An Efficient Synthesis of (Fluoromethyl)pyridylamines for Labeling with Fluorine-18

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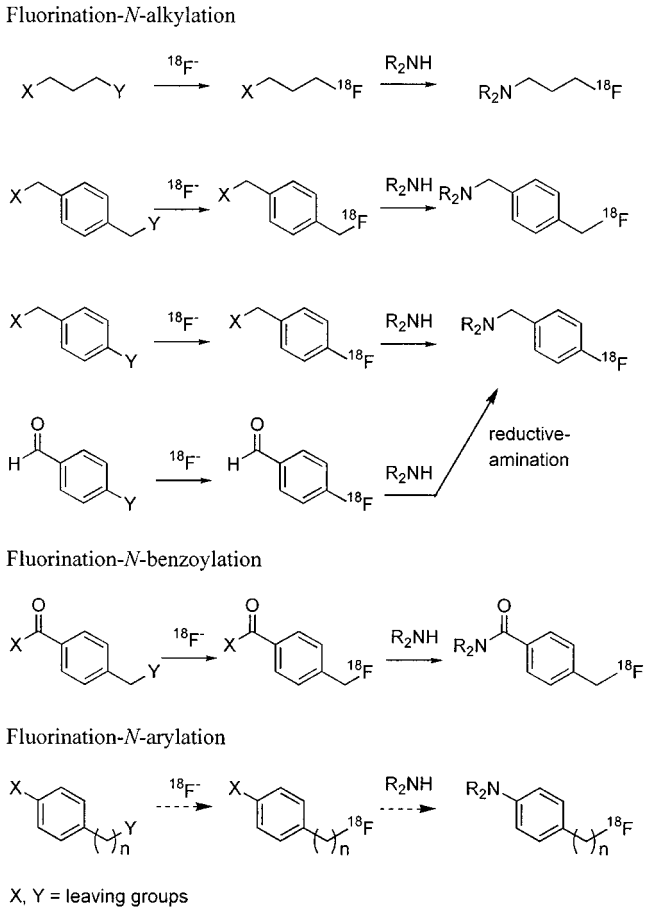
We have described a two-step method for the preparation of (fluoromethyl)pyridyl-substituted amines. The sequence involves fluoride ion displacement of methanesulfonates (mesylates) of 6-chloro-α-hydroxy-2- and -3-picolines, followed by arylation of the amine by chloropicoline. We have called this sequence fluorination−*N*-arylation. 1-Phenylpiperazine has been used as a model amine. Two key precursors for this sequence are the mesylates of 6-chloro-α-hydroxy-2- and -3-picolines. The former was synthesized in four steps from 6-chloro-2-picoline in 78% yield and the latter in three steps from 6-chloronicotinic acid in 53% yield. This fluorination−*N*-arylation sequence is sufficiently rapid and efficient for the preparation of a variety of aryl-substituted amine compounds labeled with the short half-life ($t_{1/2}$ = 110 min) positron-emitting radionuclide fluorine-18.

Introduction

Although positron-emitting radiopharmaceuticals labeled with the short-lived positron emitting radionuclide fluorine-18 ($t_{1/2}$ = 110 min) are being increasingly used in clinical diagnosis, there are few chemical processes suitable for the introduction of fluorine-18 into the organic molecules. We have described a two-step process for the preparation of [^{18}F]fluoroalkyl-substituted amines and amides that involves a fluoride ion displacement of highly reactive trifluoromethylsulfonate (triflate)-substituted alkyl halide followed by an *N*-alkylation step in 1986.[1] This amine fluoroalkyation sequence has been widely used by us and others to prepare [^{18}F]fluoroalkyl-substituted ligands for neuroreceptors.[2,3] More recently, fluorobenzylation,[4] fluorobenzoylation,[5] and (fluoromethyl)benzylation[6] methods have been developed using related fluorination−*N*-alkylation sequences (Scheme 1).

As part of a program to develop some dopamine D_4 receptor antagonists as potential imaging agents for positron emission tomography (PET), we needed a new method to introduce fluroine-18. Kulagowski et al. reported that 7-azaindole **1** is an antagonist having high affinity and selectivity for the D_4 receptor, relative to the D_2 and D_3 receptors.[7] On the basis of the structure of compound **1**, we designed compounds **2** and **3** as target compounds by introducing a [^{18}F]fluoromethyl group as

Scheme 1



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(1) (a) Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Brodack, J. W.; Welch, M. J. *Appl. Radiat. Isot.* **1986**, *37*, 1173. (b) Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Brodack, J. W.; Welch, M. J. *J. Org. Chem.* **1987**, *52*, 658.

(2) (a) Welch, M. J.; Katzenellenbogen, J. A.; Mathias, C. J.; Brodack, J. W.; Carlson, K. E.; Chi, D. Y.; Dence, C. S.; Kilbourn, M. R.; Perlmutter, J. S.; Raichle, M. E.; Ter-Pogossian, M. M. *Nucl. Med. Biol.* **1988**, *15*, 83−97. (b) Shiue, C.-Y.; Bai, L.-Q.; Teng, R.; Wolf, A. P. *J. Labeled Compd. Radiopharm.* **1987**, *24*, 53−64. (c) Kiesewetter, D. O.; Brucke, T.; Finn, R. D. *Appl. Radiat. Isot.* **1989**, *40*, 455. (d) Mulholland, G. K.; Jung, Y.-W.; Wieland, D. M.; Kilbourn, M. R.; Kuhl, D. E. *J. Labeled Compd. Radiopharm.* **1993**, *33*, 583. (e) Wilson, A. A.; Dasilva, J. N.; Houle, S. *Appl. Radiat. Isot.* **1995**, *46*, 765.

