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Preparation of Fluoroarenes in One-Pot Diazotization and Fluoro-Dediazoniation of Aminoarenes Using HF or HF-Base. The Functions of Bases in the HF Solution

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In a one-pot diazotization of anilines followed by fluoro-dediazoniation in situ using HF or HF with bases (HF-Base) as a solvent, the diazotization stage has been found to play the most important part to yield fluoroarenes effectively. Diazotization of anilines was greatly influenced by the composition of the HF solution, and greatly enhanced by employing appropriate amounts of bases, such as pyridine. On the other hand, fluoro-dediazoniation of diazonium salts, once formed, took place very readily in HF or HF-Base to produce fluoroarenes in high yield, although such bases served to slow down the rate of decomposition of diazonium salts to some extent.

Although fluoroarenes appear in a broad variety of molecules, many difficulties arise regarding the methods for introducing a fluorine atom into the aromatic nuclei effeciently and in high yield.[1] The Balz–Schiemann reaction, fluoro-dediazoniation of arenediazonium tetrafluoroborate salts derived from anilines, is known to be the most convenient and practical method available for controlled, a regiospecific introduction of fluorine into aromatic rings.[2,3] However, this procedure is somewhat troublesome, and the reproducibility for the yields of the desired fluoroarenes is at times invariably poor. A few attempts have been made to improve such a conventional two-step process using anhydrous hydrogen fluoride (HF) providing a convenient one-pot diazotization and fluoro-dediazoniation of anilines affording fluoroarenes in fairly good yields.[4–6] Even in such a convenient procedure, however, the yield of fluoroarenes was greatly influenced by a substituent on the aromatic nucleus, and tarry matter was at times formed in considerable amounts to render it difficult to apply this method satisfactorily for technical production.[7]

Recently, this procedure has been greatly improved to produce fluoroarenes in high yields while depressing the formation of undesirable tarry matter by the use of HF with bases (HF-Base).[8–11] The reaction can be postulated to be an initial formation of arenediazonium species (diazotization step) and its subsequent decomposition (fluoro-dediazoniation step) in situ in the HF solution. The acidity of the reaction media should influence both the diazotization rate of anilines,[12–14] and fluoro-dediazoniation of arenediazonium ions. So far, the dediazoniation step has been regarded as being very important for improving the yield of fluoroarenes and to suppress any undesirable products, such as tarry matter, in such a one-pot procedure.[6,10] However, there are still questionable problems regarding the formation of tarry matter, and the factors for obtaining fluoroarenes in high yield in such a one-pot procedure in an HF solution.

In this paper, discussions are focussed on one-pot diazotization and the fluoro-dediazoniation of aniline or *p*-toluidine and the fluoro-dediazoniation of benzenediazonium salt (tetrafluoroborate) using the HF solution to clarify this subject.

Experimental

A solution of anilines (aniline or *p*-toluidine) and $NaNO_2$ in HF or HF with pyridine (HF·Pyr), of which quantities are shown in Figs. 1—3 and Tables 1 and 2, was prepared at lower than −50 °C in a 100 ml FEP[15] made reactor equipped with a reflux condenser and/or a cooled trap. Then, the temperature of the solution was raised to room temperature (Stage [A]) and maintained at this temperature for 30 min or longer. The reaction mixture was then heated to the prescribed temperatures (55—90 °C) for 30 min or longer in an oil bath under stirring (Stage [B]). Next the mixture was quenched with ice-water, and the products extracted with CH_2Cl_2. The products thus obtained were indentified by ordinary spectroscopic methods. The NMR spectra of the reaction mixtures of *p*-toluidine were taken on a Bruker MSL 400 NMR spectrometer using a tube made of FEP (3ϕ) inserted in the usual NMR sample tube (5ϕ) with TMS as the external standard. Benzenediazonium tetrafluoroborate was prepared according to Starkey's methods.[16]

