

A Mild Method for the Formation and *in situ* Reaction of Imidoyl Chlorides: Conversion of Pyridine-1-oxides to 2-Aminopyridine Amides

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Supplementary Material

General experimental information: Proton and carbon 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 part per million (δ) downfield from tetramethylsilane as an internal standard. High resolution mass spectra were recorded on a Bruker 3T Fourier transform ion cyclotron resonance mass spectrometer equipped with electrospray ionization. The MH^+ signal of the analyte of interest is mass measured against the internal calibrant, polypropylene glycol (average mass (425)). 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.

General procedure: To a solution of 1.5 equivalents of secondary amide in CH_2Cl_2 (0.2 M with respect to pyridine-1-oxide) was added 2.5 equivalents of 2,6-lutidine then 1.5 equivalents of oxalyl chloride dropwise at $0^\circ C$ resulting in the evolution of gas. After stirring for 15 minutes 1 equivalent of pyridine-1-oxide was added all at once and the cooling bath was removed. After the N-oxide had been consumed as judged by TLC or LC/MS the mixture was diluted with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography using MeOH/ CH_2Cl_2 or EtOAc/hexanes solvent mixtures as indicated.

N-methyl-*N*-pyridin-2-ylacetamide (Table 1, entry 1): Purification using 0-5% MeOH/ CH_2Cl_2 gradient gave a yellow oil (58 mg, 73%): 1H -NMR (500 MHz, $CDCl_3$) δ 8.50 (d, 1 H, $J = 4.64$ Hz), 7.76 (m, 1 H), 7.30 (bs, 1 H), 7.20 (t, 1 H, $J = 7.08$ Hz), 3.39 (s, 3 H), 2.10 (s, 3 H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 171.0, 149.1, 138.4, 122.0, 120.7, 35.7, 23.3; HRMS calc for $C_8H_{11}N_2O$ 151.0866, found 151.0874.

N-benzyl-*N*-pyridin-2-ylacetamide (Table 1, entry 2): Purification using 0-5% MeOH/ CH_2Cl_2 gradient gave a mixture. A second purification using 30% EtOAc hexanes gave a pale yellow oil (94 mg, 79%): 1H -NMR (500 MHz, $CDCl_3$) δ 8.50 (d, 1 H, $J = 4.64$ Hz), 7.67 (m, 1 H), 7.28-7.06 (m, 7 H), 5.11 (s, 2 H), 2.08 (s, 3 H); ^{13}C -NMR

(100 MHz, CDCl₃) δ 149.4, 138.3, 137.8, 128.7, 128.1, 127.4, 122.3, 121.9, 51.3, 23.4; HRMS calc for C₁₄H₁₅N₂O 227.1179, found 227.1172.

N-phenyl-*N*-pyridin-2-ylacetamide (Table 1, entry 3): Purification using 25% EtOAc hexanes gave a yellow oil (63 mg, 56%): ¹H-NMR (500 MHz, CDCl₃) δ 8.43 (m, 1 H), 7.72 (m, 1 H), 7.48-7.25 (m, 6 H), 7.13 (m, 1 H), 2.11 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 171.2, 155.5, 149.0, 142.3, 138.1, 129.7, 128.6, 127.8, 121.7, 121.4, 24.5; HRMS calc for C₁₃H₁₃N₂O 213.1023, found 213.1030.

N-methyl-*N*-pyridin-2-ylbenzamide (Table 1, entry 4): Purification using 0-5% MeOH/CH₂Cl₂ gradient gave a mixture. A second purification using 25% EtOAc hexanes gave a clear oil (112 mg, 100%): ¹H-NMR (500 MHz, CDCl₃) δ 8.45 (m, 1 H), 7.43 (m, 1 H), 7.35-7.21 (m, 5 H), 7.04 (m, 1 H), 6.81 (d, 1 H, J = 8.06 Hz), 3.58 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 171.2, 157.0, 148.9, 137.5, 136.3, 130.3, 128.7, 128.2, 121.8, 121.1, 36.2; HRMS calc for C₁₃H₁₃N₂O 213.1023, found 213.1023.

N-benzyl-*N*-(4-phenylpyridin-2-yl)acetamide (Table 2, entry 1): Purification using 95:5 DCM/MeOH and then using 70:30 hexanes/EtOAc gave a colorless oil (151 mg, 86%): ¹H-NMR (500 MHz, CDCl₃) δ 8.53 (d, 1H, J = 5.1 Hz), 7.52-7.44 (m, 6 H), 7.39 (dd, 1H, J = 1.5, 5.4 Hz), 7.30-7.21 (m, 5H), 5.15 (s, 2H), 2.12 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 170.8, 156.1, 149.7, 137.9, 129.7, 129.4, 128.7, 128.2, 127.5, 127.2, 120.4, 119.8, 51.4, 23.5; HRMS calc for C₂₀H₁₈N₂O 303.1492, found 303.1467.