(3) (a) Shiue, C.-Y.; Bai, L.-Q.; Teng, R.; Wolf, A. P. *J. Labeled Compd. Radiopharm.* **1987**, *24*, 53. (b) Block, D.; Coenen, H. H.; Laufer, P.; Stoklin, G. *J. Labeled Compd. Radiopharm.* **1986**, *23*, 1042.

(4) Mach, R. H.; Scripko, J. G.; Ehrenkaufer, R. L.; Morton, T. E. *J. Labeled Compd. Radiopharm.* **1991**, *30*, 154.

(5) Eastman, R. C.; Carson, R. E.; Jacobson, K. A.; Shai, Y.; Channing, M. A.; Dunn, B. B.; Bacher, J. D.; Baas, E.; Jones, E.; Kirk, K. L.; Lesniak, M. A.; Roth, J. *Diabetes* **1992**, *41*, 855.

(6) Choe, Y. S.; Song, D. H.; Lee, K.-J.; Kim, S. E.; Choi, Y.; Lee, K. H.; Kim, B.-T.; Oh, S. J.; Chi, D. Y. *Appl. Radiat. Isot.* **1998**, *49*, 1173.

(7) Kulagowski, J. J.; Broughton, H. B.; Curtis, N. R.; Mawar, I. M.; Ridgill, M. P.; Baker, R.; Emms, F.; Freedman, S. B.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1941.

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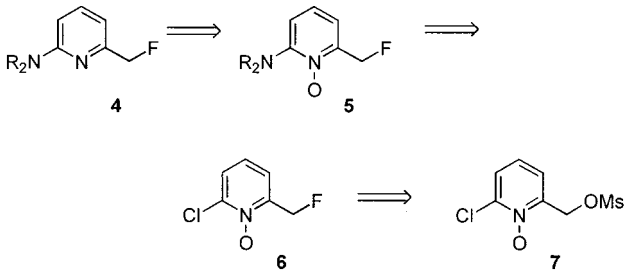
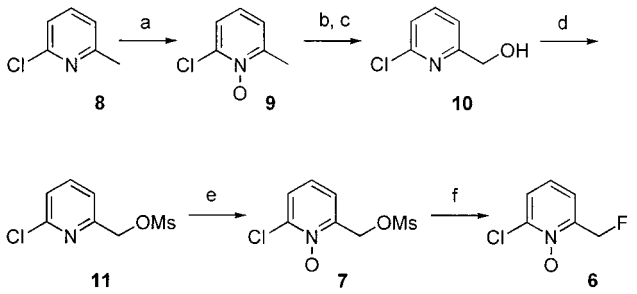
Scheme 2

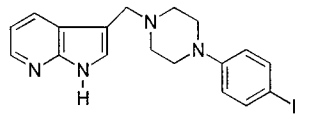


Scheme 3[a]

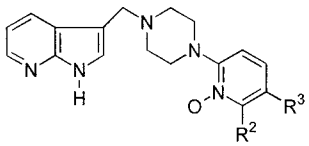


[a] Key: (a) *m*-CPBA, $CHCl_3$, 50 °C, 12 h, 99%; (b) Ac_2O, H_2SO_4, 110 °C, 3 h; (c) K_2CO_3, MeOH/H_2O, rt, 15 min, 83% from **9**; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 96%; (e) *m*-CPBA, $CHCl_3$, 50 °C, 12 h, 99%; (f) $^nBu_4NF{\cdot}xH_2O$, Et_3N, CH_3CN, reflux, 4 h, 43%.

well as nitrogen atom (including its *N*-oxide) into the phenyl ring. As shown in Scheme 1, fluorination−*N*-arylation could be a very useful method to prepare these target compounds in fluorine-18 labeled form. This procedure uses a direct nucleophilic substitution of fluoride ion, which is suitable for preparation of F-18 labeled compounds with a high specific activity, a requirement for many site-specific imaging agents.



1



2, $R^2 = CH_2{}^{18}F$, $R^3 = H$

3, $R^2 = H$, $R^3 = CH_2{}^{18}F$

Despite the usefulness of the fluorination−*N*-arylation sequence, however, there have been no reports on the use of this sequence for labeling with fluorine-18. Here, we report the first example of this fluorination−*N*-arylation sequence.

Results and Discussion

General Strategy. A retrosynthetic scheme to the 6-amino-α-fluoro-2-picoline **4** and its *N*-oxide **5** using the two-step process is outlined in Scheme 2. Compound **4** could be obtained by deoxygenation of *N*-oxide **5**. The amine can be arylated with chloropicoline *N*-oxide **6** by a nucleophilic aromatic substitution displacement (S_NAr) reaction. 6-Chloro-α-hydroxy-2-picoline *N*-oxide can be derivatized as the moderately reactive sulfonate ester (e.g., mesylate, **7**); fluoride ion displaces the mesylate, providing **6**. In this paper, we describe a method for the rapid and efficient synthesis of 6-amino-α-fluoro-2-picoline *N*-oxide using a two-step process: (1) fluoride ion displacement of a mesylate, followed by (2) *N*-arylation with 6-chloro-α-fluoro-2-picoline *N*-oxide **6**. These two reactions can be conducted as a "one-pot" reaction.

