

# **Mild and Direct Conversion of Quinoline *N*-Oxides to 2-Amidoquinolines using Primary Amides**

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**General Methods.** The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Innova 400 spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc. (Woodside N.Y.). Melting points were obtained from a Thomas Hoover Uni-Melt capillary apparatus and are uncorrected. Column chromatography purifications were carried out on Baker silica gel 40  $\mu\text{m}$  flash chromatography packing (60  $\text{\AA}$  pore diameter). Quinoline *N*-oxides were purchased from Aldrich, with the exception of 3-cyanoquinoline *N*-oxide,<sup>i</sup> phenanthridine *N*-oxide,<sup>ii</sup> 6-carboethoxyquinoline *N*-oxide,<sup>iii</sup> which were prepared according to known literature procedures. Commercially available quinoline *N*-oxide hydrate was azeotropically dried with benzene prior to use.

**General Procedure (method A).** To a stirred solution of *N*-oxide (5.0 mmol) in dichloromethane (15 mL) at room temperature was added a solution of benzoyl isocyanate (10.0 mmol) in dichloromethane (5 mL). The resulting mixture was stirred under nitrogen at the prescribed temperature (rxnT) over the prescribed amount of time (rxnt). The reaction was quenched at room temperature with methanol (500  $\mu\text{L}$ ), stirred for 15 minutes, and concentrated under vacuum. The crude residual material was purified by the prescribed procedure.

**General Procedure (method B).** To a stirred solution of amide (11.0 mmol) in the prescribed solvent (10 mL) at room temperature was added oxalyl chloride (10.0 mmol) dropwise over 5 min. The reaction mixture was heated to reflux under nitrogen for the prescribed amount of activation time (a.t.), and then cooled back to room temperature. The foregoing solution was added to a solution of *N*-oxide (5 mmol) in the same solvent (10 mL), and the resulting mixture was stirred under nitrogen at the prescribed temperature (r.T.) over the prescribed amount of time (r.t.). The reaction was quenched at room temperature with methanol (500  $\mu\text{L}$ ), stirred for 15 minutes, and

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<sup>i</sup> Vitry, C.; Vasse, J.-L.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Tetrahedron* **2001**, *57*, 3087.

<sup>ii</sup> DeRuiter, J.; Swearingen, B. E.; Wandrekar, V.; Mayfield, C. A. *J. Med. Chem.* **1989**, *32*, 1033.

<sup>iii</sup> Sagi, K.; Fujita, K.; Sugiki, M.; Takahashi, M.; Takehana, S.; Tashiro, K.; Kayahara, T.; Yamanashi, M.; Fukuda, Y.; Oono, S.; Okajima, A.; Iwata, S.; Shoji, M.; Sakurai, K. *Bioorg. Med. Chem.* **2005**, *13*, 1487.

concentrated under vacuum. The crude residual material was purified by the prescribed procedure.

**2-Benzamidoquinoline (3)- from benzoyl isocyanate.** The titled compound was prepared according to method A (r.T. = reflux; r.t. = 20h). Column chromatography (dichloromethane) of the residual material yielded **3** (955 mg, 77%) as a crystalline solid (m.p. 120-121°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.17 (brs, 1H), 8.57 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 7.5 Hz, 2H), 7.76 (t, J = 8.5 Hz, 2H), 7.60 (m, 1H), 7.50 (m, 1H), 7.44-7.40 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.44, 151.45, 146.82, 138.87, 134.42, 132.56, 130.22, 128.99, 127.82, 127.61, 127.52, 126.63, 125.45, 114.76. Exact mass calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O (M+1): 249.1028; found: 249.1024.

