# Syntheses of 2-Chloro- and 2-Amino-5-fluoropyridines and Isolation of a Novel Difluoroboryl Imidate

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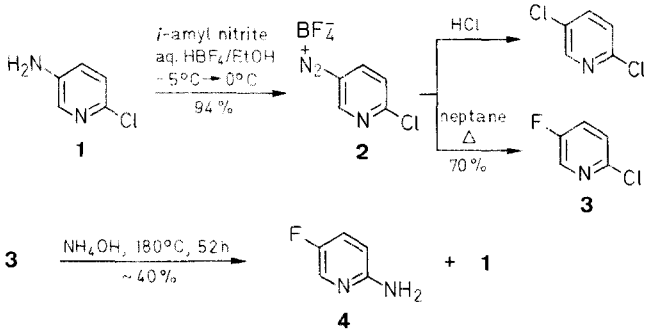
The highly volatile, weakly basic 2-chloro-5-fluoropyridine (**3**), prepared by diazotization of 5-amino-2-chloropyridine (**1**) with isoamyl nitrite/tetrafluoroboric acid followed by thermolysis (70%) has been characterized. Reaction of **3** with ammonia afforded a 3:1 mixture (40%) of **1** and 2-amino-5-fluoropyridine (**4**). An alternate, 5-step synthesis gave **4** in 33% overall yield from 2-amino-5-nitropyridine (**5**). One of the intermediates was shown to have a novel difluoroboryl imidate **10** structure.

In a project, in which a number of heterocyclic diazoates were evaluated as antitumor agents,[1] sodium 5-fluoropyridine-2-diazoate was targeted for synthesis. The synthetic precursor, 2-amino-5-fluoropyridine (**4**), was required. This aminopyridine is known[2] and has been prepared by diazotization of 5-amino-2-chloropyridine (**1**), followed by thermolysis of the resulting diazonium tetrafluoroborate **2** to give 2-chloro-5-fluoropyridine (**3**), and subsequent displacement of chlorine with ammonia. Herein are reported some aspects of our attempts to duplicate this procedure and an alternate method, by which 2-amino-5-fluoropyridine (**4**) was successfully prepared.




The starting material **1** was best prepared by hydrogenation of 2-chloro-5-nitropyridine in the presence of Raney nickel.[3] Use of 10% palladium on activated charcoal catalyst resulted in extensive dechlorination and formation of 3-aminopyridine. Reduction with tin(II) chloride[4] or iron powder[5] was more time-consuming and gave products of inferior quality.

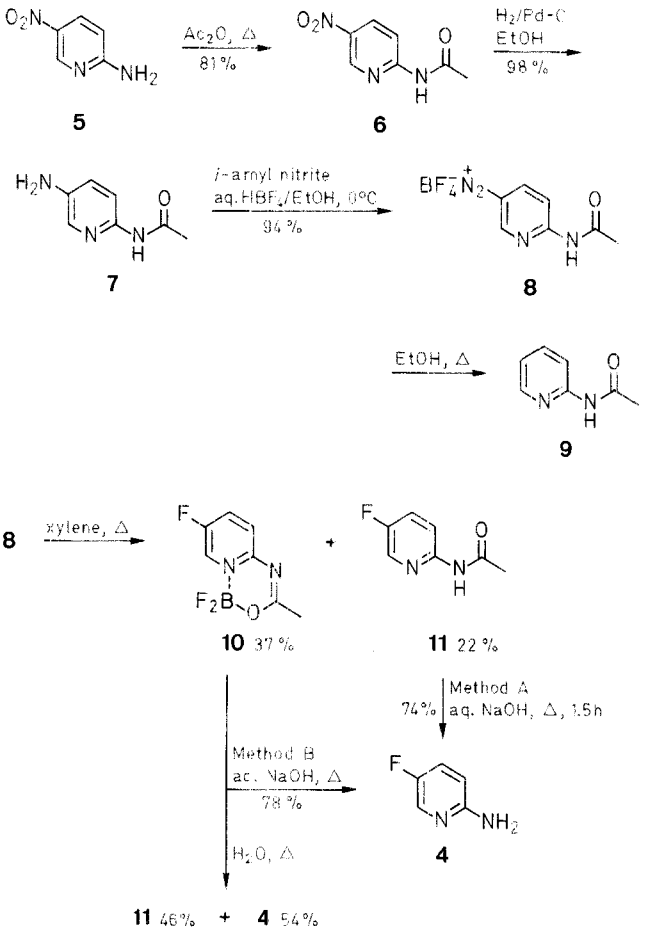
Diazotization of **1** with isoamyl nitrite proceeded smoothly under conditions similar to those reported[2] to give **2**. However, thermolysis of **2** in boiling hexane for 21 h gave only 15% of **3** which was, moreover, contaminated with 2,5-dichloropyridine as determined by GC/MS analysis. Formation of the latter is attributed to decomposition of unreacted **2** by hydrochloric acid, which was added during the workup.

