Chemistry in Hydrogen Fluoride. 6. Oxidative Fluorination of Aromatic Compounds

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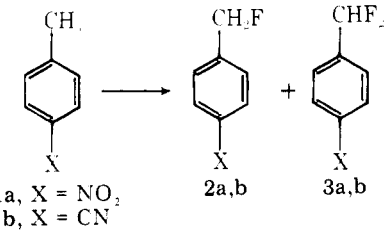
Toluene derivatives bearing electronegative substituents are fluorinated on the methyl group when reacted with lead dioxide, nickel dioxide, cobalt trifluoride, cobalt triacetate, silver difluoride, or silver(II) oxide in liquid hydrogen fluoride. For example, 4-nitrotoluene gives a mixture of 4-nitrobenzyl fluoride (**2a**) and 4-nitrobenzal fluoride (**3a**). Further reaction of **3a** with cobalt trifluoride or silver difluoride in HF results in ring fluorination. Novel 3,3,6,6-tetrafluorocyclohexa-1,4-diene derivatives are formed when acetophenone or nitrobenzene is treated with lead dioxide in HF.

The conversion of toluenes bearing electronegative substituents (nitro, cyano, carboethoxy, etc.) to the corresponding benzyl and/or benzal fluorides using lead dioxide or nickel dioxide in HF has been described.[1,2] Combined yields (not



1a, X = NO_2
b, X = CN

2a,b **3a,b** (1)

optimized) ranged from 18 to 95%. Additional substrates and reagents for this novel oxidative fluorination process are now reported.

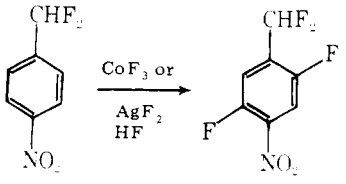
Results

Treatment of the representative substrates 4-nitrotoluene (**1a**) or 4-cyanotoluene (**1b**) with silver difluoride, silver(II) oxide, cobalt trifluoride, or cobalt triacetate in liquid HF results in fluorination of the methyl group. The results are shown in Table I.

In all cases, examination of the crude reaction mixture by fluorine NMR showed that the corresponding benzyl fluoride **2** and benzal fluoride **3** were the only fluorinated products. Varying amounts of the corresponding benzaldehyde or benzyl acetate were detected in some cases. As reported earlier, many additional oxidants including lead tetraacetate do not react with **1a** or **1b** under these conditions.

Reaction of 4-nitro-1-ethylbenzene with 3 equiv of lead dioxide in HF at 25 °C gave, in addition to the expected products **4** and **5**, the α,β-difluorinated derivative **6**. This latter product presumably arose from an HF-catalyzed elimination of HF from **4** followed by the addition of F_2 across the double bond, a known[3] reaction of PbO_2/HF.

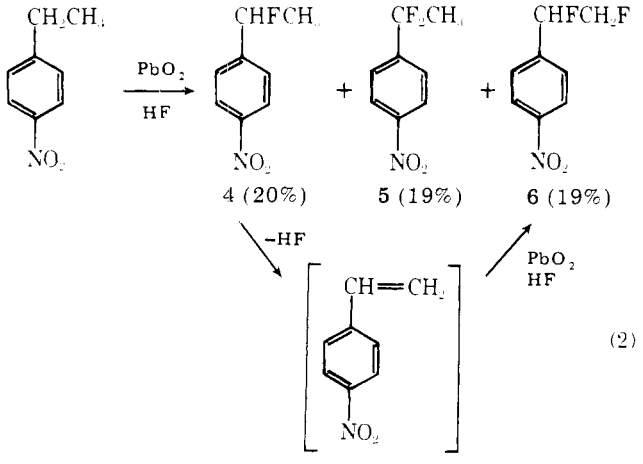
Treatment of 4-nitrobenzal fluoride (**3a**) with lead dioxide in HF at 80 °C gave only 4-nitrobenzaldehyde. However, reaction of **3a** with 2 equiv of AgF_2 or CoF_3 in liquid HF at 120 °C gave a mixture (by GLC) of 74% recovered **3a** and 26% of a new compound **7** which was isolated by preparative GLC. The elemental composition of **7** was established as