Recently, *N*-oxide compounds themselves have been shown to have reasonable metabolic stability and enhanced bioavailability.[8] Because the *N*-oxide can easily be removed by treatment with PCl_3, the (fluoromethyl)-pyridyl-substituted amine can be used either as the *N*-oxide **5** or the amine itself (**4**), thereby providing two potentially interesting compounds having a different polarity.

The S_NAr reaction has been used for the arylation of amines. As the S_NAr reaction of chlorobenzene is generally slow, the use of chlorobenzenes is not practical for labeling with fluorine-18. A comparison of the S_NAr reactions of chlorobenzene and chloropyridines with methoxide ion shows reaction rates of 2-, 3-, and 4-chloropyridine to be 2.76×10^8, 9.12×10^4, and 7.43×10^9, respectively, relative to the rate of chlorobenzene.[9a] When we have performed the S_NAr reaction of 2-chloropyridine with *N*-phenylpiperazine, the reaction has not been successful.

A comparison of S_NAr reactions of chloro-1-methylpyridinium ions with methoxide ion shows these reaction rates of 2-, 3-, and 4-chloro-1-methylpyridinium to be 1.28×10^{21}, 2.62×10^{13}, and 4.23×10^{19}, respectively, relative to the rate of chlorobenzene.[9a] Thus, *N*-methyl salts of chloropyridines react faster than their nonalkylated analogues by roughly a factor of 10^{10}. The rationale for using chloropyridinium *N*-oxide is as follows: (1) the removal of the methyl group of 1-methylpyridiniums is not always easy; (2) chloropyridinium *N*-oxides are readily deoxygenated; (3) their S_NAr reactivity is expected to be between that of chloropyridines and the chloro-1-methylpyridinium ions. (In the literature, the S_NAr reactions rates of 2-, 3-, and 4-chloropyridinium *N*-oxide with methoxide ion are 5.32×10^{12}, 1.00×10^{10}, and 8.14×10^{12}, respectively.)[9b]

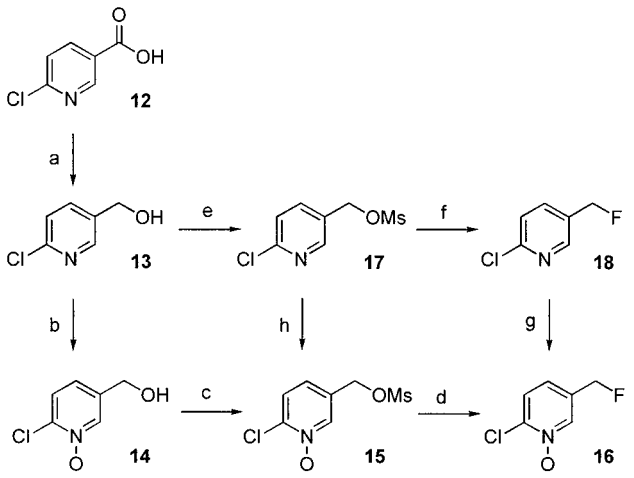
Synthesis of 6-Chloro-α-methanesulfonyloxy-2-picoline *N*-Oxide (7) and Fluorination. The preparation of 6-chloro-α-methanesulfonyloxy-2-picoline *N*-oxide **7**, the precursor of a two-step process, is shown in Scheme 3.

Overnight treatment of 6-chloro-2-picoline (**8**) with *m*-CPBA at 50 °C in chloroform provides the *N*-oxide **9** in 99% isolated yield. Use of other peroxides such as hydrogen peroxide gave lower yields. Because the *N*-oxide is very polar, it is easily lost during standard aqueous workup. However, after quenching with a minimum amount of water, removal of solvent and silica gel

(8) (a) Mallams, A. K.; Rossman, R. R.; Doll, R. J.; Girijavallabhan, V. M.; Ganguly, A. K.; Petrin, J.; Wang, L.; Patton, R.; Bishop, W. R.; Carr, D. M.; Kirschmeier, P.; Catino, J. J.; Bryant, M. S.; Chen, K.-J.; Korfmacher, W. A.; Nardo, C.; Wang, S.; Nomeir, A. A.; Lin, C.-C.; Li, Z.; Chen, J.; Lee, S.; Dell, J.; Lipari, P.; Malkowski, M.; Yaremko, B.; King, I.; Liu, M. *J. Med. Chem.* **1998**, *41*, 877. (b) Bell, I. M.; Erb, J. M.; Freidinger, R. M.; Gallicchio, S. N.; Guare, J. P.; Guidotti, M. T.; Halpin, R. A.; Hobbs, D. W.; Homnick, C. F.; Kuo, M. S.; Lis, E. V.; Mathre, D. J.; Michelson, S. R.; Pawluczyk, J. M.; Pettibone, D. J.; Reiss, D. R.; Vickers, S.; Williams, P. D.; Woyden, C. J. *J. Med. Chem.* **1998**, *41*, 2146.

(9) (a) Newkome, G. R.; Paudler, W. W. In *Contemporary Heterocyclic Chemistry*; John Wiley & Sons: New York, 1982; pp 262−263. (b) Joule, J. A.; Mills, K.; Smith, G. F. In *Heterocyclic Chemistry*, 3rd ed.; Chapman and Hall: London, 1995; p 25.