Conversion of **2** to **3** was achieved at higher temperatures (refluxing heptane). 2-Chloro-5-fluoropyridine (**3**)[6] is a highly volatile, low-melting, colorless substance, which has an odor reminiscent of iodoform and coevaporates with most solvents, including heptane and hexane. Furthermore, it is a very weak base: for the conjugate acid, a $pK_a$ value of $-1.5$ is calculated from the $pK_a$ of 2-chloropyridine (0.7) and the effect of a 3-fluoro substituent[8] on the $pK_a$ of pyridine ($\Delta = -2.2$). For successful isolation of **3**, strong acid (e.g., concentrated sulfuric acid) must be used to form the conjugate acid; the free base can be obtained in good yield only from a low-boiling solvent (e.g., diethyl ether).

Attempts to convert **3** to 2-amino-5-fluoropyridine (**4**) with aqueous ammonium hydroxide according to the published procedure[2] led to divergent results. The reaction was incomplete even after longer heating than the requisite 36 hours[9] at 180°C and afforded primarily 2-chloro-5-aminopyridine (**1**); i.e., the 5-fluoro-, not the 2-chloro-, substituent was more easily displaced. The difference in this result and those previously reported[2] may be due to the adventitious presence of a catalyst or inhibitor. In our experiments, for example, traces of copper ions may have been present since the fittings of the pressure gauge attached to the stainless steel reaction vessel were made of brass.

Since the approach of introducing the 2-amino substituent, after the 5-fluoro substituent had been placed, failed, a synthesis wherein fluorine is introduced into an appropriately substituted 2-aminopyridine derivative was developed. 2-Amino-5-fluoropyridine (**4**) was prepared in overall 33% yield (not maximized) by a 5-step sequence. The amino group of 2-amino-5-nitropyridine (**5**) was protected by acetylation to give **6**.

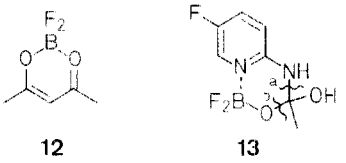
Hydrogenation (10% palladium on activated carbon) of **6** gave 2-acetamido-5-aminopyridine (**7**), which was converted to a hydrate of 2-acetamido-5-pyridinediazonium tetrafluoroborate (**8**) by treating an ethanolic suspension of **7** containing aqueous tetrafluoroboric acid with isoamyl nitrite. Each of these reactions appears to be quantitative, although some losses were incurred on purification of the products.




The diazonium fluoroborate **8** is surprisingly stable. Thus, a $^1$H-NMR spectrum recorded immediately after the preparation of a solution in deuterium oxide was the same as that recorded after 1.5 h. Boiling a hexane or benzene suspension of **8** for several hours resulted only in removal of the water of hydration. Rapid crystallization from ethanol gave analytically pure **8**. Prolonged heating of an ethanolic solution of the diazonium compound **8** resulted in the expected replacement of the diazonium moiety by hydrogen.[10] Thus 2-acetamidopyridine (**9**), obtained by neutralization of an initially formed salt, was identified by mass and $^1$H-NMR spectral comparisons and admixture melting point with an authentic sample of **9**.

