Cobalt-Catalyzed Alkyne-Nitrile Cyclotrimerization to Form Pyridines in Aqueous Solution

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Supporting Information

All reactions and manipulations were conducted under a dry argon atmosphere either using an inert atmosphere glove-box or standard Schlenk techniques. All nitriles and alkynes were purchased from Aldrich Chemical Company and purified by either vacuum distillation or recrystallization prior to use. Methanol (for cyclotrimerization reactions) was distilled from magnesium turnings, and water was Millipore quality. All NMR data were recorded on a Bruker ARX (300 MHz ^{1}H, 75 MHz ^{13}C) or a Bruker AMX (300 MHz ^{1}H, 75 MHz ^{13}C) spectrometer. NMR data for kinetic analyses were acquired on a Bruker AMX (400 MHz ^{1}H, 100 MHz ^{13}C). Chemical shifts are reported in parts per million (ppm) referenced to the ^{1}H resonance of the protonated solvent. Mass spectral data were obtained from the departmental facility at Washington State University, NeXstar Pharmaceuticals, Inc., or UC Berkeley Mass Spectral facilities. Elemental analyses were obtained from Desert Analytics, Tucson, AZ. Melting points were recorded on a Mel-Temp apparatus and are uncorrected.

Synthesis of 2. The synthesis of **2**, Cp$^\$$-d$_4$Co(COD), and Cp$^\$$Co(COD-d$_8$) were prepared as previously reported.[1]

General Cyclotrimerization Procedure: A 30 mL reaction vessel equipped with a Teflon screw cap was charged with 40 mg (125 μmol) Cp$^{\$}$Co(COD), 430 mg (5 mmol) 2-butyne-1,4-diol, 131 μL (2.5 mmol) acetonitrile and 5 mL 70/30 water/methanol. The mixture was subjected to three cycles of freeze-pump-thaw then placed into an oil bath set at 85 °C for 20 hours. After 20 hours, the bomb was cooled to ambient temperature and volatiles were removed by rotary evaporation. The remaining residue was subjected to silica column chromatography with 10% MeOH/CH_2Cl_2.

16: ^{1}H NMR (300MHz, DMSO-d_6) δ 2.54 (s, 3H), 4.64 (m, 8H), 4.95 (m, 2H), 5.09 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 22.04, 55.66, 55.93, 56.72, 62.70, 130.81, 132.26, 147.85, 155.38, 156.62; MS *m/z* (MH$^+$) 214; HRMS *m/z* (MH$^+$) for $C_{10}H_{15}NO_4$ calcd 214.1079; found 214.1079; Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.09; H, 7.06; N, 6.54; found C, 56.10; H, 7.31; N, 6.45; mp 144-146 °C

17: An equimolar mixture of *E* and *Z* isomers: ^{1}H NMR (300MHz, MeOD-d_4) δ 1.82 (dd, *J* = 1.7 Hz, 7.1 Hz, 3H), 1.97 (dd, *J* = 3.6 Hz, 1.4 Hz, 3H), 4.86 (m, 24H), 6.09 (qd, *J* = 11.6 Hz, 7.1 Hz, 3.6 Hz, 1H), 6.74 (dq, *J* = 11.6 Hz, 1.4 Hz, 1H), 6.94 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, MeOD-d_4) δ 15.40, 18.94, 57.47, 57.59, 57.76, 57.93, 58.07, 58.62, 63.90, 64.10, 128.06, 128.39, 131.49, 132.01, 132.81, 133.35, 133.78, 134.59, 150.09, 150.46, 154.92, 156.08, 158.20, 158.25; MS *m/z* (M$^+$) 239; HRMS *m/z* (MH) for $C_{12}H_{17}NO_4$ calcd 239.1158; found 239.1151

