The Smiles rearrangement in the polyfluoroaromatic series

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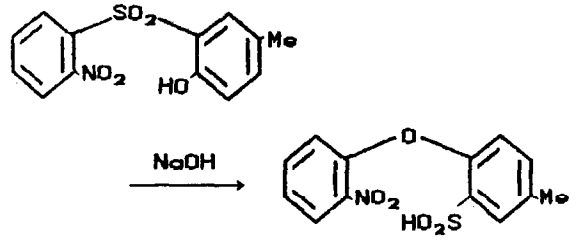
Abstract

This paper summarizes the authors' data on the reactions of polyfluoroaromatic compounds with *o*-aminophenols in DMF under neutral or basic conditions and the Smiles rearrangement of partly fluorinated *o*-aminodiaryl ethers.

The Smiles rearrangement involves inversion of side-chains attached to ring-activated aromatic systems [1, 2].

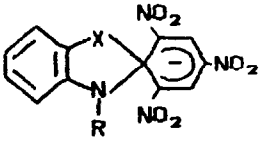
(X = O, S, SO, SO_2; YH = NHR, OH, SH, CONHR, CH_2R)

A typical rearrangement is the transformation of 2-hydroxydiphenyl sulfone into sulfinic acid [3].



The Smiles rearrangement has been studied in a well-planned manner and the following factors which influence the speed of the rearrangement have been established: (1) activation of the migrating aromatic ring; (2) replaceability of X; (3) the strength of Y^- as a nucleophilic reagent; and (4) the acidity of the Y–H function, since in most cases Y–H must be converted to the anionic Y^- form before reaction can occur [1, 2].

The mechanism of this transformation has been investigated and the presence of a stabilized spiro-Meisenheimer intermediate such as **1** established [4, 5].



(X = O, S; R = Me, Ph)

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Rearrangement of *o*-aminodiphenyl ethers into *o*-hydroxydiphenylamines was discovered by Roberts and Worms [6, 7]. The most favourable conditions for these reactions involve the use of solvents with high dielectric constants, particularly the presence of water without the addition of ionic base. The fact that *N*-acyl derivatives react progressively more slowly with increasing electron-withdrawing character of the acyl group is in accord with the conclusion that the amino group enters into the displacement reaction as such. Rearrangement of *o*-hydroxydiphenylamines to *o*-aminodiphenyl ethers has not been observed.

One problem is the intervention of the Smiles rearrangement in the synthesis of phenoxazines from two aromatic moieties. When the latter are condensed and cyclized in one step, it is sometimes difficult to decide whether the Smiles rearrangement has occurred, because initial condensation may involve either the hydroxy or the amino group depending on the reaction conditions [6, 8].

The Smiles rearrangement was unknown in the polyfluoroaromatic series until the mid-1980s, when we began investigating the reaction of polyfluorinated aromatic compounds with *o*-aminophenol as a means of synthesizing polyfluorophenoxazines [9, 10].

Some reactions of compounds of the type C_6F_5X with *o*-aminophenol in pyridine in the presence of sodium hydroxide or with potassium *o*-aminophenoxide in DMF had been reported earlier [11, 12]. These led

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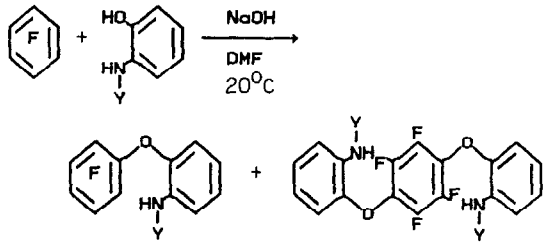
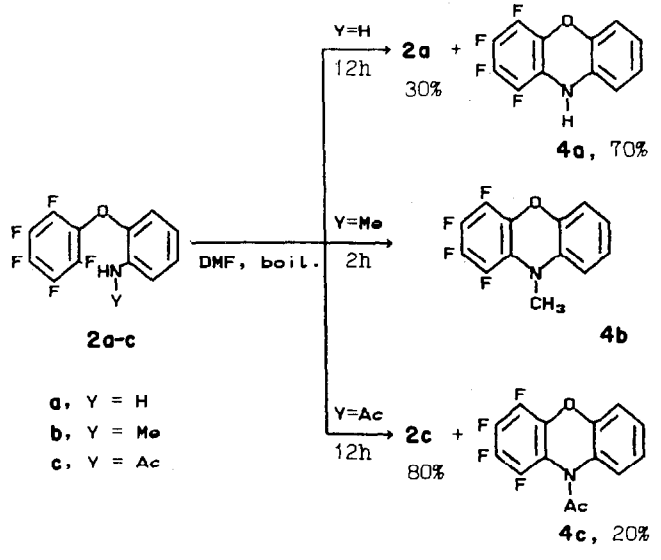
to the substitution of fluorine by the aminophenoxy group. It was shown that hexafluorobenzene failed to react with *o*-aminophenol in DMF upon heating to 80 °C [12].

