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Journal of Fluorine Chemistry 76 (1996) 59–62

JOURNAL OF FLUORINE CHEMISTRY

An improved method for fluoro-dediazoniation of arylamines substituted with polar groups

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Received 2 May 1995; accepted 29 July 1995

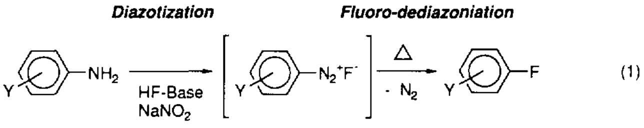
Abstract

The addition of SnX_2 ($SnCl_2$ or SnF_2), as a low redox potential reductant, at the fluoro-dediazoniation step in the deaminative fluorination of aryl amines substituted with polar groups gave high selectivities for the formation of fluoroaromatics under mild conditions. The selectivities were further increased by the addition of a nucleophilic fluoride anion source, i.e. tetrabutylammonium dihydrogen trifluoride $^nBu_4N^+\ H_2F_3^-$, along with the reductants.

Keywords: Fluoro-dediazoniation; Arylamines; Tin(II) halides; Low redox potential reductant; Deaminative fluorination; Selectivities

1. Introduction

Fluorine-containing compounds have attracted considerable interest in many fields, e.g. biologically active compounds, liquid-crystals and polymers [1]. Among fluorine-containing compounds, fluoroaromatics are one of the most important synthetic intermediates. Great efforts have been made in the development of methods for the selective synthesis of fluoroaromatics. Deaminative fluorination is a useful method for the synthesis of a wide range of substituted fluoroaromatics. In particular, one-pot deaminative fluorination in HF/base is a useful method with some advantages [2] [Eq. (1)].



(1)

However, this synthetic method has some problems. One of these is the low yield of fluoroaromatics substituted with polar groups. The diazonium salts of aryl amines substituted with polar groups (for example –OH, –OR, $-NH_2$, etc.) at the *ortho* or *para* position to the amino group are stabilized by resonance and intermolecular interaction [3]. Hence, high temperatures (> 120 °C) are usually required in the fluoro-dediazoniation reaction of these diazonium salts. Because of the high temperature in thermolysis, the yields of fluoroaromatics substituted with these polar groups are usually low. In this paper, we report a new convenient method for the highly selective synthesis of fluoroaromatics substituted with the polar groups.

2. Results and discussion

An aryl cation is produced by heterolytic cleavage [4] [Eq. (2)], followed by an S_N1-type attack by the fluoride anion during the thermolysis of diazonium salts. We assumed that the evolution of nitrogen gas from diazonium salts would proceed under mild conditions via a thermodynamically favorable homolytic cleavage path [Eq. (3)] provided that an electron transferred from the metal halides to the diazonium salt [5].

$$\mathrm{Ar{-}N^+{\equiv}N} \xrightarrow[-N_2]{} \mathrm{Ar^+} \qquad (2)$$

$$\mathrm{Ar{-}N^+{\equiv}N} \xrightarrow{+e} \mathrm{Ar{-}N{=}N\cdot} \xrightarrow[-N_2]{} \mathrm{Ar\cdot} \qquad (3)$$

Several metal halides have been examined in the one-pot deaminative fluorination reaction of 4-aminophenol (**1**) (Table 1). The yield of the diazonium salt **2**, which was determined by the absorbance at the absorption maximum of the azo-coupling compounds **4**, was quantitative. The fluoro-dediazoniation reaction proceeded smoothly above 140 °C, but the selectivity for the formation of 4-fluorophenol (**3**)

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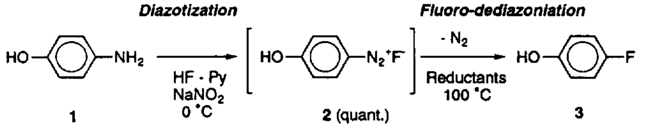
SSDI 0022-1139(95)03343-2

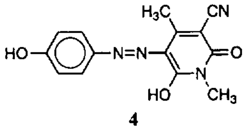
Table 1
Effect of reductants on the fluoro-dediazoniation reaction [a]



Reductants (E_0/V) [c]	Dediazoniation temp. (°C)	Time (h)	Conversion of **2** (%) [b]	Yield of **3** (%)	Selectivity of **3** (%)
–	140	3	100	40	40
–	100	3	52	33	63
–	100	6	76	41	54
$SnCl_2$ (+0.15)	100	3	98	84	86
SnF_2 (+0.15)	100	3	95	79	83
CuCl (+0.15)	100	3	52	27	52
$CoCl_2$ (+0.20)	100	3	71	45	63
$FeCl_2$ (+0.77)	100	3	63	35	56
SmI_2 (−1.55)	100	3	89	33	38

[a] Conditions: **1** = 3.0 mmol, HF/pyridine (60:40 w/w) = 6 ml, $NaNO_2$ = 3.2 mmol, reductants = 3.0 mmol.