Heating a suspension of the diazonium fluoroborate **8** in xylene at 120 °C gave a mixture, from which compounds **10** (37%) and **11** (22%) were isolated. The structure of the difluoroboryl imidate **10** was inferred from its elemental analyses and spectral data. A mass spectrum showed the parent ion [$M^{+\cdot}$ ($^{11}$B) = 202, 19% and ($^{10}$B) = 201, 5%] and fragments due to loss of masses 19 (F, 6%), 41 ($CH_3CN$, 77%), 42 ($CH_2CO$, 19%), 65 ($F_2BO$, 12%), 90 ($F_2BOCCH$, 14%), and 105 ($F_2BOCNCH_2$, 36%), among others. The *m/z* values of the fragments formed by the last two mass losses correspond to the molecular ions of 2-amino-5-fluoropyridine and 3-fluoropyridine, respectively.

NMR spectra (see Experimental Section) showed the presence of three aromatic protons, one methyl group, and two types of fluorine atoms in the ratio of 1:2. Chemical shifts of $CH_3$ and $BF_2$ ($\delta$ = 2.33 and −138.85) are similar to those observed for the difluoroboron enol ether of acetylacetone (**12**) ($\delta$ = 2.31 and −138.2).[11] The latter is decomposed by moist air, warm ethanol or upon heating[11] and thus appears to be considerably less stable than the difluoroboryl imidate **10**. While such imidates might be formed during the boron trifluoride catalyzed hydrolysis of amides, such compounds have not been previously described. The considerable stability of **10** is attributed to strong intramolecular bonding of boron to the pyridine nitrogen.




Aqueous hydrolysis (ca pH 6, 80 °C) of the difluoroboryl imidates **10** gave the fluoroamide **11** and the fluoroamine **4** in similar amounts. These products are expected to arise by cleavage of the O–C (b) and N–C (a) bonds, respectively, in the hydrolysis intermediate **13**.

Hydrolysis of **11** contaminated with **10**, or of pure **11**, with aqueous sodium hydroxide gave 2-amino-5-fluoropyridine (**4**) in high yield. In contrast to many aminopyridines, the colorless compound is stable in the presence of air and/or light, and it readily sublimes near its melting point (94 °C) or at room temperature *in vacuo*.

Reagents were purchased from Aldrich Chemical Co., except for 10% Pd/C catalyst, which was obtained from Alpha Products Division of Morton Thiokol, Inc. $HBF_4$ was purchased from Fluka Chemical Co., and silica gel adsorbent for column chromatography (70–230 mesh) and analytical TLC plates (0.2 mm) were purchased from E. Merck (Darmstadt). Melting points were determined with a Thomas Hoover Unimelt apparatus and are uncorrected. Mass spectra were obtained with either a Hewlett Packard 5985A quadrupole (Q) or with a Perkin Elmer RMU-6 magnetic sector (M) instrument operating in the EI mode (70 eV). NMR spectra were obtained at 200 MHz using a Nicolet NT-200 spectrometer; $^1$H-NMR chemical shifts are relative to internal TMS; $^{19}$F chemical shifts were measured relative to external $CF_3CO_2H$ ($\delta$ = −78.5) and are corrected to $CFCl_3$ ($\delta$ = 0); *J* values (Hz) are apparent first-order coupling constants. Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, GA. Compounds on TLC plates were detected by means of a Mineralight lamp (UVS-54).

**2-Chloro-5-pyridinediazonium Tetrafluoroborate (2):**
A stirred solution of 2-chloro-5-aminopyridine[3] (**1**; 5.55 g, 43 mmol) in EtOH (50 mL), placed in an ice-salt bath, is treated with 48% aq. $HBF_4$ (16.6 mL, 90 mmol) and cooled to −5 °C. Isoamyl nitrite (6.1 mL, 45 mmol) is added dropwise during 5 min, so that the temperature does not rise above 0 °C. After ca one-half of the nitrite has been added, the product begins to separate exothermally. Stirring is continued for an additional 30 min, and the solid is filtered and rinsed with absolute EtOH[12] and $Et_2O$. The resulting pale yellow product **2** is stored at −20 °C; yield: 8.46 g (94%); mp 105 °C (dec).

