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A Practical Synthesis of 2-((1*H*-Pyrrolo[2,3-b]pyridine-4-yl)methylamino)-5-fluoronicotinic Acid

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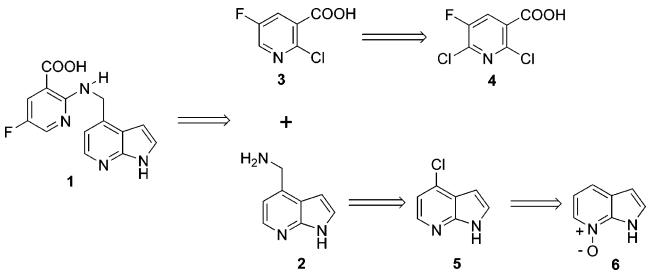
Received February 7, 2006



A practical synthesis of a key pharmaceutical intermediate, 2-[(1*H*-pyrrolo[2,3-b]pyridine-4-yl)methylamino]-5-fluoronicotinic acid (**1**), is described. To introduce the aminomethyl moiety of **2** via a palladium-catalyzed cyanation/reduction sequence, a regioselective chlorination of 7-azaindole via the *N*-oxide was developed. A highly selective monodechlorination of 2,6-dichloro-5-fluoronicotinic acid was discovered to afford the nicotinic acid **3**. The two building blocks **2** and **3** were then coupled to complete the preparation of **1**.

The 7-azaindoles constitute an important class of compounds in pharmaceuticals.[1] As part of an ongoing drug discovery program in our laboratories, we required an efficient synthesis of 2-[(1*H*-pyrrolo[2,3-b]pyridin-4-yl)methylamino]-5-fluoronicotinic acid (**1**) containing the key component 4-aminomethyl-7-azaindole (**2**). Neither the azaindole **2** nor 2-chloro-5-fluoronicotinic acid (**3**) was commercially available, thus requiring independent syntheses of these building blocks. Herein we wish to report a chromatography-free synthesis that is suitable for the preparation of kilogram quantities of **1**.

Introduction of the aminomethyl group of **2** required selective functionalization of azaindole. As chlorination of 7-azaindole *N*-oxide (**6**) has been reported to occur primarily at the 4-position with $POCl_3$[2] or $MeSO_2Cl$[3] to afford **5**, the overall approach of *N*-oxide formation, chlorination, and aminomethylation was considered to be the most practical (Scheme 1). The oxidation of 7-azaindole was investigated using oxidants reported in the literature,[4−8] such as 3-chloroperbenzoic acid (MCPBA),[4] H_2O_2/HOAc,[5] or H_2O_2/$MeReO_3$.[6] The 7-azaindole *N*-oxide (**6**) was prepared in yields ranging from 60 to 71%. The chemical conversions in all the cases were good to excellent (>90%). Due to the high solubility of the azaindole *N*-oxide **6** in water, isolation of the product was very tedious, requiring multiple extractions. For example, with MCPBA in DCM, the reaction was completed cleanly in less than 10 h. However, upon aqueous workup (eight extractions with DCM), only a 50% yield of the azaindole *N*-oxide **6** was obtained while the remaining product remained in the aqueous phase. In addition, the isolated azaindole *N*-oxide **6** was contaminated with 5% of 3-chlorobenzoic acid. Fortuitously, precipitation was observed after all the reagents were mixed. The product was isolated directly by filtration and was identified as the azaindole *N*-oxide MCBA salt **7**. After further optimization, a cosolvent mixture of DME/heptane (1:2) was found to be optimal for the isolation, affording the azaindole *N*-oxide MCBA salt **7** in 89% yield.

The conversion of azaindole *N*-oxide **6** to the chloroazaindole **5** required modification of the literature procedure[4b] using neat $POCl_3$ or $MeSO_2Cl$ in DMF to limit the formation of the major side product 3-chloro-7-azaindole. We always obtained better results with $POCl_3$ over $MeSO_2Cl$. The typical ratio of 4-chloro-7-azaindole (**5**) and 3-chloro-7-azaindole in the reaction mixture was 7:1 from azaindole *N*-oxide **6** in neat $POCl_3$. The ratio, however, improved to 12:1 when azaindole *N*-oxide MCBA salt **7** was used. Upon workup, 4-chloro-7-azaindole (**5**) was isolated in 80% yield with enrichment of the isomeric ratio to 35:1. The purity of the product was satisfactory for use in the next step without further purification.

