn(OAc)_3 \cdot 2H_2O$. The mixture was stirred at 80–85 °C for 3–5 h until the reaction was complete (monitored by ^{19}F NMR). The resulting mixture was filtered and the solid washed with ether. The combined solution was washed with aqueous $NaHCO_3$ solution and water, and dried over anhydrous Na_2SO_4. Chromatography of the crude product on a silica gel column with benzene petroleum ether as eluent gave the corresponding products **3b** [6].

5-(4-Chloro-octafluorobutyl)quinoline (**13b**): Analysis: $C_{13}H_6ClF_8N$ requires: C, 42.94; H, 1.66; N, 3.85; F, 41.80%. Found: C, 42.81; H, 1.63; N, 3.68; F, 42.24%. MS (*m*/*z*): 365; 364; 363 (M^+); 328 (M^+-Cl); 178 ($M^+-ClC_3F_6$, 100). IR (cm^{-1}): 3050; 1600; 1575; 1500; 1190. ^{1}H NMR ($CDCl_3$) δ: 9.01 (1H, d, $J=4$ Hz, 2-H); 8.56 (1H, d, $J=9$ Hz, 4-H); 8.36 (1H, d, $J=8$ Hz); 7.91 (1H, d, $J=6$ Hz); 7.80 (1H, d–d, $J_1=6$ Hz, $J_2=8$ Hz, 7-H); 7.52 (1H, d–d, $J_1=4$ Hz, $J_2=9$ Hz, 3-H) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.4 (2F); 104.0 (2F, t, CF_2Ar); 119.0 (4F, m) ppm.

8-(4-Chloro-octafluorobutyl)quinoline (**15b**): Analysis: $C_{13}H_6ClF_8N$ requires: C, 42.94; H, 1.66; M, 3.85; F, 41.80%. Found: C, 42.67; H, 1.67; N, 4.03; F, 41.96%. MS (*m*/*z*): 365; 364; 363 (M^+); 328; 178 (100). IR (cm^{-1}): 3040; 1600; 1580; 1500; 1190. ^{1}H NMR ($CDCl_3$) δ: 9.15 (1H, d, $J=4$ Hz, 2-H); 8.30 (1H, d, $J=8$ Hz, 4-H); 8.08 (2H, d, $J=8$ Hz, 5,7-H); 7.68 (1H, t, $J=8$ Hz, 6-H); 7.53 (1H, d–d, $J_1=4$ Hz, $J_2=8$ Hz, 3-H) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.4 (1F); 104.2 (2F, t, CF_2Ar); 119.0 (4F, m) ppm.

5-(6-Chlorododecafluorohexyl)quinoline (**13c**): Analysis: $C_{15}H_6ClF_{12}N$ requires: C, 38.86; H, 1.30; N, 3..02; F, 49.17%. Found: C, 38.63; H, 1.18; N, 2.85; F, 49.50%. MS (*m*/*z*) 465, 464; 463 (M^+); 428 (M^+-Cl); 178 ($M^+-ClC_5F_{10}$, 100). IR (cm^{-1}): 3050; 1600; 1575; 1500; 1200; 1140. ^{1}H NMR ($CDCl_3$) δ: 9.02 (1H, d, $J=4$ Hz); 8.56 (1H, d, $J=9$ Hz); 8.37 (1H, d, $J=8$ Hz); 7.92 (1H, d, $J=6$ Hz); 7.80 (1H, d–d, $J_1=6$ Hz, $J_2=8$ Hz); 7.52 (1H, d–d, $J_1=4$·Hz, $J_2=9$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.2 (2F); 104.5 (2F, t, CF_2Ar); 119.0–120.8 (8F, m) ppm.

8-(6-Chloro-dodecafluorohexyl)quinoline (**15c**): m.p. 70–71 °C. Analysis: $C_{15}H_6ClF_{12}N$ requires: C, 38.86; H, 1.30; N, 3.02; F, 49.17%. Found: C, 39.16; H, 1.35; N, 2.97; F, 49.03%. MS (*m*/*z*): 465; 464; 463 (M^+); 444; 428; 178 ($M^+-ClC_5F_{10}$, 100); IR (cm^{-1}) 3040; 1605; 1582; 1500; 1200; 1140. ^{1}H NMR ($CDCl_3$) δ: 9.15 (1H, d, $J=4$ Hz, 2-H); 8.29 (1H, d, $J=8$ Hz, 4-H); 8.08 (2H, d, $J=8$ Hz, 5,7-H); 7.68 (1H, t, $J=8$ Hz, 6-H); 7.53 (1H, d–d, $J_1=4$ Hz, $J_2=8$ Hz, 3-H) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.6 (2F); 104.6 (2F, t, CF_2Ar); 119.0–120.8 (8F, m) ppm.

4-Methyl-5-(4-chloro-octafluorobutyl)quinoline (**14b**): Analysis: $C_{14}H_8ClF_8N$ requires: C, 44.52; H, 2.14; N, 3.17; F, 40.24%. Found: C, 44.55; H, 2.18; N, 3.70; F, 39.59%. MS (*m*/*z*): 379; 378; 377 (M^+); 342 (M^+-Cl); 192 ($M^+-ClC_3F_6$, 100); 178. IR (cm^{-1}): 1600; 1505; 1190; 1140. ^{1}H NMR ($CDCl_3$) δ: 8.95 (1H, d, $J=6$ Hz, 2-H); 8.60 (1H, d, $J=8$ Hz, 8-H); 8.28 (1H, d, $J=6$ Hz, 6-H); 7.66–7.48 (2H, m, 3,7-H); 2.70 (3H, t, $J=4$ Hz, CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.6 (2F); 96.4 (2F, t, CF_2Ar); 118.8 (2F, m); 119.4 (2F, m) ppm.

