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NEW DEVELOPMENTS IN THE SYNTHESIS OF LOWER FLUORINATED PYRIDINES VIA DIAZOTIZATION-FLUORINATION OF AMINOPYRIDINES IN ANHYDROUS HYDROGEN FLUORIDE*

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SUMMARY

The isolation and stabilization of elusive 4-fluoropyridine as the hydrochloride salt (54% yield) from fluorodediazoniation of 4-aminopyridine in anhydrous hydrogen fluoride (AHF) is described. Unlike the low yields (0-13%) recently reported from the chlorodediazoniation of 2,6-diamino-pyridine and 3-halo-2,6-diaminopyridine, fluorodediazoniation gave high yields (49-62%) of the corresponding 2,6-difluoropyridines. In contrast, benzene analogs, i.e. m-phenylenediamine and 4-chloro-m-phenylenediamine, form only tars under similar fluorination conditions. Vicinal aminohalo-pyridines, e.g. 3-amino-2-chloropyridine and 2-amino-3,5-dichloropyridine give the corresponding fluorohalopyridine in 49-89% yield. Again, the benzene analogs, i.e. o-chloroaniline and 2,4-dichloroaniline, resist fluorination.

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INTRODUCTION

Until recently, interest in lower fluorinated pyridines had remained dormant. Quaternized 2-fluoropyridine(s) have been exploited by Mukaiyama [1] as synthons for numerous transformations to give pyridine-free products. Fluoropyridines have also been evaluated for crop protection chemicals, pharmaceuticals and biochemical reagents [2].

Exchange-fluorination of halopyridines or diazotization of aminopyridines ('fluorodediazoniation') represent the main routes to these compounds [3a,b]. (Of limited synthetic utility are techniques such as substitutive fluorination of pyridine with xenon difluoride [4], fluorodehydroxylation of 2-hydroxypyridine with cyanuric fluoride [5] and fluorodenitration of 2-nitropyridine [6]).

While the 2-step Balz-Schiemann fluorodediazoniation via pyridinediazonium fluoborates has been generally used [7,8], some examples of the in-situ route via pyridinediazonium fluorides in hydrogen fluoride have also been reported. Concentrated hydrofluoric acid medium has been found to give low yields of 2-, 3- and 4-fluoropyridine [9a-c]; higher yields have been achieved with fluoronitropyridines [10]. In contrast, comparable reactions in anhydrous hydrogen fluoride (AHF) medium have only been reported for 2-fluoropyridine and 2-fluoro-3-(and 5-)picoline [8b; 11-14].

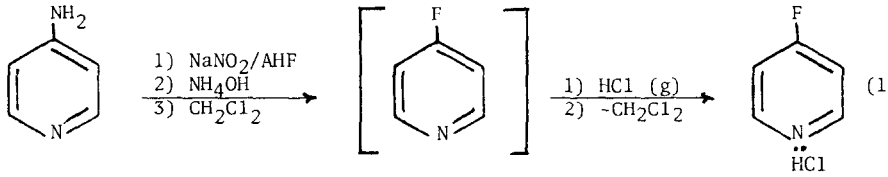
The present study extends the fluorodediazoniation technique in AHF to other aminopyridines. In several cases, the parallel reaction with benzene analogs showed surprisingly divergent behavior.

RESULTS AND DISCUSSION

4-Fluoropyridine

4-Fluoropyridine is the least stable of the 4-halopyridines [9c]. This compound undergoes facile self-condensation to give N-(4'-pyridyl)-4-fluoropyridinium fluoride [9c]; the latter is readily hydrolyzed to N-(4'-pyridyl)-4-pyridone [7; 8c]. Early attempts to prepare 4-fluoropyridine included: exchange-fluorination (KF) of 4-chloropyridine in N,N-dimethylformamide [15]; 4-nitraminopyridine with boron trifluoride-acetic acid [16]; and, fluorodediazoniation routes based on 4-aminopyridine [7, 8c, 9c].

A technique has now been developed for the diazotization-fluorination of 4-aminopyridine in AHF, followed by isolation and stabilization of 4-aminopyridine as the hydrochloride salt in 54% yield [17].



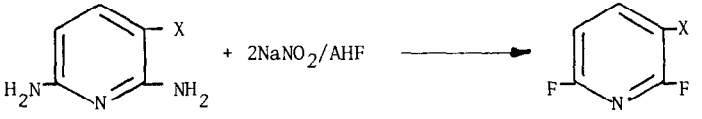
(1)

The critical isolation step involves neutralization (ammonium hydroxide) of the fluorination liquor in the presence of methylene chloride. The organic extract is separated, gaseous hydrogen chloride introduced and the solvent stripped to give the hydrochloride salt of >90% purity. (The latter has been stored for at least 5 years without decomposition).