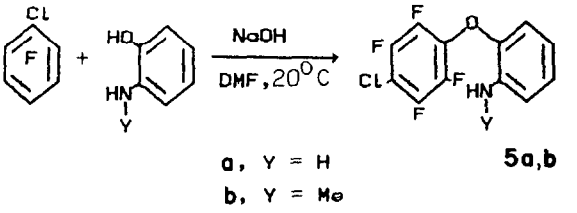
We have found that hexafluorobenzene and *o*-aminophenol or *o*-*N*-methylaminophenol react readily in DMF under basic conditions at room temperature to give *o*-aminodiphenyl ethers of type **2** with an admixture of the disubstituted product **3** [13].



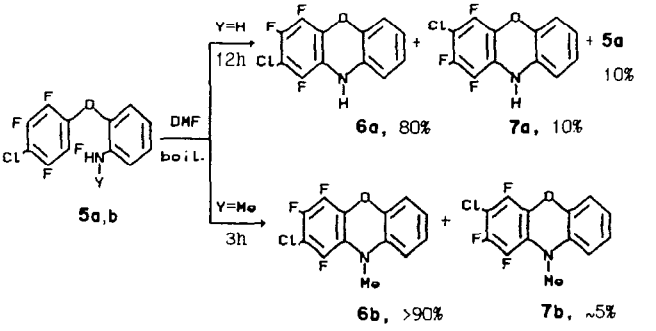
Heating ethers **2a,b** for a prolonged time under reflux in DMF leads to cyclization into the corresponding phenoxazines **4** with displacement of fluorine. *N*-Alkylation increases the rate of this transformation. The *N*-acetyl derivative **2c** [9] reacts more slowly than the free amino compound **2a**.



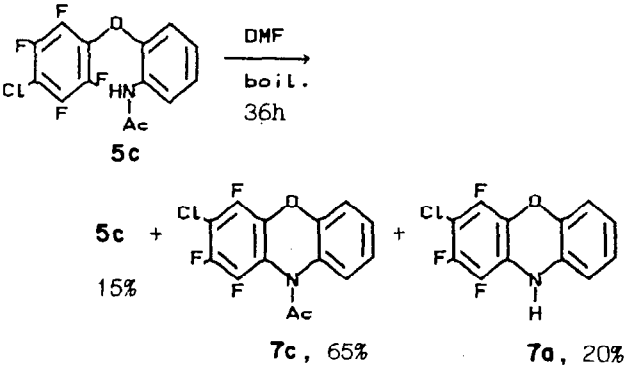
Alternative pathways for the formation of phenoxazines are shown in Scheme 1. Direct condensation at nitrogen with displacement of fluorine (route A) and displacement after Smiles rearrangement (route B) yield phenoxazines of type **4**. To answer the question whether compounds **4** are formed directly or by a Smiles rearrangement, we have prepared ethers of type **5** containing a chloro substituent in fluorinated ring.