7 (3)

$C_7H_3F_4NO_2$ by mass spectroscopy. The proton decoupled fluorine NMR spectrum showed a doublet (J = 2 Hz) at −116.8 ppm (2 fluorines), a doubled triplet (J = 2 Hz, 18 Hz) at −120.7 ppm (one fluorine), and a doublet (J = 18 Hz) at −121.0 ppm (one fluorine). The proton NMR spectrum showed a one-proton triplet (J = 55 Hz) at δ 6.97 (CHF_2) and complex two proton aromatic absorption at δ 7.3–8.6. A fluorine-decoupled proton spectrum showed three singlets of equal area at δ 6.97, 7.56, and 7.83. The data establish the structure of **7** as 2,5-difluoro-4-nitrobenzal fluoride. Both the fluorine NMR spectrum and GLC analysis of the crude product showed no 4-nitrobenzotrifluoride or other fluorinated products.

The unexpected formation of **7** suggested a search for ring fluorination reactions of aromatic compounds not substituted by alkyl groups. So far, efforts to fluorinate benzene, naphthalene, phenol, or anisole in liquid HF using lead dioxide have



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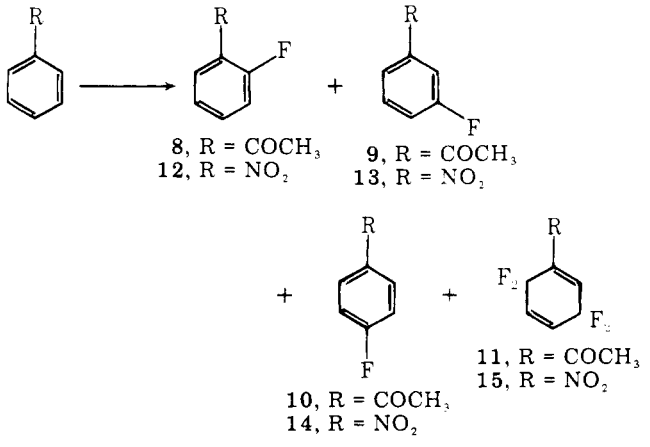

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Table I. Fluorination of 4-Nitrotoluene (1a) and 4-Cyanotoluene (1b)

substrate (mol)	oxidant (mol)	mL of HF	conditions	products[a] 1	2	3	other
1a (0.01)[e]	AgF_2 (0.02)	30	25 °C/3 h	42	51[g]	trace	
1a (0.02)	AgO (0.10)	30	80 °C/1 h	45	14		15[b,j]
1a (0.005)	AgO (0.01)	20	25 °C/3 h	65	31		
1a (0.005)	CoF_3 (0.02)	30	25 °C/17 h	0	31	59[h]	
1a (0.005)	$Co(OAc)_3$ (0.02)	30	25 °C/3 h	13	41		35[c,k]
1a (0.01)	PbO_2 (0.02)	40	25 °C/17 h	0	21	62	8[b]
1a (0.01)	NiO_2 (0.032)	40	25 °C/17 h	5	44	20	3[b]
1b (0.005)[f]	AgO (0.01)	20	0 °C/3.5 h	17	44[i]		
1b (0.005)	$Co(OAc)_3$ (0.02)	30	25 °C/3 h	26	44		22[d,l]
1b (0.01)	PbO_2 (0.03)	30	25 °C/1 h	0	67		
1b (0.01)	NiO_2 (0.03)	50	0 °C/3 h	61	19	2[m]	

[a] Percent yield by GLC analysis of distilled product mixture. [b] 4-Nitrobenzaldehyde. [c] 4-Nitrobenzyl acetate. [d] 4-Cyanobenzyl acetate. [e] Registry no. 99-99-0. [f] Registry no. 104-85-8. [g] Registry no. 500-11-8. [h] Registry no. 29848-57-5. [i] Registry no. 16473-21-5. [j] Registry no. 555-16-8. [k] Registry no. 619-90-9. [l] Registry no. 21388-95-4. [m] Registry no. 55805-10-2.