**1-Benzamidoisoquinoline (8).** The titled compound was prepared according to method A (r.T. = 20°C; r.t. = 3h). Column chromatography (10% ethyl acetate in toluene) of the residual material yielded **8** (1.20 g, 97%) as a crystalline solid (m.p. 99-100°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.92 (d, J = 8.0 Hz, 1H) 8.39 (d, J = 7.5 Hz, 2H), 7.83 (t, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.57 (brd, J = 6.5 Hz, 1H), 7.56-7.48 (m, 3H), 7.22 (brd, J = 6.5 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 137.41, 133.02 (br), 131.85, 129.43 (br), 128.37, 127.97, 127.39, 126.64. Exact mass calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O (M+1): 249.1028; found: 249.1025.

**2-Benzamido-3-cyanoquinoline (10).** The titled compound was prepared according to method A (r.T. = reflux; r.t. = 32h). Trituration of the residual material in ice-cold dichloromethane (20 mL) yielded **10** (1.24 g, 91%) as a crystalline solid (m.p. 225-227°C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.15 (s, 1H), 8.11-8.07 (m, 3H), 8.04-7.89 (m, 2H), 7.71 (t, J = 7.0 Hz, 1H), 7.64 (t, J = 7.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 167.48, 150.53, 147.91, 145.97, 134.04, 133.32, 129.58, 129.36, 129.29, 128.92, 128.66, 128.57, 125.27, 116.27, 105.62. Exact mass calcd. for C<sub>17</sub>H<sub>12</sub>N<sub>3</sub>O (M+1): 274.0980; found: 274.0993.

**6-Benzamidophenanthridine (12).** The titled compound was prepared according to method A (r.T. = 20°C; r.t. = 5min). Column chromatography (dichloromethane) of the residual material

yielded **12** (1.47 g, 99%) as a crystalline solid (m.p. 170-172°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.03 (brd, J = 7.0 Hz, 1H), 8.47 (d, J = 7.0 Hz, 2H), 8.29 (d, J = 8.5 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.60-7.45 (m, 4H), 7.44-7.36 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.61, 157.66, 138.49, 133.93, 133.33, 131.98, 129.88, 129.70, 128.33, 128.28, 125.49, 125.00, 122.86, 121.95, 120.68, 118.55. Exact mass calcd. for C<sub>20</sub>H<sub>15</sub>N<sub>2</sub>O (M+1): 299.1184; found: 299.1198.

**2-Benzamido-6-carboethoxyquinoline (14).** The titled compound was prepared according to method A (r.T. = reflux; r.t. = 22h). Column chromatography (10% ethyl acetate in toluene) of the residual material yielded **14** (1.32 g, 82%) as a crystalline solid (m.p. 122-125°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.89 (brs, 1H), 8.65 (d, J = 9.0 Hz, 1H), 8.55 (s, 1H), 8.31 (d, J = 9.0 Hz, 1H), 8.27 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 7.0 Hz, 2H), 7.84 (d, J = 9.0 Hz, 1H), 7.60 (t, J = 7.0 Hz, 1H), 7.53 (t, J = 7.0 Hz, 2H), 4.43 (q, J = 7.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.37, 153.04, 149.02, 140.08, 134.11, 132.79, 130.73, 129.89, 129.07, 128.21, 127.64, 127.24, 125.62, 115.29, 61.49, 14.60. Exact mass calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> (M+1): 321.1239; found: 321.1227.

**2-Benzamido-6-methoxyquinoline (16).** The titled compound was prepared according to method A (r.T. = reflux; r.t. = 40h). Column chromatography (10% ethyl acetate in toluene) of the residual material yielded **16** (862 mg, 62%) as a crystalline solid (m.p. 163-165°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.86 (s, 1H), 8.52 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 7.0 Hz, 2H), 7.70 (d, J = 9.0 Hz, 1H), 7.55 (t, J = 7.0 Hz, 1H), 7.47 (t, J = 7.0 Hz, 2H), 7.30 (dd, J = 9.0, 3.0 Hz, 1H), 7.07 (d, J = 3.0 Hz, 1H), 3.90 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.16, 157.17, 149.49, 142.58, 137.57, 134.52, 132.50, 130.81, 129.03, 127.51, 122.81, 114.89, 105.62, 55.77. Exact mass calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> (M+1): 279.1134; found: 279.1123.

