N-Azinylpyridinium *N*-Aminides: Intermediates for the Regioselective Synthesis of 3-Fluoro-2-aminopyridine Derivatives

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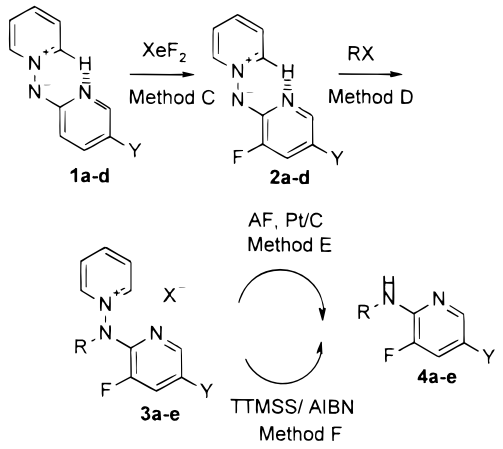
The replacement of hydrogen by fluorine in organic molecules frequently results in dramatic changes in their properties. Improvement in thermal and oxidative stability, alterations of electronic effects, and an increase of lipophilicity have been described for a large variety of molecules, with high interest in medicinal chemistry. The preparation of organofluorine compounds, however, remains a difficult area, and since fluorine itself is so reactive and difficult to control, alternative methods of incorporating fluorine into organic molecules are still required.[1−3]

On the other hand, some of our work has been concerned with reactivity of azinyl-*N*-aminides **1** toward electrophiles, especially sources of X^+ (X = Cl, Br, I) like *N*-halosuccinimides (NXS),[4] and the use of **1** as intermediates in the synthesis of 2-aminoazines. Since fluorination has not been achieved this way, we would like to report the use of xenon difluoride, as an electrophilic fluorine source, to prepare different fluoro-2-aminopyridines.[5]

Results and Discussion

Halo-2-aminopyridines are intermediates of interest in the synthesis of relevant biologically active molecules,[6] and they are usually prepared by direct halogenation of the corresponding 2-aminopyridine. However, 3- or 5-fluoro-2-aminopyridines represent special cases for which a classical method has been used (Balz−Schiemann reaction, from the corresponding amino-2-chloropyridine, and subsequent displacement of chlorine with ammonia).[7] For 5-fluoro-2-aminopyridine, an alternate five-step synthesis from 2-amino-5-nitropyridine, through a difluoroboryl imidate intermediate, has been recently reported,[8] but we found no additional reference for the 3-fluoro derivative. Both methods use the formation and decomposition of the corresponding diazonium salt with variable results. As a continuation of our interest in these kinds of compounds, we planned to study methods of preparation avoiding this step. In this context, reaction of pyridinium *N*-(pyridin-2′-yl)aminide **1a**, followed by alkylation on the exocyclic nitrogen and final fission of the N−N bond, could allow the synthesis of the target compounds (Scheme 1).

Scheme 1



Some attempts to prepare fluorinated aminides using well-known electrophiles such as *N*-fluoropyridinium salts,[9] *N*-fluorosulfonamides,[10] or *N*-fluoroazabicycles[11,12] did not generate any fluorinated product. Xenon difluoride,[13] normally used in the fluorination of vinylstannanes,[14] aromatics,[15,16] and heteroaromatics[17−19] with variable results, initially produced poor yields of **2a** [entry 1, Table 1, method A: portionwise addition at 0 °C of 1.5 mmol of solid xenon difluoride to a dispersion of potassium carbonate (1.25 mmol) and **1a** (1 mmol) in dry acetonitrile, under an atmosphere of dry argon; entry 2, Table 1, method B: dropwise addition at −40 °C of 1 mmol of xenon difluoride solution in dry acetonitrile to a dispersion of potassium carbonate (1.25 mmol) and **1a** (1 mmol) in dry acetonitrile, under an atmosphere of dry argon]. Finally, **2a** (entry 3, Table 1, method C) was satisfactorily prepared by dropwise addition, at low temperature (−40 °C), of equimolar amounts of xenon difluoride solution in dry dichloromethane to a dispersion of potassium carbonate and **1a** in dry dichloromethane, although small changes in reaction conditions and solvents[20] or reactant proportions caused dramatic changes in the reaction yield. Surprisingly, **2a** was identified as pyridinium *N*-(3′-fluoropyridin-2′-yl)aminide, while no 5-monofluoro nor difluoro derivatives were detected.[21]

