Fluorination with XeF₂.[1] 44. Effect of Geometry and Heteroatom on the Regioselectivity of Fluorine Introduction into an Aromatic Ring

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Introduction

Direct introduction of fluorine under mild reaction conditions into aromatic molecules is still only a partly solved problem, particularly if the aromatic ring is not activated.[2−6] Xenon difluoride is one of the oldest reagents used for aromatic ring functionalization, and substitution,[7−10] addition,[11−14] and in some cases side chain fluorination[10,15] were observed. It is evident that even a small structural variation in the organic substrate could completely change the course of fluorination, and the important role of solvent polarity and catalyst (HF, BF₃, BF₃·OEt₂, C₆F₅SH, TFA, TFA⁻Ag⁺, etc.) has also been pointed out.[2a,4−6]

Fluorene (**1a**) and dibenzofuran (DBF, **1b**) have been used several times[16−19] as target molecules in investigations of the effect of geometry, electronegativity of substituent, and strain on the type of transformation. These reactions involve regioselectivity at the aromatic ring or side chain functionalization with various reagents (bromination, nitration, chlorination, alkylation, acylation, and anodic and photochemical cyanation). Electrophilic substitution in fluorene occurs mainly at the 2 and 4 positions; however, the regioselectivity of functionalization of DBF depends on the reagent used. Bromination[20] and acylation[21,22] occurred mainly at position 2, functionalization at position 3 was more pronounced in anodic and photochemical cyanation,[23] but nitration strongly depends on the reagent used (93% at position 3 in 99%HNO₃/TFA[22] and 52% at position 2 in a NaNO₃, N₃⁻, AcOH/H₂SO₄ mixture[24]). Ionic attack was suggested to explain predominant substitution at position 2, and ion radicals were proposed as intermediates for 3-substituted products, while radical attack resulted in almost equal amount of four products.[23]

To obtain further information of the role of the structure of the aromatic molecule on the type of fluorine atom introduction, we found it instructive to study the reactions of fluorene (**1a**), DBF (**1b**), and structurally related biphenyl (**5a**), diphenylmethane (**4b**), and diphenylether (**5c**) with XeF₂.

Results and Discussion

First we investigated the regioselectivity of room-temperature fluorination of fluorene **1a** using XeF₂ catalyzed with BF₃·OEt₂. In a typical experiment 0.5 mmol of **1a** was dissolved at room temperature in 5 mL of CH₂Cl₂, 0.5 mmol of XeF₂ was added, and the reaction was catalyzed with a drop of BF₃·OEt₂ solution. The reaction mixture immediately turned dark blue, and xenon gas was evolved. After being stirred for 3 h, the reaction mixture was isolated and the crude reaction product analyzed by ¹H and ¹⁹F NMR spectroscopy and gas chromatography. The crude reaction mixture showed only two signals in its ¹⁹F NMR spectrum (−116.2 ppm (ddd) and −120.8 ppm (ddd) in 2:1 ratio) indicating only ring fluorination, and no evidence for side chain fluorination of the methylene carbon was found. The major product was assigned as 2-fluorofluorene (**4a**) and the minor one as 4-fluorofluorene (**2a**), while the crude reaction mixture contained only 30% of fluorinated products (as determined by ¹⁹F NMR with octafluoronaphthalene as internal standard). The regioselectivity of fluorene fluorination with XeF₂ was similar to that of nitration in acetic anhydride[25] at −43 °C (67% at C2 and 33% at C4); however, higher regioselectivity was observed in bromination, where 97% of 2-bromofluorene was formed.[26] The regioselectivity was explained by a

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Table 1. Effect of Reagent Structure on the Regioselectivity of Dibenzofuran (1b) Functionalization

Entry	Reagent	Regioselectivity				Ref
		1-	2-	3-	4-	
1	XeF$_2$	25	31	44	<1	
2	XeF$_2$, BF$_3\cdot$OEt$_2$, 0°C	23	23	54	<1	
3	XeF$_2$, BF$_3\cdot$OEt$_2$, 20°C	26	21	53	<1	
4	F-TEDA, CH$_3$CN, 70°C	27	42	31	<1	28
5	NO$_2$BF$_4$, EtNO$_2$. 0°C	22	43	33	2	22
6	NaNO$_3$,N$_3^-$,AcOH/H$_2$SO$_4$	13	52	34	1	24
7	99% HNO$_3$, CF$_3$COOH	3	4	93	1	22
8	NaCN, MeOH,anoic oxid.	8	17	71	3	23
9	NaCN, MeOH, hν	9	27	64	<0.5	23
10	ICN, MeOH, hν	32	23	24	21	23
11	PhCH$_2$Cl, AlCl$_3$, CHCl$_3$	12	50	32	6	22
12	PhCOCl, AlCl$_3$, PhNO$_2$	0.7	92	7	0.4	22
13	Br$_2$, AcOH		100			20