**2-Chloro-5-fluoropyridine (3):**
A stirred mixture of **2** (9.19 g, 44 mmol) and dry heptane[13] (50 mL) is heated at gentle reflux for 3 h, when evolution of $N_2$ has ceased. The mixture is cooled, and the reflux condenser rinsed with $Et_2O$. The upper heptane/$Et_2O$ layer is decanted/filtered, and the dark lower layer is stirred with $Et_2O$ (2 × 20 mL). Most of the $Et_2O$ of the combined organic solutions is evaporated under reduced pressure. The remaining

heptane solution is then stirred overnight with conc. $H_2SO_4$ (1.4 mL), the supernatant layer is decanted, and the $H_2SO_4$ layer is rinsed with pentane (3 × 5 mL). After residual pentane has evaporated, addition of ice to the $H_2SO_4$ solution gives a voluminous precipitate. The mixture is treated with water and 5 N aq. NaOH (10 mL) and extracted with $Et_2O$ (1 × 50 mL, 2 × 20 mL). The extracts are dried ($MgSO_4$), and the solvent is evaporated under reduced pressure to give **3** (1.01 g). The major portion of **3** is obtained by treating the $Et_2O$-extracted dark, lower layer (see above) with water and aqueous NaOH to pH 8, followed by steam distillation. The distillate (ca 100 mL) is saturated with NaCl and extracted with $Et_2O$ (1 × 30 mL, 2 × 20 mL). The extracts are dried ($MgSO_4$), and the solvent is evaporated to give **3** (3.07 g); total yield: 4.08 g (70%). After distillation at atmospheric pressure, **3** is a colorless solid; bp 147°C; mp 19.5°C; TLC ($CHCl_3$) $R_f$ = 0.85. Redistillation under reduced pressure gives analytically pure **3**; bp 74°C/50 mbar; mp 23–24°C.

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|---|---|---|---|---|---|
| $C_5H_3ClFN$ | calc. | C 45.65 | H 2.30 | N 10.65 | Cl 26.95 |
| (131.5) | found | 45.71 | 2.32 | 10.63 | 27.03 |

$^1$H-NMR ($CDCl_3$): $\delta$ = 7.29–7.42 (m, 2 H, H-3, 4); 8.26 (s, 1 H, H-6).

$^{19}$F-NMR ($CDCl_3$): $\delta$ = −130.31 (dd, $J_{F,H-4}$ = 6.8 Hz, $J_{F,H-3}$ = 4.0 Hz).

MS (Q, EI): *m/z* = 131, 133 ($M^{+\cdot}$, 100, 46); 96 [$(M-Cl)^+$, 75]; 76 [$(M-Cl-HF)^+$, 30]; 69 [$(M-Cl-HCN)^+$, 15].

**Reaction of 2-Chloro-5-fluoropyridine (3) with Ammonium Hydroxide:**
A mixture of **3** (4.0 g, 30 mmol) and conc. aq. $NH_4OH$ (50 mL) in a stainless steel vessel (75 mL) equipped with a pressure gauge is shaken in an oilbath heated to 180°C for 52 h. The cooled mixture is treated with ice and conc. HCl to pH ~ 7 and extracted sequentially with $Et_2O$ (4 × 25 mL) and $CH_2Cl_2$ (4 × 25 mL). The combined extracts are dried ($MgSO_4$) and evaporated under reduced pressure to give a solid (2.98 g), which on standing, becomes partially liquid. Extraction with pentane (5 × 10 mL) gives an insoluble solid (1.9 g); evaporation of the solvent affords slightly impure starting material **3** (0.72 g) according to $^1$H-NMR and TLC analyses. The insoluble solid fraction is fractionated by column chromatography (silica gel, 30 g, $Et_2O$). Early fractions contain small amounts of **3**, followed by mixtures (1.48 g) of ca 3:1, 1:1 ($^1$H-NMR analysis). [GC/MS analysis (J & W Scientific, Inc. DB-5 fused silica capillary column, 0.25 mm i.d. × 30 m) shows in addition to **1** and **4** the presence of several other materials.] Fractional sublimation (60°C/0.3 mbar) gives mixtures of **1** and **4**, followed by **1**; mp 75.5–77.5°C, undepressed on admixture with authentic **1**.