18: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.11 (s, 3H), 4.62 (d, *J* = 5.3 Hz, 2H), 4.67 (d, *J* = 5.3 Hz, 2H), 4.69 (d, *J* = 5.3 Hz, 2H), 4.76 (d, *J* = 5.3 Hz, 2H), 5.01 (t, *J* = 5.3 Hz, 1H), 5.06 (t, *J* = 5.3 Hz, 1H), 5.10 (t, *J* = 5.3 Hz, 1H), 5.16 (s, 1H), 5.18 (t, *J* = 5.3 Hz, 1H), 5.34 (s, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 23.41, 55.69, 56.30, 57.32, 62.93, 116.38, 130.84, 132.07, 143.61, 149.52, 156.93, 158.68; MS *m/z* (M^+) 239; HRMS *m/z* for $C_{12}H_{17}NO_4$ calcd 239.1158; found 239.1161; Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85; found C, 60.08; H, 7.09; N, 5.81; mp 131-132 °C

19: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84 (p, *J* = 7.4 Hz, 2H), 2.08 (s, 3H), 2.49 (t, *J* = 7.4 Hz, 2H), 2.81 (t, *J* = 7.4 Hz, 2H), 4.65 (m, 8H), 4.97 (m, 2H), 5.08 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 23.47, 29.83, 33.60, 42.44, 55.67, 56.06, 56.23, 62.74, 130.88, 132.04, 148.32, 156.72, 158.24, 208.54; MS *m/z* (M^+) 283; HRMS *m/z* for $C_{14}H_{21}NO_5$ calcd 283.1420; found 283.1409

20: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.29 (s, 3H), 4.58 (s, 2H), 4.67 (br. s, 8H), 5.00 (br. s, 2H), 5.13 (br. s, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 55.71, 55.83, 55.90, 57.93, 62.86, 74.00, 133.24, 133.76, 148.99, 153.71, 157.03

21: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.09 (s, 3H), 3.94 (s, 2H), 4.66 (s, 4H), 4.68 (s, 4H), 5.30 (br. s, 4H);^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 36.91, 49.21, 55.84, 56.11, 56.17, 62.82, 132.13, 132.57, 149.00, 155.41, 156.85

22: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, *J* = 7.4 Hz, 3H), 3.10 (t, *J* = 7.4 Hz, 2H), 3.42 (q, *J* = 7.4 Hz, 2H), 3.70 (t, *J* = 7.4 Hz, 2H), 4.68 (m, 8H), 5.06 (m, 2H), 5.08 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 15.16, 34.91, 55.66, 56.01, 56.30, 62.73, 65.37, 69.62, 131.09, 132.69, 148.17, 155.93, 156.87; MS *m/z* (M-$C_2H_5^+$) 242; HRMS *m/z* for $C_{11}H_{16}NO_5$ calcd 242.1028; found 242.1030

23: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.52 (d, *J* = 5.4 Hz, 2H), 4.73 (d, *J* = 5.4 Hz, 2H), 4.75 (d, *J* = 5.4 Hz, 2H), 4.82 (d, *J* = 5.4 Hz, 2H), 5.07 (t, *J* = 5.4 Hz, 1H), 5.14 (t, *J* = 5.4 Hz, 1H), 5.23 (m, 2H), 7.45 (m, 3H), 7.67 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 55.76, 56.29, 57.57, 63.02, 127.95, 129.28, 129.34, 131.32, 132.48, 140.20, 149.83, 156.80, 157.72; MS *m/z* (MH$^+$) 276; HRMS *m/z* for $C_{15}H_{17}NO_4$ calcd 276.1236; found 276.1251; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.43; H, 6.23; N, 5.09; found C, 65.24; H, 6.37; N, 4.85; mp 119-121 °C

24: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.24 (s, 2H), 4.64 (m, 8H), 5.08 (m, 4H), 7.22 (m, 5H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 41.92, 57.31, 58.41, 58.56, 62.95, 127.41, 129.65, 130.01, 131.52, 133.31, 141.06, 150.57, 157.46, 158.71; MS *m/z* (M-H$^+$) 288; HRMS (M-H$^+$) *m/z* for $C_{16}H_{18}NO_4$ calcd 288.1236; found 288.1234