The assignment of protons for the 2-iminopyridine moiety in **2a** was carried out by means of double

(1) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley-Interscience: New York 1991.
(2) Resnati, G. *Tethahedron* **1993**, *49*, 9385.
(3) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.
(4) Burgos, C.; Delgado, F.; García-Navio, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **1995**, *51*, 8649.
(5) Paquette, L. A. *Reagents for Organic Synthesis 815515*; John Wiley and Sons Ltd: New York, 1995.
(6) Randl, S.; Bouzard, D. *Heterocycles* **1992**, *34*, 2143.
(7) Saito, N.; Kurihara, T.; Yasuda, S.; Yamanaka, K.; Tsuruta, S.; Tanaka, T.; Inamori, Y. *Yakugaku Zasshi* **1968**, *88*, 1610; *Chem. Abstr.* **1969**, *70*, 87639.
(8) Hand, E. S.; Baker, D. C. *Synthesis* **1989**, 905.
(9) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.
(10) Differding, E.; Ofner, H. *Synlett.* **1991**, 187.
(11) Banks, R. E.; Mohialdin-Kyaffaf, S. N.; Lal, G. S.; Sharif, Y.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595.
(12) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791.
(13) Tius, M. A. *Tetrahedron* **1995**, *52*, 6605.
(14) Tius, M. A.; Kawakami, J. K. *Synth. Commun.* **1992**, *22*, 1461.
(15) Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1993**, *34*, 4355.
(16) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505.
(17) Anand, S. P.; Filler, R. *J. Fluorine Chem.* **1976**, *7*, 179.
(18) Filler, R. *Isr. J. Chem.* **1978**, *17*, 71.
(19) Wang, J.; Scott, I. *Tetrahedron Lett.* **1994**, *35*, 3679.
(20) Dukat, W. W.; Holloway, J. H.; Hope, E. G.; Townson, P. J.; Powell, R. L. *J. Fluorine Chem.* **1993**, *62*, 293.

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Table 1. Compounds 2−4 Obtained

entry	compd	X	Y	R	method	yield[a] (%)
1	**2a**		H		A	7
2	**2a**		H		B	15
3	**2a**		H		C	60
4	**2b**		Cl		C	15
5	**2c**		Br		C	25
6	**2d**		I		C	18
7	**3a**	Br	H	H		95[b]
8	**3b**	I	H	Me	D	83
9	**3c**	I	H	Et	D	70
10	**3d**	I	H	Pr	D	64
11	**3e**	I	Cl	Me	D	87
12	**4a**		H	H	E	94
13	**4b**		H	Me	E	84
14	**4b**		H	Me	F	73
15	**4c**		H	Et	E	89
16	**4c**		H	Et	F	70
17	**4d**		H	Pr	E	93
18	**4e**		Cl	Me	E	90

[a] Yields refer to isolated pure product. All the products were identified by spectroscopic and literature data. Method A: XeF_2, K_2CO_3, MeCN, 0 °C. Method B: XeF_2, K_2CO_3, MeCN, −40 °C. Method C: XeF_2, K_2CO_3, CH_2Cl_2, −40 °C. Method D: RX, acetone, rt. Method E: Pt/C, AF, MeOH, 80 °C. Method F: TTMSS, AIBN, *t*-BuOH, 80 °C. [b] See Experimental Section.

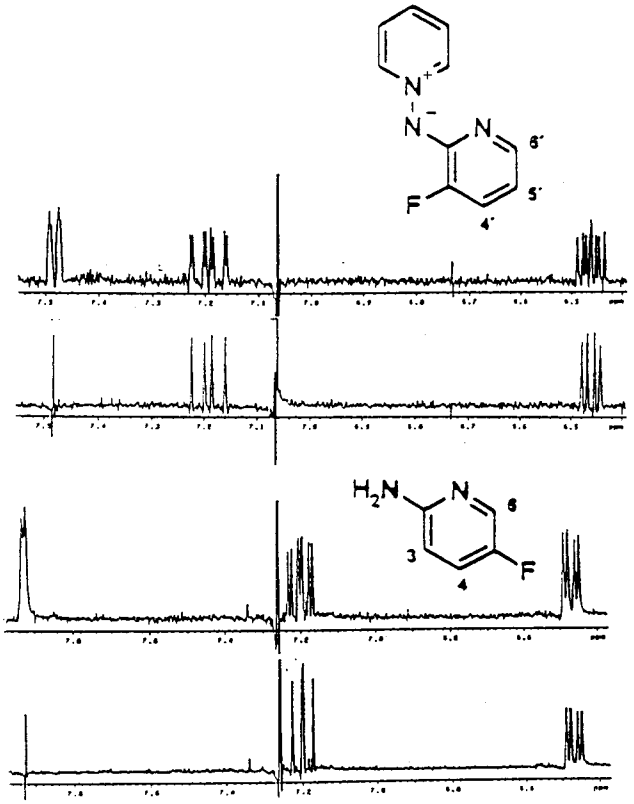


Figure 1.