2,6-Difluoropyridine

Application of the Balz-Schiemann reaction to 2,6-diaminopyridine (IA) failed to give 2,6-difluoropyridine (IIA) [18].

Surprisingly, when the bis(diazotization) of (IA) was conducted in AHF, a 62% yield of (IIA) was obtained [19]. Simultaneous introduction of fluorine into the 2- and 6- positions was also achieved with 3-halo-2,6-diaminopyridines (IB, X-Cl; IC, X=Br) to give the corresponding 3-halo-2,6-difluoropyridine (IIB; IIC) in 49-51% yield.

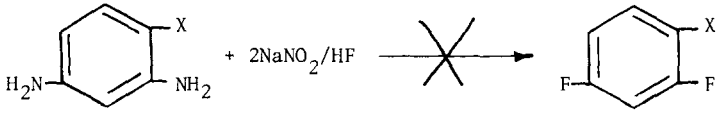


(2)

(I) (II)

A. X=H
B. X=Cl
C. X=Br

In contrast, the benzene analogs of IA and IB, m-phenylenediamine (IIIA) and 4-chloro-m-phenylenediamine (IIIB), respectively, gave tars under the same fluorination conditions. (Hopff, et al [20] demonstrated that another



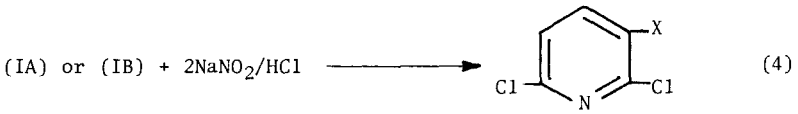
(3)

(III)

A. X=H
B. X=Cl

phenylenediamine, 1,4-diaminodurene, resisted tetrazotization-fluorination in AHF; duroquinone was obtained in 60-80% yield).

The behavior of 2,6-diaminopyridines under fluoro- and chloro-dediazoniation conditions is striking. While good yields of the 2,6-difluoropyridines (IIA-C) were obtained, Chen, et al [21] reported that chlorodediazoniation of IA or IB gave negligible amounts of the corresponding 2,6-dichloropyridine (IVA and B). (From earlier studies, Titov [22] found



(4)

(IV)

A=H (0%)

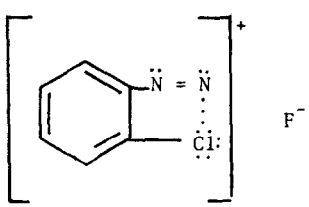
B=Cl (13%)

that nitrosation predominated from the diazotization of the hydrochloride salt of (IA) in dilute hydrochloric acid to give 3-nitroso-2,6-diaminopyridine (94% yield)).

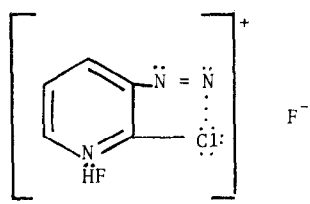
Vicinal Fluorohalopyridines

Vicinal aminohalobenzenes and -pyridines constitute another case of divergent behavior during fluorodediazoniations conducted in hydrogen fluoride.

Diazotization of o-chloroaniline in concentrated hydrofluoric acid [23] or AHF [13, 24] gives a complex mixture of high melting solids. Ferm et al [13] proposed a stable diazonium salt for o-chlorobenzenediazonium fluoride involving an unshared electron pair of the ortho-halogen with the outer nitrogen of the diazonium group (V). This complex can be decomposed at 200° to give the desired o-chlorofluorobenzene in 7-28% yield [24].



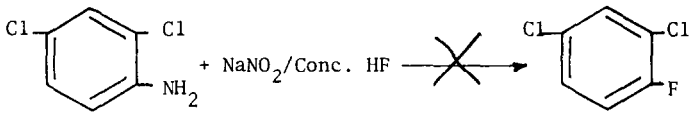
(V) (More Stable)



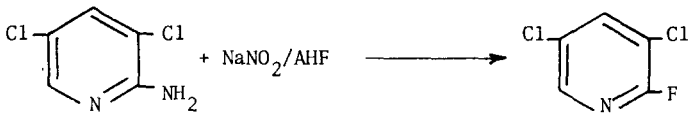
(VI) (Less Stable)

In contrast, facile fluorodediazoniation of a pyridine analog, 3-amino-2-chloropyridine, can be effected in AHF (20 to 61°) to give a 49% yield of 2-chloro-3-fluoropyridine. In this case, the proposed complex of Ferm et al [13] should be less stable since this intermediate is also a pyridinium fluoride (VI).