**2-Benzamidoquinoline (3)- from benzamide.** The titled compound was prepared according to method B using dichloromethane as the solvent (a.t. = 45min; r.T. = reflux; r.t. = 20h). Column

chromatography (10% ethyl acetate in toluene) of the residual material yielded **3** (870 mg, 70%) as a crystalline solid.

**2-(4-Methoxybenzamido)quinoline (17).** The titled compound was prepared according to method B using dichloromethane as the solvent (a.t. = 50min; r.T. = reflux; r.t. = 24h). Column chromatography (10% ethyl acetate in toluene) of the residual material yielded **17** (1.102 g, 79%) as a crystalline solid (m.p. 81-88°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.00 (brs, 1H), 8.56 (d, J = 9.0 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.5 Hz, 2H), 3.82 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 165.81, 163.12, 151.62, 146.74, 138.85, 130.23, 129.59, 127.83, 127.38, 126.53, 126.47, 125.35, 114.76, 114.22, 55.69. Exact mass calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> (M+1): 279.1134; found: 279.1143.

**2-(4-Cyanobenzamido)quinoline (18).** The titled compound was prepared according to method B using dichloromethane as the solvent (a.t. = 40min; r.T. = reflux; r.t. = 24h). Column chromatography (10% acetonitrile in toluene) of the residual material yielded **18** (1.04 g, 74%) as a crystalline solid (m.p. 240°C – dec.); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.45 (d, J = 9.0 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 8.18 (d, J = 8.5 Hz, 2H), 7.99 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.74 (m, 1H), 7.53 (m, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 166.19, 151.44, 143.06, 141.97, 137.79, 133.21, 132.26, 129.84, 128.92, 127.04, 126.13, 125.23, 118.83, 115.97, 115.49. Exact mass calcd. for C<sub>17</sub>H<sub>12</sub>N<sub>3</sub>O (M+1): 274.0980; found: 274.0992.

**2-(3-Trifluoromethylbenzamido)quinoline (19).** The titled compound was prepared according to method B using dichloromethane as the solvent (a.t. = 60min; r.T. = reflux; r.t. = 16h). Column chromatography (toluene) of the residual material yielded **19** (1.28 g, 81%) as a crystalline solid (m.p. 100-105°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.33 (brs, 1H), 8.54 (d, J = 8.5 Hz, 1H), 8.23-8.20 (m, 2H), 8.12 (d, J = 8.0 Hz, 1H), 7.82-7.74 (m, 3H), 7.62 (t, J = 7.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 165.54, 151.44, 146.35, 139.18, 135.37, 131.40 (q, J = 33 Hz), 130.87, 130.33, 129.45, 128.94, 127.83, 127.08,

126.61, 125.65, 124.84, 123.75 (q, J = 272 Hz), 114.95. Exact mass calcd. for  $C_{17}H_{12}F_3N_2O$  (M+1): 317.0902; found: 317.0912.

**2-Acetamidoquinoline (20).** The titled compound was prepared according to method B using 1,2-dichloroethane as the solvent (a.t. = 2.5h; r.T. = reflux; r.t. = 90min). Trituration of the residual material in ice-cold dichloromethane (20 mL) yielded **20** (775 mg, 83%) as a crystalline solid (m.p. 240°C – dec.);  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  8.91 (d, J = 9.0 Hz, 1H), 8.18-8.14 (m, 2H), 8.04 (t, J = 7.5 Hz, 1H), 7.81 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 9.0 Hz, 1H), 2.42 (s, 3H);  $^{13}C$  NMR (100 MHz,  $CD_3OD$ )  $\delta$  174.38, 149.79, 147.26, 134.71, 134.46, 129.09, 128.39, 124.91, 119.82, 113.54, 23.23. Exact mass calcd. for  $C_{11}H_{11}N_2O$  (M+1): 187.0871; found: 187.0873.