Scheme 4[a]



[a] Key: (a) $BH_3 \cdot S(CH_3)_2$, THF, reflux, 16 h, 79%; (b) *m*-CPBA, $CHCl_3$, 50 °C, 12 h, 92%; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min, 73%; (d) $^nBu_4NF$, Et_3N, THF, reflux, 4 h, 30%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min, 76%; (f) $^nBu_4NF$, Et_3N, THF, reflux, 4 h, 49%; (g) *m*-CPBA, $CHCl_3$, 50 °C, 12 h, 12%; (h) *m*-CPBA, $CHCl_3$, 50 °C, 12 h, 5%.

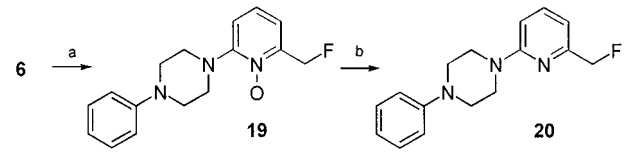
chromatography afforded *N*-oxide **9** in high yield. Upon treatment with acetic anhydride, this material underwent a novel rearrangement to provide a 2-picoline acetate,[10] which was saponified with potassium carbonate in 2:1 MeOH/H_2O to give alcohol **10** in 83% yield from **9**. Mesylation of alcohol **10**, followed by oxidation with *m*-CPBA, afforded a key intermediate, mesylate *N*-oxide **7**, in high yield.

In ^{1}H NMR, the CH_2 peaks of compounds **10**, **11**, and **7** each appeared at characteristic chemical shifts, δ 4.64, 5.29, and 5.47, respectively, resulting in easy identification. The displacement reaction of mesylate **7** with fluoride ion proceeded within 30 min at 110 °C in acetonitrile when an appropriate soluble source of fluoride ion such as *n*-Bu_4NF was used. The introduction of fluorine is easily identified by ^{1}H NMR, in which the signal for the doublet peaks of CH_2F group at 5.66 ppm is a doublet due to typical geminal coupling with fluorine (J = 46.8 Hz).

Synthesis of 6-Chloro-α-methanesulfonyloxy-3-picoline *N*-Oxide (15) and Fluorination. Reduction of 6-chloronicotinic acid with borane dimethyl sulfide was performed in THF at reflux for 16 h, providing alcohol **13**. As shown in Scheme 4, three transformation routes are possible from compound **13** to compound **16**, b−c−d, e−h−d, and e−f−g. By comparison of the *N*-oxidation steps b, h, and g, we found that step b gave high yield (92%), whereas the other steps h (5%) and g (12%) gave much lower yields. Both mesylates **17** and **15** were obtained from alcohols **13** and **14**, respectively, at 0 °C, in reasonable yield. If the reaction temperature was raised above 0 °C by adding mesyl chloride too rapidly, α-chloro-6-chloro-3-picoline was obtained.

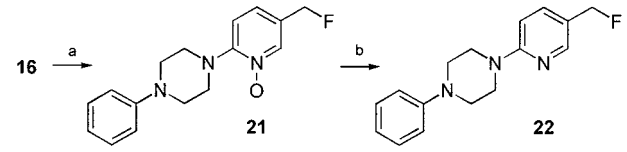
(Fluoromethyl)pyridylation of amine. 1-Phenylpiperazine was used as a model compound for the amine arylation step (Schemes 5 and 6). The reaction of both *N*-oxides **6** and **16** proceeded with moderate to good efficiency in DMF. To prepare 1-phenyl-4-(α-fluoro-3-picolin-6-yl)piperazine (**22**), we performed the S_NAr reaction of 6-chloro-α-fluoro-3-picoline (**16**) with 1-phenylpiperazine. However, the reactivity of the pyridine ring is not sufficient for this S_NAr reaction to proceed. As discussed previously in the General Strategy section, the electron density of each carbon of pyridine is changed significantly upon the formation of the *N*-oxide. The negative charge on oxygen makes the C4 and C2 (or C6) carbons negative by resonance. However, the inductive effect of the positive charge on nitrogen diminishes the resonance effect on the C2 carbon, consequently making the C2 carbon more positive. Thus, the S_NAr reaction of the *N*-oxide compound on C2 carbon proceeds more easily.

Scheme 5[a]



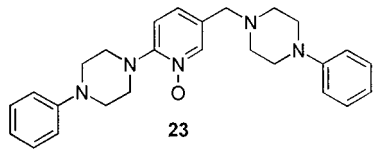
[a] Key: (a) 1-phenylpiperazine, Et_3N, DMF, 180 °C, 2 h, 53%; (b) PCl_3, $CHCl_3$, rt, 2 h, 99%.

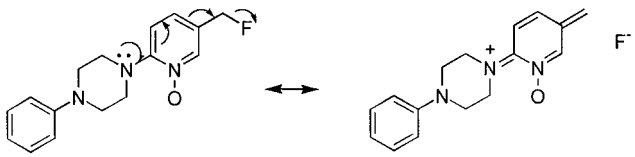
Scheme 6[a]



[a] Key: (a) 1-phenylpiperazine, Et_3N, EtOH/CH_3CN, 130 °C, 3 h, 44%; (b) PCl_3, $CHCl_3$, rt, 2 h, 99%.

The optimized yields for the S_NAr reaction of **6** and **16** were 53 and 44% (Schemes 5 and 6). In the reaction of **6**, only monoaminated product **19** was obtained. On the other hand, in the reaction of **16**, diaminated product **23** was also obtained. A possible explanation for this is that the fluoromethylene group is activated toward nucleophilic attack by hyperconjugation, which is induced by resonance donation by the lone pair electron on the nitrogen of monoaminated product **21**. Removal of *N*-oxide was carried out by the treatment of compounds **19** and **21** with phosphorus trichloride to give **20** and **22**, respectively, in quantitative yield.