[b] Determined by the absorbance of the azo-coupling compound **4** (λ_{max} = 460 nm) in aqueous MeOH.



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[c] Standard electrode potentials in an aqueous solution, see Ref. [6].

temperature of the fluoro-dediazoniation reaction, the decomposition rate became slow and the selectivity slightly increased. On the other hand, it is remarkable that fairly good selectivity was obtained at 100 °C by adding the metal halide $SnCl_2$ having a low redox potential (E_0 = +0.15 V) [6] in the fluoro-dediazoniation reaction. However, $CoCl_2$ (E_0 = +0.20 V) and $FeCl_2$ (E_0 = +0.77 V) whose redox potentials were *higher* than that of $SnCl_2$ were ineffective [1]. Reductants having a redox potential lower than 0.2 V could reduce the diazonium salt **2**. Exceptionally, in the case of SmI_2 (E_0 = −1.55 V), the selectivity decreased and the major products were benzoquinone and hydroquinone. Furthermore, CuCl (E_0 = +0.15 V), which has the same redox potential as $SnCl_2$, showed no effects [7]. It may be that CuCl is converted into CuF in HF, and that the CuF immediately disproportionates to CuF_2 and Cu (E_0 = +0.34 V) [8], which have insufficient reducing power.

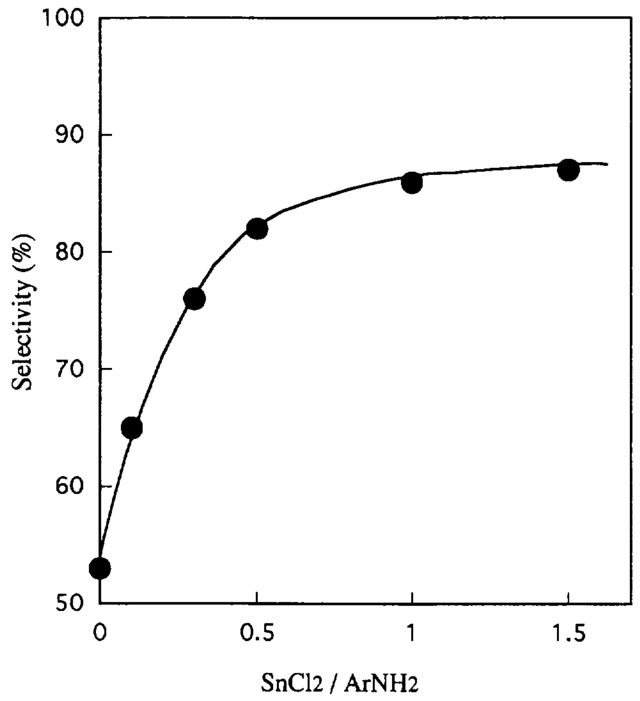

Fig. 1. The effect of the molar ratio of $SnCl_2/ArNH_2$ on the selectivity for the formation of 4-fluorophenol in the fluoro-dediazoniation reaction.

Fig. 1 shows the relationship between the molar ratio of $SnCl_2$ relative to the diazonium salt **2** and the selectivity for the formation of 4-fluorophenol (**3**). Increasing amounts of the two-electron reductant $SnCl_2$ increase the selectivity from ca. 50% up to ca. 80%, the latter value being reached when the molar ratio was 0.5. This result suggests that the reduction of the diazonium salt **2** is a single-electron-transfer process.

Furthermore, we expected that the selectivities would increase by the addition of fluoride anion sources together with the reductants. Table 2 shows the effects of the nucleophilic fluoride anion sources together with $SnCl_2$ in the fluoro-dediazoniation reaction. The selectivity increased on addition of tetrabutylammonium dihydrogen trifluoride, $^nBu_4N^+$

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[1] The quantity E_0 represents the standard electrode potentials relative to the normal hydrogen electrode (NHE) in aqueous solution at 25 °C. $Sn^{4+} + 2e^- = Sn^{2+}$; $Cu^{2+} + e^- = Cu^+$; $Co^{3+} + e^- = Co^{2+}$; $Fe^{3+} + e^- = Fe^{2+}$; $Sm^{3+} + e^- = Sm^{2+}$.