Results and Discussion

Reactions of Anilines in HF. The reactions of aniline and *p*-toluidine in HF using a one-pot procedure were always accompanied by the formation of tarry matter. As shown in Fig. 1, the yield of the corresponding fluoroarenes increased remarkably upon decreasing molar ratio of HF/anilines in the reaction of aniline and *p*-toluidine. However, the increasing use of anilines brought about difficulty in dissolving $NaNO_2$ in HF. The amount of the highest limit of anilines which enables the reaction to procced smoothly was found to be 1/19 molar ratio for HF; fluoroarenes were afforded in yields of around 90% or higher. Under the condition of a high molar ratio of HF/anilines, a considerable amount of tarry matter was produced. The temperature of a solution of aniline (5 mmol) and $NaNO_2$ in HF (450 mmol; ca. 9 cm^3), prepared at −78 °C, was allowed to rise to room temperature (Stage [A]) and was then maintained for

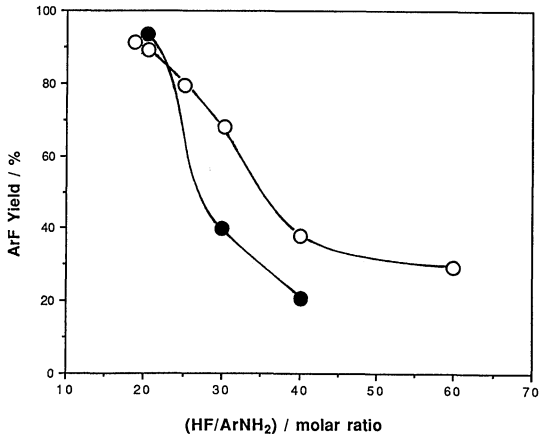


Fig. 1. The effect of $HF/ArNH_2$ molar ratio on the yield of ArF in the diazotization and fluoro-dediazoniation of $ArNH_2$ in HF. Diazotization: $ArNH_2$, 20 mmol; $NaNO_2$, 21 mmol; 0 °C for 20 min. Dediazoniation: ○; Aniline 60 °C for 1 h, ●; *p*-Toluidine 75 °C for 1 h.

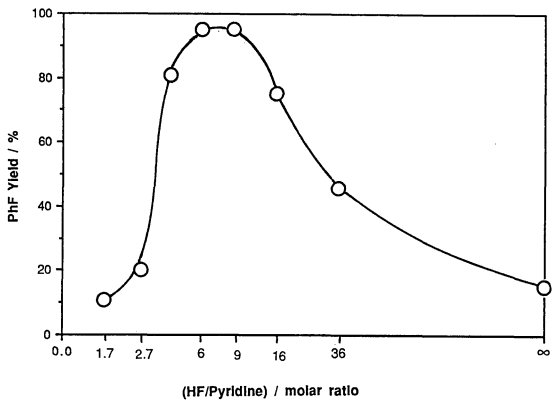


Fig. 2. The effect of HF/pyridine molar ratio of HF·Pyr on the yield of PhF in the diazotization and fluoro-dediazoniation of $PhNH_2$. Diazotization: HF, 450 mmol; $PhNH_2$, 5 mmol; $NaNO_2$, 5.5 mmol; 20 °C for 30 min. Dediazoniation: 55 °C for 1 h.

60 min. By quenching the reaction mixture with ice-water, the color of resulting solution changed to brown from deep red, and a trace amount of fluorobenzene (0.5%) was extracted with CH_2Cl_2. The addition of 1-naphtylamine to this aqueous acid solution brought about a color change to dark purple. When ammonium chloride and copper(I) chloride were added to this solution a considerable amount of chlorobenzene (85%), together with a small amount of chloro-fluoro-, difluoro- and dichlorobiphenyls (less than 2% in total) was produced. Furthermore, when this solution was neutralized with K_2CO_2, benzene (30%) and biphenyl (less than 1%) were extracted with CH_2Cl_2, together with a deep brown tarry residue (less than 2%). These results suggest the presence of benzenediazonium ion in the aqueous acid solution.