**2-(4-Methoxybenzamido)isoquinoline (21).** The titled compound was prepared according to method B using dichloromethane as the solvent (a.t. = 50min; r.T. = 20°C; r.t. = 20h). Column chromatography (10% ethyl acetate in toluene) of the residual material yielded **21** (1.14g, 82%) as a crystalline solid (m.p. 106-110°C);  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.87 (brd, J = 8.0 Hz, 1H), 8.36 (d, J = 7.5 Hz, 2H), 7.75 (t, J = 7.5 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.46 (brd, J = 6.5 Hz, 1H), 7.04 (brd, J = 6.5 Hz, 1H), 6.96 (d, J = 7.5 Hz, 2H), 3.87 (s, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  162.73, 152.7, 143.12, 137.37, 132.80 (br), 131.37 (br), 127.82, 127.32, 126.59, 113.55, 55.60. Exact mass calcd. for  $C_{17}H_{15}N_2O_2$  (M+1): 279.1134; found: 279.1137.

**2-(4-Cyanobenzamido)isoquinoline (22).** The titled compound was prepared according to method B using dichloromethane as the solvent (a.t. = 40min; r.T. = 20°C; r.t. = 40min). Crystallization of the residual material from methanol (30 mL) yielded **22** (875 mg, 64%) as a crystalline solid (m.p. 215°C – dec.);  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.99 (brd, J = 8.0 Hz, 1H), 8.52 (d, J = 8.0 Hz, 2H), 7.83 (t, J = 7.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.73-7.67 (m, 2H), 7.44 (brs, 1H), 7.12 (d, J = 6.5 Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  176.64, 158.68, 142.59, 137.42, 133.74, 132.09, 129.95, 128.36, 127.44, 126.75, 126.08, 119.14, 114.64, 113.66. Exact mass calcd. for  $C_{17}H_{12}N_3O$  (M+1): 274.0980; found: 274.0981.

**2-(3-Trifluoromethylbenzamido)isoquinoline (23).** The titled compound was prepared according to method B using dichloromethane as the solvent (a.t. = 60min; r.T. = 20°C; r.t. = 2h). Column chromatography (10% ethyl acetate in toluene) of the residual material yielded **23** (1.44g, 91%) as a crystalline solid (m.p. 164-165°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.98 (d, J = 8.5 Hz, 1H), 8.71 (s, 1H), 8.60 (d, J = 7.5 Hz, 1H), 7.81 (t, J = 7.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.72-7.67 (m, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 6.5 Hz, 1H), 7.10 (d, J = 6.5 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.95 (br), 158.55 (br), 139.34 (br), 137.36, 133.51 (br), 132.71 (br), 131.69, 130.62 (q, J = 32 Hz), 129.50, 128.75, 128.54, 128.25, 128.09, 127.44, 126.65, 126.43 (br), 125.98, 124.47 (q, J = 273 Hz), 113.38 (br). Exact mass calcd. for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O (M+1): 317.0902; found: 317.0915.

**2-Acetamidoisoquinoline (24).** The titled compound was prepared according to method B using 1,2-dichloroethane as the solvent (a.t. = 2.5h; r.T. = 20°C; r.t. = 24h). Trituration of the residual material in ice-cold dichloromethane (20 mL) yielded **24** (875 mg, 94%) as a crystalline solid (m.p. 240°C – dec.); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.87 (d, J = 8.5, 1H), 8.20-8.14 (m, 2H), 8.10 (d, J = 7.0 Hz, 1H), 8.01 (m, 1H), 7.95 (d, J = 7.0 Hz, 1H), 2.56 (s, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) δ 174.59, 148.97, 139.05, 136.10, 130.40, 128.33, 127.46, 125.16, 119.39, 118.12, 23.76. Exact mass calcd. for C<sub>11</sub>H<sub>11</sub>N<sub>2</sub>O (M+1): 187.0871; found: 187.0869.



























