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INTERACTION OF POLYFLUOROAROMATIC COMPOUNDS WITH o-AMINOPHENOL. THE SMILES REARRANGEMENT IN THE POLYFLUOROAROMATIC SERIES

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SUMMARY

The reactions of polyfluoroaromatic compounds containing an electron-attracting substituent other than fluorine in the aromatic ring with o-aminophenol proceed at the amino or hydroxy group and lead to the corresponding hydroxydiarylamines (in neutral media) or aminodiaryl ethers (in alkaline media). The latter compounds, unlike 2,3,4,5,6-pentafluoro-2'-aminodiphenyl ether, are transformed in dimethylformamide (DMFA) to isomeric polyfluoro-2-hydroxydiarylamines (the Smiles rearrangement). The increased electron-attracting capacity of substituent leads to the decreased activation energy and increased rearrangement rate constants.

INTRODUCTION

The reactions of aromatic and heteroaromatic compounds containing an activated halogen atom with aminophenols may proceed at the amino or hydroxy group and lead, depending on the medium basicity, to hydroxydiarylamines or aminodiaryl ethers [1-9]. The latter route takes place in the presence of a strong base [1,2,7,9] or with an alkaline metal phenoxide as a reagent [8]. Interaction with o-aminophenol may be complicated by the transformation of o-aminodiphenyl ethers to o-hydroxydiphenylamines (the Smiles rearrangement) [1-3,10,11].

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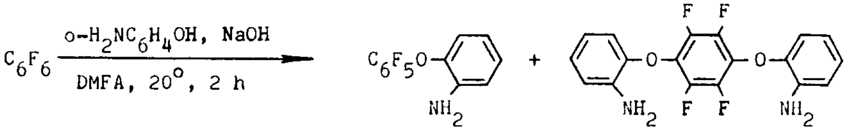
The reactions of polyfluoroaromatic compounds of the type C_6F_5X (X=F,H,Cl) with o-aminophenol in pyridine in the presence of NaOH have been reported [12,13]. They lead to substitution of fluorine by the aminophenoxy group. The possibility for the reactions to produce diarylamines has not been studied. In the present study we have investigated the reactions of hexafluorobenzene, pentafluoronitrobenzene, octafluorotoluene and pentafluoropyridine with o-aminophenol in DMFA, in neutral and alkaline media.

RESULTS AND DISCUSSION

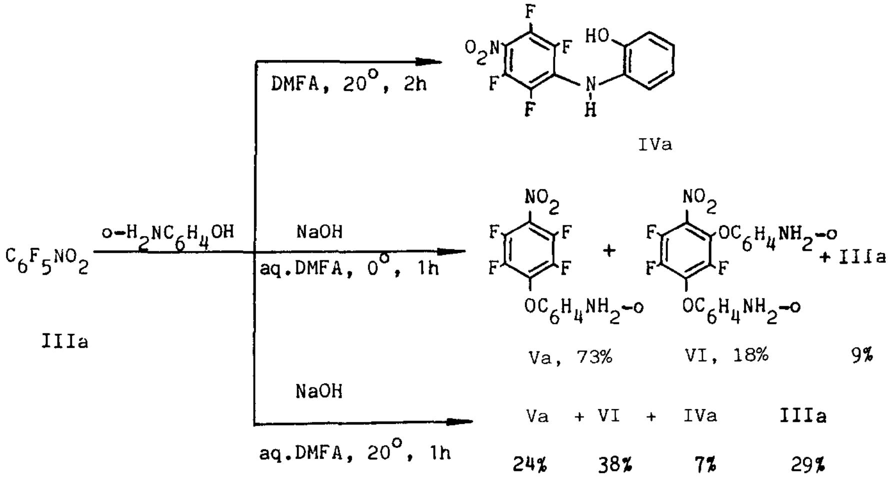
Hexafluorobenzene does not react with o-aminophenol in DMFA upon heating to 80°. This is consistent with the known data on the inactivity of polyfluoroaromatic compounds containing no additional electron-attracting group with aromatic amines [14,15]. In the alkaline medium promoting formation of nucleophile $H_2NC_6H_4O^-$ the reaction proceeds at room temperature to form a mixture of the products of substitution of one and two fluorine atoms by the o-aminophenoxy group (I,II). The disubstituted compound (II), as expected, contains the aminophenoxy substituents at positions 1 and 4. The reaction mixture contained no isomeric hydroxydiarylamines.



