An Unexpected Route to Fluorinated Anisoles

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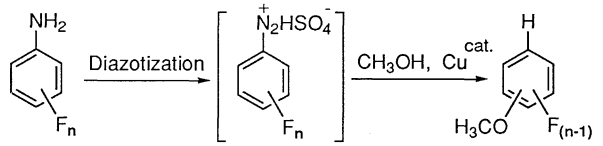
We found a new one-pot procedure for the synthesis of polyfluoroanisoles from polyfluoroanilines. The reaction involves aromatic nucleophilic substitution of *o*- or *p*-fluorine of benzenediazonium salt with methoxy group followed by reductive removal of the diazonium group.

Recently fluorophenols have been used in pharmaceutical and agricultural chemistry as principal materials, but a synthesis of them is not easy by known methods.[1] In particular a synthesis of meta-fluorophenols starting from phenols is difficult because fluorination of phenols gives predominantly *o*- and *p*-fluorophenols. We wish to disclose here a new one-pot procedure for the synthesis of *m*-fluoroanisoles, which can be converted to fluorophenols, starting from polyfluoroanilines via the diazonium salt (Scheme 1).



1 2 3

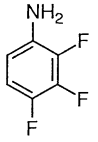
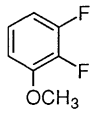
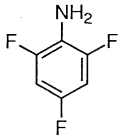
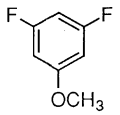
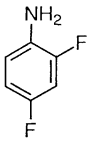
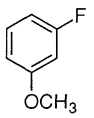
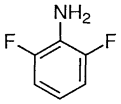
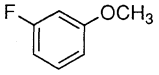
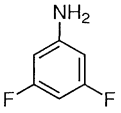
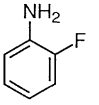
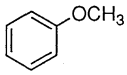
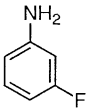
Scheme 1.

Diazotization of 2,6-difluoroaniline in 50% sulfuric acid and stirring with a large excess of methanol and a catalytic amount of copper powder at 20 °C afforded 56% of 3-fluoro-anisole.[2] The structure of the product was identified by comparison of its ^1H and ^{19}F NMR spectrum with those of authentic samples, and the yield was determined by gas chromatography and NMR.

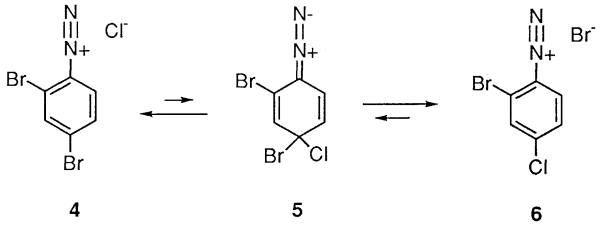
The reaction was extended to other fluorinated anilines and the results are shown in Table 1. Fluorine in para- to the diazonium group was substituted preferentially (entries 1-3); *o*-fluorine became involved in the reaction only in the absence of *p*-fluorine (entries 4 and 6). *m*-Fluoroanilines did not afford the corresponding anisoles presumably because *m*-fluorine group in the diazonium group was less reactive (entries 5 and 7). The yields of the fluoroanisoles are good to moderate with a sharp decrease for *o*-fluorobenzenediazonium ion (entry 6). It is noted that products driven from exchange of two fluorines by methoxy were not isolated, suggesting that the first methoxy group deactivates further substitution.

Electron-attracting substituents increase the inclination of aryl halides to nucleophilic substitution.[3] The determination of N-terminal amino acids in peptides and proteins by reaction with 2,4-dinitrofluorobenzene[4] is a popular example. The diazonium cation exceeds the nitro group in the electron-withdrawing effect. The observation by Hantzsch that 2,4-dibromoaniline on diazotization in hydrochloric acid gives rise to 2-bromo-4-chlorobenzenediazonium salt (Scheme 2) is nearly a hundred years old;[5] **5** is the suspected additive intermediate. On treating

Table 1. Conversions of Fluorinated Anilines into Fluorinated Anisoles

Entry	Aniline **1**	Conditions	Anisole **3**	%Yield[a]
1		20 °C, 30 min		78 (80)
2		20 °C, 30 min		68 (78)
3		20 °C, 2 h		60 (75)
4		20 °C, 2 h		56
5		20 °C, 2 h		0
6		50 °C, 2 h		8
7		50 °C, 2 h		0

[a]The yields refer to methanol as reducing agent (Note 2), those in brackets to reduction with hypophosphorous acid (Note 9).

