# Tetrabutyl Ammonium Salt-Induced Denitration of Nitropyridines: Synthesis of Fluoro-, Hydroxy-, and Methoxypyridines

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## Supplementary information

### General Methods.

General experiment information: Proton, Carbon, and Fluorine NMR spectra were recorded on Varian Unity 400 or VRX-400 spectrometers (400 MHz) or Varian Unity or Varian Plus (500 MHz) spectrometers. Chemical shifts are reported in parts per million (δ) downfield from TMS as an internal standard. TBAF (1M in THF) and TBAOH (40% in water) were obtained from Aldrich. TBAOMe (20% in MeOH) was obtained from Fluka. Other solvents and reagents were obtained from commercial sources and used without further purification. The reported yields are the actual isolated yields of purified material and are not optimized. Flash chromatography was performed on an ISCO combiflash system employing prepacked silica columns (Isco Redi-sep). Filtration thru silica gel plugs were carried out using Fisher 230-400 mesh silica gel. Analytical HPLC: Waters' LC/MS comprised of a 2695 LC with a gradient from 5% MeCN/H2O to 100% MeCN (0.05% TFA) in 4 minutes, using a YMC Pro C18, 3x50 mm column. UV detection was performed at 215 nM. Data is reported in the format: retention time (% purity).

**3-Bromo-2-fluoropyridine (Table 1, entry 1):**[1] $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, 1 H), 8.16 (dd, 1 H), 8.49 (dd, 1 H); $^{19}$F NMR ($CDCl_3$) δ −107.3 (m). HPLC 1.66 min (100%).

**5-Bromo-2-fluoropyridine (Table 1, entry 2):**[2] $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.87 (dd, 1 H), 7.87 (m, 1 H), 8.29 (bs, 1 H). HPLC 1.42 min (96%).

**3-Ethoxy-2-fluoropyridine (Table 1, entry 3):** To a solution of 538 mg (3.2 mmol) of 3-ethoxy-2-nitro-pyridine in 6.4 ml of DMF was added a solution of 1M TBAF in THF (12.8 ml). The solution was stirred and heated under nitrogen at 70 ºC for 24 hours. The reaction mixture was then cooled and poured into 50 ml of 1:1 water:brine and extracted with three 30-ml portions of ethyl acetate. The combined ethyl acetate extracts were washed three times with water and once with brine, then dried over sodium sulfate, and filtered. Removal of solvent *in vacuo* gave 711 mg of crude fluoro-denitration product. Purification by flash chromatography on silical gel using 5 to 7% ethyl acetate in hexane gave 318 mg (70%) of 2-fluoro-3-ethoxy pyridine. $^{1}$H NMR (400 MHz, $CDCl_3$ ) δ 1.48 (t, 3H), 4.12 (q, 2 H), 7.10 (dd, 1 H), 7.26 (t, 1 H), 7.74 (d, 1 H); $^{13}$C NMR (CDCl3) δ 14.6, 65.0, 121.9, 122.6, 137.0, 142.3, 153.7; $^{19}$F NMR ($CDCl_3$) δ −84.5 (d); EI-MS: 141. HPLC 1.30 min (98.7%).

**2-Cyano-3-fluoropyridine (Table 1, entry 6):**[3] To a solution of 2-cyano-3-nitro pyridine (468 mg, 3.14 mmol) in 6.2 ml of DMF was added a solution of 1M TBAF in THF (6.3 mmol). The resulting reddish-brown solution was stirred at room temperature for 30 minutes. The reaction mixture was then poured into 50 ml of a 1:1 mixture of water and brine and extracted with three 40-ml portions of ethyl acetate. The combined ethyl acetate extracts were washed with two 25-ml portions of water and one with brine. The extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 440 mg of crude product. The crude reaction product was purified by flash chromatography on silica gel using 5 to 10% ethyl acetate in hexane to afford 244 mg (63%) of 2-cyano-3-fluoro pyridine. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 2 H), 8.57 (d, 1 H); $^{19}$F NMR (CDCl3) δ -90.5 (dd,); $^{13}$C NMR (CDCl3) δ 112.9 (1C, -CN), 123.0 (1C, C-2), 124.6 (1C, C-4), 128.7 (1C, C-5), 147.0 (1C, C-6), 161.3 (1C, C-3). EI-MS: 122. HPLC 1.06 min (99.7%).

**2-Chloro-4-fluoropyridine (Table 1, entry 7):** $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.01 (t, 1 H), 7.11 (d, 1 H), 8.38 (dd, 1 H); $^{19}$F NMR ($CDCl_3$) δ −99.8 (q); $^{13}$C NMR ($CDCl_3$)

δ 111.0 (1C, C-5), 112.5 (1C, C-3), 151.6 (1C, C-6), 153.1 (1C, C-2), 169.3 (1C, C-4). Mass spectrum not obtained; compound too volatile. HPLC 1.35 min (100%).