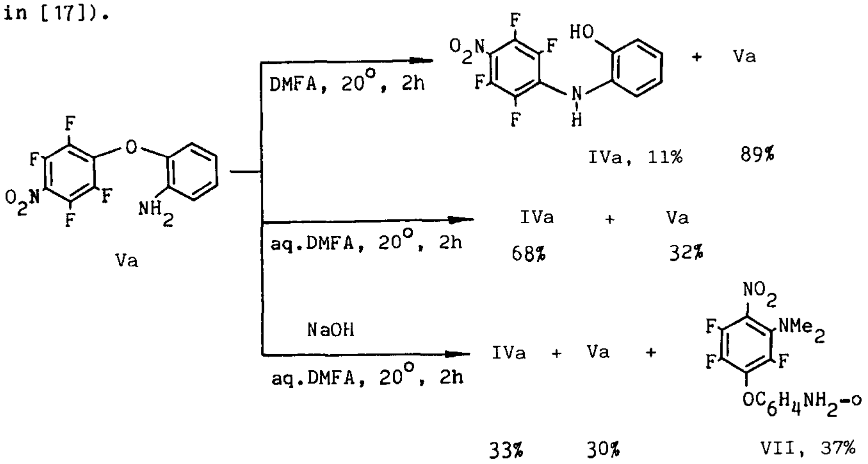
I, 88%

II, 12%

In contrast to hexafluorobenzene, pentafluoronitrobenzene (IIIa) in which the nucleophilic mobility of fluorine atoms is significantly higher [16] easily reacts with o-aminophenol both in the presence of alkali and without it. In neutral media the reaction proceeds completely at the amino group forming o-hydroxydiarylamine (IVa). In the presence of aqueous NaOH at 0° the reaction gives 4-nitro-2,3,5,6-tetrafluoro-2'-aminodiphenyl ether (Va) with an admixture of the 2,4-disubstituted compound (VI). The reaction conducted at 20° leads to diarylamine (IVa) in addition to compounds (Va) and (VI).



The formation of diarylamine (IVa) in the last reaction may result from either the partial interaction at the amino group of the reagent or the Smiles rearrangement of compound (Va).* In support of the second supposition prolonged keeping (30 h) of diphenyl ether (Va) in DMFA at room temperature leads to its transformation to compound (IVa). In the presence of NaOH the rearrangement also takes place but is complicated by substitution of fluorine in the starting ether (Va) by the dimethylamino group (the ability of DMFA to act as a donor of the Me_2N group was reported in [17]).



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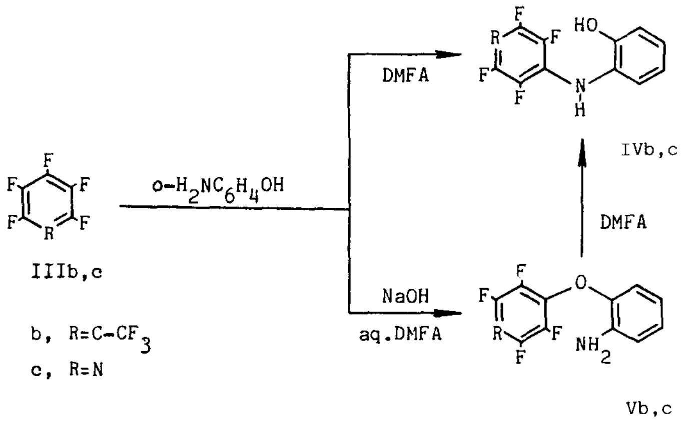
* Earlier we have described the intervention of the Smiles rearrangement in the process of cyclization of polyfluoro-o-acylamidodiphenyl ethers to phenoxazine derivatives [13].

A very important factor determining the occurence of the Smiles rearrangement is the activation of the migrating aromatic nucleus [10]. In the case of diaryl ethers containing a free amino group in the o-position, the rearrangement only takes place if the migrating aryl has at least two nitro groups in the conjugated positions [2,10,18]. We have shown the pentafluoro-2-aminodiphenyl ether (I) to be stable upon heating in DMFA, unlike its nitrosubstituted analogue (Va). It seems important to show the possibility of the Smiles rearrangement for the polyfluoroaromatic compounds containing an electron accepting fragment other than the nitro group. In this connection we investigated the reaction of octafluorotoluene (IIIb) and pentafluoropyridine (IIIc) with o-aminophenol in DMFA.