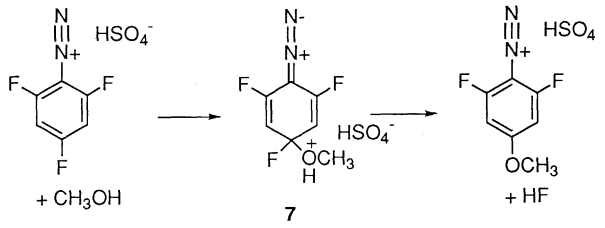


4 5 6

Scheme 2.

2,4,6- tribromobenzenediazonium chloride with high hydrogen chloride concentration, all three bromine atoms are replaced by chlorine. The rate of exchange of fluorine by methoxy in the reaction of 4-substituted fluorobenzenes with CH_3O^- / CH_3OH at 0 °C is for R = N_2^+ 300000 times faster than for R = NO_2.[6]

Fluorine substitution increases the electron deficiency of the benzenediazonium ion. As formulated for one of our examples, methanol (not methoxide) is sufficiently active for attack at 20 °C; **7** is the supposed intermediate which loses H^+ and F^- (Scheme 3).



Scheme 3.

In the reaction of aromatic diazonium salts with alcohols, reductive N_2 elimination competes with the formation of aryl ethers. Substitution by halogen or nitro groups promotes the reduction which is a radical chain reaction; frequently, copper catalysis was observed.[7,8] Ethanol is superior to methanol as a reducing reagent. Nevertheless, 2,4,6-tribromobenzenediazonium salt is reduced by methanol, tribromobenzene being formed.

Hypophosphorus acid is the reagent of choice for the replacement of the diazonium group by hydrogen.[7] Indeed, we could increase the yield of polyfluoroanisoles when the solution of the diazonium salt was first treated with methanol (30 min, 30 °C) and then with hypophosphorous acid (2 h, 20 °C),[9] as shown in Table 1.

Although nucleophilic substitution of diazonium salt had been studied,[5] its application to organic synthesis has not been reported. This report is the first example of the preparation of fluoro-anisoles by use of diazonium ion as an efficient activator for the aromatic nucleophilic substitution.

In conclusion, we found a new method for the preparation of fluorinated anisoles from polyfluoroanilines. The reaction is of particular value for the synthesis of 3-fluoroanisoles.

References and Notes

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2 In a typical procedure, 2,6-difluoroaniline (10 g, 77 mmol) was diazotized in 50% sulfuric acid (20 g, 100 mmol H_2SO_4) by using nitrosyl hydrogen sulfate prepared from conc. H_2SO_4 (40 g, 410 mmol) and $NaNO_2$ (5.88 g, 85 mmol). After the solution was being stirred at 30 °C or below, methanol (200 g, 6.24 mol) and copper powder (0.10 g, 16 mmol) were added. After the stirring was continued for 2 h at 20 °C, water (100 ml) was added to stop the reaction. And the mixture was extracted with dichloromethane (100 ml). In the concentrated organic phase, 3-fluoroanisole was analyzed by GC and NMR to determine the yield.

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7 N. Kornblum, *Org. Reactions*, **2**, 262 (1944).

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9 An example is described: The diazotization as in Note 2 is followed by addition of CH_3OH (200 g, 6.24 mol) and stirring for 30 min at 30 °C. Then 50% H_3PO_2 (10.2 g, 77 mmol) and Cu powder (0.1 g) were added and stirred for 2 h at 20 °C. Work-up as in Note 2.