Table II. Oxidative Aromatic Ring Fluorination

substrate (g, mol)	oxidant (mol)	mL of HF	conditions	fluorine containing products (%)[a]			
acetophenone[b] (2.4, 0.02)	PbO_2 (0.04)	30	25 °C/5 h	**8**[d] (3)	**9**[f] (0)	**10**[h] (24)	**11**[j] (73)
acetophenone (2.4, 0.02)	CoF_3 (0.04)	30	25 °C/5 h	**8** (42)	**9** (5)	**10** (5)	**11** (48)
nitrobenzene[l] (4.92, 0.04)	PbO_2 (0.04)	60	50 °C/18 h	**12**[e] (3)	**13**[g] (7)	**14**[i] (40)	**15**[k] (50)

[a] Relative product percent by integration of the fluorine NMR spectrum of crude product. NMR peak assignments are (in $CDCl_3$, ppm from $CFCl_3$): **8**, −106.1; **9**, −112.7; **10**, −110.1; **11**, −95.3 and −96.8; **12**, −118.6; **13**, −109.7; **14**, −102.7; **15**, −94.3 and −101.1. [b] Registry no. 98-86-2. [c] Registry no. 98-95-3. [d] Registry no. 445-27-2. [e] Registry no. 455-36-7. [f] Registry no. 403-42-9. [g] Registry no. 69291-63-0. [h] Registry no. 1493-27-2. [i] Registry no. 402-67-5. [j] Registry no. 350-46-9. [k] Registry no. 69291-64-1.

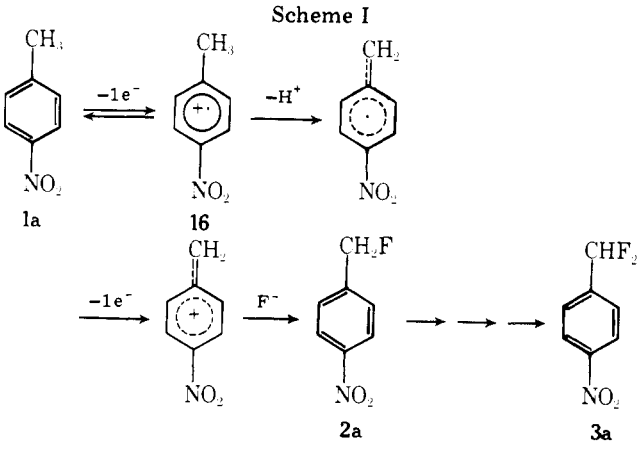
given only tars or in some cases partial recovery of the starting material. However, treatment of acetophenone with 2 equiv of lead dioxide or cobalt trifluoride in liquid HF at 25 °C gave a crude product showing several absorptions in its F NMR spectrum. Three of the absorptions could readily be assigned to the monofluoroacetophenone isomers **8**, **9**, and **10**. The remaining absorption consisted of equal area doubled doublets, proton decoupled (J = 6 Hz) at −95.3 and −96.8 ppm relative to $CFCl_3$. The relative proportions of the four fluorinated products were determined by integration of the spectrum. Results are in Table II. A preparative scale experiment (Experimental Section) using 2 equiv of lead dioxide permitted isolation in 9% yield of the compound **11**, responsible for these latter absorptions. Unreacted acetophenone (46%) was recovered. The structure of **11** was assigned as 1-acetyl-3,3,6,6-tetrafluorocyclohexa-1,4-diene on the basis of its analytical and spectroscopic properties (Experimental Section).

Similarly, nitrobenzene gave **12**, **13**, **14**, and **15** when treated with lead dioxide in HF at 50 °C (Table II). A preparative scale experiment gave **15** in about 5% isolated yield plus substantial amounts of unreacted nitrobenzene.