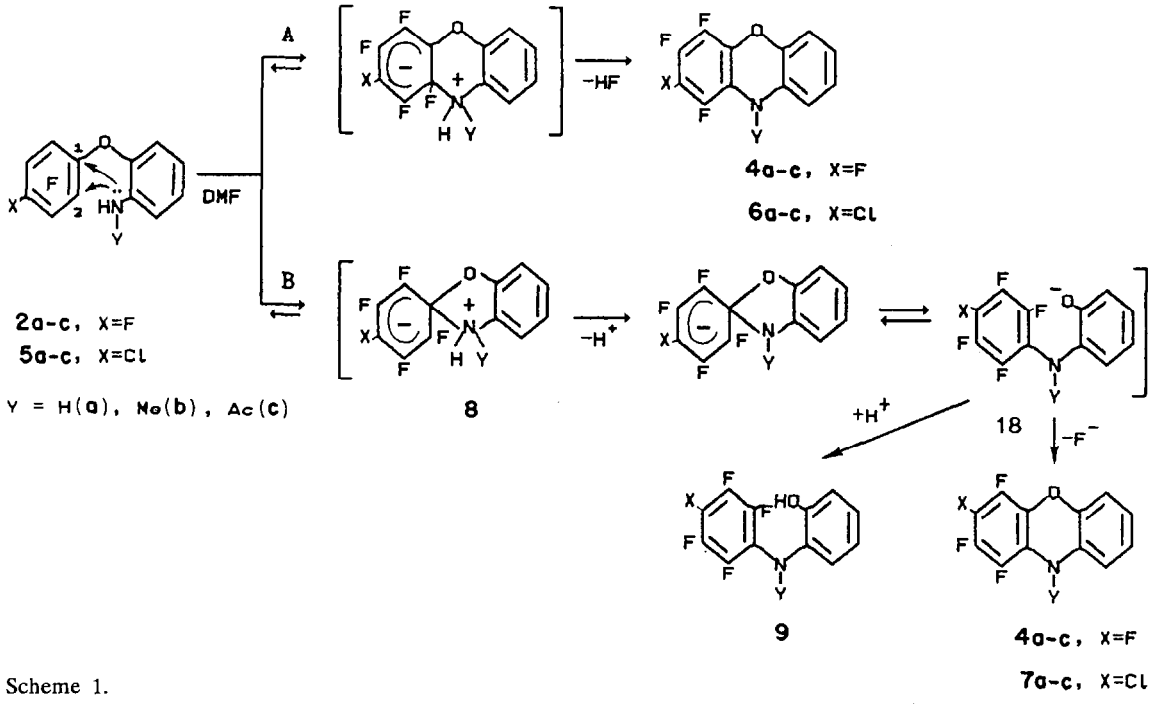
Heating amino and *N*-methylamino ethers **5a,b** in DMF affords phenoxazines **6a,b** with admixtures of the rearranged isomers **7a,b**. These data indicate that route A with direct cyclization of ethers **5a,b** is favoured.



The reverse situation is seen for the *N*-acetyl ether **5c** [10] which rearranges in DMF before yielding phenoxazine **7c**. Direct cyclization of ether **5c** does not occur under the reaction conditions. Phenoxazine **7a** is probably the product of the deacylation of compound **7c** under the conditions employed. Ethers **5a–c** exhibit the following reactivity order: **5b** > **5a** > **5c**.



These results may be explained in the terms of Scheme 1. One suggestion is that route B is favoured by the formation of spiro complex **8** by intramolecular nucleophilic attack on the position *para* to the chlorine since this is consistent with the orientation of nucleophilic substitution in the polyfluoroaromatic series [14]. This route is realized for ether **5c** as far as the weakly nucleophilic acetylamino group is concerned. The other direction of transformation of compound **5a,b** when the latter contains the more nucleophilic amino or *N*-methylamino group can be attributed to the rate-limiting deprotonation of the zwitterionic spiro complex **8**. Under these circumstances, route A with attack on the less



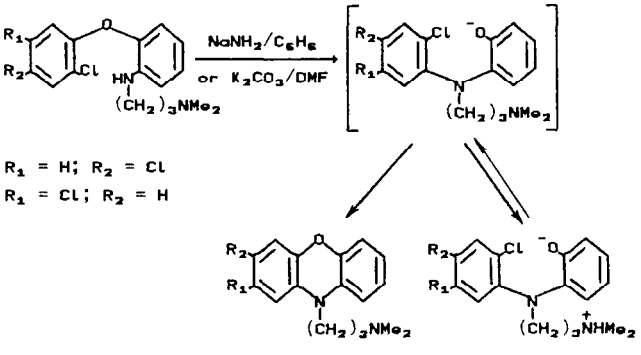
Scheme 1.

electrophilic 2-position becomes more favourable. The realization of route A requires the involvement of a rapid equilibrium step in the formation of intermediate **8**. The reactivity order of compounds **5a** and **5b** in process A can be explained in terms of a mechanism nucleophilic polyfluoroaromatic substitution [14].

