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Aromatic nucleophilic substitution in perfluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran

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Abstract

Aromatic fluorine atoms in perfluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**1**) readily undergo substitution with common nucleophiles such as MeO^-, HS^-, HO^-, NC^-, N_3^- and *tert*-BuN^- anions. Depending on the nature of the nucleophile one or two fluorines are substituted. The double substitution is favoured by strong bases and prolonged reaction time. Replacement of one fluorine by an electron-donating group, MeO, SH, OH, NH_2 or *tert*-$BuNH_2$, hinders the replacement of the second fluorine while introduction of an electron-withdrawing group, e.g., CN or N_3 enhances the nucleophilic reactivity of the remaining aromatic fluorine such that disubstituted derivatives are formed exclusively.

Keywords: Perfluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran; Aromatic nucleophilic substitution; Fluorine substitution

1. Introduction

Nucleophilic substitution of a halogen in an aromatic ring usually requires the presence of either a strong electron-withdrawing substituent such as nitro or sulpho group or a powerful nucleophile, e.g., NH_2^- anion [1]. Perfluoroalkyl groups, e.g., CF_3 group *para* to an aromatic halogen, increase the rate of its nucleophilic substitution by three orders of magnitude but rather drastic reaction conditions are required [2]. From among substituents on an aromatic ring, fluorine atom shows the best leaving-group ability [1]. A long time ago we reported that aromatic fluorines in octafluoro-1,3-dihydroisobenzofuran showed enhanced nucleophilic reactivity; substitutions with methoxide and hydroxide ions proceeded readily at ambient temperature [3]. This paper describes substitution of aromatic fluorines in perfluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**1**) [4] by common nucleophiles. The benzene ring in compound **1** is annulated with two tetrafluoro-dihydrofuran rings of which the CF_2 groups act as four electron-withdrawing substituents.

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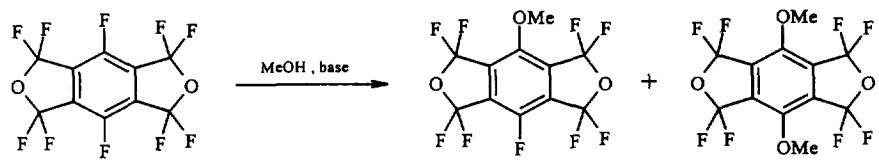
2. Results and discussion

The attempted reaction of **1** with neat refluxing methanol failed; however, in the presence of a base substitution of one or two aromatic fluorines took place readily at reflux or even at ambient temperature to give either monomethoxy derivative **2** or dimethoxy derivative **3** or a mixture of them in a ratio depending on the nature of base and on the reaction conditions (Scheme 1, Table 1). When a weak base, e.g., KCN, Na_2S or PhSK, was used only one aromatic fluorine was substituted to give exclusively monomethoxy derivative **2**. Strong bases, KOH or NEt_3, and prolonged reaction time favour double substitution leading to predominant or exclusive formation of dimethoxy derivative **3**. The double substi-



1 **2** **3**

Scheme 1.

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Table 1
The base catalysed reactions of perfluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**1**) with methanol

Base	Reaction conditions	Products (GLC %)*	
		2	**3**
NEt_3	reflux, 1 h	60	40
NEt_3	reflux, 5 h	2	98
KCN	reflux, 1 h	100	0
KOH	reflux, 2 h	0	100
Na_2S	reflux, 2 h	96**	0
PhSK	reflux, 2 h	97	0
tert-$BuNH_2$	r.t., 1 h	84	15
tert-$BuNH_2$	r.t., 20 h	16	83
tert-$BuNH_2$	reflux, 0.5 h	6	94

*, Total yields > 95%.
, About 4% of thiophenol **4 was formed.

Table 2
The reactions of perfluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**1**) with nucleophiles

Nucleophile	Rection conditions	Product		
		No.	Yield (%)	m.p. (°C)
Na_2S	DMF, r.t., 10 min*	**4**	93	134–135 (subl.)
NH_3**	EtOH, r.t., 15 min*	**5**	93	166 (hexane)
NaN_3	MeCN, TEBA, r.t., 15 min*	**6**	95	decomp.
KCN	MeCN, 30°C, 3 h	**7**	94	257 (subl.)
tert-$BuNH_2$[a]	dioxane, r.t., 20 h	**8**	91	80–80.5 (a/w)
tert-$BuNH_2$**	reflux, 2 h	**9**	94	120 (a/w)
KOH	C_6H_6, 50% aq. KOH, TEBA, reflux, 2 h	**10**	88	151–152 (subl.)