resonance experiments and by decoupling spectra and literature data for the 5-fluoro-2-aminopyridine, obtained according to Baker et al.[8] For compound **2a**, on saturating the unambiguous H6′ signal, at 7.48 ppm, signals at 7.20 ppm (H4′) and 6.40 ppm (H5′) were simplified into two doublet of doublets. However, for 5-fluoro-2-aminopyridine, on saturating H6 signal at 7.92 ppm, the H3 signal at 6.46 ppm did not change (Figure 1). The 3-fluorine position was confirmed in the ^{1}H NMR spectra by the multiplicity of the methyl group in compound **3b** (Y = H, R = Me, and X = I, Scheme 1), which appears as a doublet due to the *long-range* coupling with F, and in the

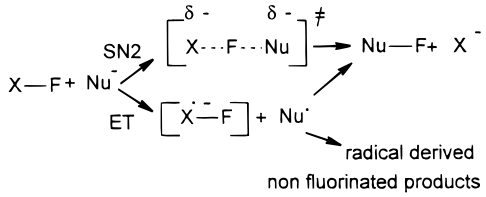
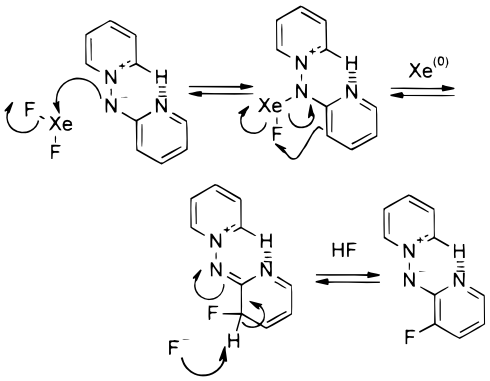


Figure 2. Possible pathways in the reaction $Nu^- + XF$.[22]

Scheme 2



^{13}C NMR spectra in compounds **3b**−**e** by the small coupling constant between fluorine in the 3-position and the alkyl group attached on the exocyclic nitrogen.

There has been a considerable dispute about the possible mechanism of electrophilic fluorination, whether it could be a simple fluorine transfer or a two-step pathway, where an electron-transfer precedes a fluorine radical attack (Figure 2).[22] Independent of the path involved in the process, we would suggest a reaction course as described in Scheme 2, which agrees with the formation of the most sterically hindered α-isomer[23] and with the production of HF during the reaction process.

Fluorination was tried with other aminides (**1b**, Y = Cl; **1c**, Y = Br; **1d**, Y = I, Scheme 1) under similar conditions, yielding aminides **2b**−**d** with lower yields.[24] Traces of 3,5-dibromo derivative (≈5%) were detected in the preparation of **2c**, probably related with a previously described ipso substitution.[4]

The direct alkylation of heterocyclic aminides is usually unsatisfactory as a preparative method as it mainly occurs at the most basic endocyclic nitrogen.[25] However,

(21) Initially, the crude reaction mixture was tested by ^{1}H NMR. Reaction of **1a** with xenon difluoride leads to **2a** as the only fluorinated identifiable product. Since xenon difluoride is also a strong oxidant agent, competition between the fluorofunctionalization and oxidation processes can take place: small amounts of highly colored products were observed that were removed during the chromatographic procedure (for byproducts $R_f \approx 0.2$, for compound **2a** $R_f \approx 0.6$, silica gel, ethanol). On the other hand, fluorination of **2a** with xenon difluoride does not provide the difluoro derivative compound, but only oxidized byproducts were observed. In this way, no fluorinated compounds were detected in the reaction with other aminides, as pyridinium *N*-(pyrimidin-2′-yl)aminide.

(22) Differding, E.; Rüegg, G. M. *Tetrahedron Lett.* **1991**, *32*, 3815.