N-[4-(benzyloxy)pyridin-2-yl]-*N*-methylacetamide (Table 2, entry 2): Purification using 95:5 DCM/MeOH gave a colorless oil (91 mg, 67%): ¹H-NMR (500 MHz, CDCl₃) δ 8.31 (d, 1H, J = 5.6 Hz), 7.43-7.35 (m, 5H), 6.85 (bs, 1H), 6.81 (dd, 1H, J = 2., 2., 5.8 Hz), 5.14 (s, 2H), 3.34 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 170.9, 166.6, 158.0, 150.0, 135.5, 129.0, 128.7, 127.71, 127.68, 109.4, 107.4, 70.4, 35.7, 23.2; HRMS calc for C₁₅H₁₆N₂O₂ 257.1285, found 257.1277.

N-methyl-*N*-(4-methylpyridin-2-yl)acetamide (Table 2, entry 3): Purification using 90% EtOAc hexanes gave a yellow oil (62 mg, 61%): ¹H-NMR (500 MHz, CDCl₃) δ 8.34 (d, 1 H, J = 5.13 Hz), 7.08 (bs, 1 H), 7.03 (d, 1 H, J = 4.64 Hz), 3.35 (s, 3 H), 2.40 (s, 3 H), 2.07 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 170.9, 150.0, 148.8, 123.2, 121.4, 35.7, 23.2, 21.2; HRMS calc for C₉H₁₂N₂O 164.0950, found 164.0948.

N-methyl-*N*-(3-methylpyridin-2-yl)acetamide (Table 2, entry 4, major): Purification using 80% EtOAc hexanes gave a yellow solid (30 mg, 40%): ¹H-NMR (500 MHz, CDCl₃) δ 8.41 (d, 1 H, J = 3.42 Hz), 7.67 (d, 1 H, J = 7.33 Hz), 7.26 (m, 1 H), 3.22 (s, 3 H), 2.29 (s, 3 H), 1.80 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 170.5, 155.5, 147.7, 140.6, 130.6, 123.9, 34.4, 22.2, 17.3; HRMS calc for C₉H₁₂N₂O 164.0950, found 164.0953.

N-methyl-*N*-(5-methylpyridin-2-yl)acetamide (Table 2, entry 4, minor): Purification using 80% EtOAc hexanes gave a yellow oil (18 mg, 24%): ¹H-NMR (500 MHz, CDCl₃) δ 8.32 (s, 1 H), 7.56 (d, 1 H, J = 7.81 Hz), 7.14 (bs, 1 H), 3.34 (s, 3 H), 2.36 (s, 3 H), 2.04

(s, 3 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 170.9, 149.4, 139.0, 120.3, 35.7, 23.1, 18.1; HRMS calc for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}$ 164.0950, found 164.0948.

N-benzyl-*N*-(6-methylpyridin-2-yl)acetamide (Table 2, entry 5): Purification using 30% EtOAc in hexanes gave a colorless oil (290 mg, 74%): ^1H -NMR (500 MHz, CDCl_3) δ 7.52 (t, 1H, J = 7.8 Hz), 7.27 (m, 5H), 7.3 (d, 1H, J = 7.6 Hz), 6.80 (bs, 1H), 5.08 (s, 2H), 2.54 (s, 3H), 2.05 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ 170.6, 158.8, 154.8, 138.4, 138.0, 128.8, 128.6, 128.3, 127.3, 121.9, 118.9, 51.3, 24.5, 23.3; HRMS calc for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ 241.1335, found 241.1333.

N-methyl-*N*-quinolin-2-ylacetamide (Table 2, entry 6): Purification using 30% EtOAc hexanes gave a pale yellow solid (50 mg, 73%): ^1H -NMR (500 MHz, CDCl_3) δ 8.20 (d, 1 H, J = 8.54 Hz), 7.99 (d, 1 H, J = 8.54 Hz), 7.83 (d, 1 H, J = 8.05 Hz), 7.74 (t, 1 H, J = 7.57 Hz), 7.56 (t, 1 H, 7.81 Hz), 7.46 (bs, 1 H), 3.51 (s, 3 H), 2.21 (s, 3 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 171.3, 155.4, 147.1, 138.4, 130.3, 128.9, 127.6, 126.8, 126.7, 119.0, 35.6, 23.8; HRMS calc for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}$ 201.1023, found 201.1031.

N-isoquinolin-1-yl-*N*-methylacetamide (Table 2, entry 7): Purification using 0-5% MeOH/ CH_2Cl_2 gradient gave a brown oil (62 mg, 90%): ^1H -NMR (500 MHz, CDCl_3) δ 8.46 (d, 1 H, J = 5.62 Hz), 7.95 (m, 2 H), 7.79-7.67 (m, 3 H), 3.41 (s, 3 H), 1.79 (s, 3 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 171.1, 155.5, 142.1, 138.7, 131.3, 128.9, 127.6, 125.3, 124.6, 121.7, 35.8, 22.7; HRMS calc for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}$ 201.1023, found 201.1033.