MS (M, EI): *m/z* = 128, 130 ($M^{+\cdot}$, 100, 35); 101, 103 [$(M-HCN)^+$, 10, 4]; 93 [$(M-Cl)^+$, 44]; 66 [$(M-Cl-HCN)^+$, 49].

**2-Acetamido-5-nitropyridine (6):**
2-Amino-5-nitropyridine (**5**; 10.0 g, 72 mmol) and $Ac_2O$ (25 mL) are heated for 1.5 h in an oil bath at 130°C. The solution is partly cooled, treated with water (15 mL), and heated again for 0.5 h to hydrolyze excess $Ac_2O$. Volatiles are removed under reduced pressure, and the residue is treated with water (25 mL) to give **6** (12.5 g). Crystallization from EtOH affords nearly colorless needles; yield: 10.5 g (81%); mp 195–196°C (Lit.[14] mp 196°C); TLC ($CHCl_3$) $R_f$ = 0.25.

**2-Acetamido-5-aminopyridine (7):**
A solution of **6** (1.1 g, 6.1 mmol) in EtOH (100 mL) is hydrogenated in the presence of 10% Pd/C (0.1 g) in a Paar apparatus for 3.5 h. The mixture is filtered through Celite, and the solvent is evaporated *in vacuo* to give **7** as a light yellow solid; yield: 0.90 g (98%); mp 152–153°C (Lit.[14] mp 154°C); homogeneous by TLC (10% MeOH/$CHCl_3$, $R_f$ = ~0.2). The compound is sensitive to air and/or light.

**2-Acetamido-5-pyridinediazonium Tetrafluoroborate (8):**
A stirred mixture of **7** (0.80 g, 5.3 mmol), EtOH (10 mL) and 48% aq. $HBF_4$ (2 mL), cooled in an icebath, is treated dropwise with isoamyl nitrite (0.8 mL, 6.0 mmol) and then stirred for 75 min. The mixture is diluted with $Et_2O$ (10 mL). Filtration and rinsing with $Et_2O$ gives a hydrate of **8** as light tan needles; yield: 1.33 g (ca. 94%). Water of hydration is removed by boiling the solid with hexane. Analytically pure **8** is obtained by treating the compound (0.50 g) with boiling anhydrous EtOH (40 mL), filtering the hot mixture, rapidly cooling the filtrate in ice, and filtration of the resulting colorless needles (0.27 g); mp 132.5°C (dec). A $^1$H-NMR spectrum of a freshly prepared $D_2O$ solution is the same after 1.5 h; on briefly heating this solution at 100°C, decomposition occurs.

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|---|---|---|---|---|---|
| $C_7H_7BF_4N_4O$ | calc. | C 33.63 | H 2.82 | N 22.41 | |
| (250.0) | found | 33.79 | 2.85 | 22.33 | |

$^1$H-NMR ($CDCl_3$/DMSO-$d_6$, ~2:1): $\delta$ = 1.95 (s, 3 H, $CH_3$), 8.18 (d, 1 H, H-3, $J_{3,4}$ = 9.5 Hz); 8.57 (dd, 1 H, H-4, $J_{3,4}$ = 9.5 Hz, $J_{4,6}$ = 1.9 Hz); 9.22 (d, 1 H, H-6, $J_{4,6}$ = 1.9 Hz); 11.56 (s, 1 H, NH).
$^1$H-NMR (DMSO-$d_6$): $\delta$ = 2.25 (s, 3 H, $CH_3$); 8.49 (d, 1 H, H-3); 8.88 (dd, 1 H); 9.52 (d, 1 H, H-6) 11.85 (s, 1 H).