Smiles rearrangements with a rate-limiting deprotonation of a zwitterionic complex of type **8** are known. Base-catalyzed kinetics are exhibited in these cases [15, 16]. It is reasonable to suppose that adding a base to the reaction mixture must increase the contribution of route A in the formation of ether **5a** or **5b**. We have demonstrated experimentally that heating ether **5b** in DMF in the presence of potassium carbonate affords the rearranged phenoxazine **7b** and the unrearranged isomer **6b** in a 9:1 ratio. The ability of CO_3^{2-} anions, in conjunction with the K^+ cation, to take part in a proton-transfer process is well known [17].

$$\mathbf{5b} \xrightarrow[130\ ^\circ C,\ 1\ h]{K_2CO_3,\ DMF} \underset{(10\%)}{\mathbf{6b}} + \underset{(90\%)}{\mathbf{7b}}$$

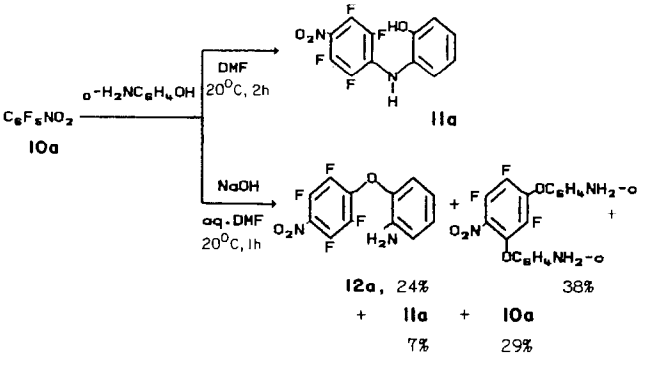
We believe that the transformations described above include the first examples of a Smiles rearrangement in the polyfluoroaromatic series. Most Smiles rearrangements require strong activation by the presence of electron-attracting substituents in the migrating aromatic ring. In the case of diaryl ethers with a free *o*-amino group, rearrangement only takes place if the migrating aryl has at least two nitro groups in conjugated positions [1]. As shown by other workers [8, 18], *o*-(*N*-alkylamino)diaryl ethers containing only chlorine atoms in the migrating aromatic ring undergo a Smiles rearrangement with sodium amide in benzene or with potassium carbonate in DMF. It is reasonable to assume that the activating effect of halogen atoms in ethers **5** is sufficient to allow the Smiles rearrangement to occur.



The sole argument in favour of occurrence of a Smiles rearrangement with the diaryl ethers **5a–c** is the structure of phenoxazine **7**. *o*-Hydroxydiarylamines of type **9** – the product of the rearrangement of ethers **5** – were not observed in the reaction mixture. In order to arrest these reactions at the diarylamine stage and to obtain additional evidence for the Smiles rearrangement, we have investigated the interaction of *o*-aminophenol with polyfluoroaromatic compounds containing an electron-attracting substituent in the fluorinated aromatic ring.

In contrast to hexafluorobenzene, pentafluoronitrobenzene (**10a**) in which the nucleophilic mobility of

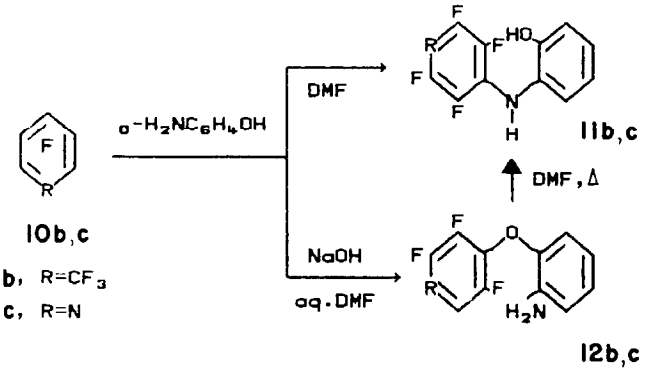
fluorine is significantly greater readily reacts with *o*-aminophenol both in the presence of alkali and in its absence. In neutral media, the reaction proceeds exclusively at the amino group forming *o*-hydroxydiphenylamine (**11a**) [13, 19].