The introduction of the dimethylamino group of **2** from the 4-chloro-7-azaindole (**5**) was accomplished by a two-step process. As a cyano moiety is an excellent precursor to an aminomethyl group through reduction, a palladium-catalyzed coupling of the chloride with cyanide was developed. Applying Jin and Confalone's conditions[7] to **5** using a Pd-dppf catalyst system and zinc cyanide, the 4-cyano-7-azaindole (**8**) was prepared in 70% isolated yield. The 4-cyano-7-azaindole (**8**) was then subjected to LAH reduction[8] to afford 4-aminomethyl-

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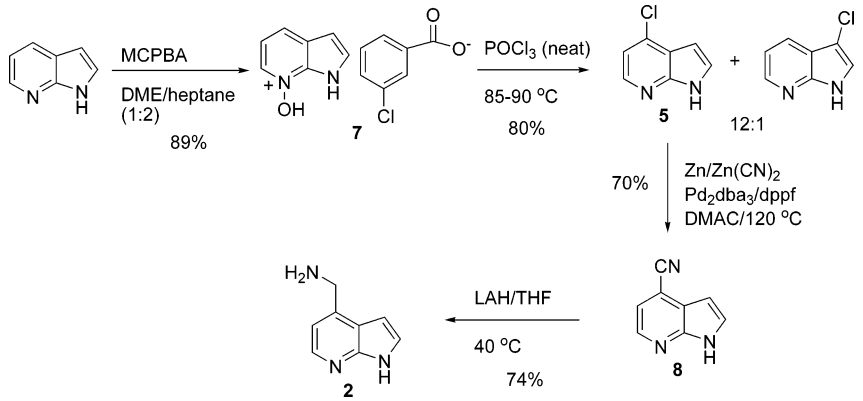
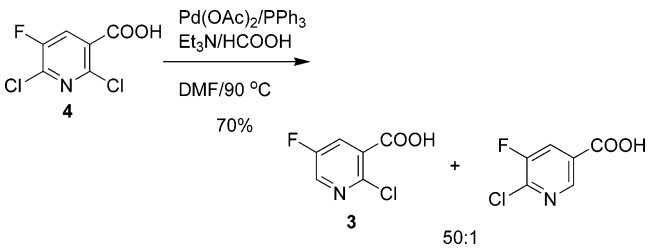
10.1021/jo0602571 CCC: $33.50
Published on Web 04/05/2006

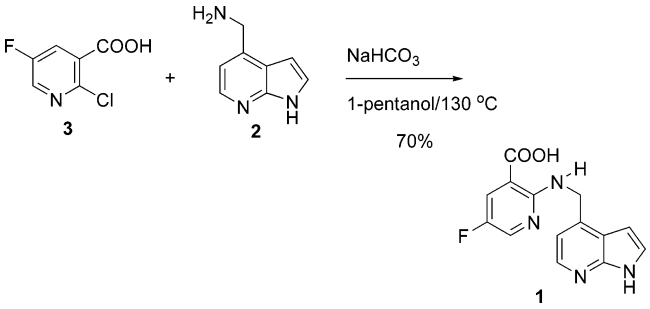
SCHEME 1. Preparation of 4-Aminomethyl-7-azaindole (2)



SCHEME 2. Selective Dechlorination of 2,6-Dichloro-5-fluoronicotinic Acid (3)



SCHEME 3. Coupling of 2 and 3



7-azaindole (**2**) in 74% yield. Various catalytic hydrogenation methods using Pd[9] or Ni[10] were also tested but were unsatisfactory, producing several byproducts.

There are two known routes for preparing 2-chloro-5-fluoronicotinic acid (**3**).[11,12] Each requires four steps from commercially available starting materials. In a Rhone Poulenc patented process,[11] the acid **3** was prepared from 2-hydroxynicotinic acid by applying a nitration, chlorination, nitro reduction, and Sandmeyer reaction sequence in an overall 7.9% yield. In an Abbott process,[12] only the yield for a Raney nickel reduction (30%) was reported for a four-step sequence, including esterification, selective displacement with NaSMe, Raney nickel reduction, and saponification, from 2,6-dichloro-5-fluoronicotinic acid (**4**).

