Journal of Fluorine Chemistry, 51 (1991) 299–304

Received: October 4, 1990; accepted: December 12, 1990

PRELIMINARY NOTE

The Preparation of p-Fluorophenols from p-Aminophenols: Diazotization and Fluorodediazoniation in Pyridine-HF.

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SUMMARY

A facile preparation of p-fluorophenols is described by the diazotization of p-aminophenols and fluorodediazoniation in situ using HF in a pyridine solution (Pyridine-HF) under carefully controlled conditions.

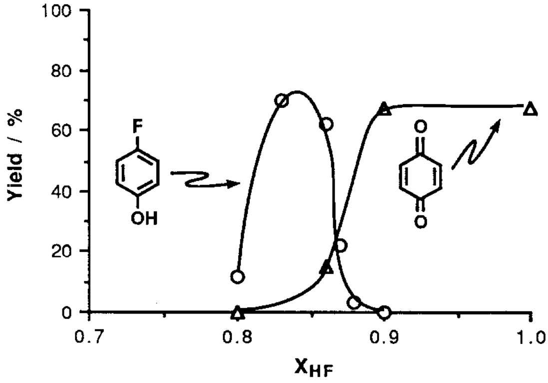
p-Fluorophenols can be expected to be useful intermediates for medical and agricultural chemicals [1]. The Balz-Schiemann reaction, fluorodediazoniation of arene diazonium tetrafluoroborates, is one of the most convenient and practical methods available for controlled, regio specific introduction of fluorine into aromatic rings [2]. However, attempts to prepare p-hydroxybenzene diazonium tetrafluoroborate were reported to fail under the usual conditions [3]. The corresponding diazonium fluorosilicate salt was produced in good yields, but only gave p-fluorophenol in 5% yield by its thermal decomposition [4]. On the other hand, quinonediazide dimer was obtained in the reaction of p-aminophenol with $NaNO_2$ using HBF_4, and decomposed to produce p-fluorophenol at 136 °C in a yield of 32% based on the starting p-aminophenol [5].

We report here on a facile preparation of p-fluorophenols by a one-pot diazotization of p-aminophenols with $NaNO_2$, followed by the thermal treatment of the reaction mixture in Pyridine-HF (fluorodediazoniation).

0022-1139/91/$3.50

To p-aminophenol (5 mmol) in Pyridine-HF (HF:450 mmol) in a 100 ml **FEP* reactor** equipped with a reflux condenser, a solution of $NaNO_2$ (5.1 mmol) in Pyridine-HF (HF:450 mmol) prepared at -78 °C was cautiously added dropwise at the desired temperatures, of which values are shown in Fig. 2, for 30 min under stirring [Stage A]. Then, to decompose the reaction mixture, the temperature was raised to 20-140 °C for 30 min in an oil bath under stirring [Stage B]. The resultant solution was quenched with ice-water,and the products were extracted with ether and washed with aqueous NaCl to remove pyridine. After neutralizing the ether layer with $NaHCO_3$ and drying over $MgSO_4$, the products were identified by ordinary spectroscopic methods.

As shown in Fig. 1, when the solution was heated at 20-100 °C for 30 min having been prepared at Stage A under the conditions of -50 °C for 30 min in the presence of Pyridine-HF having HF mole fractions(X_{HF}) of more than 0.9 a considerable amount of benzoquinone was produced with no formation of p-fluorophenol. When heating was carried out for the solution of Pyridine-HF with X_{HF}=0.9 at 140 °C, however, it gave a considerable amount of tarry matter. On the other hand, when the heating was carried out at 20-100 °C for the solution which



Condts. at Stage A:
Substrate, 5 mmol;
HF, 900 mmol;
$NaNO_2$, 5.1 mmol.;
Temp., -50 °C for 30 min.
Condts. at Stage B:
○ Temp., 140 °C for 1 h;
△ Temp., 20~100 °C for 30 min.

Fig. 1. Effects of HF Mole Fractions in Pyridine-HF at Stage A and Temperature at Stage B on the Reaction of 4-Aminophenol.