On the other hand, when the solution prepared in Stage [A] was heated at a temperature higher than 50 °C for 30 min, fluorobenzene boiled off together with NO_X and a considerable amount of HF (ca. 5 cm^3) which condensed in a cooled trap during the reaction. After quenching the reaction mixture with ice-water, fairly large quantities (40% or more) of a tarry matter and fluorobenzene were obtained together with some (2% or less) fluoro- and difluorobiphenyls. The total yield of fluorobenzene was 15—30% (reproducibility is poor). Tarry matter (Found: C, 82.37; H, 4.97; N, 10.64; F, 2.06%; IR(KBr) 3390(N–H), 3030, 1620, 1500, 1300, 820(*p*-substituted aryl)) thus obtained was insoluble in both CH_2Cl_2 and aqueous acid layer and was composed of black particles that resembled sand. The empirical formula of this material was $C_6H_{4.3}N_{0.7}F_{0.1}$, which is similar to that of poly aniline ($C_6H_{4.5-5}N$).[17] The remaining solution containing the tarry matter was neutralized with K_2CO_3 to change the color to slightly dark brown. From this solution, aniline (20%) together with benzene, biphenyl, aminobiphenyls, diaminobiphenyls, and phenylazoanilines (2% or less in total) were extracted with CH_2Cl_2. A small amount of brown tarry matter was also obtained from the extracts after the evaporation of CH_2Cl_2.

Reactions in HF with Pyridine (HF·Pyr). The reaction of aniline with $NaNO_2$ was carried out using the HF·Pyr solution with various molar ratio of HF/pyridine (N).[18] When the solution with N=6 prepared at Stage [A] remained at room temperature, the reaction gradually took place to increase the yield of fluorobenzene (5% for 1 h and 30% for 24 h). Interestingly, fluorobenzene, together with phenol, was obtained increasingly from the solution of the ice-water-quenched reaction mixture by standing for some time at room temperature (PhF 27%, PhOH 51% for 24 h, and PhF 31%, PhOH 57% for 48 h).

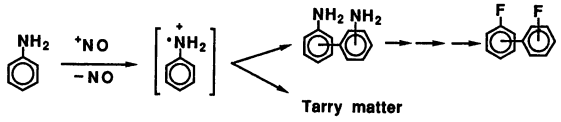
When the solution obtained at Stage [A] was heated, the yield of fluorobenzene after the usual work-up was greatly influenced by the composition of the HF·Pyr, as shown in Fig. 2. Under the conditions of 55 °C for 1 h, fluorobenzene was produced in low yields, accompanying the formation of various kinds of complicated compounds in the case of the HF·Pyr with N>9. However, it was obtained in nearly quantitative yield using a solution with 6<N<9, although small amounts of fluorobiphenyls, difluorobiphenyls and *p*-nitrofluorobenzene[19] (less than 2% in total) were found. In the case of HF·Pyr (N<6), a remarkable decrease in the yield of fluorobenzene was observed (9% at N=1.7) with the formation of phenylpyridines (55% at N=1.7) and 2- or 4-phenylazoanilines (ratio 1:5, 8% in total at N=1.7) with unidentified variable products. When a solution with N=6 prepared at Stage [A], which is stable up to 90 °C, was heated immediately at 55—90 °C for 1 h, a nearly quantitative yield of fluorobenzene was obtained. The

solution with N=9, which is stable up to 55 °C, also gave also a quantitative yield of fluorobenzene by immediate treatment at 55 °C. However, since this solution was not stable at 90 °C, considerable amounts of HF together with NO_X were released in the reaction at 90 °C leading to a decrease in yield of fluorobenzene (83%) with some formation of difluorobiphenyls and fluoronitrobenzenes. On the other hand, when this solution was allowed to stand at 0 °C for 1 h or longer, the subsequent reaction at 90 °C gave rise to an increasing yield of fluorobenzene (89% for 1 h and 95% for 2 h). These results suggest that the rate of diazotization of aniline in HF·Pyr with N=9 is much slower than that with N=6, although immediate heating of the solution (N=9) at 55 °C gives fluorobenzene effectively without the occurrence of undesirable reactions, since the diazotization rate of unaltered aniline at 55 °C seems to be reconciled with the fluorodediazoniation rate of the resultant benzenediazonium ion.