Table 2
The effect of nucleophilic F^- sources on the fluoro-dediazoniation step in the synthesis of 4-fluorophenol (**3**) [a]

Entry No.	Nucleophilic F^- sources	SnX_2	Conversion of **2** [b] (%)	Yield of **3** (%)	Selectivity of **3** (%)
	–	–	76	41	54
2	–	$SnCl_2$	98	84	86
3	$^nBu_4N^+\ H_2F_3^-$	$SnCl_2$	98	90	92
4	$^nBu_4N^+\ F^-$	$SnCl_2$	94	80	85
5	CsF	$SnCl_2$	95	78	82
6	KF [c]	$SnCl_2$	95	77	81

[a] Diazotiation conditions; **1** = 3.0 mmol, HF/pyridine (60:40 w/w) = 6 ml, $NaNO_2$ = 3.2 mmol, 0–10 °C, 0.5 h. Fluoro-dediazoniation conditions; $SnCl_2$ = 3.0 mmol, nucleophilic F^- sources = 3.0 mmol, 100 °C, 3 h.

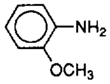
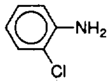
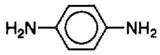
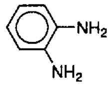
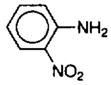
[b] The quantity of **2** was determined by the absorbance of the azo-coupling compound **4**. The yield of **2** was 100%.

[c] Spray-dry KF.

$H_2F_3^-$ [9], which was known to be a highly nucleophilic fluoride anion source (Entry No. 3) [10]. Other nucleophilic fluoride anion sources, tetrabutylammonium fluoride (Entry No. 4), CsF (Entry No. 5) or spray-dry KF (Entry No. 6), which were less nucleophilic than $^nBu_4N^+\ H_2F_3^-$ [10], showed no effect. The yield of 4-fluorophenol was low (38%) when only tetrabutylammonium dihydrogen trifluoride $^nBu_4N^+\ H_2F_3^-$ was added in the fluoro-dediazoniation reaction.

As summarized in Table 3, this new synthetic method using $SnCl_2$ as a reductant and tetrabutylammonium dihydrogen trifluoride as the nucleophilic fluoride anion source at the fluoro-dediazoniation reaction step was effective for several aniline derivatives substituted with polar groups. The yields of the methoxy (Entry No. 1), chloro (Entry No. 2), amino (Entry Nos. 3 and 4) or nitro (Entry No. 5) group substituted fluorobenzenes in the presence of $SnCl_2$ and $^nBu_4N^+\ H_2F_3^-$ were higher than those observed in the absence of $SnCl_2$ and $^nBu_4N^+\ H_2F_3^-$.

Table 3
Deaminative fluorination of aromatic amines substituted with polar groups

Entry	Ar–NH_2	Yield of Ar–F (%)	
		HF/Py [a]	HF/Py/$SnCl_2$ and n-$Bu_4N^+\ H_2F_3^-$ [b]
1		20	71
2		52	80
3		60	89
4		15	77
5		23	71

[a] Reactions in HF/pyridine (60:40 w/w) solution.

[b] $SnCl_2$ and $^nBu_4N^+\ H_2F_3^-$ were added to the HF/pyridine reaction solution at the fluoro-dediazoniation step.

In conclusion, we have demonstrated that the addition of SnX_2 ($SnCl_2$ or SnF_2) as a low redox potential reductant at the fluoro-dediazoniation step promoted the reaction under mild conditions and gave high selectivities for the formation of fluoroaromatics. The selectivities were further increased by the addition of the nucleophilic fluoride anion source, tetrabutylammonium dihydrogen trifluoride, $^nBu_4N^+\ H_2F_3^-$, together with the reductants. Further investigation of the reaction mechanisms are ongoing.

3. Experimental details

A typical experimental procedure was as follows. To a HF/pyridine (60:40 w/w) solution (6 ml) in an FEP (tetrafluoroethylene/hexafluoropropene copolymer) vessel were added 4-aminophenol (**1**) (3.0 mmol) and sodium nitrite (3.2 mmol) at 0–5 °C. The reaction mixture was stirred at 5–10 °C for 30 min. At this diazotization reaction step, an aliquot of the solution was separated and reacted with an aqueous methanol solution ($H_2O/MeOH$ = 6:94 v/v; 10 ml) of 1,4-dimethyl-3-cyanopyridine (122 mg), AcONa (58 mg) and NaOH (80 Mg) at a pH value of ca. 5. This azo-coupling reaction was very fast and quantitative at room temperature. The yield of the diazonium salt **2** was determined from the absorbance at maximum absorption (460 nm).

$SnCl_2$ (3.0 mmol) and tetrabutylammonium dihydrogen trifluoride, $Bu_4N^+\ H_2F_3^-$, (3.0 mmol) were added to the diazotization reaction solution at 10 °C and the latter stirred at 100 °C for 3 h. When the temperature was raised, the evolution of nitrogen gas was observed. After cooling, a small aliquot was separated for the determination of the diazonium salt **2**. The fluoro-dediazoniation reaction mixture was quenched with ice-water and the products extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the products were identified by comparing the IR, ^1H NMR and ^{19}F NMR spectra with those of authentic samples.

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