(23) Polishchuk, V. R.; German, L. S. *Tetrahedron Lett.* **1972**, *51*, 5169.

(24) The negative charge on the exocyclic nitrogen facilates the reaction of the pyridine nucleus toward electrophiles. This ability is decreased for compounds **2a**−**e** due to the high electronegativity of halogen atom in the 5-position. Lower yields for fluorination in 5-haloaminides could be partially attributed to this effect. On the other hand, coordination of the xenon difluoride to the halogen in 5-position could also be an undesirable effect, but some attempts of fluorination increasing concentration of xenon difluoride did produce complex mixtures.

(25) Goerdeler, J.; Roth, W. *Ber.* **1963**, *96*, 534.

in pyridinium-N-(2′-azinyl)aminides, endocyclic nitrogen is partially blocked by an intramolecular hydrogen bond, making the alkylation regioselective on the exocyclic nitrogen.[26] Fluorinated aminides **2** were reacted, at room temperature, with the corresponding alkyl halide producing *N*-alkyl derivatives **3b**−**d** in good yields.

In a preceding paper,[4] we reported the N−N bond fission in halogenated aminides using formic acid/triethylamine in the presence of platinum on carbon. In that way, the unsubstituted 3-fluoro-2-aminopyridine **4a** (R = H, Y = H, Scheme 1) could be obtained. However, in the present case involving *N*-alkyl derivatives, better results were obtained using ammonium formate (AF)[27] (method E) or tris(trimethylsilyl)silane (TTMSS)/AIBN[28−30] as a radical-reducing agent (method F). The results are summarized in Table 1. All the fluoro-2-aminopyridines obtained were readily decomposed by moist air by warm ethanol, or upon heating and, thus, appear to be considerably less stable than the pyridinium salts **3**. The latter compounds can be used as stable and handy precursors of the aminopyridine derivatives.

Experimental Section

General Methods. All experiments were carried out under an atmosphere of dry argon. ^{1}H, ^{13}C, and ^{19}F spectra were recorded on a Varian UNITY 300 MHz spectrometer.

The following compounds were prepared according to literature procedures: pyridinium *N*-(pyridin-2′-yl)aminide **1a**,[26] pyridinium *N*-(5′-chloropyridin-2′-yl)aminide **1b**,[4] pyridinium *N*-(5′-bromopyridin-2′-yl)aminide **1c**,[4] and pyridinium *N*-(5′-iodopyridin-2′-yl)aminide **1d.**[4]

General Procedure for the Preparation of Pyridinium *N*-(3′-Fluoropyridin-2′-yl)aminides 2a−d. Method C (Scheme 1, Table 1). A solution of XeF_2 (0.100 g, 0.58 mmol) in 20 mL of dry dichloromethane was added dropwise (rate of addition 0.5 mL/min) to a stirred suspension of **1** (0.58 mmol) and anhydrous K_2CO_3 (0.100 g, 0.72 mmol) in 4 mL of dry dichloromethane at −40 °C. After being stirred for 30 min, distilled water (5 mL) was added dropwise at the same temperature. Then, the reaction mixture was allowed to warm to room temperature. After separation of the organic layer, the aqueous solution was extracted with ethyl acetate. All the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, providing a crude product that was purified using flash chromatography (silica gel, ethanol) to yield the corresponding aminide **2**.

Pyridinium *N*-(3′-fluoropyridin-2′-yl)aminide (2a): orange plates (60%); mp 120−1 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (dd, 2H, J = 6.5, 1.1 Hz), 8.18 (t, 1H, J = 7.7 Hz), 7.90 (t, 2H, J = 7.1 Hz), 7.49 (d, 1H, J = 5.1 Hz), 7.21 (ddd, 1H, J = 11.8, 7.7, 1.4 Hz), 6.46 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 155.9 (d, J = 8.3 Hz), 148.6 (d, J = 253.7 Hz), 145.6, 142.1 (d, J = 5.5 Hz), 139.2, 128.7, 121.4 (d, J = 16.5 Hz), 111.7; ^{19}F NMR (282 MHz, $CFCl_3$ internal standard, CD_3OD) δ −139.10 (dd, J = 11.9, 3.4 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 189 (33, M^+), 79 (26). Anal. Calcd for $C_{10}H_8N_3F$: C, 63.49; H, 4.26; N, 22.21. Found: C, 63.26; H, 4.38; N, 22.19.