The Rate of Diazotization of *p*-Toluidine in HF. *p*-Toluidine was employed as a substrate to make NMR spectroscopic analysis easier,[20] in order to examine the rate of diazotization in the HF solution.

As shown in Table 1, the protonation of *p*-toluidine took place almost exclusively at its amino group in a solution with a composition of 25 or more moles of HF to one mole of *p*-toluidine prepared at 0 °C (Entries 3, 9, 13). However, when such a solution was heated (Entries 7, 11) or diluted with water (Entry 12), a fair amount of arenediazonium ion was found in the resultant solutions. This evidence indicates that a stronger protonation towards a nitrogen atom in *p*-toluidine tends to prevent its nitrosation with NO^+ to form *N*-nitrosoanilinium ion. In a solution having a HF/*p*-toluidine molar ratio less than 25 (Entries 1, 2), on the other hand, the diazotization of *p*-toluidine was found to take place remarkably, even at 0 °C. This may be because of the dilution of HF by *p*-toluidine, which reduces the acidity of the HF solution to accelerate the diazotization of *p*-toluidine.

The rate of diazotization of anilines is known to be decreased with the increasing acidity of reaction medium with an H_0 value of higher than −4.[12–14,21] Such a rate decrease at high acidities was explained by assuming that the rate-limiting step is the deprotonation of the *N*-nitrosoanilinium ion to afford benzenediazonium ion.[14,21] Judging from our experimental results, the rate-limiting step in highly concentrated acidic media, such as HF with an H_0 value of −10,[22] should exist at least before the formation of *N*-nitrosoanilinium ion, since this ion and arenediazonium ion were not observed in the solution with HF/*p*-toluidine ratio of 40—60 at 0 °C (Entries 9, 13). Raising the temperature of such a solution, on the other hand, brought about some formation of arenediazonium ion (Entries 10, 11) with the generation of nitrogen monoxide (NO),[23] and caused highly variable reactions giving biaryls, arylazoanilines, and tarry matter. Although the formation of azo compounds can be well explained by the reaction of arenediazonium ion with an unaltered anilines,[25] the formation of diaminobiphenyls and difluorobiphenyls[26] can not currently be well elucidated. However,



Scheme 1.

Table 1. Products Found in the Diazotization of *p*-Toluidine in HF

Entry	Solution (HF/*p*-Toluidine/$NaNO_2$)[a]			Products[b] composition			
	Composition HF/*p*-toluidine /molar ratio	Standing conditions		*p*-TolNH_3^+	*p*-TolN_2^+	Others	*p*-TolF
		°C	min	%	%	%	%
1	5[c]	5	0	29.5	70	0.5	0
2	10	5	120	18	80	5	Trace
3	25	0	0	85	15	0	0
4	25	0	20	70	28	2	0
5	25	0	60	48	48	4	Trace
6	25	0	120	46	49	5	Trace
7	25	20	20	34	57	9	Trace
8	25	20	60	15	77	8	Trace
9	40	0	0	100	0	0	0
10	40	20	60	96	3.3	1.7	0
11	40	40	60	37	53	14	Some[e]
12	40[d]	0	0	0	91	9	0
13	60	0	120	100	0	0	0

a) *p*-Toluidine, 20 mmol; $NaNO_2$, 21 mmol. b) *p*-TolNH_3^+; *p*-Tolylammonium ion, *p*-TolN_2^+; *p*-Methylbenzenediazonium ion, *p*-TolF; *p*-Methylfluorobenzene. c) $NaNO_2$ did not dissolve in HF completely. d) Water (100 mmol) was added to this solution. e) Less than 3%.