Boiling the ethanolic mother liquor for 0.5 h and concentrating the solution (to ~4 mL) gives a salt of 2-acetamidopyridine (mp 182–186°C), which is dissolved in water and treated with aq. NaOH to pH ~ 10. Extraction with $CHCl_3$ yields the free base **9**, identified by TLC (5% MeOH/$CHCl_3$, $R_f$ = ~0.5) and $^1$H-NMR spectral comparisons with an authentic sample, prepared by acetylation of 2-aminopyridine.[15]

**Thermolysis of 2-Acetamido-5-pyridinediazonium Tetrafluoroborate (8); Formation of Difluoroboryl *N*-(5-fluoro-2-pyridyl)acetimidate (10):**
Crude diazonium fluoroborate **8** (5.0 g, ca 20 mmol) is boiled with dry benzene (ca. 40 mL) in order to azeotropically remove water. Residual benzene is displaced with dry xylene (30 mL), and the mixture is then heated under reflux for 1.75 h. The solution is decanted from a gum and evaporated *in vacuo* to give a residue consisting primarily of **10** (0.90 g). The gum is extracted with hot, dry benzene (15 mL). Concentration of this extract (to ca 1.2 mL) gives a second crop of **10** (0.23 g). The residue obtained by evaporating the benzene mother liquors *in vacuo* is recrystallized from hexane to give a third crop of **10** (0.35 g); total yield: 1.48 g (37%). Two crystallizations from hexane afford an analytical sample; mp 111.5–112.5°C; TLC (5% MeOH/$CHCl_3$) $R_f$ = ~0.8.

| | | | | | |
|---|---|---|---|---|---|
| $C_7H_6BF_3N_2O$ | calc. | C 41.64 | H 3.00 | N 13.87 | |
| (201.9) | found | 41.79 | 3.06 | 13.75 | |

$^1$H-NMR ($CDCl_3$): $\delta$ = 2.33 (s, 3 H, $CH_3$); 7.39 [dd, 1 H, H-3, $J_{3,4}$ = 9.1 Hz, $J_{F,H-3}$ = 4.7 Hz (the width of these lines is about double that of the lines due to H-4, so that unresolved coupling with H-6 is likely; the single broad peak observed for H-6, expected to be a triplet ($J_{4,6}$ and $J_{F,H-6}$ = 2.4 Hz), also implies coupling of H-3 and H-6 ($J \leq 2.4$ Hz)]; 7.9 (ddd, 1 H, H-4, $J_{3,4}$ = 9.1 Hz, $J_{4,6}$ = 2.4 Hz, $J_{F,H-4}$ = 7.0 Hz; overlap gives 7 lines); 8.19 (br, 1 H, H-6).

$^{19}$F-NMR ($CDCl_3$): $\delta$ = −127.21 (ddd, 1 F, F-5, $J_{F,H-3}$ = 4.7 Hz, $J_{F,H-4}$ = 7.0 Hz, $J_{F,H-6}$ = 2.4 Hz; overlap gives 7 lines); −138.85 (m, 2 F, $F_2B$).

MS (M, EI): See text.

The xylene-insoluble gum is treated with water and $Na_2CO_3$, and the mixture is extracted with $CHCl_3$ (4 × 20 mL). The extracts are dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (1.43 g) that is percolated through silica gel (30 g) with 5% MeOH/$CHCl_3$. Early fractions contain **11** (0.94 g). Sublimation (85°C/0.2 mbar), followed by crystallization from water (charcoal), gives pure **11**; yield: 0.64 g (21%).

**2-Acetamido-5-fluoropyridine (11):**
A solution of **10** (0.37 g, ~1.8 mmol) in water (5 mL) is prepared by heating for 10 min. The solution is cooled and treated with solid $Na_2CO_3$ (0.2 g) to pH ~ 10 to give a precipitate. After cooling to 0°C, the mixture is filtered, and the solid is rinsed with water to afford **11** (90 mg, mp 118–120°C). A second crop (40 mg) precipitates, when the filtrate is saturated with NaCl; total yield: 130 mg (~46%). After standing for 2 d, the aqueous filtrate has pH ~ 7. The pH is increased to ~ 10 by treating with NaOH and the mixture is extracted with $CHCl_3$ (3 × 10 mL). The combined extracts are dried ($MgSO_4$) and evaporated to dryness to give a residue of **4** contaminated with **11** according to TLC and $^1$H-NMR analyses; yield: 0.11 g (ca. 54%).