Discussion

The synthesis of benzyl and benzal fluorides is limited to toluenes having electronegative substituents because of the rapid polymerization of more activated benzyl fluorides in liquid HF. However, the substrates which give the highest yields (for example, **1a**, **1b**, and 4-methylbenzamide[1]) have functional groups amenable to a variety of further synthetic transformations, and this process is the only known method for the direct conversion of toluenes to their fluorinated derivatives. Lead dioxide is the reagent of choice. It is commercially available, inexpensive, and completely unreactive with HF alone. It appears to give the best yields of fluorinated products, although the yields from the various reagents have not been optimized. Cobalt trifluoride and silver difluoride are also stable in HF alone at room temperature, whereas

Scheme I



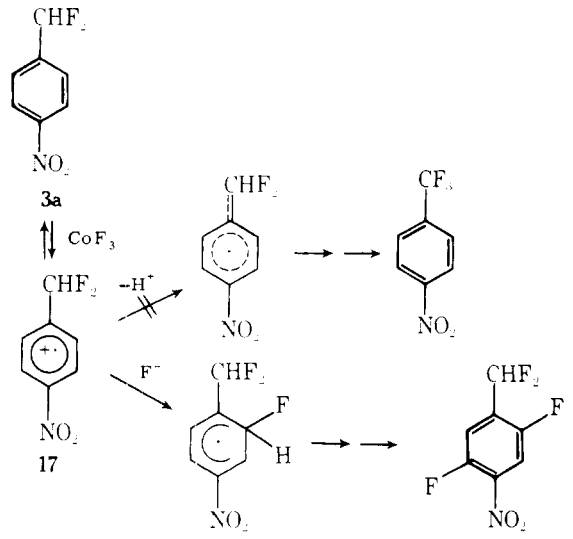
nickel dioxide, cobalt triacetate, and silver oxide lose their oxidizing ability after a short time. The decomposition of nickel dioxide, often after an induction period, occurs with vigorous gas evolution. Oxidations with this reagent are usually conducted in neutral or alkaline media.[4]

The aromatic ring fluorinations are principally of mechanistic interest (see below) although the cyclohexadiene derivatives **11** and **15** are novel examples of a little known class of compounds, the fluorine analogues of quinones.[5] Product isolation is relatively straightforward as both **11** and **15** are more volatile than their precursors.

We have previously suggested[1] a cation radical mechanism[6] (Scheme I) for the formation of the benzyl and benzal fluorides. Loss of a proton from the cation radical intermediate **16** must be faster than capture of this species by fluoride ion in order to account for the observed products.

In the reaction of **1a** with cobalt trifluoride in HF,[7] a total of four fluorine atoms can be introduced. The first two are selectively introduced on the methyl group, the second two on the aromatic ring. Ring fluorination occurs only after difluorination of the methyl group. To account for this result,

Scheme II



the process of Scheme II is proposed. A one-electron oxidation[7] of **3a** would generate the cation radical **17**. Unlike **16**, this species is reluctant to lose a proton, presumably because of the known[8] thermodynamic disadvantage which accrues to a system containing a CF_2 group when that group is converted from sp^3 to sp^2 hybridization. The radical cation **17** thus has sufficient lifetime to allow capture by fluoride ion. Orientation of the ring fluoride substitutents is exclusively para; the powerful para directing effect on a fluorine attached directly to an aromatic ring is well known.[9]

In aromatic compounds not bearing alkyl substituents, of course, only ring fluorination can result. This was, in fact, observed with acetophenone and nitrobenzene, albeit in low yield. Interestingly, only products having one or four fluorines were detected, suggesting that fluorination of the intermediate compounds must be fast. The tetrafluoride is no longer aromatic and presumably has a very high oxidation potential.

Some comment concerning the oxidizing agents appears worthwhile. The activation of metal oxidants by strong acids (e.g., trifluoroacetic acid) has been reported.[6] Additional enhancement has now been observed using HF as the solvent since neither **1a** nor nitrobenzene undergo reaction with lead dioxide or nickel dioxide in trifluoroacetic acid under conditions where significant reaction occurs in HF.[10] Clearly, exceptionally powerful oxidants must be generated from the metal species in HF in order to account for reaction with compounds as deactivated as **3a**.

The homogeneous reagent produced by dissolution of lead tetraacetate in HF[11] does not react with **1a** at 25 °C. It is apparently unable to function as a one-electron oxidant under these conditions as required by the mechanism in Scheme I. By contrast, the highly insoluble lead dioxide[12] does react with **1a** in HF at 25 °C. The heterogeneous reagent, although formally a two-electron oxidant (the inorganic product is a mixture of PbO and PbF_2 by elemental analysis), apparently can accept a single electron from **1a** into its lattice. The insolubility of lead dioxide may, in fact, be a requirement for successful reaction under these conditions. Similar comments presumably also apply to nickel dioxide, although the unstable nature of the NiO_2/HF mixture makes solubility measurements impractical. The soluble reagents which do work (the cobalt and silver salts) are one-electron oxidants.

