

The Bamberger reaction in hydrogen fluoride: the use of mild reductive metals for the preparation of fluoroaromatic amines

Marc Tordeux, Claude Wakselman *

SIRCOB, Bât. Lavoisier, Université de Versailles, 45 Avenue des Etats-Unis, 78000 Versailles, France

Received 9 January 1995; accepted 13 February 1995

Abstract

The reduction of nitroaromatic compounds by various metals (tin, lead, bismuth) in liquid hydrogen fluoride under an inert atmosphere leads to fluoroaromatic amines, in accord with the Bamberger reaction. Generally, a co-solvent such as pentane or methylene chloride is used. Some non-fluorinated arylamines are also formed by a competitive direct reduction of the *N*-arylhydroxylamine intermediate. Of the mild reductive metals studied, bismuth was the most selective.

Keywords: Bamberger reaction; Hydrogen fluoride; Mild reductive metals; Fluoroaromatic amines; NMR spectroscopy

1. Introduction

A great deal of effort has been directed towards the selective introduction of fluorine into aromatic compounds [1]. Generally, reagents which can behave as sources of electrophilic fluorine are unstable and expensive. Classical methods (Balz–Schiemann reaction, halogen-exchange procedure, fluorodenitration, etc.) based on the use of the cheap nucleophilic fluoride anion are not appropriate for the introduction of fluorine into unsubstituted positions in aromatic rings, with the exception of the Bamberger rearrangement [2] in anhydrous hydrogen fluoride [3–6].

For example, reduction of nitrobenzene in HF gives *p*-fluoroaniline which can be used as a precursor for numerous fluoroaromatic compounds. The formation of this fluoroaniline may be explained by protonation of the *N*-phenylhydroxylamine intermediate, followed by selective attack of fluoride anion on the *para* position of the delocalized cation so formed (Scheme 1).

Because of the importance of the concomitant formation of the corresponding unfluorinated aniline by competitive reduction of the *N*-phenylhydroxylamine, several reductive systems have been studied, e.g. catalytic reduction with hydrogen [7], phosphorus, sulfur or their derivatives [8], carbon monoxide [9] or electrochemical reduction [10]. Metals such as iron, zinc or tin have also been tested but no fluorinated products have been obtained [11]. Since this fail-

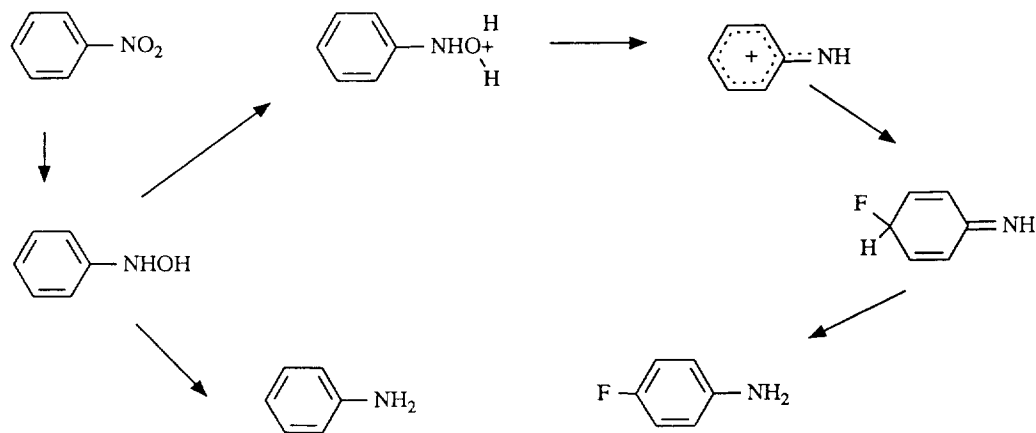
ure could be the result of a very fast reduction, a further investigation of the action of mild reductive metals in moderate conditions was warranted. We report here that fluoroaromatic amines can be obtained by the use of metals, such as tin, lead or bismuth in liquid hydrogen fluoride under an inert atmosphere (Scheme 2).