As well as pentafluoronitrobenzene (IIIa), but unlike hexafluorobenzene, compounds (IIIb,c) react with o-aminophenol both in alkaline and neutral media . In the latter case polyfluoro-2-hydroxydiarylamines (IVb,c) are formed in high yields. In the presence of aqueous alkali at 20° or below the reaction proceeds at the hydroxy group of the reagent giving the o-aminosubstituted diaryl ethers (Vb,c) (see Table 4). The higher temperature leads to the rearrangement of these compounds to amines (IVb,c).



To investigate the relative ability of compounds (Va-c) to undergo the Smiles rearrangement we determined the comparative rates of their transformations by ^{19}F NMR spectroscopy. Kinetic runs were carried out in DMFA in the temperature range of 60° to 120° . The analysis of the ^{19}F NMR spectra of the reaction mixtures has shown the rearrangement of the ethers (V) to amines (IV) to be the single type of conversion. The conversion degree was determined from a change in the integral intensity ratio of fluorine signals in the NMR spectra of the mixtures of compounds (V) and (IV). The rearrangement rate constants were calculated from the first-order equation

$$k = \frac{1}{t} \ln \frac{C_o}{C} = \frac{1}{t} \ln \left(1 + \frac{H_{amine}}{H_{ether}}\right) \qquad (1)$$

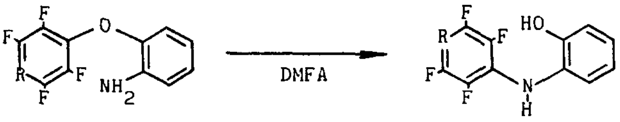
where H_{amine} is the integral intensity of fluorine 3 and 5 (or 2 and 6) signals in the spectrum of diarylamine (IV);

H_{ether} - the integral intensity of fluorine 3 and 5 (or 2 and 6) signals in the spectrum of diaryl ether (V);

t - time (s).

TABLE 1

Rearrangement of o-aminodiaryl ethers (V) in DMFA



Va-c IVa-c

Compound, (R)	T, °C	Rate constant ($10^4 k$), s^{-1}	E, kcal/mole	log A
Va	60	2.17		
($C\text{-}NO_2$)	70	3.93		
	80	7.59		
	90	12.20	14.0 ± 0.5	5.55
Vb	90	0.12		
($C\text{-}CF_3$)	100	0.21		
	110	0.53		
	120	1.03	20.9 ± 1.5	7.63
Vc	70	0.82		
(N)	80	1.66		
	90	3.34		
	100	7,21	18.3 ± 0.6	7.58

The calculated rate constants and Arrhenius parameters are reported in Table 1. As might be expected the rearrangement rate increases and the activation energy decreases with increasing the activating power of group R^{*} (the relative rate constants at 90° are given in brackets) :

$$C\text{-}CF_3\ (1) < N\ (27) < C\text{-}NO_2\ (100)$$

An example of the activating effect of water on the rearrangement of o-aminodiphenyl ethers in organic solvents had been reported [1]. We have also observed the transformation of compound (Va) to (IVa) to proceed faster upon addition of 20% of water to DMFA. The kinetic studies of the rearrangement of dyaryl ethers (Va,c) whose molecules contain the nitro group or the pyridine ring in aqueous DMFA have confirmed the activating action of water. However for compound (Vb) containing trifluoromethyl group a certain decrease of the reaction rate is observed (see Table 2).

TABLE 2

Rearrangement of o-aminodiaryl ethers (V) in DMFA-H_2O

Compound (R)	T,°C	Rate constant, ($10^4 k, s^{-1}$)	$\frac{k_{DMFA-H_2O}}{k_{DMFA}}$
Va, ($C\text{-}NO_2$)	60	11.8	5.4
Vb ($C\text{-}CF_3$)	100	0.15	0.7
Vc (N)	70	1.01	1.2

It is known that addition of protic solvents to the polar aprotic ones may produce the deactivating effect on the nucleophilic substitution reactions [21]. The increased rearrangement rate of ethers (Va,c) in aq.DMFA seems to result from the increased electron accepting nature of group R due to hydrogen bonding with water molecules.

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[*] The comparative data on the activating effect of groups in the reactions of nucleophilic substitution of fluorine by the amino group are reported in [19,20].