**2-Cyano-4-fluoropyridine (Table 1, entry 8):** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 1 H), 7.48 (dd, 1 H), 8.72 (dd, 1 H); $^{13}$C NMR ($CDCl_3$) δ 115.4, 117.2, 136.2, 153.9, 167.4, 169.6; $^{19}$F NMR ($CDCl_3$) δ −98.7 (q). HPLC 1.03 min (100%).

**2-Nitro-3-(3-aminobenzyloxy)pyridine 1:** To a solution of 3-*t*-butoxycarbonyl-amino benzyl alcohol (670 mg, 3.0 mmol) in 8 ml of THF was added 2-nitro-3-hydroxy-pyridine (420 mg., 3.0 mmol) in one portion. The resulting mixture was cooled to 0 °C under nitrogen, and then triphenylphosphine (866 mg, 3.3 mmol) and diethylazodicarboxylate (575 mg., 3.3 mmol) were added in succession. After 2.5 hours at 0 °C, the solvent was removed *in vacuo*, and the residue was azeotroped with 25 ml of toluene. Purification by flash chromatography on silica gel using chloroform gave 202 mg of the desired compound: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9 H), 5.23 (s, 2 H), 6.57 (s, 1 H), 7.08 (br s, 1 H), 7.32 (m, 2 H), 7.48 (m, 3 H), 8.08 (dd, 1 H).

To a solution of 2-nitro-3-(3-*t*-butoxycarbonyl-aminobenzyloxy) pyridine (636 mg, 1.84 mmol) in 11 ml of ethyl acetate at 0°C was added excess hydrogen chloride gas. The solution was stirred at 0° for 45 minutes and the solvent was removed *in vacuo*. The residue re-dissolved in 100 ml of ethyl acetate and washed with 50% sodium bicarbonate solution and brine. The extracts were dried over sodium sulfate, filtered, and concentration *in vacuo* to give 460 mg of the title compound which was used directly in the next step.

**2-Fluoro-3-(3-aminobenzyloxy)pyridine 2:** $^{1}$H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 2 H), 5.08 (s, 2 H), 6.64 (d, 1 H), 6.78 (m, 2 H), 7.05 (m, 1 H), 7.15 (t, 1 H), 7.28 (m, 1 H), 7.73 (d, 1 H); $^{13}$C NMR ($CDCl_3$) δ 71.4, 113.9, 115.3, 117.5, 122.0, 123.8, 129.9, 137.3, 137.8, 142.0, 147.2, 154.1; $^{19}$F NMR ($CDCl_3$) δ −84 (s); HRMS calc. for $C_{12}H_{11}FN_2O$: 219.0928 Found: 219.0921. HPLC 1.10 min (100%).

**5-Bromo-pyridin-2-ol (Table 2, entry 1):**[4] To a solution of 2-nitro-5-bromo- pyridine (270 mg, 1.33 mmol) in 2 ml of THF under nitrogen was added 1.72 mL (~2 eq.) of TBAOH (40% in water). After 12 hours at room temperature, the mixture was concentrated and the residue was filtered through a plug of silica gel (EtOAc) to afford 80 mg (35%) of 2-hydroxy-5-bromo-pyridine: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, 1 H), 7.47 (d, 1 H), 7.50 (dd, 1 H). HPLC 0.67 min (98%).

**2-Chloro-4-hydroxypyridine (Table 2, entry 4):**[5] $^1$H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, 1 H), 6.80 (bd, 1 H), 8.02 (d, 1 H). HPLC 1.49 min (99%).

**5-Bromo-2-methoxypyridine (Table 3, entry 1):**[4] To a solution of 2-nitro-5-bromo-pyridine (501 mg, 2.46 mmol) in 3 ml of THF under nitrogen was added 0.87 mL (1.05 eq.) of TBAOMe (20% in MeOH). After 30 minutes at room temperature, the mixture was filtered through a plug of silica gel to afford 320 mg (69%) of 2-methoxy-5-bromo-pyridine as a clear oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3 H), 6.66 (d, 1 H), 7.63 (d, 1 H), 8.20 (s, 1 H). HPLC 2.09 min (99%).

**3-Ethoxy-2-methoxypyridine (Table 3, entry 2):** $^1$H NMR (400 MHz, $CDCl_3$) δ 1.48 (t, 3 H), 4.02 (s, 3 H), 4.09 (q, 2 H), 6.82 (dd, 1 H), 7.04 (d, 1 H), 7.73 (d, 1 H): $^{13}$C NMR ($CDCl_3$) δ 14.8, 53.8, 64.4, 116.9, 118.5, 137.2, 143.6, 154.9; HRMS calc for $C_8H_{11}NO_2$ 154.0863, found 154.0861. HPLC 1.26 min (100%).

**3-Methoxypyridine-2-carbonitrile (Table 3, entry 3):**[3] $^1$H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3 H), 7.38 (d, 1 H), 7.50 (dd, 1 H), 8.30 (d, 1 H). EI-MS: 134. HPLC 1.09 min (100%).

**2-Chloro-4-methoxypyridine (Table 3, entry 4):**[6] $^1$H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 6.76 (d, 1 H), 6.85 (s, 1 H), 8.19 (d, 1 H). ES-MS: 144.0207. HPLC 1.26 min (100%).

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