One might suspect that fluorine in the "benzylic position" in compounds **20** and **22** might not be stable toward in vivo metabolism due to the electron deficiency generated by the pyridine ring. Although some radiotracers, such as 3-(4-([^{18}F]fluoromethyl)phenyl)ecgonine[11] and

(10) Ochiai, E. In *Aromatic Amine Oxides*; Elsevier: New York, 1967; pp 290−302.

([^{18}F]fluoromethyl)benzoylated insulin,[5] which have benzylic fluoride, showed good in vivo stability, in general benzylic fluorides do not have good in vivo stability. However, according to our experience, the in vivo stability of fluorine-substituted radiopharmaceuticals depends on the position as well as the electronic density of the methylene group of benzylic fluoride.[12] In this regard, one might expect (fluoromethyl)pyridines to be more stable than the corresponding fluorobenzyl compounds. However, the introduction of amino groups such as phenylpiperazinyl on the C6 position of the pyridine ring will increase the electron density of pyridine ring, which may increase its metabolic lability. To avoid the instability of benzylic fluoride, we are applying this method to homologated compounds such as 6-chloro-2-(2-fluoroethyl)pyridine *N*-oxide and 6-chloro-2-(3-fluoropropyl)pyridine *N*-oxide.

In conclusion, the method—fluorination−*N*-arylation—that we have described for the preparation of (fluoromethyl)pyridine-substituted amines is sufficiently rapid and efficient that it appears suitable for the prepararion of a variety of aryl-substituted amine compounds labeled with the short half-life ($t_{1/2}$ = 110 min) positron-emitting radionuclide fluorine-18. Elsewhere, we will report a detailed study of this two-step method with regard to its applicability for labeling with fluorine-18.

Experimental Section

General Methods. All reagents and solvents were obtained from Lancaster and Aldrich Chemical Co. Dimethylformamide (DMF) was distilled before use and stored over 4 Å molecular sieves. ^{1}H NMR spectra were recorded at 200 MHz, and ^{13}C NMR spectra were recorded at 50 MHz. Low-resolution electron impact (EI) and chemical ionization (CI) mass spectra were recorded at Inha University Facility. Elemental analyses were carried out at Inha University Microanalytical Laboratory.

6-Chloro-2-picoline *N*-Oxide (9). To 6-chloro-2-picoline (2.00 g, 15.75 mmol) in chloroform (10 mL) was added *m*-CPBA (6.32 g, 23.62 mmol) at room temperature. The reaction mixture was heated to 50 °C for 12 h. The reaction was quenched by adding water (2 mL). After evaporation of solvent in vacuo, flash column chromatography (50% EtOAc/hexane) provided **9** (2.10 g, 99%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.54 (s, 3H), 7.08 (t, 1H, J = 7.8 Hz), 7.19 (d, 1H, J = 6.4 Hz), 7.38 (d, 1H, J = 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.68, 122.66, 122.97, 123.51, 140.26, 149.27; MS (EI) m/z 143 (M^+); HRMS calcd for C_6H_6ClNO 144.0216, found 144.0217.

6-Chloro-α-hydroxy-2-picoline (10). To 6-chloro-2-picoline *N*-oxide (944 mg, 6.60 mmol) in acetic anhydride (20 mL) was added concentrated sulfuric acid (three drops) at room temperature. This mixture was heated to 110 °C for 3 h and then allowed to stand at room temperature overnight. The reaction mixture was extracted with ethyl acetate and washed ($NaHCO_3$, H_2O, brine). The organic layer was dried (Na_2SO_4) and concentrated. Crude acetate was taken up in 20 mL of methanol and 10 mL of H_2O, and potassium carbonate (3.0 g) was added. After 15 min, the solvent was evaporated, and the residue was dissolved in methylene chloride. The solution was dried (Na_2SO_4) and concentrated. Flash column chromatography (50% EtOAc/hexane) provided **10** (815 mg, 83%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.64 (s, 2H), 7.09 (d, 1H, J = 7.6 Hz), 7.24 (d, 1H, J = 7.6 Hz), 7.55 (t, 1H, J = 7.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 62.46, 117.43, 121.01, 137.87, 148.80, 159.78; MS (CI) m/z 144 (MH^+). Anal. Calcd for C_6H_6ClNO: C, 50.20; H, 4.21; N, 9.76. Found: C, 49.99; H, 4.24; N, 9.75.

6-Chloro-α-methanesulfonyloxy-2-picoline (11). To 6-chloro-α-hydroxy-2-picoline (1.23 g, 8.60 mmol) in methylene chloride (20 mL) were added triethylamine (1.80 mL, 12.90 mmol) and methanesulfonyl chloride (666 μL, 8.60 mmol) at 0 °C. After 30 min, the reaction mixture was quenched with H_2O. The reaction mixture was extracted with methylene chloride, and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (80% EtOAc/hexane) provided **11** (1.82 g, 96%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.14 (s, 3H), 5.29 (s, 2H), 7.35 (d, 1H, J = 8.2 Hz), 7.43 (d, 1H, J = 6.8 Hz), 7.75 (t, 1H, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.35, 68.71, 119.03, 122.66, 138.13, 152.90; MS (EI) m/z 221 (M^+). Anal. Calcd for $C_7H_8ClNO_3S$: C, 37.93; H, 3.64; N, 6.32; S, 14.47. Found: C, 38.25; H, 3.73; N, 6.30; S, 14.41.

