A Convenient One-Pot Synthesis of 1,8-Naphthyridones

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Supporting Information. Reactions were carried out under an atmosphere of dry nitrogen. Reagents and solvents were used as received from commercial sources. Acetonitrile contained <100 µg/mL water as determined by Karl-Fischer titration. All reactions were monitored by HPLC analysis using Phenomenex (Luna 5u Phenyl – Hexyl) 4.60 x 250 mm column, eluent: CH₃CN / 0.1% H₃PO₄ buffer. Initial conditions 40% CH₃CN with a gradient to 80% CH₃CN over 15 min. Flow rate: 1ml/min, UV detection at 220nm.

General Procedure for the preparation of 1,8-Naphthyridones. To 70 mL acetonitrile was first charged triethylamine (31.51 mL, 227.28 mmol, 4.0 equiv.) followed by ethyl-3,3-dimethylaminoacrylate (12.20 mL, 85.23 mmol, 1.5 equiv.) and then 2-chloronicotinoyl chloride (10.00 g, 56.82 mmol 1 equiv.). The reaction mixture was heated to reflux and maintained at this temperature for 3h. At the end of the three hours a sample was taken in order to determine total consumption of starting material via the use of HPLC. At this point the reaction temperature was brought below reflux and 3-aminobenzonitrile (**entry a**, 6.73 g, 56.82 mmol, 1.0 equiv.) was charged. The reaction was then brought back to reflux and given the required amount of time in order to convert to the desired 1,8-naphthyridone. Once complete conversion had occurred, the heat was removed and the reaction was cooled to RT before adding water (140 mL) to crystallize product. After complete addition of water the slurry was aged for 30 min and then filtered. The cake was washed with acetonitrile/ H₂O (140 mL 50:50) and then dried overnight under vacuum at 40 °C to yield ethyl-1-(3-cyanophenyl)-1,4-dihydro[1,8]naphthyridin-4-one-3-carboxylate as a colorless solid **3-a** (12.19 g, 67% yield). m.p. 267 – 269 °C. ¹H NMR (400 MHz, DMSO-d₆) 8.73 (s, 1H), 8.69 (dd, J=4.8, 2.0 Hz, 1H), 8.61 (dd, J=8.0, 2.0 Hz, 1H), 8.20 (t, J=2.0 Hz, 1H), 8.03 (dt, J=8.0, 1.2 Hz, 1H), 7.99 (ddd, J=8.0, 2.0, 1.2 Hz, 1H), 7.80 (t, J=8.0 Hz, 1H), 7.57 (dd, J=8.0, 4.8 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 1.27 (t, J=7.2 Hz, 3H); ¹³C NMR (DMSO-d₆, 100 MHz) δ 174.1, 164.2, 153.1, 150.2, 149.5, 141.2, 136.3 (2 x C), 133.8, 133.2, 132.4, 131.0, 122.5, 122.1, 118.3, 112.5, 60.5, 14.6; Anal. Calcd for C₁₈H₁₃N₃O₃: C, 67.71; H, 4.10; N, 13.16; O, 15.03. Found: C, 67.45; H, 3.92; N, 13.09.

3-b (13.53 g, 64% yield) m.p. 220 – 222 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.70 (dd, J=4.4, 2.0 Hz, 1H), 8.64 (s, 1H), 8.60 (dd, J=8.0, 2.0 Hz, 1H), 7.93 (t, J=2.0 Hz, 1H), 7.76

(ddd, J=8.0, 2.0, 1.2 Hz, 1H), 7.64 (ddd, J=8.0, 2.0, 1.2 Hz, 1H), 7.56 (dd, J=8.0, 4.4 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 174.1, 164.2, 153.1, 150.3, 149.6, 142.0, 136.2, 132.4, 131.5, 131.4, 127.7, 122.6, 121.9, 121.9, 112.2, 60.5, 14.6; Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{BrN}_2\text{O}_3$: C, 54.71; H, 3.51; Br, 21.41; N, 7.51; O, 12.86. Found: C, 54.82; H, 3.26; Br, 21.25; N, 7.41.