*, Exothermic effect.
**, Large excess.
[a], Stoichiometric amount.
a/w, ethanol/water.

tution proceeded rapidly at reflux temperature (r.t.) in the presence of *tert*-$BuNH_2$ affording **3** as the major product.

In reactions with methanol, generally the bases acted exclusively as the catalysts: they did not substitute aromatic fluorines. The only exception was the reaction in the presence of Na_2S in which a small amount of thiophenol **4** was formed. Substitutions with the bases occured readily when compound **1** was reacted with a neat base, e.g., *tert*-$BuNH_2$, or in a polar aprotic solvent such as DMF or acetonitrile (Table 2). The reactions with Na_2S, NH_3 and NaN_3 proceeded at ambient temperature within minutes affording, respectively, thiophenol **4**, amine **5** and diazide **6** in more than 90% yields. The less nucleophilic reagents, KCN and *tert*-$BuNH_2$, required a longer reaction time and/or the reflux temperature, nevertheless the corresponding dicyano derivative **7**, and mono- and diamino **8** and **9** were also obtained in high yields. The substitution of fluorine with hydroxide to give phenol **10** was achieved by refluxing compound **1** in a two-phase system, benzene—50% aqueous NaOH, in the presence of a catalytic amount of tetrabutylammonium chloride (TEBA) (Scheme 2).

The substitution of the first aromatic fluorine in **1** with an electron-withdrawing group, N_3 or CN, effectively increases the rate of the substitution of the second fluorine such that in reactions with NaN_3 and KCN disubstituted products **6** and **7** were formed exclusively. In contrast, introduction of electron-donating substituents, MeO, SH, OH, NH_2 or the amino group, strongly retards substitution of the remaining aromatic fluorine; preparation of the diamino derivative **9** required refluxing of **1** with large excess of *tert*-$BuNH_2$ but the attempted double substitutions with the OH, SH and NH_2 groups failed.

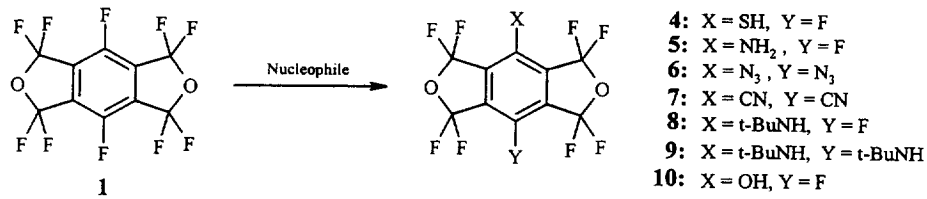
Phenol **10**, in spite of its expected high acidity, undergoes extraction from its alkaline water solutions into organic solvents (Et_2O); this behaviour could be attributed to high hydrophobic properties caused by the presence of four CF_2 groups in the molecule. It is well known that introduction of fluoroalkyl groups into an organic molecule effectively increases its hydrophobic properties [5]. Hydrophobic properties of the CF_3-substituted compounds were often observed in this laboratory, e.g., 3,5-bis(trifluoromethyl)phenol could be steam distilled [6] and 1,2,2-trimethyl-3-trifluoromethyl-1-cyclopentanoyl fluoride reacts with aqueous bases only very sluggishly [7].

Amines **5**, **8** and **9** could not be extracted from their ether solutions with 5% hydrochloric acid. This behaviour is a result of a combination of low basicity [5], high lipophilicity [5] and, in the case of **8** and **9**, may also be the result of steric inhibition of the protonation of the nitrogen atoms.

The results of the present investigations and those reported earlier [3] show that the presence of two or more CF_2 groups on an aromatic ring effectively increases the rate of nucleophilic substitution of aromatic fluorine atoms.