6-Chloro-α-methanesulfonyloxy-2-picoline *N*-Oxide (7). To 6-chloro-α-methanesulfonyloxy-2-picoline (679 mg, 3.07 mmol) in chloroform (10 mL) was added *m*-CPBA (795 mg, 4.61 mmol) at room temperature, and then the mixture was heated to 50 °C for 12 h. The reaction mixture was dried (Na_2SO_4) and concentrated. The product **7** was obtained as a yellow solid (342 mg, 47%) by flash column chromatography (cosolvents: 80% EtOAc/hexane, 2% MeOH/CH_2Cl_2) and recrystallization (40% EtOAc/hexane): mp 98.5−98.8 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.20 (s, 3H), 5.47 (s, 2H), 7.29 (t, 1H, J = 7.9 Hz), 7.53 (t, 2H, J = 8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.94, 63.81, 121.09, 123.76, 124.87, 140.50, 144.97; MS (EI) m/z 237 (M^+). Anal. Calcd. for $C_7H_8ClNO_4S$: C, 35.38; H, 3.39; N, 5.89; S, 13.49. Found: C, 35.60; H, 3.40; N, 5.85; S, 13.14.

6-Chloro-α-fluoro-2-picoline *N*-Oxide (6). To 6-chloro-α-methanesulfonyloxy-2-picoline *N*-oxide (461 mg, 1.95 mmol) in acetonitrile (10 mL) was added tetra-*n*-butylammonium fluoride hydrate (615 mg, 1.95 mmol), and the mixture was heated at 80 °C for 4 h (or 110 °C for 30 min in a pressure bottle). The reaction mixture was extracted with ethyl acetate and washed (H_2O, brine), and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (80% EtOAc/hexane) provided **6** (136 mg, 43%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.66 (d, 2H, J = 46.8 Hz), 7.31 (t, 1H, J = 7.6 Hz), 7.45 (d, 1H, J = 7.4 Hz), 7.52 (d, 1H, J = 7.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 77.19 (d, J = 171.9 Hz), 118.50, 118.67, 123.76; MS (CI) m/z 162 (MH^+). Anal. Calcd for C_6H_5ClFNO: C, 44.61; H, 3.12; N, 8.67. Found: C, 45.01; H, 3.39; N, 8.80.

α-Fluoro-6-(4-phenylpiperazinyl)-2-picoline *N*-Oxide (19). In a 5 mL Reacti·vial, to 6-chloro-α-fluoro-2-picoline *N*-oxide (47 mg, 0.29 mmol) in 1.5 mL of DMF were added triethylamine (61 μL, 0.44 mmol) and 1-phenylpiperazine (45 μL, 0.29 mmol), and then the reaction mixture was heated 180 °C for 2 h. After the reaction mixture was cooled to room temperature, it was extracted with methylene chloride, washed (H_2O, brine), and dried (Na_2SO_4). After the organic layer was removed by vacuum, flash column chromatography (80% EtOAc/hexane) provided **19** (33 mg, 40%) as a brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.31−3.51 (m, 8H), 5.58 (d, 2H, J = 47.4 Hz), 6.80−6.93 (m, 4H), 7.07 (d, 1H, J = 9.0 Hz), 7.19−7.30 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.12, 47.47, 77.48 (d, J = 170.7 Hz), 112.70, 112.88, 114.90, 118.69, 125.24, 127.59, 149.58, 152.61; MS (CI) m/z 288 (MH^+); HRMS calcd for $C_{16}H_{18}FN_3O$ 288.1512, found 288.1519.

α-Fluoro-6-(4-phenylpiperazinyl)-2-picoline (20). In a 5 mL Reacti·vial, to α-fluoro-6-(4-phenylpiperazinyl)-2-picoline *N*-oxide (33 mg, 0.11 mmol) in 2 mL of chloroform was added trichlorophosphine (12 μL, 0.14 mmol), and then the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with chloroform, washed (H_2O, brine), and dried (Na_2SO_4). After the organic layer was removed by vacuum, flash column chromatography (10% EtOAc/hexane) provided **20** (30 mg, 99%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.29 (t, 4H, J = 5.1 Hz), 3.71 (t, 4H, J = 5.2 Hz),

(11) Barrio, J. R.; Petric A.; Satyamurthy, N.; Huang, S. C.; Yu, D. C. *J. Nucl. Med.* **1994**, *35S*, 83P.

(12) Oh, S. J.; Choe, Y. S.; Kim, S. E.; Choi, Y.; Lee, K. H.; Ha, H. J.; Kim, B.-T.; Lee, K. C.; Chi, D. Y. *J. Labeled Compd. Radiopharm.* **1997**, *40*, 26−28.

5.33 (d, 2H, J = 47.2 Hz), 6.64 (d, 1H, J = 8.4 Hz), 6.80 (d, 1H, J = 7.4 Hz), 6.86−7.00 (m, 3H), 7.26−7.34 (m, 2H), 7.55 (t, 1H, J = 7.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.48, 47.51, 83.10 (d, J = 168.4 Hz), 104.60, 108.28, 114.71, 118.41, 127.51, 136.56; MS (EI) m/z 271 (M^+); HRMS calcd for $C_{16}H_{18}FN_3$ 271.1485, found 271.1484.