EXPERIMENTAL

^{19}F and ^{1}H NMR spectra were recorded on a 'Varian A 56/60 A' spectrometer in THF and $CDCl_3$ respectively. Internal standards were hexafluorobenzene and hexamethyldisiloxane. The kinetic measurements were carried out on a 'Bruker WP-200 SY' (188,28 MHz) spectrometer. IR spectra were recorded on a 'UR-20' spectrophotometer for 1% solutions in $CHCl_3$.

DMFA was dried over molecular sieves 4A and 9A and contained 0.3% of water ; aq.DMFA contained 20% of water.

Reaction of hexafluorobenzene with o-aminophenol

To 0.50 g of powdered NaOH in 10 ml DMFA was added 1.10 g of o-aminophenol and then was dropped in a solution of 1.86 g of hexafluorobenzene in 2 ml of DMFA at 20°. The mixture was stirred for 2 h, poured into 200 ml of water and extracted with ether. The ethereal solution was washed with water, dried ($CaCl_2$) and evaporated to yield the product analysed by ^{19}F NMR spectroscopy. It was separated by chromatography on a silica gel column (L 100/160). Elution with benzene gave (i) 2,3,4,5,6-pentafluoro-2'aminodiphenyl ether (I), the yield was 73%, m.p. 72-73°, identical with the authentic sample [12], and (ii) 1,4-bis(o-aminophenoxy)-tetrafluorobenzene (II) (nc), the yield was 9%, m.p. 173-174° (from benzene). Found: C,59.29; H, 3.30; F, 20.65; N, 7.28%. $C_{18}H_{12}F_4N_2O_2$ requires C, 59.34; H, 3.34; F, 20.86; N, 7.69%. IR, ν,cm^{-1} : 3400,3480 (NH_2). ^{19}F NMR showed a singlet at 7.4 ppm.

Reaction of compounds (III) with o-aminophenol

1. 1.0 Mmol of compound (III) and 1.1 mmol (1.20 g) of o-aminophenol were stirred in 20 ml of DMFA. The mixture was poured into water and extracted with ether. The combined ether layers were washed with water, dried ($CaCl_2$) and evaporated. The reaction conditions and characteristics of obtained compounds IV are shown in Table 3.

TABLE 3

Polyfluorinated o-hydroxydiarylamines and o-aminodiaryl ethers

Comp. No	React. conditions		Yield %	M.p., °C (solvent)	Found/Calcd, %				Formule	IR, ν, cm^{-1}	^{19}F NMR δ, ppm
	Temp., °C	Time, h			C	H	F	N			
IVa(nc)	20	2	63	163–165 (benzene)	47.75 47.69	2.10 2.00	25.30 25.15	8.94 9.27	$C_{12}H_6F_4N_2O_3$	3405 (NH) 3600 (OH)	7.3 (2F) 14.0 (2F)
IVb(nc)	100	10	85	87–88 (petr. ether)	47.85 48.01	1.97 1.86	40.70 40.90	4.31 4.13	$C_{13}H_6F_7NO$	3410 (NH) 3600 (OH)	8.5 (2F) 18.4 (2F) 109.2 (3F)
IVc(nc)	20	5	85	116–118 (benzene-petr. ether)	51.58 51.17	2.48 2.34	29.90 29.44	10.69 10.85	$C_{11}H_6F_4N_2O$	3420 (NH) 3600 (OH)	3.2 (2F) 67.3 (2F)
Va(nc)	0	1	59	66–68 (petr. ether)	47.49 47.69	1.86 2.00	25.20 25.15	8.98 9.27	$C_{12}H_6F_4N_2O_3$	3400, 3500 (NH_2)	9.9 (2F) 15.8 (2F)
Vb(nc)	20	5	77	65–67 (petr. ether)	47.99 48.01	2.05 1.86	41.51 40.90	4.31 4.13	$C_{13}H_6F_7NO$	3400, 3480 (NH_2)	9.5 (2F) 21.4 (2F) 107.8 (3F)
Vc(nc)	0	1	89	42–44*	51.25 51.17	2.31 2.34	29.57 29.44	10.79 10.85	$C_{11}H_6F_4N_2O$	3410, 3490 (NH_2)	6.4 (2F) 72.2 (2F)

