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OXIDATIVE FLUORINATION OF AROMATIC COMPOUNDS IN LIQUID HYDROGEN FLUORIDE‡

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SUMMARY

Toluene derivatives bearing electronegative substituents are cleanly fluorinated on the methyl group by reaction with lead dioxide or nickel dioxide in liquid HF. For example, 4-nitrotoluene gives in high yield a mixture of 4-nitrobenzyl fluoride and 4-nitrobenzal fluoride. Aromatic cation radicals are proposed as intermediates.

INTRODUCTION

Methods for the direct conversion of C-H to CF bonds include electrochemical fluorination,[1] and reactions with high valent metal fluorides[2] such as CoF_3, elemental fluorine[3] or perchloryl fluoride.[4] In general, they require highly

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specialized equipment, are not selective[5] and tolerate few functional groups. They often result in polyfluorination of the organic molecule. In this report, a selective mono- or difluorination on the methyl group of electronegatively substituted toluenes by reaction with either lead dioxide or nickel dioxide in anhydrous liquid HF is described.

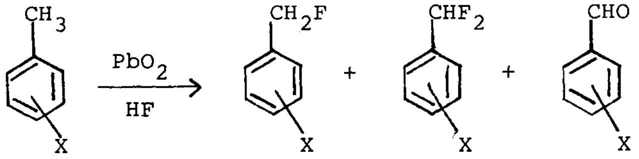
RESULTS

Moderate to good yields of benzyl (**2a-k**) and benzal fluorides (**3a-k**) were obtained from the electronegatively substituted toluenes **1a-k** on reaction with lead dioxide[6] in liquid HF at or below room temperature (Table 1). All compounds had NMR, ir and mass spectra fully in accord with the assigned structure.[7] The benzyl fluorides and benzal fluorides showed characteristic fluorine NMR signals at -211 to -217 ppm (triplet) and -112 to -115 ppm (doublet), respectively, which collapsed to singlets on proton decoupling. In all cases, fluorine NMR spectra of the crude reaction mixtures showed that **2** and **3** accounted for at least 95% of the fluorinated products. In addition to **2** and **3**, small amounts of the corresponding aldehydes **4** were isolated in some cases. Reaction of **1a** with PbO_2/HF at

80° for several hours afforded only **4a**. The aldehydes probably derive from hydrolysis of the benzal fluorides by water generated in the reaction.

Toluene, 4-chlorotoluene and 4-*tert*-butyltoluene were rapidly consumed under the reaction conditions but no fluorinated products were isolated. This is presumably due to HF-catalyzed polymerization of benzyl fluoride and its activated derivatives. *p*-Methylaniline and 4-picoline failed to react.

Using 4-nitrotoluene (**1a**) as the standard substrate, a number of common oxidants were screened for their ability to cause the oxidative fluorination in HF at 25°. In addition to lead dioxide, nickel dioxide[8] was



1a-k **2a-k** **3a-k** **4a-k**

a, X = *p*-NO_2
b, X = *o*-NO_2
c, X = *m*-NO_2
d, X = *p*-CN
e, X = *p*-CHO
f, X = *p*COOH
g, X = *p*-CO_2CH_3
h, X = *p*-COPh
i, X = *p*-$CONH_2$
j, X = *p*-SO_2OCH_3
k, X = 3,4-di-NO_2

was active, while red lead oxide, lead tetra-acetate, cobalt(III) oxide, cerium dioxide, mercuric oxide,[9] thallium trioxide, vanadium

TABLE 1

Reaction of substituted toluenes with PbO_2 or NiO_2 in HF

Substrate (mmol)	Oxidant (mmol)	Conditions	Yield[a] % **2**	**3**	**4**
1a (10)	PbO_2 (20)	25°, 17 h	16	47	6
1a (60)	" (220)	46°, 17 h	-	67	-
1a (10)	" (10)	25°, 4 h	84	11	-
1b (10)	" (30)	25°, 5 h	-	40	-
1c (80)	" (250)	25°, 17 h	13	2	23
1d (10)	" (30)	25°, 1 h	-	46	-
1e (20)	" (60)	0°, 2 h	-	29	5
1f (10)	" (30)	25°, 3 h	-	60	-
1g (10)	" (30)	0°, 1 h	-	18	-
1h (10)	" (30)	25°, 1 h	28[b]	39[b]	-
1i (10)	" (30)	0°, 1 h	88	9	-
1i (10)	" (30)	25°, 2 h	51	46	-
1j (10)	" (30)	0°, 3 h	25	31	-
1k (10)	" (30)	25°, 1 h	75[c]	-	-
1a (10)	NiO_2 (30)	25°, 18 h	44	22	3
1d (10)	NiO_2 (30)	0°, 3 h	48	5	-

a. By glpc analysis of distilled product mixture, unless otherwise indicated.