The divergent behavior of vicinal aminohalobenzenes and -pyridines is also shown when 2,4-dichloroaniline and 2-amino-3,5-dichloropyridine are diazotized in hydrogen fluoride. In the former case, Van de Lande [25] obtained tars, while the latter substrate gave an 89% yield of 3,5-dichloro-2-fluoropyridine in the present study.



(5)



(89%) (6)

4-Chloro-m-phenylenediamine (IIIB) and 3-halo-2,6-diaminopyridine (IB; IC) are additional examples of the contrasting behavior of vicinal amino-halobenzenes and -pyridines. (3-Amino-2-iodobenzoic acid may represent the sole exception to unfavorable fluorodediazoniation with vicinal amino-halobenzenes. 3-Fluoro-2-iodobenzoic acid was obtained in 62.5% yield with sodium nitrite and 48% hydrofluoric acid [26]).

EXPERIMENTAL

CAUTION: Spontaneous decomposition (nitrogen evolution) of pyridyldiazonium fluoride may occur during addition of sodium nitrite at 0°! Shenk et al [12] also noted such decomposition during diazotization (nitrosyl chloride) of 2-aminopyridine in AHF at 20-23°.

In some instances, an ammonium bifluoride/AHF medium was used [27]. We have found this system as useful as Olah's pyridine/AHF medium [28] for fluorodediazoniation reactions.

Fluorination experiments were performed in a 1-liter type 304 stainless steel reaction flask (SGA Scientific. Bloomfield, N.J.).

4-Fluoropyridine

A solution of 4-aminopyridine (1.0 Mol, 94.1 g; Reilly) and AHF (20 Mol, 400 g) was diazotized with sodium nitrite (1.2 Mol, 82.8 g) and the mixture heated at 30-50° (1.5 h). The fluorination liquor was added to a mixture of ammonium hydroxide (final pH 10) and methylene chloride at -10°. The organic extract (lower) was treated with silica gel and hydrogen chloride gas introduced. Stripping of methylene chloride (25°/30-50 torr) gave a yellow powder, 72 g (54% yield) of 4-fluoropyridine hydrochloride, m.p. 100° (with gas evolution). ^{1}H spectrum (DMSO): chemical shifts and coupling constants consistent for this salt, along with 7% impurity. (See [29] for ^{13}C chemical shifts and ^{13}C-F coupling constants for 4-fluoropyridine and -hydrochloride from a sample made by the above process).

4-Fluoropyridine can be liberated by neutralization of the hydrochloride salt in a suspension of methylene chloride-water (0°) containing potassium carbonate. The dried (sodium sulfate) organic layer should be stored at 0° prior to use.

2,6-Difluoropyridines

a. 2,6-Difluoropyridine (IIA)

A mixture consisting of 2,6-diaminopyridine (1.0 Mol, 109.1 g; Reilly) AHF (20 Mol, 400 g) and sodium nitrite (2.25 Mol, 155.3 g) was heated to 70° (14 h). The neutralized (ammonium hydroxide) fluorination liquor was steam-distilled to give 71.4 g of 2,6-difluoropyridine (IIA) (62.1% yield); GLC (10% Carbowax 20M), 99.4%; b.p. 125°; n_D^{24} 1.4362. Reported for (IIA): b.p. 124.5°; n_D^{25} 1.4349 [30].

b. 3-Chloro-2,6-difluoropyridine (IIB)

3-Chloro-2,6-diaminopyridine (IB) was prepared in 60% yield by controlled chlorination of (IA) with hydrogen peroxide-hydrochloric acid [31].

Steam distillation of the neutralized fluorination mixture from (IB) (1.0 Mol, 143.5 g), AHF (20.0 Mol, 400 g), ammonium bifluoride (1.0 Mol,

57.1 g) and sodium nitrite (2.25 Mol, 155.3 g) gave 3-chloro-2,6-difluoropyridine (IIB), 76.2 g (51% yield); GLC (20% QF-1), 98.5%; b.p. 150.5-151.5°, n_D^{24} 1.4739. Reported for (IIB): b.p. 151° (760 torr) [32]. IR: bands corresponded with literature values for (IIB) [32]. Both ^{19}F and ^{1}H spectra were consistent with the structure assigned for (IIB).

c. 3-Bromo-2,6-difluoropyridine (IIC)

3-Bromo-2,6-diaminopyridine (IC) was prepared in 76% yield by controlled bromination of (IA) with hydrogen peroxide-hydrobromic acid [31].