Scheme 1

Ratio	2	3	4
1a: Y= CH$_2$	1	/	2
1b: Y= O	1	1	2

Ph—Y—Ph	Yield	Regioselectivity	
		Ortho (6)	Para (7)
5a: Y= —	46%	1	0.9
5b: Y= CH$_2$	20%	1	1.2
5c: Y= O	44%	1	1.6

larger coefficient of electron density at C2 (0.390) than at C4 (0.278) in its HOMO established by MNDO calculation.[25] On the other hand, the regioselectivity of fluorine introduction was lower than that in the case of indan,[19] where only β-attack was observed in fluorination with XeF$_2$.[9]

It has been demonstrated that dibenzofuran (**1b**) is an interesting model compound in which ionic attack occurred predominantly at position 2, while functionalization at position 3 was ascribed to the formation of an ion radical intermediate. Calculated HOMO electron densities for DBF are on the order[22] of 0.301 for 3, 0.125 for 1, 0.061 for 2 and 0.041 for 4. On the other hand, the relative energies (kcal/mol) of protonated dibenzofurans are in the following order:[22] 0.0 for 2 > 0.69 for 4 > 3.05 for 3 > 3.23 for 1. Recently it has been demonstrated that various substituted dibenzofurans could be converted to ion radicals, and their structures were confirmed by EPR spectroscopy[27] (the spectrum observed in the oxidation of DBF, however, corresponds to the anthracene ion radical). Normalization of theoretical spin densities over positions 1 to 4 in the DBF radical cation gave the following distributions for the $^2A_2$ state:[27] 1−18%, 2−6%, 3−59%, and 4−16% and for the $^2B_1$ state 1−12%, 2−37%, 3−17%, and 4−32%. The experimentally established spin density distribution was as follows:[27] 1−25%, 2−1%, 3−67%, and 4−7%. XeF$_2$ reacted with DBF (**1b**) in CH$_2$Cl$_2$ at room temperature without a catalyst, but the yield of fluorinated products could be enhanced with BF$_3\cdot$OEt$_2$ as catalyst (from 17% to 30%). The crude reaction mixture showed three major signals at −113.7 ppm (ddd), −118.8 ppm (ddd), and −121.0 ppm (ddd) and one minor one at −137.0 ppm (ddd). The three major products were isolated by preparative TLC and GLC, and on the basis of their spectroscopic data and comparison with literature data and independently prepared samples, they were identified as 1-fluorodibenzofuran (**2b**), 2-fluorodibenzofuran (**3b**) and 3-fluorodibenzofuran (**4b**). As is evident from Table 1 the presence of BF$_3\cdot$OEt$_2$ increased fluorine attack at position 3 (entries 2 and 3), and the regioselectivity was also different (attack at positions 2 and 3) from that observed in fluorination with F-TEDA[28] in
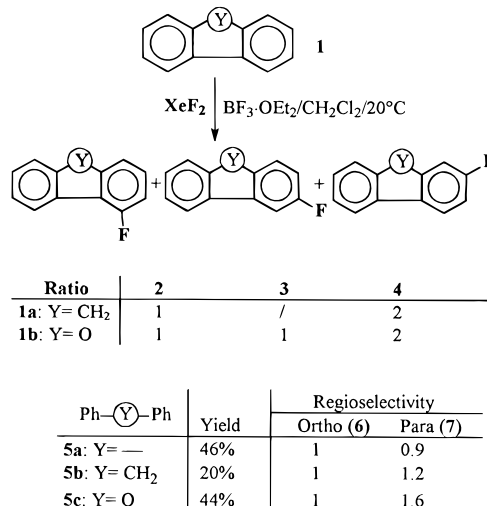
acetonitrile at 70 °C (entry 4). From the table it is apparent that the regioselectivity of DBF ring functionalization strongly depends on the reagent structure. It is evident that free radical attack gave almost equimolar amounts of four products (entry 10), ionic attack gave mainly 2-substituted product (entries 12 and 13), and the higher amount of the 3-substituted derivative observed in alkylation (entry 11) was explained by a difference in the relative stability of the σ-complex intermediate[22] (late transition state). Almost exclusive formation of 3-substituted product in nitration in TFA (entry 7) was explained by the formation of an ion radical, and a similar predominance of attack at position 3 was also observed in reaction of an ion radical generated either electrochemically (entry 8) or photochemically (entry 9).

Finally we studied the regioselectivity of fluorine introduction into structurally related biphenyl (**5a**), diphenylmethane (**5b**), and diphenyl ether (**5c**). Functionalization of biphenyl (**5a**) also depends on the reagent used, and fluorination with XeF$_2$ (Scheme 1) is very similar to nitration, where ortho attack is predominant[29] (p:o is 0.46). On the other hand, in bromination para attack prevailed.[30] In the reaction of XeF$_2$ with diphenylmethane (**5b**), para attack slightly prevailed (no fluorination in the meta position or the methylene was detected) and a regioselectivity similar to that for nitration in acetic anhydride at room temperature[31] (p:o = 1.2) was observed, while in chlorination with molecular chlorine a higher proportion of ortho attack was observed[32] (p:o = 0.86). Substitution of the CH$_2$ group by oxygen (**5c**) increased the para regioselectivity in diphenyl ether fluorination (p:o = 1.6) (Scheme 1), nitration was less regioselective[31] (p:o = 1.0), and again very high predominance of para attack was observed in bromination.[33]