Pyridinium *N*-(5′-chloro-3′-fluoropyridin-2′-yl)aminide (2b): yellow oil (15%); ^{1}H NMR (300 MHz, CD_3OD) δ 8.77 (dd, 2H, J = 6.9, 1.1 Hz), 8.16 (tt, 1H, J = 7.7, 1.1 Hz), 7.87 (dd, 2H, J = 7.7, 6.9 Hz), 7.45 (d, 1H, J = 2.2 Hz), 7.25 (dd, 1H, J = 11.0, 2.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 154.8 (d, J = 6.8 Hz), 147.5 (d, J = 259.5 Hz), 145.3, 140.0 (d, J = 4.6 Hz), 139.1, 128.3, 121.5 (d, J = 19.2 Hz), 116.1 (d, J = 2.2 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 225 (8, M^+), 223 (32, M^+), 79 (99).

Pyridinium *N*-(5′-bromo-3′-fluoropyridin-2′-yl)aminide (2c): yellow oil (25%); ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (dd, 2H, J = 7.0, 1.2 Hz), 8.14 (tt, 1H, J = 7.7, 1.2 Hz), 7.86 (dd, 2H, J = 7.7, 7.0 Hz), 7.50 (d, 1H, J = 1.8 Hz), 7.32 (dd, 1H, J = 11.0, 1.8 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 269 (2, M^+), 267 (2, M^+), 81 (35), 79 (100), 78 (51).

Pyridinium *N*-(3′-fluoro-5′-iodopyridin-2′-yl)aminide (2d): orange oil (18%); ^{1}H NMR (300 MHz, CD_3OD) δ 8.72 (dd, 2H, J = 6.9, 1.2 Hz), 8.12 (t, 1H, J = 7.7 Hz), 7.85 (dd, 2H, J = 7.7, 6.9 Hz), 7.59 (d, 1H, J = 1.8 Hz), 7.36 (dd, 1H, J = 11.0, 1.8 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 315 (48, M^+), 188 (12), 127 (59), 79 (100).

***N*-(3′-Fluoropyridin-2′-ylamino)pyridinium Bromide Hydrobromide (3a).** To a stirred solution of 0.189 g of **2a** (1 mmol) in 5 mL of ethanol was added dropwise in an ice−water bath 3 mL of HBr 40% in water. The solution was evaporated in vacuo to dryness, and the crude product **3a** was crystallized from absolute ethanol: white powder (95%); mp 216−20 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 9.11 (dd, 2H, J = 6.9, 1.4 Hz), 8.79 (tt, 1H, J = 7.9, 1.4 Hz), 8.26 (bt, 2H, J = 7.3 Hz), 7.85 (d, 1H, J = 4.2 Hz), 7.68 (ddd, 1H, J = 10.8, 8.1, 1.2 Hz), 7.10 (ddd, 1H, J = 8.1, 4.2, 3.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 148.9, 148.2 (d, J = 255.1 Hz), 147.9, 146.5 (d, J = 12.9 Hz), 143.4 (d, J = 5.7 Hz), 130.2, 124.9 (d, J = 15.2 Hz), 120.7 (d, J = 2.5 Hz). Anal. Calcd for $C_{10}H_{10}N_3Br_2F$: C, 34.22; H, 2.87; N, 11.97. Found: C, 33.88; H, 3.14; N, 12.24.

General Procedure for the Preparation of *N*-Alkyl-*N*-(3′-Fluoropyridin-2′-yl-amino)pyridinium Derivatives 3b−e. Method D (Scheme 1, Table 1). Alkyl iodide (1.82 mmol) was added via a syringe to a stirred solution of corresponding **2** (1.22 mmol) in 10 mL of dry acetone. The solution was stirred at room temperature until full consumption of **2** (1 day for compound **3b**, 3 days for compounds **3c**−**d**). The resulting suspension was filtered, and the solid was washed with ether and crystallized from absolute ethanol.