3-c (11.86 g, 64% yield) m.p. 203 – 203 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 8.69 (dd, J=4.4, 2.0 Hz, 1H), 8.60 (dd, J=8.0, 2.0 Hz, 1H), 8.59 (s, 1H), 7.54 (dd, J=8.0, 4.4 Hz, 1H), 7.48 (t, J=8.0 Hz, 1H), 7.23 (t, J=2.0 Hz, 1H), 7.15 (brd, J=8.0 Hz, 1H), 7.12 (dd, J=8.0, 2.0 Hz, 1H), 4.22 (q, J=7.2 Hz, 2H), 3.80 (s, 3H), 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 174.1, 164.2, 160.2, 153.2, 150.4, 149.7, 141.9, 136.2, 130.5, 122.6, 121.9, 120.3, 115.2, 114.1, 111.9, 60.5, 55.9, 14.6; Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$: C, 66.66; H, 4.97; N, 8.64; O, 19.73. Found: C, 66.59; H, 4.75; N, 8.65.

3-d (13.06 g, 62% yield) m.p. 197 – 199 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 8.68 (dd, J=4.4, 2.0 Hz, 1H), 8.63 (s, 1H), 8.61 (dd, J=8.0, 2.0 Hz, 1H), 7.79 (d, J=8.4 Hz, 2H), 7.57 (d, J=8.4 Hz, 2H), 7.56 (dd, J=8.0, 4.4 Hz, 1H), 4.22 (q, J=7.2 Hz, 2H), 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 174.1, 164.2, 153.1, 150.3, 149.6, 140.0, 136.2, 132.6, 130.6, 122.6, 122.5, 121.9, 112.2, 60.5, 14.6; Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{BrN}_2\text{O}_4$: C, 54.71; H, 3.51; Br, 21.41; N, 7.51; O, 12.86. Found: C, 54.85, H, 3.36; Br, 21.51; N, 7.41.

3-e (9.08 g, 43% yield) m.p. 183 – 184 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 8.69 (dd, J=4.4, 2.0 Hz, 1H), 8.63 (dd, J=8.0, 2.0 Hz, 1H), 8.62 (s, 1H), 7.88 (dd, J=7.8, 1.6 Hz, 1H), 7.77 (dd, J= 7.8, 1.6 Hz, 1H), 7.62 (td, J=7.8, 1.6 Hz, 1H), 7.57 (dd, J=8.0, 4.4 Hz, 1H), 7.53 (td, J=7.8, 1.6 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C

NMR (DMSO- d_6 , 100 MHz) δ 174.1, 164.0, 153.5, 150.1, 149.5, 139.6, 136.3, 133.6, 131.8, 131.0, 129.5, 122.5, 122.4, 122.0, 112.7, 60.6, 14.5; Anal. Calcd for $C_{17}H_{13}BrN_2O_3$: C, 54.71; H, 3.51; Br, 21.41; N, 7.51; O, 12.86. Found: C, 54.89; H, 3.36; Br, 21.66; N, 7.35.

3-f (5.10 g, 26% yield) m.p. 164 – 166 °C; 1H NMR (400 MHz, DMSO- d_6) δ 8.70 (dd, $J=4.4, 2.0$ Hz, 1H), 8.62 (dd, $J=8.0, 2.0$ Hz, 1H), 8.59 (s, 1H), 7.73 (dd, $J=8.0, 1.6$ Hz, 1H), 7.54 (dd, $J=8.0, 4.4$ Hz, 1H), 7.53 (td, $J=8.0, 1.6$ Hz, 1H), 7.39 (td, $J=8.0, 1.6$ Hz, 1H), 7.32 (dd, $J=8.0, 1.6$ Hz, 1H), 4.22 (q, $J=7.0$ Hz, 2H), 1.25 (t, $J=7.0$ Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 174.1, 164.1, 153.4, 151.6, 150.6, 146.4, 138.7, 136.2, 131.3, 130.1, 129.6, 127.8, 122.8, 121.8, 111.7, 60.5, 36.0, 31.8, 14.5; Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99; O, 13.70. Found: C, 71.70; H, 6.39; N, 7.94.