* after distillation at 126–128°/3mm

2. o-Aminophenol (1.20 g, 1.1 mmol) was added to sodium hydroxide (0.44 g, 1.1 mmol) in 10 ml of water. The mixture was warmed to temperature listed in Table 3 or 4 and a solution of 1.0 mmol of compound (III) in 10 ml of DMFA was dropped in. Pouring into water, acidification and extraction with ether afforded the product which was analysed by the ^{19}F NMR spectroscopy and then was separated by column chromatography (silica gel L 100/160; benzene). The yields, analytical and spectral data of obtained ether (V) are given in Table 3. The column separation of mixture obtained from compound (IIIa) gave also 2,4-di(2-aminophenoxy)-3,5,6-trifluoronitrobenzene (VI) (nc), m.p. 133-136° (from benzene). Found: F, 14.15; N, 10.45%. $C_{18}H_{12}F_3N_3O_4$ requires F, 14.57; N, 10.75%. IR, ν, cm^{-1}: 3400, 3480 (NH_2). ^{19}F NMR, δ, ppm: 11.0, 14.2, 20.6.

TABLE 4

Reaction of compounds (III) with o-aminophenol in DMFA in the presence of NaOH

Starting	Reaction conditions		Products ratio, % (from ^{19}F NMR spectra)			
compound	Temp., °C	Time, h	(III)	(V)	(IV)	(VI)
(IIIa)	0	1	9	73	-	18
	20	1	29	24	7	38*
(IIIb)	20	5	-	100	-	
	100	1	-	100	-	
	100	5	-	86	14	
(IIIc)	0	1	-	100	-	
	20	1	-	100	-	
	50	1	-	81	19	

* Reaction mixture contains ~2% of 2,4,6-triaryloxydifluoronitrobenzene.

Rearrangement of diaryl ethers (V)

1. 0.20 g of compound (Va) were stirred in aq.DMFA (5 ml) at 20° for 30 h. The mixture was poured into water and extracted with ether. The ethereal layers were washed with water, dried ($CaCl_2$) and evaporated to yield 0.20 g of amine (IVa).

2. 0.20 g of compound (Va) in 5 ml of dry or aqueous DMFA were stirred at 20° for 2 h. The product obtained as in exp.1 was analysed by ^{19}F NMR spectroscopy.

3. 0.20 g of compound (Va) were added to a solution of NaOH (0.03 g) in aq.DMFA (5 ml). The mixture was stirred at 20° for 2 h, poured into water, neutralized with 10% hydrochloric acid and extracted with ether. Washing, drying and evaporation left a residue which was analysed and separated by column chromatography (silica gel L 100/160, benzene) to give 3-dimethylamino-4-nitro-2,5,6-trifluoro-2'-aminodiphenyl ether (VII) (nc), m.p. 66-68° (from petrol.ether). Found: C, 51.74; H, 3.70; F, 17,37; N, 12.78%. $C_{14}H_{12}F_3N_3O_3$ requires C, 51,38; H, 3.81; F, 17.42; N, 12.84%. IR,ν, cm^{-1}: 3400, 3500 (NH_2). ^1H NMR,δ, ppm: 2.79 (CH_3), 4.11 (NH) and 6.54-6.98 (Ar). ^{19}F NMR,δ, ppm: 8.5 (F^6), 12.3 (F^5) and 25.3 (F^2).

4. A solution of compound (Vb) (0.20 g) in 5 ml of DMFA was kept at 120° for 10 h. The usual procedure gave 0.18 g of compound (IVb).

5. The compound (Vc) (0.20 g) in 5 ml of DMFA was heated at 100° for 1.5 h to give 0.20 g of amine (IVc) after the usual procedure.

Kinetic measurements

The reactions were carried out and controlled in well-stoppered tubes for recording the ^{19}F NMR spectra containing 0.10 g of ether (V) in 0.25 ml of DMFA. The thermostat temperatures were steady to within ± 0.1°C. The starting compound and product ratio was determined by ^{19}F NMR spectroscopy. The reaction was stopped by rapid cooling to -30°, the ^{19}F NMR spectrum was recorded and the tube was immersed in the thermostat immediately. Reactions were followed to at least 70% completion and each run was duplicated. The rate constants of rearrangement (k) were calculated from the formula (1) for 5-6 points at each temperature and averaged by least squares method. The error of the determination of k didn't exceed 2.7%. Values of rate constants (k) were determined at four temperatures and used in determining the

Arrhenius parameters (E and log A). The rate constants and Arrhenius parameters are given in Table 1 and 2.

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