***N*-[(3′-Fluoropyridin-2′-yl)methylamino]pyridinium iodide (3b):** white powder (83%); mp 132−4 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 9.32 (d, 2H, J = 5.4 Hz), 8.78 (t, 1H, J = 7.8 Hz), 8.27 (bt, 2H, J = 7.3 Hz), 8.11 (d, 1H, J = 4.7 Hz), 7.69 (ddd, 1H, J = 11.9, 8.2, 1.4 Hz), 7.30 (ddd, 1H, J = 8.2, 4.7, 3.2 Hz), 3.78 (d, 3H, J = 1.1 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 150.8 (d, J = 259.2 Hz), 148.9, 148.8, 146.9 (d, J = 9.7 Hz), 144.8 (d, J = 5.5 Hz), 130.7, 126.9 (d, J = 17.4 Hz), 123.9 (d, J = 2.7 Hz), 43.8 (d, J = 5.5 Hz). Anal. Calcd for $C_{11}H_{11}N_3IF$: C, 39.90; H, 3.35; N, 12.69. Found: C, 39.69; H, 3.33; N, 12.23.

***N*-[(3′-Fluoropyridin-2′-yl)ethylamino]pyridinium iodide (3c):** white powder (70%); mp 108−10 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 9.33 (d, 2H, J = 5.1 Hz), 8.77 (t, 1H, J = 7.7 Hz), 8.27 (bt, 2H, J = 7.3 Hz), 8.15 (d, 1H, J = 4.7 Hz), 7.69 (ddd, 1H, J = 11.9, 8.1, 1.4 Hz), 7.32 (ddd, 1H, J = 8.1, 4.7, 3.4 Hz), 4.19 (bq, 2H, J = 7.1 Hz), 1.27 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 151.3 (d, J = 257.5 Hz), 149.2, 148.7, 146.3 (d, J = 9.1 Hz), 144.6 (d, J = 5.5 Hz), 130.6, 126.9 (d, J = 17.3 Hz), 124.2 (d, J = 2.0 Hz), 51.9 (d, J = 2.7 Hz), 12.8. Anal. Calcd for $C_{12}H_{13}N_3IF$: C, 41.76; H, 3.80; N, 12.17. Found: C, 41.49; H, 3.43; N, 12.26.

***N*-[(3′-Fluoropyridin-2′-yl)propylamino]pyridinium iodide (3d):** white powder (64%); mp 168−70 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 9.34 (d, 2H, J = 5.4 Hz), 8.80 (t, 1H, J = 7.8 Hz), 8.27 (bt, 2H, J = 7.1 Hz), 8.13 (d, 1H, J = 4.7 Hz), 7.70 (ddd, 1H, J = 11.5, 8.1, 1.4 Hz), 7.32 (ddd, 1H, J = 8.1, 4.7, 3.4 Hz), 4.08 (bt, 2H, J = 7.3 Hz), 1.63 (m, 2H), 1.06 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 151.3, 149.1, 148.8, 146.5 (d, J = 9.1 Hz), 144.7 (d, J = 5.0 Hz), 130.6, 127.0 (d, J = 18.1 Hz), 124.2, 58.9, 21.5, 11.7. Anal. Calcd for $C_{13}H_{15}N_3IF$: C, 43.47; H, 4.21; N, 11.70. Found: C, 43.49; H, 4.33; N, 11.45.

***N*-[(5′-Chloro-3′-fluoropyridin-2′-yl)methylamino]pyridinium iodide (3e):** white powder (87%); mp 142−3 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 9.34 (dd, 2H, J = 4.9, 1.4 Hz), 8.76 (tt, 1H, J = 7.8, 1.4 Hz), 8.29 (dt, 2H, J = 7.8, 4.9 Hz), 8.16 (d, 1H, J = 1.8 Hz), 7.90 (dd, 1H, J = 11.1, 1.8 Hz), 3.78 (d, 3H, J = 1.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 154.8 (d, J = 6.7 Hz), 147.8 (d, J = 258.8 Hz), 145.6, 140.3, 139.6, 128.7, 121.8 (d, J =

(26) Carceller, R.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J.; Fajardo, M.; Gómez-Sal, P.; Gago, F. *Tetrahedron* **1994**, *50*, 4995.
(27) Cortese, N. A.; Heck, R. F. *J. Org. Chem*. **1977**, *42*, 3491.
(28) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem*. **1988**, *53*, 3641.
(29) Lesage, M.; Chatgilialoglu, C.; Griller, D. *Tetrahedron Lett*. **1989**, *30*, 2733.
(30) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem*. **1991**, *56*, 678.

18.0 Hz), 116.5, 59.0 (d, J = 3.2 Hz). Anal. Calcd for $C_{11}H_{10}N_3ICIF$: C, 36.14; H, 2.76; N, 11.49. Found: C, 36.49; H, 3.03; N, 11.27.