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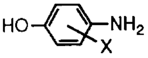
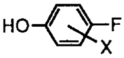
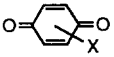
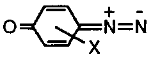
* FEP stands for tetrafluoroethylene-hexafluoropropylene copolymer and is commercially available.

was prepared by the use of Pyridine-HF with X_{HF}=0.86-0.83 at Stage A, a lesser amount of benzoquinone was formed than that in the reaction using Pyridine-HF with X_{HF}=0.9. When such solutions were heated at 140 °C, p-fluorophenol was obtained in fairly good yields. However, the yield of p-fluorophenol decreased remarkably with the increasing amount of pyridine in HF at Stage A.

TABLE 1

Diazotization and Dediazoniation of Aminophenols in Pyridine-HF (X_{HF}=0.86)

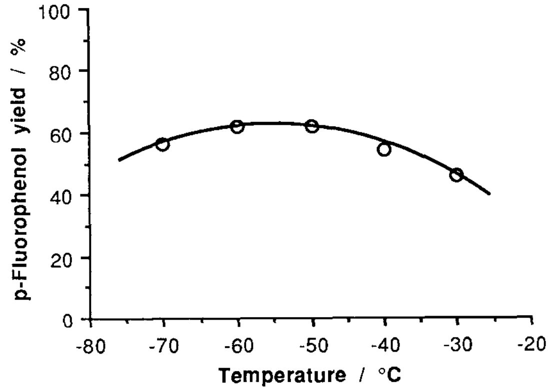
Substrate	React. Temp./°C[a]	Product Distributions/%[b]		
 X:				
H	20-120	0	80	0
H	140	72	0	0
2-CH_3	100	0	85	0
2-CH_3	140	80	0	0
3-CH_3	100	0	85	0
3-CH_3	140	82	0	0
2-CO_2H	20	0	0	90
2-CO_2H	140	85	0	0
3-CO_2H	20	0	0	0
3-CO_2H	140	0	0	0
2-NO_2	20	0	0	51
2-NO_2	140	44	0	0
3-NO_2	20	0	0	0
3-NO_2	140	0	0	0

[a] Dediazoniation time, 60 min.; Diazotization temp., -50 °C for 30 min.; Substrate, 5 mmol; HF, 100 mmol; $NaNO_2$, 5.1 mmol.

[b] Isolated yields based on substrate.

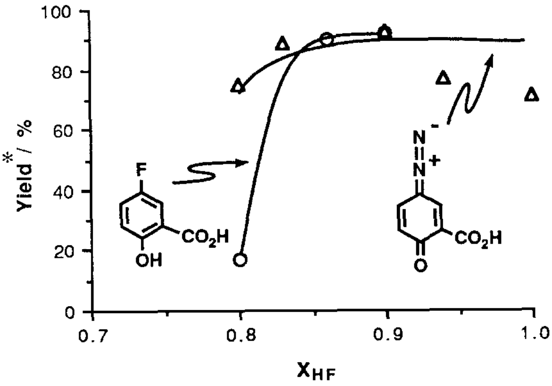
Similar results were observed in the reaction of 4-aminomethylphenols to produce the corresponding fluorophenols in good yields as shown in Table 1.

It is worth noting that the temperature at Stage A influenced the yield of p-fluorophenol as shown in Fig. 2.



Condts. at Stage A:
Substrate, 5 mmol;
$NaNO_2$, 5.1 mmol;
HF-Pyridine, X_{HF}=0.86;
HF, 900 mmol;
Time, 30 min.
Condts. at Stage B:
Temp., 140 °C for 1 h.

Fig. 2. Effect of Temperature at Stage A on the Reaction of 4-Aminophenol.