2. Results and discussion

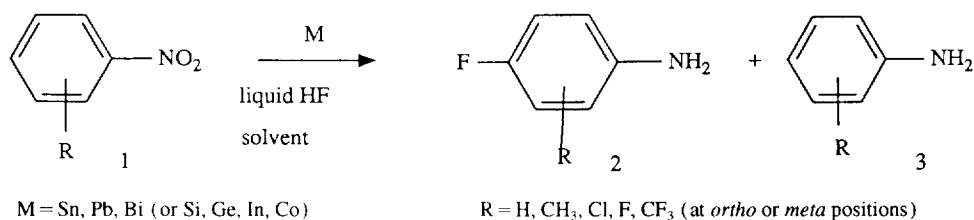
The experiments were performed in liquid hydrogen fluoride cooled approximately to -10°C under inert atmosphere. The nitroaromatic compound was placed in this medium generally diluted in a co-solvent (pentane or methylene chloride). The metallic powder was then added in small portions. The reaction was exothermic and occurred probably between 0°C and 20°C . After elimination of HF and hydrolysis, the residue was analyzed by GLC and ^1H and ^{19}F NMR spectroscopy. The results obtained with nitrobenzene are summarized in Table 1.

Numerous metals were tested. A weak transformation was observed with silicon, germanium, cobalt and indium. Better results were obtained with tin, lead and bismuth. Use of a co-solvent was generally beneficial, especially in the case of methylene chloride. Protection against oxygen was also favourable, probably owing to the instability of the *N*-phenylhydroxylamine intermediate. Inversion of the addition order of reagents was detrimental; when nitrobenzene was added to a suspension of an efficient metal in liquid hydrogen

* Corresponding author.



Scheme 1.



Optional solvent: pentane or methylene chloride (reactions performed under an argon atmosphere)

Scheme 2.

Table 1
Reduction of nitrobenzene by metallic powders in liquid hydrogen fluoride under an argon atmosphere

Metal	Solvent	Product	Ratio of 2/3			Yield of 2 (%)	
			Crude (g)	1 ^a	2 ^a		3 ^a
Sn	–	0.3	> 1	63	37	63:37	17
Sn	pentane	0.2	> 1	86	14	86:14	15
Sn	CH ₂ Cl ₂	0.7	3	90	7	92:8	57
Pb	–	0.2	20	72	8	90:10	13
Pb	pentane	0.4	15	79	6	91:9	28
Pb	CH ₂ Cl ₂	0.6	13	77	10	88:12	42
Bi	CH ₂ Cl ₂	0.5	–	97	3	97:3	45
Si	CH ₂ Cl ₂	0.2	7	23	70	25:75	4
Ge	CH ₂ Cl ₂	0.5	> 1	36	74	36:74	16
Co	–	0.3	20	41	39	51:49	11
In	CH ₂ Cl ₂	0.4	–	68	32	68:32	25

^a Relative proportions of compounds 1, 2 and 3.

fluoride, the reaction was more exothermic and the yield lower. It was not necessary to use a pressure-resistant reactor because the temperature of the reaction was lower than the HF boiling point. In fact, all experiments were performed in plastic bottles. Yields obtained under these conditions were moderate.

This reaction was not limited to the preparation of *p*-fluoroaniline. Other fluoroaromatic amines were obtained starting from nitrobenzene bearing halogen, alkyl or perfluoroalkyl

substituents at the *ortho* or *meta* positions (Table 2). However, the yield and selectivity were low when an electron-withdrawing group was present on the aromatic ring as in the case of the trifluoromethyl substituent. A better result was observed when an electron-donating group, such as methyl, was attached to the ring. The reaction is compatible with the presence of halogen substituents as shown by the reduction of 2-fluoronitrobenzene to 2,4-difluoroaniline. The influence of the nature of the substituent on the reaction selectivity has

Table 2
Reduction of substituted nitrobenzenes by metallic powders in liquid hydrogen fluoride under an argon atmosphere

R	Metal	Solvent	Product				Ratio of 2/3	Yield of 2 (%)
			Crude (g)	1 ^a	2 ^a	3 ^a		
2-Me	Pb	–	0.65	>1	93	7	93:7	48
3-Me	Pb	–	0.65	>1	85	15	85:15	44
2-Cl	Pb	–	0.55	3	90	7	93:7	35
3-Cl	Pb	–	0.55	–	85	15	85:15	34
2-F	Bi	CH ₂ Cl ₂	0.9	1	94	5	95:5	65
2-CF ₃	Bi	CH ₂ Cl ₂	0.3	6	67	27	71:29	12
3-CF ₃	Bi	CH ₂ Cl ₂	0.6	>1	34	66	34:66	13

^a Relative proportions of compounds 1, 2 and 3.

already been commented upon; in the catalytic hydrogenation method, direct reduction of the nitro group was predominant when an electron-withdrawing substituent was present in the ring, particularly at the 3-position [11]. A similar trend was observed in the bismuth reduction of 3-trifluoromethylnitrobenzene (Table 2). However, this over-reduction was only a minor pathway when the trifluoromethyl group was attached at the 2-position of the ring.