b. Isolated by silica gel chromatography: **2h** m.p. 71.5-73°, m/e = 232.0707 (calcd. 232.0699); **3h**, oil, m/e = 214.0807 (calcd. 214.0793).

c. Recrystallized from CCl_4, m.p. 37.5-38.5° m/e = 218.0149 (calcd. 218.0139).

pentoxide, vanadium(V) oxyfluoride, potassium permanganate, selenium dioxide, potassium bromate, bromine, potassium persulfate, antimony pentafluoride, palladium diacetate or ozone either failed to react or gave unfluorinated products.

4-Nitrotoluene-α-D_3 was prepared by nitration of toluene α-D_3 with sodium nitrate in trifluoroacetic acid followed by separation of the isomers by preparative glpc. A deuterium isotope effect (k_{CH_3}/k_{CD_3}) for the reaction of **1a** with lead dioxide in HF at 0° was measured by allowing a mixture of **1a** and **1a**-αD_3 to compete for limited PbO_2. Samples of the starting mixture and recovered starting material were analyzed for deuterium content by mass spectroscopy. Molar percent conversion was measured by glpc with correction for detector response. The ratio k_{CH_3}/k_{CD_3} was calculated from the data in Table 2 giving values of +4.77 and +4.81 in two separate measurements. Fluorine NMR of the crude product mixtures showed a triplet (J = 47 Hz, $-CH_2F$) at -216.23 ppm and a quintet (J = 7.5 Hz, $-CD_2F$) at -217.16 ppm as the only detectable absorptions. A control experiment using pure 1a-αD_3 indicated the absence of hydrogen-deuterium exchange under the reaction conditions.

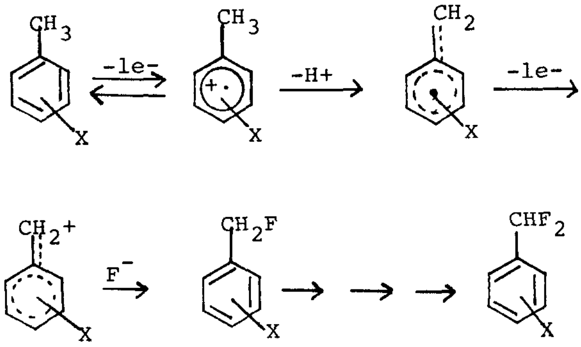
TABLE 2

Reaction of **1a** and **1a**-αD_3 with PbO_2 in HF

Exp	Conversion %	Starting Mixture % D_3	Recovered Starting Material % D_3
1	36	67.5	83.1
2	38	66.8	83.6

DISCUSSION

The mechanism of this novel fluorination process has not been studied in detail. However, the general area of oxidative substitution reactions of aromatic compounds has been extensively investigated.[10] The involvement of aromatic cation radical intermediates is well documented, especially in cases where side chain substitution is observed. In the present case, it is tempting to write an analogous mechanism for the formation of the benzyl and benzal fluorides[11] (Eq. 2). The deuterium isotope effect is in line with earlier studies[12] on the side chain oxidation of toluene and suggests a reversible oxidation followed by a rate limiting proton loss from the cation radical intermediate.



(Eq. 2)

HF is important as a source of fluoride ion and as an activator for the oxidant. Lead dioxide, for example, does not react with **1a** under more weakly acid conditions, such as in trifluoroacetic acid. Clearly, an exceptionally powerful electrophile is generated by the combination of lead dioxide and liquid hydrogen fluoride to oxidize such highly deactivated compounds as dinitro derivative **1k**.

Mechanisms other than Equation 2 can be written and details of the process, especially the nature of the oxidant, remain obscure. Nevertheless, this work demonstrates, in principle, that organic compounds can be directly and selectively fluorinated under exceptionally mild conditions.