25: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 4.19 (s, 2H), 4.63 (m, 8H), 4.99 (m, 3H), 5.11 (m, 1H), 6.77 (m, 2H), 6.98 (m, 1H), 7.16 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, MeOD-d_3) δ 35.82, 55.99. 57.54, 58.11, 58.37, 63.66, 111.46, 121.52, 128.79, 129.29, 130.76, 132.50, 134.18, 150.68, 158.15, 158.46, 159.58; MS *m/z* (M$^+$) 319; HRMS *m/z* for $C_{17}H_{21}NO_5$ calcd 319.1420; found 319.1406; Anal calcd for $C_{17}H_{21}NO_5$: C, 63.90; H, 6.63; N, 4.39; found C, 64.22; H, 6.84; N, 4.34; mp 145-147 °C

26: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.11 (m, 2H), 2.53 (m, 4H), 3.96 (s, 2H), 4.97 (m, 8H), 5.32 (m, 2H), 5.42 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 22.87, 31.97, 35.13, 37.21, 55.66, 56.04, 56.34, 62.59, 124.60, 131.20, 132.36, 142.76, 148.54, 156.34, 156.73; MS *m/z* (M^+) 279; HRMS *m/z* for $C_{15}H_{21}NO_4$ calcd 279.1471; found 279.1471

27: ^{1}H NMR (300 MHz, Pyridine-d_5) δ 1.68 (p, *J* = 6 Hz, 4H), 3.74 (t, *J* = 6 Hz, 4H), 5.11 (s, 2H), 5.14 (s, 2H), 5.19 (s, 2H), 5.42 (s, 2H), 6.05 (br. s, 1H), 6.65 (br. s, 2H), 6.85 (br. s, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 25.42, 50.23, 55.63, 56.21, 56.71, 62.25, 118.71, 122.66, 151.10, 154.60, 157.67; MS *m/z* (M^+) 239; HRMS *m/z* for $C_{13}H_{20}N_2O_4$ calcd 268.1423; found 268.1400; Anal.calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44; found C, 57.99; H, 7.49; N, 10.18; mp 178-180 °C

Kinetics. Experiments were conducted in silanized 5 mm NMR tubes that were sealed under vacuum using a propane torch. In a typical experiment, **2** (12.5 µL of a 100 mM solution in methanol-d_4), **4** (6.5 µL, 125 µmol), **28** (15 µL, 250 µmol), methanol (5 µL as an internal integration standard), methanol-d_4 (132.5 µL) and D_2O (350 µL) were combined in an NMR tube and freeze-pump-thawed- three cycles. The tube was then place in the spectrometer which was set at 85 °C and equilibrated for approximately three minutes, after which time ^{1}H NMR data were collected for three half-lives.

Double Isotopic Crossover Experiment. In a 10 mL round bottom flask, **4** (10 µL, 191 µmol), **3** (34 mg, 382 µmol), Cp$^{\$}$-$d_4$Co(COD) (47 µL of a 100 mM solution in methanol-d_4, 4.7 µmol), Cp$^{\$}$Co(COD-$d_8$) (47 µL of a 100 mM solution in methanol-d_4, 4.7 µmol), D_2O (1.05 mL) and methanol-d_4 were combined and thoroughly mixed. The sample was then aliquotted into two separate, silanized 5 mm NMR tubes equipped with Teflon screw caps, one tube containing 500 µL, the other 1.00 mL. A 200 µL aliquot was removed from the tube containing 1.00 mL, dried *in-vacuo* and sealed under vacuum in a glass capillary. The tubes were freeze-pump-thawed three times, and a ^{1}H NMR was taken at t=0 of both tubes. The tubes were then placed in a constant temperature bath set at 85 °C. The reaction was monitored by ^{1}H NMR, withdrawing 200 µL aliquots from the tube containing the larger volume at one half-life, two half-lives, and three half-lives. The aliquots were treated as described above and submitted for mass spectral analysis. The experiment was repeated three times and gave reproducible results.

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[1] Sigman, M.S.; Fatland, A.W.; Eaton, B.E. *J. Am. Chem. Soc.* **1998**, *120*, 5130