General Procedure for the Preparation of the Unsubstituted and *N*-Alkyl-Substituted *N*-(3-Fluoro-pyridin-2-yl)amines 4a−e. Method E (Scheme 1, Table 1). A stirred dispersion of corresponding **3** (1 mmol) and 0.125 g of Pt/C (5%) in 37 mL of dry methanol was heated to reflux. Ammonium formate was portionwise added to the mixture, at the same temperature, until full consumption of **3** (for compounds **4b**−**e**, 3 mmol at the beginning and 3 mmol after 3 h, and the mixture was refluxed with stirring for another 4 h). A similar procedure was used for compound **4a**, but after 12 h, TLC analysis showed that little or no reduction had been produced by the ammonium formate. Subsequent additions of 2 mmol/day (total addition 20 mmol) provided the reduction product after 7 days. Then, the reaction mixture was allowed reach room temperature, and the catalyst was removed by filtration through a Celite pad under an argon atmosphere. The filtrate was concentrated under reduced pressure. Then, dry dichloromethane (5 mL) was added to the residue, the mixture was filtered under argon atmosphere, and the filtrate was concentrated again. The process was repeated twice, affording the desired compounds **4**. An analytical sample of **4** was purified by preparative TLC (silica gel, hexanes/ethyl acetate 3:7). Pure amine was obtained as a wax solid (**4a**) or colorless oil (**4b**−**e**).

Method F. A solution of AIBN (0.328 g, 2 mmol) and TTMSS (0.498 g, 2 mmol) in 30 mL of dry *tert*-butyl alcohol was added dropwise to a stirred suspension of the corresponding **3** (1 mmol) and K_2CO_3 (0.276 g, 2 mmol), at 80 °C. The mixture was stirred 1 h at the same temperature. After evaporation in vacuo, the crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 8:2), yielding **4**.

3-Fluoropyridin-2-ylamine (4a): wax solid; method E (94%); mp 46−48 °C (lit.[8] mp 47−49 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 1H, J = 5.2 Hz), 7.10 (ddd, 1H, J = 10.9, 7.9, 1.4 Hz), 6.55 (ddd, 1H, J = 7.9, 5.2, 4.5 Hz), 4.90 (bs, 2H).

(3-Fluoropyridin-2-yl)methylamine (4b): colorless oil, method E (84%), method F (73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 1H, J = 4.8 Hz), 7.10 (ddd, 1H, J = 9.5, 7.7, 1.5 Hz), 6.49 (ddd, 1H, J = 7.7, 4.8, 3.5 Hz), 4.80 (bs, 1H), 3.03 (d, 3H, J = 5.2 Hz); MS (EI, 70 eV) m/z (relative intensity) 126 (8, M^+), 97 (31).

(3-Fluoropyridin-2-yl)ethylamine (4c): colorless oil, method E (89%), method F (70%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, 1H, J = 4.8, 1.4 Hz), 7.07 (ddd, 1H, J = 11.7, 7.8, 1.4 Hz), 6.63 (ddd, 1H, J = 7.8, 4.8, 4.3 Hz), 4.80 (bs, 1H), 3.59 (qi, 2H, J = 7.3 Hz), 0.94 (t, 3H, J = 7.3 Hz); MS (EI, 70 eV) m/z (relative intensity) 140 (10, M^+), 125 (100), 96 (35).

(3-Fluoropyridin-2-yl)propylamine (4d): colorless oil, method E (90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, 1H, J = 4.7, 1.4 Hz), 7.08 (ddd, 1H, J = 11.5, 7.7, 1.4 Hz), 6.46 (ddd, 1H, J = 7.7, 4.7, 3.0 Hz), 4.90 (bs, 1H), 4.07 (t, 2H, J = 7.3 Hz), 1.41 (qi, 2H, J = 7.3 Hz), 0.97 (t, 3H, J = 7.3 Hz); MS (EI, 70 eV) m/z (relative intensity) 154 (15, M^+), 125 (93), 96 (36).

(5-Chloro-3-fluoropyridin-2-yl)methylamine (4e): colorless oil, method E (90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, 1H, J = 1.8 Hz), 7.15 (dd, 1H, J = 10.4, 1.8 Hz), 4.70 (bs, 1H), 3.01 (d, 3H, J = 4.6 Hz); MS (EI, 70 eV) m/z (relative intensity) 162 (1, M^+), 160 (1, M^+), 95 (14).

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