Steam distillation of the neutralized fluorination mixture for (IC) (1.0 Mol, 188.0 g), AHF (20.0 Mol, 400 g), ammonium bifluoride (1.0 Mol, 57.1 g) and sodium nitrite (2.25 Mol, 155.3 g) gave 3-bromo-2,6-difluoropyridine (IIC), 94.6 g (49% yield); GLC (20% QF-1), 99.8%; b.p. 169.5° (760 torr), n_D^{25} 1.5047. MS: m/e, 193 ($C_5H_2F_2Br^{79}N$ has m/e, 193). Analysis: Found: C, 30.35; H, 1.18; N, 7.15%. C_5H_2BrFN requires C, 30.96; H, 1.04; N, 7.22%. Both ^{19}F and ^{1}H spectra were consistent with the structure assigned for (IIC). IR (liquid): 3100 (w), 1605 (s), 1580 (s), 1455 (s), 1430 (s), 1420 (s), 1400 (m), 1310 (s), 1270 (s), 1220 (s), 1115 (w), 1050 (s), 1000 (s), 820 (s), 730 (s), 655 (w), 640 (s), 550 (w), 530 (w) cm^{-1}.

Vicinal Fluorohalopyridines

a. 2-Chloro-3-fluoropyridine

A mixture consisting of 3-amino-2-chloropyridine [33] (1.0 Mol, 128.6 g), AHF (20 Mol, 400 g) and sodium nitrite (1.2 Mol, 82.8 g) was heated at 20-61° (7 h). Steam distillation of the neutralized mixture gave a 49% yield of 2-chloro-3-fluoropyridine. GLC (10% Carbowax 20M), 94.3%. IR: bands corresponded with literature values [34]. Both ^{1}H and ^{19}F spectra were consistent for the structure assigned to 2-chloro-3-fluoropyridine.

b. 2-Fluoro-3,5-dichloropyridine

From 2-amino-3,5-dichloropyridine (1.0 Mol, 163.0 g; Aldrich), AHF (22 Mol, 440 g), ammonium bifluoride (1.25 Mol, 71.4 g) and sodium nitrite (1.2 Mol, 82.8 g) heated at 21-64° (4 h) was obtained 2-fluoro-3,5-dichloropyridine, 146.9 g (88.6% yield); GLC (10% Carbowax M/T), 99.8%; m.p. 42-3°.

Reported for 2-fluoro-3,5-dichloropyridine: m.p. 42-3° [35]. Both ^{19}F and ^{1}H spectra were consistent with the assigned structure of this product and corresponded with literature values [35].

Attempted Fluorodediazoniations

a. m-Phenylenediamine (IIIA)

Only tars were obtained from heating (55-75°; 13 h) (IIIA) (1.0 Mol, 108.1 g; du Pont), AHF (20.0 Mol, 400 g) and sodium nitrite (2.25 Mol, 155.3 g).

b. 4-Chloro-m-phenylenediamine (IIIB)

Tars were also obtained from (IIIB) (1.0 Mol, 142.6 g; Aldrich), AHF (20.0 Mol, 400 g), ammonium bifluoride (1.0 Mol, 57.1 g) and sodium nitrite (2.25 Mol, 155.3 g) which had been heated at 31-84° (10.5 h).

REFERENCES

1 T. Mukaiyama, Agnew. Chem. Int. Ed. Engl., 18 (1979) 707
2 M. M. Boudakian, in M. Grayson and D. Eckroth (Editors), Kirk-Othmer: Encyclopedia of Chemical Technology, Vol. 10, 3rd edn, J. Wiley, New York, 1980, Fluorinated Aromatic Compounds, p. 901.
3 a. H. E. Mertel, in E. Klingsberg (Editor), Pyridine and Its Derivative, Vol. 14, Part 2, Interscience, New York, 1961, Ch. 6, Halopyridines, p. 299.
b. M. M. Boudakian, in R. Abramovitch (Editor), Pyridine and Its Derivatives, Vol. 14, Part 2 (Supplement), Wiley-Interscience, New York, 1974, Ch. 6, Halopyridines, p. 407.
4 S. P. Anand and R. Filler, J. Fluorine Chem., 7, (1976) 179. See also D. R. MacKenzie, 7th International Symposium on Fluorine Chemistry. Santa Cruz, California. July 1973. Paper O-26.
5 A. Dorlars, U.S. Pat. 2,975,179 (1961).
6 G. Bartoli, A. Latrofa, F. Naso and P. E. Todesco, J. Chem. Soc. Perkin Trans. I, (1972) 2671.
7 A. Roe and G. F. Hawkins, J. Am. Chem. Soc., 69 (1947) 2443.