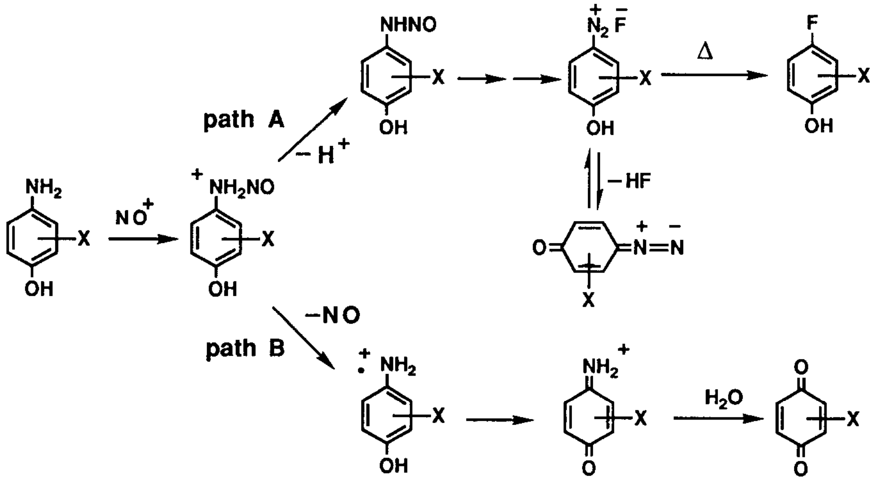
Condts. at Stage A:
Substrate, 5 mmol;
$NaNO_2$, 5.1 mmol;
HF, 900 mmol;
Temp., -50 °C for 30 min.
Condts. at Stage B:
○ Temp., 140 °C for 1 h;
△ Temp., 20 °C for 30 min.
*) Isolated yield

Fig. 3. Effects of X_{HF} in Pyridine-HF at Stage A and Temperature at Stage B on the Reaction of 2-Carboxyl-4-aminophenol.

On the other hand, as shown in Fig. 3, when 2-carboxy-4-aminophenol was treated with $NaNO_2$ in Pyridine-HF and then decomposed at 20 °C for 30 min, the corresponding quinonediazide was obtained in good yields without the formation of any other compounds such as benzoquinones. However, when such solutions were heated at 140 °C for 1 h and then quenched with water, 2-carboxy-4-fluorophenol was obtained in good yields. Similar results were observed in the reaction of 2-nitro-4-aminophenol as seen in Table 1. Increased amounts of pyridine in HF decreased the yields of the corresponding fluorophenols as was observed in the reactions of p-aminophenol or 4-aminomethylphenols. 3-Carboxy-4-aminophenol did not undergo reactions to give these types of products under the conditions employed, whilst 3-nitro-4-aminophenol gave a considerable amount of tarry materials at 100 °C in Stage B.

Quinonediazide dimer tetrafluoroborate salt was prepared in white crystalline form in good yield by the Danek method [5]. When the decomposition of this salt was carried out at 140 °C in Pyridine-HF with X_{HF}=0.86-0.83, p-fluorophenol was obtained in 180% yield based on the salt, corresponding to more than 80% yield based on p-aminophenol. This evidence indicates that quinonediazide may be a synthon of the diazonium salt derived from the p-aminophenol.

Judging from these experimental results, diazotization of p-aminophenols and dediazoniation <u>in situ</u> using HF-Pyridine may be illustrated as shown in the following Scheme.



Scheme.

The yield of p-fluorophenols is greatly dependent on the rate of diazotization of the corresponding p-aminophenols (Stage A). For the diazotization of p-aminophenols to proceed, namely **path A** to give N-nitrosoaminophenols by the deprotonation of the initially formed N-nitrosoanilinium cation, the composition of HF-Pyridine and the temperature must be controlled carefully. Otherwise, **path B** is followed to form a radical cation by the generation of nitrogen monoxide (NO) from the initially formed N-nitrosoanilinium cation [6], which in turn gives benzoquinone by subsequent hydrolysis. Electron-withdrawing substituents such as carboxyl or nitro groups at the 2-position in aminophenols favors **path A** to form the corresponding quinonediazide. Fluorodediazoniation of these diazonium salts or quinonediazides, once formed, takes place readily in HF-Pyridine at 140 °C to afford the corresponding fluorophenols. Unsuccessful results observed in the reaction of 3-carboxyl- and 3-nitro-4-aminophenol are due possibly to intramolecular competition for the intermediate which formed in the course of diazotization of the substrate.

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