6-Chloro-α-hydroxy-3-picoline (13). To 6-chloronicotinic acid (1.98 g, 12.61 mmol) in dried THF (30 mL) was added borane dimethyl sulfide complex (2.35 mL, 26.40 mmol), and then the mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature, quenched with 10% HCl, extracted with ethyl acetate, washed (H_2O, brine), and dried (Na_2SO_4). After the organic layer was evaporated, flash column chromatography (60% EtOAc/hexane) provided **13** (1.43 g, 79%) as a white solid: mp 53.8−54.2 °C; 1H NMR (200 MHz, $CDCl_3$) δ 4.52 (s, 2H), 7.14 (d, 1H, J = 8.2 Hz), 7.55 (dd, 1H, J = 8.2, 2.4 Hz), 8.11 (d, 1H, J = 2.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 59.26, 122.47, 134.40, 136.34, 146.10, 148.10; MS (CI) m/z 144 (MH^+). Anal. Calcd for C_6H_6NO: C, 50.20; H, 4.21; N, 9.76. Found: C, 50.56; H, 4.40; N, 9.71.

6-Chloro-α-methanesulfonyloxy-3-picoline (17). To 6-chloro-α-hydroxy-3-picoline (1.43 g, 10.00 mmol) in methylene chloride (25 mL) were added triethylamine (1531 μL, 10.99 mmol) and methanesulfonyl chloride (773 μL, 9.99 mmol) at 0 °C for 20 min. The reaction mixture was quenched with H_2O and extracted with methylene chloride. After the organic layer was dried (Na_2SO_4) and evaporated, flash column chromatography (60% EtOAc/hexane) provided mesylate **17** (1.68 g, 76%) as a white solid: mp 75.6−75.9 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.04 (s, 3H), 5.24 (s, 2H), 7.40 (d, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 7.6 Hz), 8.44 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.35, 68.77, 119.12, 122.73, 138.25; MS (CI) m/z 222 (MH^+). Anal. Calcd. for $C_7H_8ClNO_3S$: C, 37.93; H, 3.64; N, 6.32; S, 14.47. Found: C, 37.86; H, 3.29; N, 6.23; S, 14.54.

6-Chloro-α-fluoro-3-picoline (18). To 6-chloro-α-methanesulfonyloxy-3-picoline (6.34 g, 2.87 mmol) in dried THF (30 mL) was added tetra-*n*-butylammonium fluoride (1 M THF solution, 8.0.29 mmol), and the mixture was refluxed for 4 h. The reaction mixture was extracted with methylene chloride and washed (H_2O, brine). After the organic layer was dried (Na_2SO_4) and evaporated, flash column chromatography (60% EtOAc/hexane) provided **18** (2.04 g, 49%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30 (d, 2H, J = 4 7.6 Hz, CH_2), 7.26 (d, 1H, J = 8.4 Hz, C4−H), 7.60 (d, 1H, J = 8.4 Hz, C3-H), 8.29 (s, 1H, C6-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 79.52 (d, J = 167.3 Hz), 122.63, 129.01 (d, J = 18.2 Hz, C3), 136.44 (d, J = 5.3 Hz, C4), 147.00 (d, J = 6.5 Hz, C2), 150.12; MS (CI) m/z 146 (MH^+); HRMS calcd for C_6H_5ClFN 146.0173, found 146.0169.

6-Chloro-α-fluoro-3-picoline *N*-Oxide (16). To 6-chloro-α-fluoro-3-picoline (328 mg, 2.26 mmol) in chloroform (10 mL) was added *m*-CPBA (586 mg, 3.39 mmol) at room temperature. This mixture was heated at 50 °C for 12 h. The reaction mixture was dried (Na_2SO_4) and concentrated. Flash column chromatography (2% MeOH/CH_2Cl_2) provided **16** (57 mg, 12%) as a pale brown solid: mp 99.4−99.8 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30 (d, 2H, J = 46.6 Hz), 7.15 (d, 1H, J = 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 8.32 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 78.44 (d, J = 171.8 Hz), 122.34 (d, J = 6.1 Hz), 125.39, 132.08 (d, J = 19.0 Hz), 137.15 (d, J = 8.0 Hz), 140.21; MS (CI) m/z 162 (MH^+). Anal. Calcd for C_6H_5FClNO: C, 44.61; H, 3.12; N, 8.67. Found: C, 44.43; H, 3.32; N, 8.28.

6-Chloro-α-hydroxy-3-picoline *N*-Oxide (14). To 6-chloro-α-hydroxy-3-picoline (700 mg, 4.90 mmol) in chloroform (20 mL) was added *m*-CPBA (1839 mg, 5.86 mmol) at room temperature. This mixture was heated to 50 °C for 12 h. The reaction mixture was dried (Na_2SO_4) and concentrated. Flash column chromatography (10% MeOH/CH_2Cl_2) provided **14** (719 mg, 92%) as a white solid: mp 101.1−101.4 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.61 (s, 2H), 7.16 (dd, 1H, J = 8.4, 2.0 Hz), 7.35 (d, 1H, J = 8.4 Hz), 8.29 (d, 1H, J = 2.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 59.09, 124.64, 125.06, 131.13, 137.31, 138.26; MS (EI) m/z 159 (M^+); HRMS calcd for $C_6H_6ClNO_2$ 159.0087, found 159.0089.

