## SYNTHESIS OF POLYFLUOROPHENOXAZINES: SMILES' REARRANGEMENT

# ACTIVATED BY FLUORINE ATOMS

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We have previously described [1] the synthesis of 1,2,3,4-tetra- and octafluorophenoxazines from hexafluorobenzene, based on the preparation and intramolecular cyclization of polyfluoro-2-acetylaminodiphenyl ethers. In the present paper we report an analogous approach to the preparation of polyfluorosubstituted phenoxazines from pentafluorobenzene (Ia) and pentafluorochlorobenzene (Ib). Reaction of o-aminophenol with compounds (Ia, b) was carried out under the same conditions that were employed for reaction with  $C_6F_6$  [2]. This resulted in the preparation of tetrafluoro-2-aminodiphenyl ethers (IIa, b), each of which contained, as anticipated [3], an o-NH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>O group para to the X substituent. Heating the acetyl derivatives of these ethers (IIIa, b) with K<sub>2</sub>CO<sub>3</sub> in DMFA, followed by deacetylation in acidic media, resulted in the preparation of 1,2,4-trifluoro-3-X-phenoxazines (Va, b), rather than compounds of type (IV).



The structures of the phenoxazines (V) were confirmed by elemental analysis, as well as by IR, UV, and NMR spectroscopic analysis. For instance, the <sup>19</sup>F-NMR spectrum of phenoxazine (Va) contains three signals of equal intensities at -2.1 (ddd), 19.1 (dd), and 23.0 (dd) ppm. The presence of a H atom in the fluorinated portion of the molecule simplifies the spectral interpretation; the signal at -2.1 ppm, characterized by spin-spin coupling constants Jo-F,F = 22 Hz and Jp-F-F = 11 Hz, as well as Jm-F,H = 7 Hz (this coupling constant was also seen in the PMR spectrum), is assigned to the F<sup>1</sup> fluorine atom. The chemical shift value for this atom, as calculated by additivity rules [4], should be -1.6 ppm.\* The significant upfield shift (21.6 ppm) of this signal relative to F<sup>1</sup> in the spectrum of 10-acety1-1,2,4-trifluorophenoxazine (VIa), is consistent with the distribution of  $\pi$ -electron density in phenoxazine [5], as well as with the <sup>13</sup>C-NMR data of the latter compound and its N-acety1 derivative [6].

Trifluorophenoxazine, synthesized from pentafluorochlorobenzene (Ib), exhibits a <sup>19</sup>F-NMR spectrum which is very similar to that of compound (Va), which permits its structure assignment as (Vb).

The change which is observed in the relative positions of the OAr and X substituents apparently occurs at the intramolecular cyclization stage of the 2-acetylaminodiphenyl ethers (IIIa, b), i.e., formation of the phenoxazine system precedes Smiles' rearrangement. Based on general principles [7-9] which have been enunciated previously, it is assumed that attack

\*The chemical shift value for  $F^4$ , calculated for structure (IVa), is 6.0 ppm.

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		mp, °c		Fou	nd/Calc.	, %		Molecular	IR spectrum,	δ <sup>19</sup> F, ppm (rela-
Compound	Yield, %	(solvent)	C	н	CI	Ŀ	N	formula	v, cm <sup>-1</sup>	tive intensities)
(IIa)	41	48-50 hexane	<u>55,81</u> 56,07	$\frac{2,62}{2,74}$	I	$\frac{30,38}{29,55}$	5,33 $5,44$	C <sub>12</sub> H <sub>7</sub> F <sub>4</sub> NO	3410 m , 3480 m <sup>(</sup> NH <sub>2</sub> )	$7,8; 23,9 \\ (1:1)$
(q11)	13	63-66 (Petroleum ether, bp 70-	$\frac{48,94}{49,42}$	$\frac{2,15}{2,07}$	$\frac{12,24}{12,16}$	$\frac{26,51}{26,06}$	4,83	C <sub>12</sub> H <sub>6</sub> ClF <sub>4</sub> NO	3400 m , 3480 m (NH <sub>2</sub> )	9,2; 21,2 (1:1)
(IIIa)	94	100°C) 118-121 118-121 (petroleum ether, bp 70-	55.69 56,19	$\frac{3,16}{3,03}$		$\frac{25,92}{25,37}$	4.77 4,68	$C_{14}H_9F_4NO_2$	1700 s (C=0), 3440 m (NH)	$^{8,2;}_{(1:1)}$ 24,2
(q,111)	98	100°C) 122-125 (Petroleum ether bp 70-100°C)	50,84 50,39	$\frac{2,94}{2,42}$	<u>10,63</u> 11,10	22,45 22,78	$\frac{4,42}{4,20}$	C <sub>14</sub> H <sub>8</sub> CIF <sub>4</sub> NO <sub>2</sub>	1700 s (C=O) 3440 m (NH)	$\begin{array}{c} 9,6; \ 22,0\\ (1:1) \end{array}$
(Va) *	a,90 5,92	144-146 sublimation at 150°C (6 mm)	<u>61.00</u> 60.77	2.57 2,55		$\frac{24,21}{24,03}$	5,80 5,91	C <sub>12</sub> H <sub>6</sub> F <sub>3</sub> NO	3340 m (NH)	$\begin{array}{c} -2,1; \ 19,1 \ 23,0 \ (1:1:1) \end{array}$
(Vb) †	a,95 b,92	168-171 sublimation at 140°C (3 mm)	$\frac{52,63}{53,06}$	$\frac{1.67}{1.68}$	$\frac{13,22}{13,05}$	$\frac{20,64}{20,98}$	$\frac{5,43}{5,16}$	C <sub>12</sub> H <sub>5</sub> ClF <sub>3</sub> NO	(HN) <b>u</b> 0768	$egin{array}{cccc} -0.8; & 16.7; & 20.2 \ (1:1:1) \end{array}$
(VIa)	69	106–108 (EtOH)	$60,21 \\ 60,22$	$\frac{3.17}{2,89}$		$\frac{20,04}{20,41}$	5,09 5,02	$G_{14}H_8F_3NO_2$	1710 s (C=0)	19.5; 22,0; 25,2 (1:1:1)
(q IA)	61	127-130 (EtOH)	53,31 53,61	2,23	$\frac{11.35}{11,30}$	$\frac{18,51}{18,17}$	4,34 4,47	C <sub>14</sub> H <sub>7</sub> ClF <sub>3</sub> NO <sub>2</sub>	1710 s (G=0)	$\begin{array}{c} 19,2; \ 21,6; \ 22,4 \\ (1:1:1) \end{array}$