EXPERIMENTAL

Anhydrous hydrogen fluoride was used as received from Air Products. Nickel dioxide, prepared by a literature procedure,[8] was standardized by iodometric titration immediately before use. All other reagents were commercial samples, used as received. Proton NMR spectra were obtained on a Varian A-60 instrument in $CDCl_3$ with TMS 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. Glpc data was obtained on a Hewlett-Packard 5700A instrument using a 6 ft X 1/8 in 10% UCW-982 or a 10 ft X 1/4 in 10% SE-30 column. Gas chromatography/mass spectroscopy (gc/ms) data was obtained on a Du Pont 21490 instrument equipped with a VG 2040 data system.

Procedure

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.

Reactions at room temperature or below were run in a 200 ml Kel-F® vessel attached to a vacuum line constructed from Kel-F® and Teflon®. Reactions at higher temperatures were run in Hastelloy shaker tubes. In general, the organic substrate, oxidant and cosolvent, if any, were introduced into the reaction vessel which was closed, evacuated and cooled in dry ice/acetone or liquid N_2. The required amount of HF was distilled into the vessel from a commercial cylinder. The resulting mixture was raised to the reaction temperature and agitated for the required time period (cf Table 1). The HF was removed by water aspirator. The residue in the vessel was triturated with several portions of organic solvent (usually CH_2Cl_2). The organic solution was either treated with sodium fluoride powder or washed with dilute aqueous sodium bicarbonate to remove traces of HF. The solvent was removed on a rotary evaporator to give the crude product. After preliminary purification, it was analyzed, usually as a mixture of benzyl and benzal fluoride, by a combination of glpc, gc/ms, and proton and fluorine NMR spectroscopy. The results are contained in Table 1. The properties of the products agreed well with those previously reported[7]. A representative example of the procedure is given below. The highly reactive nature of NiO_2 necessitated the use of a somewhat different procedure as illustrated in the second example given below.

Preparation of 4-Nitrobenzalfluoride

A 360 ml Hastelloy bomb tube was charged with 8.2 g (0.06 mole) of 4-nitrotoluene and 52.0 g (0.22 mole) of lead dioxide. The bomb was cooled in dry ice/acetone, evacuated, and charged with 150 g of hydrogen fluoride. The was agitated for 17 h with an inside temperature of 30-46°. The hydrogen fluoride was removed using an aspirator. The residue was triturated with five 100-ml portions of methylene chloride. The combined methylene chloride solutions were treated with NaF powder to remove traces of HF, filtered and concentrated on a rotary evaporator.

The residue was distilled to give 7.0 g (67%) of 4-nitrobenzal fluoride, b.p. 83° (1.9 mm), proton NMR (δ) 6.93 (t, J = 57 Hz, 1H); 8.18 (q, 4H); fluorine NMR (δ) -113.4 (d, J = 57 Hz).

Reaction of 4-Nitrotoluene with NiO_2 in HF

A 200 ml Kel-F® vessel was charged with 1.37 g (0.010 mole) of 4-nitrotoluene. The vessel was evacuated, cooled in liquid N_2 and charged with 50 ml of hydrogen fluoride by vacuum transfer from a commercial cyclinder. The vessel was connected by a T-tube and mercury bubbler to a source of dry nitrogen and immersed in a dry ice/acetone bath. Nickel dioxide (8.0 g, activity 3.96 X 10^{-3} g-atom O_2/g by iodometric titration (0.032 mole)) was added in several portions over 15 min to the vigorously stirred HF solution. The resulting mixture was allowed to warm to room temperature. After 18 h, the HF was removed on the aspirator. The residue was slurried with 5 X 75 ml of methylene chloride and quickly filtered through a sintered glass funnel. The filtrate was treated with NaF powder for 1 h, filtered and concentrated on a rotary evaporator to 1.52 g of dark oil. Vapor bath distillation at 1 mm using xylene as the heating fluid gave 1.2 g of light yellow oil. Glpc analysis (6 ft X 1/8 in 10% UCW982 column, He carrier gas at 40 ml/min, oven temperature = 125°) showed three components, identified by comparison with authentic samples as p-nitrobenzal fluoride (39%), p-nitrobenzyl fluoride (60%), p-nitrobenzaldehyde (6%).

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