These current literature syntheses of 2-chloro-5-fluoronicotinic acid (**3**) suffer from low yields and are not scalable. To gain access to **3**, the selective monodechlorination of the commercially available 2,6-dichloro-5-fluoronicotinic acid (**4**) at the 6-position was explored (Scheme 2). We initially screened a hydrogenation process[13] by applying a variety of different Pd/C catalysts without success. The selectivity was poor in all the cases, resulting in a mixture of chlorinated products. However, it was gratifying to find that selective dechlorination of **4** to 2-chloro-5-fluoronicotinic acid (**3**) occurred cleanly under homogeneous conditions using $Pd(OAc)_2/Et_3N/HCOOH$.[9] The selectivity was about 50:1 in favor of the 6-position. The desired isomer 2-chloro-5-fluoronicotinic acid (**2**) was isolated in 70% yield.

Final coupling of 4-aminomethyl-7-azaindole (**2**) and 2-chloro-5-fluoronicotinic acid (**3**) went smoothly to produce the desired product **1** in 70% isolated yield (Scheme 3). Several factors[14] were critical for the coupling reaction to be successful. A high reaction concentration (1.9 mol/L) and 2 equiv of 4-aminomethyl-7-azaindole (**2**) were essential for the reaction to go to completion. The reaction was slow, requiring elevated temperatures (130 °C) and a long reaction time (48 h). 1-Pentanol was the best solvent, while major decomposition occurred in other high boiling solvents, such as DMF, DMAC, and DMSO. $NaHCO_3$ was the best base as inferior results were obtained in the cases of other common bases, such as Et_3N, Hunig's base, Na_2CO_3, and KOtBu.

In conclusion, we have developed a practical synthesis of the 4-substituted 7-azaindole **1** and its intermediates in high yield and purity. The process is suitable for large-scale production. The key steps include the highly selective monodechlorination of **4** to afford **3** and a much improved chlorination of the *N*-oxide intermediate **7**.

Experimental Section

7-Azaindole *N*-Oxide 3-chlorobenzoate (7). To a solution of 7-azaindole (19.83 kg, 167.9 mol) in DME/heptane (1:2, 294 L) was added 3-chloroperbenzoic acid (85 wt %, 46.2 kg, 194.9 mol)

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(14) Preliminary reaction parameters were established during the preparation of a structurally similar compound, AMG 706, and details of those results will be published elsewhere.

portionwise at 8 to 26 °C. Precipitation occurred after half of the 3-chloroperbenzoic acid was added. The slurry was stirred at room temperature for 2.5 h. The precipitate was filtered and washed with DME/heptane (1:2, 100 L). The product was dried to yield an off-white solid (43.58 kg, 89.2%). mp 144.1−146.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (1H, bs), 12.53 (1H, s), 8.16 (1H, d, J = 6.2 Hz), 7.86−7.93 (2H, m), 7.63−7.72 (2H, m), 7.54 (1H, t, J = 8.0 Hz), 7.46 (1H, d, J = 3.0 Hz), 7.07 (1, dd, J = 6.3, 1.4 Hz), 6.58 (1H, d, J = 3.1 Hz), 6.39 (1H, d, J = 3.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 138.6, 133.7, 133.3, 132.5, 131.5, 130.9, 129.2, 128.2, 126.9, 124.4, 120.6, 116.5, 102.6. Anal. Calcd for $C_{14}H_{11}ClN_2O_3$: C, 57.84; H, 3.81; N, 9.64. Found: C, 57.88; H, 3.83; N, 9.79.