3. Experimental details

Melting points were determined in capillaries and are uncorrected. ^1H and ^{19}F NMR spectra were recorded in $CDCl_3$



1

4: X = SH, Y = F
5: X = NH_2, Y = F
6: X = N_3, Y = N_3
7: X = CN, Y = CN
8: X = t-BuNH, Y = F
9: X = t-BuNH, Y = t-BuNH
10: X = OH, Y = F

Scheme 2.

with a Varian Gemini 200 spectrometer at 200 and 188 MHz, respectively. Chemical shifts are quoted in ppm relative to internal TMS for protons (positive downfield) and relative to internal $CFCl_3$ for fluorine nuclei (positive upfield). IR spectra were measured in KBr with a Perkin-Elmer 1640 apparatus. The reactions were monitored with a Shimadzu GC-14A chromatograph using a 3.5 m×2 mm column packed with 5% silicone oil SE-52 on Chromosorb G.

3.1. Reactions of perfluoro-1,3,5,7-tetrahydrobenzo[1,2-c:4,5-c']difuran (1) with methanol. General procedure

Compound **1** (510 mg, 1.5 mmol) and a base (1.5–4 mmol) were refluxed in methanol (10 ml) for 1–5 h. The reaction course was monitored by GLC. After completion of the reaction (total consumption of **1**), methanol was removed on a rotary evaporator and the residue was matured with water (30 ml). A white precipitate formed which was filtered off, washed with water and dried under vacuum over KOH pellets. Reactions condition, yields and ratios of mono- and dimethoxy substituted compounds **2** and **3** are given in Table 1. The analytical samples were obtained by vacuum sublimation (0.2–0.4 Torr, 70–80°C).

1,1,3,3,4,5,5,7,7-Nonafluoro-8-methoxy-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**2**): m.p. 89–90°C. Analysis: Found: C, 37.1; H, 0.9; F, 48.3%. $C_{11}H_3F_9O_3$ requires: C, 37.3; H, 0.9; F, 48.3%. ^{1}H NMR δ: 4.26 (narrow pentet, $^6J_{HF}$=1.2 Hz, CH_3O). ^{19}F NMR δ: 64.7 (s, 2×CF_2); 69.1 (broad, 2×CF_2), 130.4 (s, aromatic F). IR (KBr) (cm^{-1}): 3004 and 2957 (CH_3).

1,1,3,3,5,5,7,7-Octafluoro-4,8-dimethoxy-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**3**): m.p. 161°C. Analysis. Found: C, 39.2; H, 1.7; F, 41.5%. $C_{12}H_6F_8O_4$ requires: C, 39.4; H, 1.7; F, 41.5%. ^{1}H NMR δ: 4.17 (broad s, 2×CH_3O). ^{19}F NMR δ: 65.9 (s, 4×CF_2). IR (KBr) (cm^{-1}): 3035 and 2984 (CH_3).

3.2. Reactions of perfluoro-1,3,5,7-tetrahydrobenzo[1,2-c:4,5-c']difuran (1) with nucleophiles. General procedure for compounds 4–9

The reactions were run on a 1–5.5 mmol scale. Reactants, their ratios, solvents, reaction conditions, yields and melting points of the products are listed in Table 2. Compound **1**, a nucleophile, TEBA (20 mg) and a solvent (3–5 ml) were stirred together under conditions given in Table 2 (in some cases an exothermic effect and/or colour change occurred) then poured into water (50–100 ml, in the case of Na_2S a few drops of 10% aq. HCl was added). Compounds **4–9** formed white crystalline precipitates which were filtered off, washed with water and dried under vacuum over KOH pellets. Analytical samples were obtained by vacuum sublimation (60–80°C, 0.1 Torr) or by crystallisation.

1,1,3,3,4,5,5,7,7-Nonafluoro-8-mercapto-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**4**). Analysis: Found: C, 33.8; H, 0.3; F, 48.2; S, 8.9%. $C_{10}H_1F_9O_2S$ requires: C, 33.7; H, 0.3; F, 48.0; S, 9.0%. ^{1}H NMR δ: 4.23 (s, SH). ^{19}F NMR δ: 68.9 (d, $^4J_{FF}$=3.3 Hz, 2×CF_2); 72.0 (s, 2×CF_2), 124.1 (narrow pentet, $^4J_{FF}$=3.3 Hz, aromatic F). IR (KBr) (cm^{-1}): 2604 (SH).