Similarity in the regioselectivity of the dibenzofuran (**1a**) toward nitration,[22] anodic and photochemical cyanation,[23] and XeF$_2$ functionalization suggests that the formation of an ion radical intermediate is the most probable intermediate. Free radical type of functional-

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ization is less probable due to the absence of fluorine attack at position 4, which is characteristic of radical attack, as in photochemically initiated cyanation[23] with ICN where almost equal amounts of four substituted products were observed (Table 1, entry 10). Nitration of monosubstituted aromatic molecules has been extensively studied, and the formation of ion radicals as intermediates has been suggested.[34–40] Similarity in the regioselectivity of nitration and XeF_2 functionalization of studied aromatic molecules supported the formation of ion radicals, which were also observed in the fluorination of some aromatic molecules.[7,8]

Experimental Section

Fluorene (Janssen Chimica), 2-fluorofluorene (Fluorochem Limited), biphenyl (Fluka), diphenymethane (Fluka), diphenyl ether (Fluka), dibenzofuran (Matheson Coleman), $BF_3 \cdot OEt_2$ (Merck), and octafluoronaphthalene (Fluorochem) were obtained from commercial sources. XeF_2 was prepared by photosynthetic methods,[41] and its purity was better than 99.5%. Acetonitrile (Merck) and methylene chloride (Merck) were purified by distillation and stored over molecular sieves. ^1H and ^{19}F NMR spectra were recorded by a Varian EM360L spectrometer at 60 or 56.45 MHz with Me_4Si or CCl_3F as internal standards, gas chromatography was carried out on Varian Models 3700 and 3300, and TLC was carried out on Merck PSC-Fertigplatten silica gel F-254.

Fluorination with XeF_2. In 25 mL plastic bottle was dissolved 0.5 mmol of substrate (**1a**, **1b**, **5a**, **5b**, **5c**) in 5 mL of CH_2Cl_2. The 0.5 mmol of XeF_2 was added and the reaction catalyzed with a drop of $BF_3 \cdot OEt_2$. After being stirred for 3 h at room temperature, the reaction mixture was diluted with 25 mL of CH_2Cl_2, washed with water (10 mL) and a saturated solution of $NaHCO_3$ (10 mL), and dried over Na_2SO_4 and the solvent was removed under reduced pressure. Yields of fluorinated products were determined by ^1H and ^{19}F NMR spectros-

copy with octafluoronaphthalene as internal reference and calculated on the basis of starting substrate. Complete exclusion of ambient light had no effect on the conversion and product distribution. Products were isolated by preparative TLC or GC, and the structure was determined on the basis of spectroscopic data and by comparison with commercial samples, literature data, or independently prepared samples.

Fluorination of Fluorene (1a). The crude reaction mixture (77 mg) was isolated containing 30% of fluorinated products (ratio of **2a:4a** = 1:2): 4-fluorofluorene[42] (**2a**), $\delta_F = -120.8$ ppm (m); 2-fluorofluorene[42] (**4a**), $\delta_F = -116.2$ ppm (ddd).

Fluorination of Biphenyl (5a). The crude reaction mixture (79 mg) was isolated containing 46% of fluorinated products (ratio of **6a:7a** = 1:0.9): 2-fluorobiphenyl[43] (**6a**), $\delta_F = -116.0$ ppm (m); 4-fluorobiphenyl[43] (**7a**), $\delta_F = -118.2$ ppm (m).

Fluorination of Diphenylmethane (5b). The crude reaction mixture (80 mg) was isolated containing 20% of fluorinated products (ratio of **6b:7b** = 1:1.2): 2-fluorodiphenylmethane[44] (**6b**), $\delta_F = -118.5$ ppm (m); 4-fluorodiphenymethane[45] (**7b**), $\delta_F = -117.7$ ppm (dd).

Fluorination of Diphenyl Ether (5c). The crude reaction mixture (87 mg) was isolated containing 44% of fluorinated products (ratio of **6c:7c** = 1:1.6): 2-fluorodiphenyl ether[46] (**6c**), $\delta_F = -130.5$ ppm (m); 4-fluorodiphenyl ether[46] (**7c**), $\delta_F = -120.0$ ppm (dd).

Fluorination of Dibenzofuran (1b). The crude reaction mixture (89 mg) was isolated containing 30% of fluorinated products (ratio of **2b:3b:4b** = 1:1:2): 1-fluorodibenzofuran[28] (**2b**), $\delta_F -118.8$ ppm (ddd, $J = 12, 6, 1$ Hz); 2-fluorodibenzofuran[47] (**3b**), $\delta_F = -121.0$ ppm (ddd, $J = 9, 5$ Hz); 3-fluorodibenzofuran[47] (**4b**), $\delta_F = -113.7$ ppm (ddd, $J = 9, 5$ Hz).

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