In the presence of aqueous alkali at 20 °C, the reaction gives 4-NO_2-2,3,5,6-tetrafluoro-2'-aminodiphenyl ether (**12a**) in admixture with the 2,4-disubstituted compound and *o*-hydroxydiphenylamine (**11a**). The latter may be formed directly or via a Smiles rearrangement of the diphenyl ether **12a**. In support of the latter version, prolonged storage of compound **12a** in DMF at room temperature leads to its transformation to diphenylamine (**11a**).

Isolation of the Smiles rearrangement product in the case of ether **12a** has suggested the possibility of obtaining information about the influence on the reactivity of substituents introduced into the migrating aromatic ring or into the *o*-amino group in the diaryl ether structure.

We have found that octafluorotoluene (**10b**) and pentafluoropyridine (**10c**) react with *o*-aminophenol in DMF in a similar manner to the nitrobenzene **10a**. The *o*-aminosubstituted diaryl ethers **12b, c** obtained in alkaline media rearranged to *o*-hydroxydiarylamines **11b, c** upon heating in DMF [19].



Analysis of the ^{19}NMR spectra of the reaction mixtures obtained has shown that the rearrangement of ether **12** to amine **11** is a single type of conversion. The relative ability of compounds **12a–c** to undergo the Smiles rearrangement in DMF has been investigated over the temperature range 60–120 °C. The degree of conversion was determined from the change in the integral intensity ratio of the fluorine signals in the NMR spectra of mixtures of compounds **12** and **11**, the rearrangement rate constants being calculated from the first-order equation:

$$k = \frac{1}{t}\ln\left(\frac{C_0}{C}\right) = \frac{1}{t}\ln\left(1 + \frac{H_{amine}}{H_{ether}}\right)$$

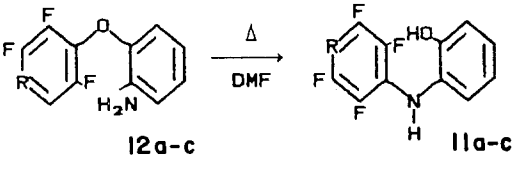
where H_{amine} is the integral intensity of the signals of fluorines 3 and 5 (or 2 and 6) in the spectrum of diarylamine **11**, H_{ether} is the integral intensity of the signals of fluorines 3 and 5 (or 2 and 6) in the spectrum of diarylether **12** and t is the time in seconds.

The calculated rate constants are listed in Table 1. As expected, the rate of rearrangement increases with increasing activating power of the group R (the relative rate constants at 90 °C are given in brackets): viz $C-CF_3(1) < N(27) < C-NO_2(100)$.

In earlier work, Roberts and Worms showed that the order of reactivity of *N*-acylaminodiphenyl ether also depends on the order in which nucleophilicity of the acylamino group decreases [7]. We have thus investigated the effects of *N*-acylation and *N*-alkylation on the rearrangement rate of 4-NO_2-2,3,5,6-tetrafluoro-2'-aminodiphenyl ether in DMF.

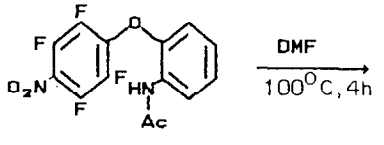
o-Acetamidodiphenyl ether (**13**) was obtained by refluxing compounds **12a** with acetyl chloride in benzene [20]. Heating this ether in DMF afforded a mixture containing *o*-hydroxydiphenylamine (**14**), compound **15**

TABLE 1. Rearrangement of *o*-aminodiaryl ethers **12** in DMF



Compound (R)	Temp. (°C)	Rate constant ($\times 10^4$) (s^{-1})
12a (C–NO_2)	60	2.17
	70	3.93
	80	7.59
	90	12.20
12b (C–CF_3)	90	0.12
	100	0.21
	110	0.53
	120	1.03
12c (N)	70	0.82
	80	1.66
	90	3.34
	100	7.21

with the acetyl group at the oxygen and phenoxazine **16**. Obviously we are dealing here with the case of a Smiles rearrangement combined with acetyl group migration from nitrogen to oxygen.