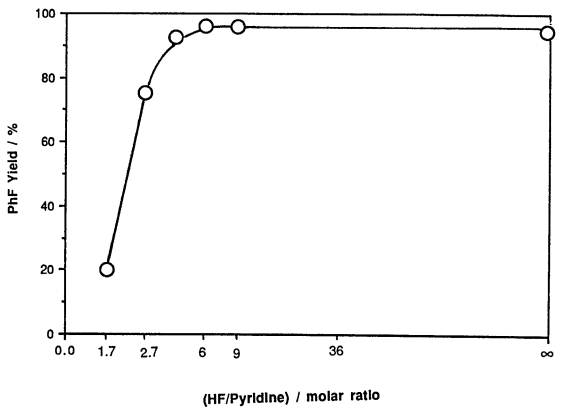


Fig. 3. The effect of HF/pyridine molar ratio of HF·Pyr on the yield of PhF in the fluoro-dediazoniation of PhN_2BF_4. Reaction conditions: HF, 450 mmol; PhN_2BF_4, 5 mmol; 55 °C for 1 h.

the generation of NO in this reaction sugests the oxygenation of anilines with NO^+ to give an active precursor, such as anilinium cation radical, for the formation of diaminobiphenyls and difluorobiphenyls, and also that of tarry matter as shown in Scheme 1.

Reactions of a Benzenediazonium Salt in HF or HF·Pyr. The decomposition of benzenediazonium tetrafluoroborate PhN_2BF_4 in polar solvents is known to give nucleophilic products with solvents, mainly such as phenol and aryl ethers together with a small amount of fluoro-dediazoniation product, namely fluorobenzene.[27] On the other hand, when the reaction was carried out in nonpolar solvents, such as dodecane, the decomposition of PhN_2BF_4 was observed to take place very slowly, but almost exclusively to give fluorobenzene in a yield of 43% at 50 °C for 30 min. However, it was performed successfully to afford fluorobenzene in high yields using HF or the HF·Pyr with $N>6$, as shown in Fig. 3.

Good first-order plots were obtained at a rate of such fluoro-dediazoniation of PhN_2BF_4 in the HF·Pyr with $N>4$. The rate constant was increased with the increasing value of N, as shown in Table 2. Though the activation energies were calculated to be the same (30.0 kcal mol^{-1}) in these solutions, the activation entropy was found to increase slightly with decreasing value of N in the HF·Pyr (23.5 and 20.0 cal K^{-1} mol^{-1} for $N=35$ and 6 respectively). This may be related to the viscosity of the HF·Pyr, which decreases with increasing value of N. However, when using HF·Pyr with $N<6$, the reaction of pyridine with PhN_2^+ occurred remarkably to give phenylpyridines (70% at $N=1.7$) with a decreasing yield of fluorobenzene (20% at $N=1.7$).

Consequently, both stages of diazotization of anilines and fluoro-dediazoniation of the corresponding arenediazonium salts are influenced by the composition of the HF·Pyr employed. The yield of fluorobenzenes in a one-pot procedure using HF[4–6] or HF-Base,[8–11] is greatly dependent on the rate of the former stage.

Table 2. Fluoro-Dediazoniation Rate Constants of PhN_2BF_4 in HF·Pyr[a]

HF/Pyridine mole ratio	$k\times10^5$ s^{-1}
36	3.80
16	3.02
9	2.12
6	1.54
4	0.88

a) Reaction Conditions: PhN_2BF_4, 5 mmol; HF, 450 mmol; 20 °C.

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18) The addition of $NaNO_2$ to the HF·Pyr solution did not result in a vigorous rise temperature as was observed in the case of HF. Thus, clean and almost colorless solutions were readily obtained (Stage [A]) by the use of the HF·Pyr with $N=9$ or below.
19) The yield of *p*-nitrofluorobenzene was increased when an increasing amount of $NaNO_2$ was employed. The oxidation of NO^+ may take place to produce NO_2^+ under the present conditions, since no fluoronitrobenzene was observed under the conditions in an atmosphere of argon.
20) The chemical shifts of protons on the aromatic ring of *p*-toluidine, which gave typical AA'XX' spectra, were observed to shorten its $\Delta\nu_{AX}$ in HF solution. Here the increasing amount of HF made $\Delta\nu_{AX}$ smaller to give a single

peak in the solution of HF/*p*-toluidine molar ratio of more than 60.

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