There is a discrepancy between our experiments using tin (Table 1) and the negative results obtained by Moilliet with the same metal [1]. This difference could be due to a temperature effect and to the use of an inert atmosphere and a co-solvent in order to moderate the reaction.

Of all the metals tested, bismuth, which is seldom used in reduction reactions, appeared the most selective. Its use allowed the mild reduction of nitroaromatic compounds to nearly pure fluoroaromatic amines when the nucleus was not substituted by strong electron-withdrawing groups.

3. Experimental details

3.1. General procedure

Warning! Because of the hazards associated with hydrogen fluoride, extreme care should be exercised in working with it and all reactions should be carried out in efficient hoods. NMR spectra (¹H, ¹⁹F) were recorded in deuteriochloroform on a Bruker AC-200 spectrometer (at 200 and 188 MHz). The internal reference for the ¹⁹F spectra was CCl₃F. GC analyses were accomplished with a gas chromatograph equipped with a 30 m × 0.25 mm (i.d.) column (Crompack CP Sil 19 CB 10, 19 μm methyl silicon). Preparative GLC were performed using an 8 ft × 3/8 in column packed with 30% SE30 Chromosorb PAW 45/60.

The reactions were carried out in a 100 ml plastic (high-density polyethylene or polypropylene) flask equipped with a magnetic stirrer. A Teflon inlet, outlet tubes and a dropping funnel were inserted through its cap. The flask was cooled by an ice-salt bath and 20 ml of anhydrous liquid hydrogen fluoride were introduced. The flask was then placed under an

argon atmosphere and 0.01 mol of the nitroaromatic compound (1.2 g in the case of nitrobenzene), generally diluted in 5 ml of a co-solvent (pentane or methylene chloride), was added. With stirring, 0.021 mol of metallic powder was added in small portions over a period of 1 h. The cooling bath was then removed and the hydrogen fluoride conducted away by means of a nitrogen stream at room temperature. The residue was poured into a glass flask containing 100 g of ice, the aqueous phase was neutralized with solid soda to a pH value of 10 and extracted with diethyl ether. After filtration, the organic phase was washed with 20 ml of a saturated sodium hydrogen carbonate solution and dried over magnesium sulphate. After removal of the solvent under vacuum, the residue was analyzed by GLC and by ¹H and ¹⁹F NMR spectroscopy. Pure fluoroaromatic amines were isolated by preparative GLC. Their ¹H and ¹⁹F NMR characteristics were as follows:

4-Fluoroaniline: ¹H NMR δ: 6.88; 6.57 (*J*_{HH} = 8.8 Hz) ppm. ¹⁹F NMR δ: –126.5 (tt, *J*_{FH} = 8.8, 4.5 Hz) ppm.

4-Fluoro-2-methylaniline: ¹H NMR δ: 6.58 (tm, *J* = 8.6 Hz, H-3, H-5); 6.40 (dd, *J*_{HH} = 8.4, *J*_{FH} = 5.6 Hz, H-6); 1.95 (CH₃) ppm. ¹⁹F NMR δ: –126 (td, *J*_{FH} = 8.8, 5.6 Hz) ppm.

4-Fluoro-3-methylaniline: ¹H NMR δ: 6.6 (t, *J* = 8.8 Hz, H-5); 6.26 (ddd, *J*_{HH} = 8, *J*_{FH or HH} = 3.9, 3.1 Hz, H-6); 6.3 (t, *J* = 3.4 Hz, H-2); 2.3 (CH₃, *J*_{FH} = 1.8 Hz) ppm. ¹⁹F NMR δ: –129.3 (m) ppm.

