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A NOVEL SYNTHESIS OF FLUOROAROMATICS

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In contrast to other halogenation techniques, methods for the selective introduction of fluorine into unsubstituted positions of aromatic species are scarce. Direct fluorination usually involves highly reactive species that do not offer convenience of handling; i.e., elemental fluorine,[1,2] inert gas fluorides,[3] or high valent metal fluorides.[1] A recent report by Taylor and co-workers[4] describes thallation of selected aromatic species followed by fluorine introduction. In addition, other investigators have reported the reaction of arylhydroxylamines with anhydrous hydrogen fluoride, giving moderate yields of p-fluoroanilines.[5,6] This is analogous to rearrangements involving other hydrogen halides studied earlier by Bamberger.[7] The arylhydroxylamine procedure is inconvenient because of the concomitant formation of the corresponding unfluorinated aniline, as well as the symetrical azo and azoxy compounds. Considerable tar is formed rendering product isolation difficult. Because of closeness of boiling points, separation of the fluorinated and non-fluorinated anilines is quite difficult.

We wish to report a new method for the introduction of a single fluorine into an unsubstituted aromatic position. It has been our observation that aromatic azides in neutral solvents react smoothly with anhydrous hydrogen fluoride to afford good yields of p-fluoroanilines. This reaction type was also reported by Bamberger for other hydrogen halides.[7] Of particular interest is the fact that while Bamberger reported both ortho and para attack with other hydrogen halides, we observe strictly para attack with hydrogen fluoride. It has been suggested that the Bamberger rearrangement proceeds via a nitrenium ion whether arylhydroxylamine or arylazide serves as precursor.[8]

The azide procedure, in contrast to the arylhydroxylamine method, provides clean monofluorinated products. Overall yields range between 45-72% (purified) and most functional groups are readily tolerated; e.g., alkyl, halogen, alkoxy, acyl, cyano, and trifluoromethyl. Steric considerations do not appear to be critical, although solvent choice is of utmost importance. To date, the only satisfactory solvents have been inert and non-basic relative to HF. For example, alkanes, cycloalkanes, and halogenated hydrocarbons are satisfactory, whereas aromatics, ethers, acetic acid and alcohols are unsatisfactory. As described below the potentially hazardous azides are formed in situ and need not be isolated. The reaction sequence of aryl amine → [diazonium salt in water] → [aryl azide in organic medium] → p-fluoroarylamine is easily carried out in a few hours in what is essentially a one-step operation.

A typical procedure involves treating a cold, two-phase mixture of aryl diazonium salt in water (prepared in situ from the aniline) and n-hexane with a solution of sodium azide in water. The azide as it forms is extracted into the hexane layer which after two hours is

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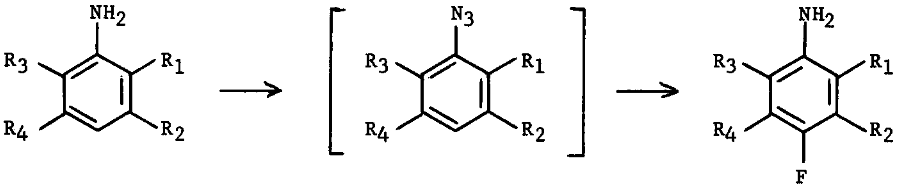
separated and charged to a plastic vessel containing excess anhydrous hydrogen fluoride. After four hours the reaction is quenched and rendered alkaline, and the fluoraniline isolated by extraction and purified by either distillation or crystallization (see Table).



In conclusion, we feel we have developed a valuable and needed technique for the selective introduction of fluorine into aromatic substrates.

Substituted Aniline Substrate				Overall Yield of p-F-Aniline (purified)
R_1	R_2	R_3	R_4	
H	H	H	H	52% (B.P. 88-90°C at 40 mm)
CH_3	H	CH_3	H	54% (B.P. 139-141°C at 40 mm)
H	CH_3	H	CH_3	60% (B.P. 127-130°C at 40 mm)
Cl	H	H	H	54% (B.P. 120-122°C at 40 mm)
F	H	H	H	72% (B.P. 90-92°C at 40 mm)
H	CN	H	H	53% (M.P. 88-89°C)
H	$\overset{O}{\overset{\parallel}{C}}CH_3$	H	H	70% (M.P. 68-70°C)
H	OCH_3	H	H	53% (B.P. 150-152°C at 40 mm)
CF_3	H	H	H	45% (B.P. 89-90°C at 40 mm)

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9. Satisfactory microanalyses have been obtained for all reported fluoroanilines. In addition, infrared, ^1H NMR and ^{19}F NMR spectra are in good accord with the assigned structures. No attempts have been made to optimize yields and the only by-products observed were non-volatile materials.