4-Chloro-7-azaindole (5). To 7-azaindole *N*-oxide 3-chlorobenzoate (**7**) (43.4 kg, 149.3 mol) was added $POCl_3$ (170.4 kg) at room temperature. The solution was heated to 55 °C, and then heating was removed. The temperature slowly went up to 74 °C in about 1 h without external heating. The mixture was further heated to 85−90 °C for 18 h. *Caution: Two exothermic events were observed during a DSC study of the reaction mixture, one at 50−60 °C and the other at 105−110 °C. To prevent a runaway reaction on scale, the solution was first heated to 55 °C and then heated slowly to 85−90 °C.* The solution was cooled to 50 °C, and $POCl_3$ was distilled off in vacuo. The residue was dissolved in acetonitrile (100 L) and quenched with slow addition of H_2O (100 L) while keeping the temperature under 50 °C. The mixture was basified to pH 9 with 50% NaOH solution. The slurry was allowed to cool to room temperature, and the precipitates were filtered. The wet cake was reslurried with H_2O (200 L), filtered, and dried to afford the product (18.15 kg, 80%). mp 175.3−177.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (1H, s), 8.18 (1H, d, J = 5.2 Hz), 7.59 (1H, d, J = 3.2 Hz), 7.16 (1H, d, J = 5.2 Hz), 6.50 (1H, d, J = 3.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.0, 143.1, 134.0, 127.2, 118.6, 115.14, 97.89. Anal. Calcd for $C_7H_5ClN_2$: C, 55.10; H, 3.30; N, 18.36. Found: C, 55.20; H, 3.30; N, 18.32.

4-Cyano-7-azaindole (8). A suspension of 4-chloro-7-azaindole (**5**) (18.15 kg, 118.9 mol) in dimethylacetamide (100 L) was degassed by pulling vacuum on the reactor and then filling with nitrogen. To this suspension was added zinc powder (0.72 kg, 11 mol), diphenylphosphinoferrocene (2.09 kg, 3.77 mol), zinc cyanide (8.2 kg, 69.8 mol), and tris(dibenzylideneacetone) dipalladium (1.74 kg, 1.9 mol) at room temperature. The mixture was heated at 120 °C for 2 h and was cooled to 100 °C. Water (306 L) was added over 45 min at 90−100 °C. The mixture was then cooled to room temperature over 3 h. The crude product was filtered and was washed with H_2O (2 × 68 L). To a solution of 3 N HCl (75 L) was added the product wet cake, and the mixture was stirred for 3 h at room temperature. The insolubles were removed by filtration. To the filtrate was added 50% NaOH until pH 12 was reached. Filtration and drying afforded the pure product (12.28 kg, 70%). mp 195.1−197.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (1H, s), 8.45 (1H, d, J = 4.9 Hz), 7.88 (1H, d, J = 3.4 Hz), 7.58 (1H, d, J = 4.9 Hz), 6.70 (1H, d, J = 3.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.5, 142.4, 130.2, 119.6, 118.2, 116.9, 98.3. Anal. Calcd for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.35. Found: C, 66.91; H, 3.38; N, 28.99.

4-Aminomethyl-7-azaindole (2). To a solution of LAH (3.15 kg, 82.9 mol) in THF (108 L) was added 4-cyano-7-azaindole (5.9 kg, 40.0 mol) in portions over 45 min. The mixture was heated to 40 °C for 1 h. The reaction mixture was cooled to 10 °C and was quenched with 25% NaOH (13 L). The mixture was then filtered through a bed of silica gel. To the filtrate was added a saturated HCl solution in 1-propanol (10.65 kg) at room temperature. The product precipitated as the dihydrochloride salt and was isolated by filtration. To a solution of the dihydrochloride salt in H_2O (22.7 L) was added solid NaOH (2.6 kg, 65 mol). The temperature rose to 60 °C. The solution was stirred until the product started to crystallize. The mixture was then cooled to room temperature. The product was isolated by filtration and washed with H_2O (10 L) (3.54 kg, 74%). mp 131.7−133.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (1H, bs), 8.17 (1H, d, J = 5.3 Hz), 7.41 (1H, d, J = 3.5 Hz), 7.12 (1H, d, J = 5.3 Hz), 6.55 (1H, d, J = 3.5 Hz), 4.02 (1H, s), 1.92 (2H, bs). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 148.3, 144.6, 142.7, 125.0, 117.9, 112.9, 98.1, 42.8. Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.15; H, 6.31; N, 28.22.