4-Methyl-8-(4-chloro-octafluorobutyl)quinoline (**16b**): Analysis: $C_{14}H_8ClF_8N$ requires: C, 44.52; H, 2.14; N, 3.17; F, 40.24%. Found: C, 44.58; H, 2.11; N, 3.58; F, 40.17%. MS (*m*/*z*): 379; 378; 377 (M^+); 358; 342; 192 ($M^+-ClC_3F_6$, 100); 178. IR (cm^{-1}): 1605; 1580; 1500; 1190. ^{1}H NMR ($CDCl_3$) δ: 9.15 (1H, d, $J=6$ Hz, 2-H); 8.26 (1H, d, $J=8$ Hz); 7.89 (2H, d, $J=8$ Hz); 7.55 (1H, m); 2.60 (3H, s, CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.4 (2F); 104.8 (2F, t, CF_2Ar); 118.5 (2F, m); 119.4 (2F, m) ppm.

5-(4-Chloro-octafluorobutyl)isoquinoline (**17b**): Analysis: $C_{13}H_6ClF_8N$ requires: C, 42.94; H, 1.66; N, 3.85; F, 41.08%. Found: C, 42.52; H, 1.58; N, 3.89; F, 41.30%. MS (*m*/*z*): 365; 364; 363 (M^+); 328 (M^+-Cl); 178 ($M^+-ClC_3F_6$, 100); 128. IR (cm^{-1}): 3050; 1625; 1598; 1498; 1200. ^{1}H NMR ($CDCl_3$) δ: 9.36 (1H, s, 1-H); 8.65 (1H, d, $J=6$ Hz, 4-H); 8.21 (1H, d, $J=8$ Hz, 6-H); 8.06–7.95 (2H, m, 3,8-H); 7.72 (1H, t, $J=8$ Hz, 7-H) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.0 (2F); 104.8 (2F, t, CF_2Ar); 118.6 (4F, m) ppm.

8-(4-Chloro-octafluorobutyl)isoquinoline (**18b**): Analysis: $C_{13}H_6ClF_8N$ requires: C, 42.94; H, 1.66; N, 3.85; F, 41.80%. Found: C, 42.50; H, 1.60; N, 3.91; F, 41.84%. MS (*m*/*z*): 365; 364; 363 (M^+); 344; 328; 178 ($M^+-ClC_3F_6$, 100). IR (cm^{-1}): 3050; 1630; 1598; 1500; 1450; 1200. ^{1}H NMR ($CDCl_3$) δ: 9.67 (1H, s, 1-H); 8.66 (1H, d, $J=6$ Hz, 3-H); 8.06 (1H, d, $J=8$ Hz); 7.94 (1H, d, $J=8$ Hz); 7.79 (1H, d–d, $J_1=4$ Hz, $J_2=6$ Hz, 6-H); 7.76 (1H, d, $J=6$ Hz, 4-H) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.0 (2F); 103.0 (2F, t, CF_2Ar); 118.6 (4F, m) ppm.

5-(6-Chloro-dodecafluorohexyl)isoquinoline (**17c**): Analysis: $C_{15}H_6ClF_{12}N$ requires: C, 38.86; H, 1.30; N, 3.02; F, 49.17%. Found: C, 39.04; H, 1.41; N, 2.89; F, 48.85%. MS (*m*/*z*): 465; 464; 463 (M^+); 444; 428 (M^+-Cl); 178 ($M^+-ClC_5F_{10}$, 100); 128. IR (cm^{-1}): 3050; 1630; 1600; 1500; 1200; 1140. ^{1}H NMR ($CDCl_3$) δ: 9.35 (1H, s); 8.64 (1H, d, $J=6$ Hz); 8.20 (1H, d, $J=8$ Hz); 8.05–7.95 (2H, m); 7.72 (1H, t, $J=8$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.2 (2F); 104.8 (2F, t, CF_2Ar); 119.0–121.0 (8F, m) ppm.

8-(6-Chloro-dodecafluorohexyl)isoquinoline (**18c**): Analysis: $C_{15}H_6ClF_{12}N$ requires: C, 38.86; H, 1.30; N, 3.02; F, 49.17%. Found: C, 38.68; H, 1.26; N, 2.84; F, 49.46%. MS (*m*/*z*): 465; 464; 463 (M^+); 428; 178 ($M^+ - ClC_5F_{10}$, 100). IR (cm^{-1}): 3050; 1625; 1595; 1500; 1450; 1200. ^1H NMR ($CDCl_3$) δ: 9.67 (1H, s); 8.66 (1H, d, $J=6$ Hz); 8.06 (1H, d, $J=6$ Hz); 7.95 (1H, d, $J=8$ Hz); 7.79 (1H, d–d, $J_1=4$ Hz, $J_2=6$ Hz); 7.75 (1H, d, $J=6$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.2 (2F); 103.2 (2F, t, CF_2Ar); 119.0–120.8 (8F, m) ppm.

Acknowledgement

This work was partially supported by the National Natural Science Foundation of China.

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