2-Chloro-4-fluoroaniline: ¹H NMR δ: 7.0 (dd, *J*_{FH} = 8.3 Hz; *J*_{H3-H5} = 2.8 Hz, H-3); 6.75 (td, *J* = 8.5, 2.8 Hz, H-5); 6.68 (dd, *J*_{HH} = 9 Hz, *J*_{FH} = 5.6 Hz) ppm. ¹⁹F NMR δ: –124.8 (td, *J*_{FH} = 8, 5.6 Hz) ppm.

3-Chloro-4-fluoroaniline: ¹H NMR δ: 6.89 (t, *J* = 8.7 Hz, H-5); 6.65 (dd, *J*_{FH} = 6.0 Hz, *J*_{H2-H6} = 2.9 Hz, H-2); 6.45 (ddd, *J*_{H5-H6} = 8.8, *J*_{H2-H6} = 2.9 Hz, *J*_{HF} = 3.8 Hz, H-6) ppm. ¹⁹F NMR δ: –130 (ddd, *J*_{FH} = 8, 6, 3.8 Hz) ppm.

4-Fluoro-2-trifluoromethylaniline: ¹H NMR δ: 7.07 (dd, *J* = 8.9, 2.9 Hz, H-3); 6.91 (td, *J* = 8.4, 2.9 Hz, H-5); 6.60 (dd, *J*_{H5-H6} = 8.8, *J*_{HF} = 4.8 Hz, H-6) ppm. ¹⁹F NMR δ: (1F, td, *J*_{FH} = 8.1, 4.5 Hz); –63.2 (3F) ppm.

4-Fluoro-3-trifluoromethylaniline: ¹H NMR δ: 6.9–6.7 (m, 3H) ppm. ¹⁹F NMR δ: –129.9 (1F, m; after total protons decoupling: q, *J*_{FF} = 12.7 Hz); –61.9 (3F, d) ppm.

2,4-Difluoroaniline: ^1H NMR δ : 6.75 (m) ppm. ^{19}F NMR δ : -124.1 (1F, large q, $J=7.4$ Hz); -131.1 (large dd, $J=11.0, 6.2$ Hz) ppm.

Acknowledgement

We thank the Rhône-Poulenc Co. for financial support.

References

- [1] J.S. Moilliet, in R.E. Banks, B.E. Smart and J.C. Tatlow (eds.), *Organofluorine Chemistry. Principles and Commercial Applications*, Plenum, New York, 1994.
- [2] (a) J. March, *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 4th edn., John Wiley, New York, 1992, p. 674; (b) T.P. Simonova, V.D. Nefedov, M.A. Toropova and N.F. Kirilov, *Russ. Chem. Rev.*, 61 (1992) 584.
- [3] A.I. Titov and A.N. Baryshnikova, *Zh. Obshch. Khim.*, 23 (1953) 346; [*Chem. Abs.*, 48 (1954) 2623f].
- [4] D.A. Fidler, J.S. Logan and M.M. Boudakian, *J. Org. Chem.*, 26 (1961) 4014.
- [5] P.H. Scott, C.P. Smith, E. Kober and J.W. Churchill, *Tetrahedron Lett.*, (1970) 1153.
- [6] T.B. Patrick, J.A. Schield and D.G. Kirchner, *J. Org. Chem.*, 39 (1974) 1758.
- [7] D.A. Fidler (to Olin Matheson Chem. Corp.), US Pat. 2 884 458, 1959; [*Chem. Abs.*, 53 (1959) 17 055d].
- [8] J.W. Churchill, E.H. Kober and P.H. Scott (to Olin Matheson Chem. Corp.), US Pat. 3 558 707, 1970; [*Chem. Abs.*, 74 (1971) 125 126c].
- [9] J.W. Churchill, P.H. Scott and H. Kober (to Olin Matheson Chem. Corp.), US Pat. 3 639 482, 1972; [*Chem. Abs.*, 73 (1970) 109 468a].
- [10] S. Wawzonek, R. Berkey and D.T. Thomson, *J. Electrochem. Soc.*, 103 (1956) 513.
- [11] I.K. Jones and J.S. Moilliet, *13th Int. Symp. Fluorine Chem.*, Bochum, Germany, 3 September 1991; Summary: *J. Fluorine Chem.*, 54 (1991) 322.