2-Chloro-5-fluoronicotinic Acid (3). To a 12-L round-bottomed flask were added dimethylacetamide (3.24 L), $Pd(OAc)_2$ (5.89 g, 0.262 mol), PPh_3 (134.9 g, 0.51 mol), Et_3N (2.15 L, 15.4 mol), HCOOH (95 wt %, 430 mL, 10.3 mol), and 2,6-dichloro-5-fluoronicotinc acid (1.08 kg, 5.14 mol). The reaction mixture was heated at 60 °C for 7 h. The heating was stopped, and brine (13 L) was added. The mixture was cooled to room temperature over 12 h. The mixture was filtered through a pad of Celite and was rinsed with brine (2 × 1 L). HCl (12 N, 1 L) was added into the filtrate slowly to pH 0−1. The mixture was extracted with isopropyl acetate (2 × 10.8 L). The organic phase was dried (Na_2SO_4). The isopropyl acetate was evaporated under reduced pressure. 1,2-Dichloroethane (2.5 L) was added to the residue. The mixture was heated at reflux (87 °C) for 1 h and was cooled to −15 °C over 12 h. The slurry was filtered and dried in an oven under vacuum for 24 h to afford the pure product (632 g, 70%). mp 132.9−134.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.15 (1H, bs), 8.63 (1H, d, J = 3.1 Hz), 8.20 (1H, dd, J = 8.8, 3.1 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 157.9 (d, $^1J_{C-F}$ = 256.1 Hz), 142.7, 139.9 (d, $^2J_{C-F}$ = 25.8 Hz), 129.3 (d, $^3J_{C-F}$ = 4.3 Hz), 127.1 (d, $^2J_{C-F}$ = 21.5 Hz). ^{19}F NMR (DMSO-d_6) δ −129.1 (d, J = 9.1 Hz). Anal. Calcd for $C_6H_3ClFNO_2$: C, 41.05; H, 1.72; N, 7.98. Found: C, 40.92; H, 1.83; N, 7.79.

2-((1*H*-Pyrrolo[2,3-b]pyridine-4-yl)methylamino)-5-fluoronicotinic Acid (1). A mixture of 2-chloro-5-fluoronicotinic acid (50 g, 0.29 mol), 4-aminomethyl-7-azaindole (88 g, 0.6 mol), and $NaHCO_3$ (76 g, 0.9 mol) in pentanol (150 mL) was heated to 130 °C for 48 h. MeOH (150 mL) and H_2O (150 mL) were added to the mixture. The mixture was cooled to room temperature over 5 h. HCl (12 N) was added slowly to adjust the pH to 4−5. The mixture was stirred further for 1 h. Filtration and washing with H_2O (500 mL) afforded the product. The solid was slurried in MeOH (250 mL) at 70 °C for 4 h. The mixture was cooled to room temperature and filtered to provide the pure product as an off-white solid (57 g, 70%). mp 215.0−217.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.54 (bs, 1H), 8.26 (d, J = 3.1 Hz, 1H), 8.13 (d, J = 4.9 Hz, 1H), 7.96 (dd, J = 8.8, 3.1, 1H), 7.43 (t, J = 2.9 Hz, 1H), 6.92 (J = 4.9 Hz, 1H), 6.55 (dd, J = 3.3, 1.9 Hz, 1H), 4.96 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.1, 155.2, 150.9 (d, $^1J_{C-F}$ = 239.7 Hz), 148.5, 142.6, 140.6 (d, $^2J_{C-F}$ = 24.1 Hz), 140.5, 126.5 (d, $^2J_{C-F}$ = 20.7 Hz), 125.5, 117.9, 113.0, 106.3, 98.1, 41.9. ^{19}F NMR (DMSO-d_6) δ −144.7 (d, J = 9.1 Hz). Anal. Calcd for $C_{14}H_{11}FN_4O_2$: C, 58.74; H, 3.87; N, 19.57. Found: C, 58.51; H, 4.00; N, 19.88.

Supporting Information Available: ^{1}H, ^{13}C, and ^{19}F NMR spectra for compounds **1** and **3**, and ^{1}H and ^{13}C NMR for compounds **2**, **5**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0602571