8-Amino-1,1,3,3,4,5,5,7,7-nonafluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**5**). Analysis: Found: C, 35.7; H, 0.6; F, 50.4; N, 4.1%. $C_{10}H_2F_9NO_2$ requires: C, 35.4; H, 0.6; F, 50.1; N, 4.1%. ^{1}H NMR δ: 4.78 (s, NH_2). ^{19}F NMR δ: 69.2 (s, 2×CF_2); 72.1 (s, 2×CF_2), 137.5 (s, aromatic F). IR (KBr) (cm^{-1}): 3543.3, 3505.0 and 3446.3 (NH_2).

4,8-Diazido-1,1,3,3,5,5,7,7-octafluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**6**). Analysis: Found: C, 31.1; F, 39.0; N, 21.9%. $C_{10}F_8N_6O_2$ requires: C, 31.0; F, 39.21; N, 21.7%. ^{19}F NMR δ: 65.6 (s, 4×CF_2). IR (KBr) (cm^{-1}): 2120.5 (vs, NH_2).

4,8-Dicyano-1,1,3,3,5,5,7,7-octafluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**7**). Analysis: Found: C, 40.6; F, 42.6; N, 7.8%. $C_{20}F_8N_2O_2$ requires: C, 40.5; F, 42.7; N, 7.8%. ^{19}F NMR δ: 70.2 (s, 4×CF_2). IR (KBr) (cm^{-1}): 2253 (w, NH_2).

8-*tert*-Butylamino-1,1,3,3,4,5,5,7,7-nonafluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**8**). Analysis: Found: C, 42.6; H, 2.7; F, 43.2; N, 3.4%. $C_{14}H_{10}F_9NO_2$ requires: C, 42.5; H, 2.6; F, 43.3; N, 3.5%. ^{1}H NMR δ: 1.37 (s, CH_3); 3.96 (s, NH). ^{19}F NMR δ: 67.8 (s, 2×CF_2); 69.3 (s, 2×CF_2), 131.5 (narrow pentet, $^4J_{FF}$=3.5 Hz, aromatic F). IR (KBr) (cm^{-1}): 3410.1 (NH); 2976.7 and 2935.4 (CH_3).

4,8-Di-*tert*-Butylamino-1,1,3,3,5,5,7,7-octafluoro-1,3,5,7-tetrahydrobenzo[1,2-*c*:4,5-*c'*]difuran (**9**). Analysis: Found: C, 48.2; H, 4.5; F, 33.8; N, 6.3%. $C_{18}H_{20}F_8N_2O_2$ requires: C, 48.2; H, 4.5; F, 33.9; N, 6.3%. ^{1}H NMR δ: 1.32 (s, CH_3); 3.62 (s, NH). ^{19}F NMR δ: 68.1 (s, 4×CF_2). IR (KBr) (cm^{-1}): 3400.4 (NH); 2979.0, 2939.6 and 2880.5 (CH_3).

3.3. 1,1,3,3,4,5,5,7,7-Nonafluoro-8-hydroxy-1,3,5,7-tetrahydrobenzo[1,2-c:4,5-c']difuran (10)

Compound **1** (510 mg, 1.5 mmol), TEBA (20 mg), benzene (6 ml) and 50% aqueous NaOH (3 ml) were vigorously agitated at reflux temperature for 2 h. The reaction mixture was allowed to cool to ambient temperature then water (15 ml) and ether (15 ml) were added. The organic layer was separated, the aqueous layer was extracted with ether (15 ml) and the combined organic solution was washed with 5% aq. HCl (5 ml), followed by water, and dried over $MgSO_4$. The solvents were removed on a rotary evaporator to give **10** as a white crystalline solid (450 mg, yield: 88%). The analytical sample was obtained by vacuum sublimation (80°C, 0.2 Torr). m.p. 151–152°C. Analysis: Found: C, 35.2; H, 0.3; F, 50.2. $C_{10}H_1F_9O_3$ requires: C, 35.3; H, 0.3; F, 50.3%. ^{1}H NMR δ: 4.37 (broad, OH). ^{19}F NMR δ: 69.1 (s, 2×CF_2); 69.8 (s, 2×CF_2), 132.05 (s, aromatic F). IR (KBr) (cm^{-1}): 3598 (OH).

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