Experimental Section

Anhydrous hydrogen fluoride was used as received from Air Products. Nickel dioxide,[13] cobalt triacetate,[14] and silver(II) oxide[15] were prepared by the indicated literature procedures and analyzed by iodometric titration immediately before use. Cobalt trifluoride (Ozark-Mahonig), silver difluoride (Ozark-Mahonig), and all other reagents were used as received. Proton NMR spectra were obtained on a Varian A-60 instrument in $CDCl_3$ with Me_4Si as internal standard. Fluorine NMR spectra were obtained on a Varian XL-100 instrument operated at 94.1 MHz using $CFCl_3$ as internal standard. Negative chemical shifts refer to signals upfield from the standard. GLC data were obtained on a Hewlett-Packard 5700A instrument.

Caution! Hydrogen fluoride is extremely corrosive to human tissue, contact resulting in painful, slow-healing burns. Laboratory work with HF should be conducted only in an efficient hood with operator wearing full face shield and protective clothing.

Procedure. The fluorination of substituted toluenes was conducted as described earlier. Conditions and results are contained in Table I. Properties of the products agree well with those previously reported.

Preparation of 1-Acetyl-3,3,6,6-tetrafluorocyclohexa-1,4-diene (11). A 200-mL Hastelloy pressure vessel was charged with 47.8 g (0.2 mol) of lead dioxide and 12.0 g (0.1 mol) of acetophenone. The vessel was closed, cooled in dry ice/acetone, evacuated, and charged with 100 g of HF. The mixture was agitated at room temperature for 4 h. The HF was removed by aspirator vacuum. The residue was triturated with 4 × 100 mL portions of methylene chloride. The combined methylene chloride solutions were treated with ~50 g of sodium fluoride powder to remove traces of HF and filtered. The filtrate was combined with that from a second identical run and concentrated on a rotary evaporator to 22.9 g of dark liquid. Distillation of the liquid through a 10-in. spinning band column of Teflon fluorocarbon resin gave 3.4 g (9%) of **11**: bp 74 °C (15 mm); ^1H NMR ($CDCl_3$) δ 2.52 (3 H, t, J = 1 Hz), 6.33 (2 H, m), 6.98 (1 H, m); F NMR (δ, $CDCl_3$) −96.77 (2 F), −95.27 (2 F). Anal. Calcd for $C_8H_6F_4O$: C, 49.48; H, 3.09; F, 39.18. Found: C, 49.73; H, 3.27; F, 38.10.

Continued distillation gave 9.1 g of recovered acetophenone.

Preparation of 1-Nitro-3,3,6,6-tetrafluorocyclohexa-1,4-diene (15). Following the above procedure, a mixture of 12.3 g (0.1 mol) of nitrobenzene, 35.9 g (0.15 mol) of lead dioxide, and 100 g of HF was agitated for 17 h at 50 °C in a pressure vessel. The combined product from two runs was distilled, as above, giving 1.8 g of faintly yellow oil, bp 89–91 °C (40 mm), identified as **15**: ^1H NMR ($CDCl_3$) δ 6.25–6.53 (2 H, m), 7.30–7.68 (1 H, m); F NMR ($CDCl_3$) δ −94.55 (2 F), −101.44 (2 F); IR (film) 3.24 (olefinic C–H), 5.98, 6.03 (C=C), 6.39 and 7.44 ($-NO_2$), 8.5–10 μm (C–F). Anal. Calcd for $C_6H_3F_4NO_2$: C, 36.56; H, 1.53; F, 38.56. Found: C, 36.41; H, 1.80; F, 36.10.

Registry No.—**4**, 64747-67-7; **5**, 32471-55-9; **6**, 74747-68-8; **7**, 69291-65-2; 4-nitro-1-ethylbenzene, 100-12-9; hydrogen fluoride, 7664-39-3.

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