The combined crops of **11** are recrystallized from water (charcoal) to give long needles; mp 121.5–123°C; TLC (5% (MeOH/$CHCl_3$) $R_f$ = 0.65. Sublimation (80°C/0.2 mbar) affords an analytical sample.

| | | | | | |
|---|---|---|---|---|---|
| $C_7H_7FN_2O$ | calc. | C 54.54 | H 4.58 | N 18.17 | |
| (154.1) | found | 54.35 | 4.59 | 18.10 | |

$^1$H-NMR ($CDCl_3$): $\delta$ = 2.21 (s, 3 H, $CH_3$); 7.45 (ddd, 1 H, H-4, $J_{3,4}$ = 9.2 Hz, $J_{4,6}$ = 2.9 Hz, $J_{F,H-4}$ = 7.5 Hz); 8.12 (d, 1 H, H-6, $J_{4,6}$ = 2.9 Hz); 8.26 (dd, 1 H, H-3, $J_{3,4}$ = 9.2 Hz, $J_{F,H-3}$ = 4.2 Hz); 8.83 (br, 1 H, NH).
$^{19}$F-NMR ($CDCl_3$): $\delta$ = −133.13 (dd, $J_{F,H-3}$ = 4.2 Hz, $J_{F,H-4}$ = 7.5 Hz).

**2-Amino-5-fluoropyridine (4):**

Method A: A mixture of **11** (0.69 g, 4.5 mmol) and 1.6 N aq. NaOH (7.5 mL) is heated under reflux for 1.5 h to give a pale yellow solution, which on standing for 4 d at ambient temperature deposits a solid. The mixture is extracted with $CHCl_3$ (2 × 10 mL), the aqueous phase is saturated with NaCl and again extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers are dried ($MgSO_4$) and evaporated *in vacuo* to give a colorless solid (0.50 g), which is extracted with boiling hexane (75 mL). When the extract is concentrated by boiling (to ~ 8 mL), exothermal crystallization occurs to give nearly colorless plates of **4**; yield: 0.37 g (74%); TLC (5% MeOH/$CHCl_3$) $R_f$ = ~ 0.5. Sublimation (45 °C/0.2 mbar) affords analytically pure **4**; mp 93–93.7 °C (Lit.[2] mp 96–98 °C).

$^1$H-NMR ($CDCl_3$): $\delta$ = 6.46 (dd, 1 H, H-3, $J_{3,4}$ = 8.9 Hz, $J_{F,H-3}$ = 3.5 Hz); 7.20 (ddd, 1 H, H-4, $J_{3,4}$ = 8.9 Hz; $J_{4,6}$ = 2.9 Hz, $J_{F,H-4}$ = 7.9 Hz); 7.92 (d, 1 H, H-6, $J_{4,6}$ = 2.9 Hz).

$^{19}$F-NMR ($CDCL_3$): $\delta$ = −143.1 (dd, $J_{F,H-3}$ = 3.5 Hz, $J_{F,H-4}$ = 7.9 Hz).

MS (Q, EI); *m/z* = 112 ($M^+$, 100); 85 [$(M-HCN)^+$, 52]

Method B: A mixture of **10** (0.72 g, 3.6 mmol) and water (5 mL) is heated at 80 °C for 0.5 h, 5 N aq. NaOH (2.65 mL) is added, heating is continued for 2.2 h, water (5 mL) is added, and the hot solution is clarified by filtration through a heated funnel. The solid, which separates on cooling, is filtered. The filtrate is saturated with NaCl and extracted with $CHCl_3$ (4 × 10 mL). The dried ($MgSO_4$) extracts are evaporated to give a residue that is combined with the separated solid and recrystallized from heptane; yield: 0.31 g (78%).

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