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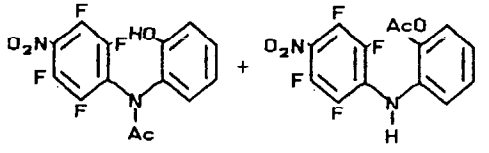
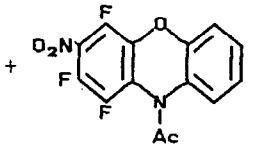
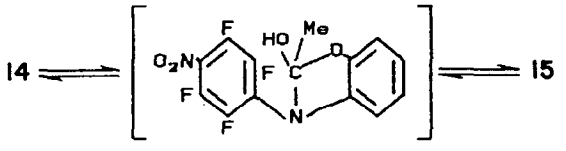


14, 47% **15**, 13%



16, 40%

In DMF the individual compounds **14** and **15** equilibrate in a 74:26 ratio. We believe that N ⇌ O migration of the acyl group involves the formation of an intermediate structure of type **17** [21]:



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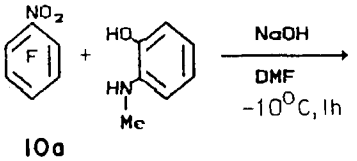
Prolonged heating of compound **14** in DMF at 100 °C did not yield the corresponding phenoxazine **16**. Obviously, the latter is obtained by cyclization of the corresponding phenoxy anion of type **18** (Scheme 1).

Since ether **13** rearranges before yielding compounds **15** and **16**, we determined the transformation rate of ether **13** from the change in the integral intensity of the fluorine signals in the NMR spectra with time. First-order kinetics were observed and the value of rate constant at 90 °C has been estimated (Table 2).

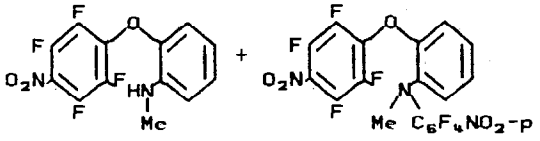
TABLE 2. Rearrangement rate constants of 4-NO_2-2,3,5,6-tetrafluoro-2'-NHY-diphenyl ethers in DMF

Compound	Y	Rate constant at 90 °C ($\times 10^4$) (s^{-1})
12a	H	12.2
19	Me	7.4
13	Ac	1.32

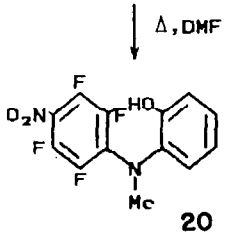
The alkylated diphenyl ether **19** was obtained from pentafluoronitrobenzene (**10a**) in alkaline media and we have determined the kinetics of its rearrangement to diphenylamine **20** in DMF. The rate constant as determined at 90 °C is reported in Table 2.



10a



19, 71%



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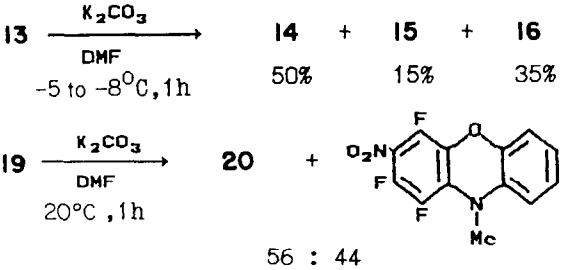
Thus the *N*-acetylated (**13**) and *N*-methylated (**19**) derivatives rearrange in neutral solution more slowly than the free amino parent ether **12a**. The effect of *N*-substitution may be interpreted in terms of the mechanism reported in Scheme 1 if it is assumed that the formation of a zwitterionic complex of type **8** is rate-limiting in the case of acetamido compound **13** but that deprotonation of intermediate **8** becomes rate-determining for ether **19** with the more nucleophilic methylamino group. According to this view, compounds **13** and **19** rearrange faster in the presence of potassium carbonate. The case of the free amino compound **12a** is probably intermediate.



Thus, we have demonstrated the ability of polyfluorinated *o*-aminodiaryl ethers to undergo the Smiles rearrangement and have studied the influence exerted on the reaction rate by substituents in the migrating aromatic nucleus and at the nitrogen of the *o*-amino group. In our opinion, rearrangements of this type are

of significant importance in reactions of polyfluoroaromatic compounds with various bifunctional nucleophilic reagents.

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