TABLE 1

$\begin{array}{c} 12.9; \ 23,0\\ (1:1) \end{array}$	12.7; 18.2 (1:1)	-1.8; 13.8 (3:2)	11,6; 21,9 (1:1)	12,2; 18,9 (1:1)	-3.7; -1.8; 12.7 (1:2:2)	.d (Н <sup>3</sup> . Јнг2 =
 3420m (NH)	3420 m (NH)	3440 m (NH)	3430 m (NH) 3620m (OH)	3430 m .(NH) 3620m (OH)	3420 m (NH) 3610 m (OH)	s (NH). 630 t.
 C <sub>13</sub> H <sub>9</sub> F4NO	C <sub>13</sub> H <sub>8</sub> ClF <sub>4</sub> NO	C <sub>13</sub> H <sub>8</sub> F <sub>5</sub> NO	C <sub>12</sub> H <sub>7</sub> F <sub>4</sub> NO	C12H6ClF4NO	C12H6F5NO	): 5.39 br.
 5,11	4.27 4,58	4,64 4,84	5.67 5,45	4,97	5,02 5,09	á. pom)
 28,35 28,02	$\frac{24,85}{24,86}$	$\frac{32,92}{32,85}$	29,11 29,55	26,07 26,06	34,34 34,52	ctrum (
	$\frac{11,21}{11,60}$			$\frac{12,05}{12,16}$		PMR spe
3,55 3,34	2,69	2,78	2,76	2.02	2,36	83).
57.48 57,37	51.65 51,08	$\frac{54.04}{53,99}$	<u>55.58</u> 56,04	49,54 49,42	52,79 52,37	315 (3,
49-51 hexane	64-66 hexane	61-62 hexane	5456 hexane	84-86 hexane	85–87 hexane	239 (4.75),
 71	67	44	52	09	59	(log ɛ):
 IIa)	(IIb)	IIc)	111a)	(q111	1111 c)	ax, nm

• 2 • 2  $J_{HF4} = 11 \text{ Hz}$ ,  $J_{HF1} = 7 \text{ Hz}$ ), 6.42-6.95 (Harom $\uparrow\lambda \text{max}$ , nm (log  $\varepsilon$ ): 242 (4.65), 317 (3.89).

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of the N atom of the acetylamino group occurs at position 1 of the fluorinated aromatic ring. The 2-hydroxydiarylamine which is formed as a result undergoes cyclization via intramolecular nucleophilic substitution of the o-F atom



The synthesis of phenoxazines based on the Smiles' rearrangement of 2-aminosubstituted diphenyl ethers has been observed often in the case of cyclization reactions carried out in strong base, and also under conditions similar to those employed here  $(K_2CO_3, DMFA)$  [8, 10, 11]. A sufficient degree of activation of the migrating aromatic ring is believed to be necessary for its (Smiles' rearrangement) occurrence. The presence of electron withdrawing fluorine atoms provides this activation in the cases reported here.