8 Fluoropyridines can also be made via:
a. Pyridinediazonium hexafluorophosphates: K. G. Rutherford, W. Redmond and J. Rigamonti, J. Org. Chem., 26 (1961) 5149.
b. Pyridinediazonium hexafluorosilicates: R. D. Beaty and W. K. R. Musgrave, J. Chem. Soc., (1952) 875.
c. Pyridinediazonium hexafluoroantimonates: C. Sellers and H. Suschitzky, ibid (C), (1968) 2317.

9 a. A. E. Chichibabin and M. D. Rjazancev, J. Russ. Phys. Chem. Soc., 46 (1915) 1571. Chem. Abstr., 10 (1916) 2898.
b. A. Binz and C. Räth, Ann., 486 (1931) 95.
c. J. P. Wibaut and W. J. Holmes-Kamminga, Bull. Soc. Chim. France, (1958) 424.

10 T. Talik and Z. Talik, Rocz. Chem., 47 (1973) 441.

11 J. H. Simons and D. F. Herman, 112th National Meeting, American Chemical Society, Sept. 1947, Div. Ind. & Eng. Chem., Abstracts, p. 13J.

12 W. J. Shenk, Jr. and G. B. Pellon, U.S. Pat. 2,563,796 (1951).

13 R. L. Ferm and C. A. Vander Werf, J. Am. Chem. Soc., 72 (1950) 4809.

14 J. T. Minor, G. F. Hawkins, C. A. Vander Werf and A. Roe, J. Am. Chem. Soc., 71 (1949) 1125.

15 K. Thomas and D. Jerchel in W. Foerst (Editor), Newer Methods of Preparative Organic Chemistry, Vol. 3, Academic Press, New York, 1964, p. 74.

16 T. Talik and Z. Talik, Rocz. Chem., 44 (1970) 1249.

17 M. M. Boudakian, U.S. Pat. 3,703,521 (1972). Concurrent modifications of the Balz-Schiemann reaction gave a 22% yield of 4-fluoropyridine. J. J. Lyle and R. W. Taft, J. Heterocyclic Chem., 9 (1972) 745. P. B. Desai, J. Chem. Soc. Perkin Trans. II, (1973) 1865.

18 Unpublished Results. A. Roe, Organic Reactions, 5 (1949) 227.

19 M. M. Boudakian and S. J. Chiras, U.S. Pat. 3,798,228 (1974).

20 H. Hopff, P. Doswald and B. K. Manukian, Helv. Chim. Acta, 44 (1961) 1231.

21 T. K. Chen and W. T. Flowers, J. Chem. Soc. Chem. Comm., (1980) 1139.

22 A. I. Titov, J. Gen. Chem. (U.S.S.R.), 8 (1938) 1483. Chem. Abstr., 33 (1939) 4248.

23 J. H. Slothouwer, Rec. trav. chim., 33 (1914) 324. Chem. Abstr., 9 (1915) 1314.

24 W. A. Gay, U.S. Pat. 3,950,444 (1976).

25 C. A. Van de Lande, Rec. trav. chim., 51 (1932) 98. Chem. Abstr., 26 (1932) 1258.

26 W. M. Stanley, E. McMahon and R. Adams, J. Am. Chem. Soc., 55 (1933) 706.

27 M. M. Boudakian, U.S. Pat. 4,075,252 (1978).

28 G. A. Olah and J. Welch, J. Am. Chem. Soc., 97 (1975) 208.

29 R. L. Lichter and R. E. Wasylishen, J. Am. Chem. Soc., 97 (1975) 1808.

30 G. C. Finger, L. D. Starr, A. Roe and W. J. Link, J. Org. Chem., 27 (1962) 3965.

31 M. M. Boudakian, U.S. Pat. 3,849,429 (1974).

32 F. Mutterer and C. D. Weis, Helv. Chim. Acta, 59 (1976) 229.

33 O. v. Schickh, A. Binz and A. Schulz, Chem. Ber., 69 (1936) 2593.

34 W. J. Link, R. F. Borne and F. L. Setliffe, J. Heterocyclic Chem., 4 (1967) 641.

35 G. C. Finger, L. D. Starr, D. R. Dickerson, H. S. Gutowsky and J. Hamer, J. Org. Chem., 28 (1963) 1666.