6-Chloro-α-methanesulfonyloxy-3-picoline *N*-Oxide (15). To 6-chloro-α-methanesulfonyloxy-3-picoline (602 mg, 2.72 mmol) in chloroform (10 mL) was added *m*-CPBA (705 mg, 4.09 mmol) at room temperature. This mixture was heated to 50 °C for 12 h. The reaction mixture was dried (Na_2SO_4) and concentrated. Flash column chromatography (2% MeOH/CH_2Cl_2) provided **15** (31 mg, 5%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.01 (s, 3H), 5.09 (s, 2H), 7.23 (dd, 1H, J = 8.4, 1.4 Hz), 7.44 (d, 1H, J = 8.4 Hz), 8.35 (d, 1H, J = 1.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.13, 64.63, 124.84, 125.62, 130.42, 138.28, 140.25; MS (EI) m/z 237 (M^+). Anal. Calcd for $C_7H_8ClNO_4S$: C, 35.38; H, 3.39; N, 5.89; S, 13.49. Found: C, 35.62; H, 3.34; N, 5.80.

6-Chloro-α-methanesulfonyloxy-3-picoline *N*-Oxide (15). To 6-chloro-α-hydroxy-3-picoline *N*-oxide (303 mg, 1.91 mmol) in methylene chloride (15 mL) were added triethylamine (397 μL, 2.85 mmol) and methanesulfonyl chloride (146 μL, 1.90 mmol) to 0 °C for 20 min. The reaction mixture was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% MeOH/CH_2Cl_2) provided **15** (328 mg, 73%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.01 (s, 3H), 5.09 (s, 2H), 7.23 (dd, 1H, J = 8.4, 1.4 Hz), 7.44 (d, 1H, J = 8.4 Hz), 8.35 (d, 1H, J = 1.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.13, 64.63, 124.84, 125.62, 130.42, 138.28, 140.25; MS (EI) m/z 237 (M^+). Anal. Calcd for $C_7H_8ClNO_4S$: C, 35.38; H, 3.39; N, 5.89; S, 13.49. Found: C, 35.62; H, 3.34; N, 5.80.

6-Chloro-α-fluoro-3-picoline *N*-Oxide (16). To 6-chloro-α-methanesulfonyloxy-3-picoline *N*-oxide (98 mg, 0.41 mmol) in acetonitrile (2 mL) were added triethylamine (86 μL, 0.62 mmol) and tetra-*n*-butylammonium fluoride•trihydrate (130 mg, 0.41 mmol) at room temperature. This mixture was refluxed for 3 h. The reaction mixture was concentrated. Flash column chromatography (80% EtOAc/hexane) provided **16** (20 mg, 30%) as a pale brown solid: mp 99.4−99.8 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30 (d, 2H, J = 46.6 Hz), 7.15 (d, 1H, J = 8.4 Hz), 7.47 (d, 1H, J = 8.4 Hz), 8.32 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 78.44 (d, J = 171.8 Hz), 122.34 (d, J = 6.1 Hz), 125.39, 132.08 (d, J = 19.0 Hz), 137.15 (d, J = 8.0 Hz), 140.21; MS (CI) m/z 162 (MH^+). Anal. Calcd for C_6H_5FClNO: C, 44.61; H, 3.12; N, 8.67. Found: C, 44.43; H, 3.32; N, 8.28.

α-Fluoro-6-(4-phenylpiperazinyl)-3-picoline *N*-Oxide (21). To 6-chloro-α-fluoro-3-picoline *N*-oxide (57 mg, 0.35 mmol) in 5 mL of acetonitrile and 5 mL of ethanol was added triethylamine (54 μL, 0.39 mmol) and 1-phenylpiperazine (53 μL, 0.35 mmol), and then the reaction mixture was heated 130 °C for 3 h. After the reaction mixture was cooled to room temperature, it was extracted with methylene chloride, washed (H_2O, brine), and dried (Na_2SO_4). After the organic layer was removed by vacuum, flash column chromatography (5% MeOH/CH_2Cl_2) provided **21** (42 mg, 44%) as a brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.38−3.62 (m, 8H), 5.27 (d, 2H, J = 47.6 Hz), 6.90−7.00 (m, 5H), 7.23−7.34 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.18, 47.53, 77.51 (J = 169.9 Hz), 111.42, 112.67, 112.84, 114.87, 118.66, 125.10, 127.55, 149.51; MS (CI) m/z 288 (MH^+); HRMS calcd for $C_{16}H_{18}FN_3O$ 288.1512, found 288.1511.

α-Fluoro-6-(4-phenylpiperazinyl)-3-picoline (22). In a 5 mL Reacti•vial, to α-fluoro-6-(4-phenylpiperazinyl)-3-picoline *N*-oxide (23 mg, 0.08 mmol) in 2 mL of chloroform was added trichlorophosphine (8.4 μL, 0.10 mmol), and then the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with chloroform, washed (H_2O, brine), and dried (Na_2SO_4). After the organic layer was removed by vacuum, flash column chromatography (10% EtOAc/hexane) provided **22** (0.08 mg, 99%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.29 (t, 4H, J = 5.2 Hz), 3.71 (t, 4H, J = 5.2 Hz), 5.33 (d, 2H, J = 47.2 Hz), 6.64 (d, 1H, J = 8.4 Hz), 6.78−7.00 (m, 4H), 7.26−7.34 (m, 2H), 7.55 (t, 1H, J = 7.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.48, 47.51, 83.10 (d, J = 168.4 Hz), 104.60, 108.28, 114.71, 118.41, 127.51, 136.56; MS (CI) m/z 272 (MH^+); HRMS calcd for $C_{16}H_{18}FN_3$ 272.1563, found 272.1567.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **6**, **7**, **8**−**11**, and **13**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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