It is known that o-hydroxydiphenylamines are unreactive to Smiles' rearrangements [7, 8]. Based on this fact, we have synthesized phenoxazines (Va, b) by an independent method, according to the scheme shown below. This procedure involves the preparation of o-methoxy-diarylamines (VII) from  $O_6F_5X$  (Ia-c) and o-anisidine [12], followed by demethylation to give the o-hydroxydiarylamines (VIII), and cyclization of the latter upon heating in DMFA to generate (V).



1,2,3,4-Tetrafluorophenoxazine (Vc) prepared in this manner form  $C_6F_6$  (Ic) was identical to that described in [1]. The properties of the compounds prepared in this paper are summarized in Table 1.

The reaction demonstrated here appears to the best of our knowledge to be the first example of a Smiles' rearrangement in a polyfluoroaromatic system. The probability of its occurrence must be considered when carrying out intramolecular nucleophilic substitution reactions of fluorine as part of the synthesis of a variety of heterocycles.

#### EXPERIMENTAL

UV spectra were recorded on a Specord UV-VIs spectrophotometer for EtOH solutions; IR spectra were obtained on a UR-20 spectrophotometer for solutions in CHCl<sub>3</sub> or CCl<sub>4</sub>. PMR spectra were recorded on a Bruker HX-90 (90 MHz) spectrometer for CDCl<sub>3</sub> solutions; chemical shifts (<sup>1</sup>H) are reported on the  $\delta$  scale. <sup>19</sup>F-NMR spectra were obtained on a Varian A56/60 A (56.4 MHz) spectrometer for THF solutions. <sup>19</sup>F chemical shift values are reported in ppm from C<sub>6</sub>F<sub>6</sub>.

<u>Tetrafluoro-2-aminodiphenyl Ethers (II)</u>. A solution of 0.1 mole of (Ia, b) and 0.1 mole o-aminophenol in 100 ml of pyridine was stirred and treated with 0.15 mole of finely powdered NaOH. The mixture was refluxed for 2 h, poured into water, and neutralized with 10% HCl to pH 5-6, and then extracted with ether. The ether extract was washed with water, dried over  $CaCl_2$ , and evaporated. The residue was subjected to column chromatography on  $Al_2O_3$  (activity II) in benzene.

<u>Tetrafluoro-2-acetylaminodiphenyl Ethers (III)</u>. A mixture of 3 mmole ether (IIa, b) and 4 mmole acetyl chloride in 10 ml dry benzene was refluxed 2 h, evaporated, and the residue was washed with petroleum ether.

<u>10-Acetyltrifluorophenoxazines (VI)</u>. A mixture of 1.0 g (IIIa, b) and 1 g calcined (fused)  $K_2CO_3$  in 20 ml anhydrous DMFA was stirred for 1 h at 70-80°C, poured into water, acidified with 10% HCl, and extracted with ether. The product, isolated in a conventional manner from the ether solution, was washed with petroleum ether.

<u>Polyfluoro-2-methoxydiphenylamine (VII)</u>. A mixture of 2.7 g NaH (55% suspension in oil) and 0.05 mole o-anisidine in 60 ml dry dioxane was refluxed 1.5 h; the mixture was cooled to 80°C and treated with a solution of 0.025 mole of (Ia-c) in 10 ml of dioxane. The mixture was stirred at this temperature for 5 h.\* After being cooled, the mixture was poured onto 500 ml 1 N HCl, extracted with ether, and evaporated. The residue was dissolved in petroleum ether and passed through a column of SiO<sub>2</sub> (grade L 100/160).

<u>Polyfluoro-2-hydroxydiphenylamines (VIII)</u>. A mixture of 2.0 g (VII) and 2.0 g  $AlCl_3$  in 50 ml of dry benzene was refluxed for 2 h. The mixture was poured onto ice diluted with HCl and extracted with benzene. The product which was isolated from the benzene extract was washed with hexane.<sup>†</sup>

<u>Preparation of Polyfluorophenoxazines</u>. a) A mixture of 0.5 g (IVa, b) in 10 ml 20% HCl and 5 ml EtOH was refluxed for 2 h. The mixture was poured onto water and the precipitate was removed by filtration.

b) A mixture of 0.5 g compound (VIIIa-c) and 0.5 g calcined  $K_2CO_3$  or KF in 10 ml of dry DMFA was stirred at 80-90°C for 1 h, poured into water, and the precipitate was removed by filtration.

1,2,3,4-Tetrafluorophenoxazine (Vc), prepared in 92% yield, was identical with respect to mp and IR spectrum with a sample prepared according to [1].

#### CONCLUSIONS

1. Two methods have been described for the preparation of 1,2,4-trifluoro-3-X-phenox-azines (X = H, Cl) from pentafluoro- and pentafluorochlorobenzene.

2. Intramolecular cyclization of 2,3,5,6-tetrafluoro-4-X-2'-acetylaminodiphenyl ethers to give phenoxazine derivatives occurs with Smiles' rearrangement.

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<sup>\*</sup>In the case of (VIIb), reflux.

<sup>+</sup>Product (VIIIc) was distilled under vacuum.