SUPPORTING INFORMATION

Synthesis of 4-Cyano Pyrroles via Mild Knorr Reactions with β -Ketonitriles

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General. Useful HPLC method for analyzing the following reactions. Column: Zorbax SB-C8, 250 x 4.5 mm, 5 μ m. UV = 218 nm. Oven temperature : 40 $^{\circ}$ C. Flow rate : 1.5 mL/min.. Mobile phase: A: 0.001% H_3PO_4 in water (1 mL of 85% H_3PO_4 /1L of water; pH ~2.3), B: CH_3CN . T = 0 min. 5% B to 50% B over 10 min. (gradient), T = 10 min. 50% B to 95% B until 15 min. (gradient), T = 15 min. 95% B until 20 min. (isocratic).

3-(4-Bromo-phenyl)-4-cyano-5-methyl-1H-pyrrole-2-carboxylic acid ethyl ester (**21**).

Under a nitrogen atmosphere, a mixture of EtOAc (4.6 mL, 47.5 mmol), CH_3CN (3.0 mL, 57.0 mmol), and THF (5 mL) was prepared. 1M $t\text{BuOK}$ in THF (52.2 mL, 52.2 mmol) was added dropwise at ambient temperature over 1.25 h. The resulting thick, light yellow precipitate of the potassium enolate was diluted with THF (5 mL). In a separate flask, α -isonitroso- β -ketoester **4** (5.7 g, 18.9 mmol) was dissolved in EtOH (50 mL) and cooled to 10 $^{\circ}$ C. Zinc dust (3.9 g, 60.1 mmol) was added and the resulting mixture stirred for 20 min, then further cooled to 5 $^{\circ}$ C. A mixture of AcOH (13.7 g, 228 mmol) and H_2O (6 mL) was charged to an addition funnel, then added in 10 drop portions (30 drops total) until the reduction initiated (exotherm to 10 $^{\circ}$ C). The remaining AcOH/ H_2O was added dropwise over 30 minutes while controlling the pot temperature in the 5-10 $^{\circ}$ C range. The resulting mixture was stirred at 5 $^{\circ}$ C for 0.5 h, then cooled to -5-10 $^{\circ}$ C using an ice/acetone bath. The enolate mixture from above was cooled to 0-5 $^{\circ}$ C and dissolved in DMSO (30 mL). This solution was transferred via cannula to the cold reduction product, and the resulting mixture stirred at 0-5 $^{\circ}$ C for 15 minutes. After stirring overnight (15 h) while equilibrating to ambient temperature, the mixture was diluted with EtOAc (50 mL), filtered to remove solids, and concentrated *in vacuo* to remove the THF, EtOH, and EtOAc. The resulting DMSO mixture was diluted with isopropyl alcohol (30 mL) followed by the dropwise addition of H_2O (60 mL) over 1 h. The resulting precipitate was stirred at ambient temperature for 0.5 h and filtered. The solids were rinsed with H_2O (2 x 60 mL) followed by hexanes (2 x 50 mL), and then vacuum dried at 40 $^{\circ}$ C to afford 5.3 g of crude product. The material was further purified by treating with isopropyl alcohol (106 mL). After heating to reflux, the mixture was treated with H_2O (2.6 mL)

and then allowed to cool slowly to ambient temperature. The resulting solids were filtered and rinsed with H₂O (2 x 25 mL) followed by hexanes (25 mL). After vacuum drying at 40 °C, 5.0 g of white crystals were recovered (79.5% yield). mp 235.4 °C

IR 3265, 2987, 2219, 1662, 1571, 1519, 1480, 1431 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.16 (3H, t, *J* = 7.1 Hz), 2.42 (3H, s), 4.17 (2H, q, *J* = 7.1 Hz), 7.40 (2H, d, *J* = 8.2 Hz), 7.64 (2H, d, *J* = 8.2 Hz), 12.65 (1H, s). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 12.3, 14.4, 60.7, 94.1, 116.0, 118.3, 121.8, 131.2, 131.7, 131.8, 132.3, 142.0, 159.9. Anal. Calcd for C₁₅H₁₃BrN₂O₂: C, 54.07; H, 3.93; Br, 23.98; N, 8.41. Found: C, 54.03; H, 3.92; Br, 23.77; N, 8.34.

3-(4-Bromo-phenyl)-4-cyano-5-isopropyl-1H-pyrrole-2-carboxylic acid ethyl ester (**22**).

Under a nitrogen atmosphere, ethyl isobutyrate (6.4 mL, 47.4 mmol) was added to 1M ^{*t*}BuOK in THF (52.2 mL, 52.2 mmol) over 10 min. The resulting mixture was stirred at ambient temperature for 5 min. A mixture of CH₃CN (3.0 mL, 57.0 mmol) and THF (7 mL) was then added over 1.5 h, keeping the pot temperature below 27 °C. The reaction mixture was allowed to stir overnight (15 h) at ambient temperature. In a separate flask, α-isonitroso-β-ketoester **4** (5.7 g, 18.9 mmol) was dissolved in EtOH (50 mL) and cooled to 10 °C. Zinc dust (3.9 g, 60.1 mmol) was added and the resulting mixture stirred for 20 min, then further cooled to 5 °C. A mixture of AcOH (13.7 g, 228 mmol) and H₂O (6 mL) was charged to an addition funnel, then added in 10 drop portions (30 drops total) until initiation is noted (exotherm to 10 °C). The remaining AcOH/H₂O was added dropwise over 30 minutes while controlling the pot temperature in the 5-10 °C range. The resulting mixture was stirred at 5 °C for 0.5 h, then cooled to -5-10 °C using an ice/acetone bath. The potassium enolate mixture from above was cooled to 0-5 °C and dissolved in DMSO (30 mL). This solution was transferred via cannula to the cold reduction product, and the resulting mixture stirred at 0-5 °C for 15 minutes. After stirring overnight (15 h) while equilibrating to ambient temperature, the mixture was diluted with EtOAc (50 mL), filtered to remove solids, and concentrated *in vacuo* to remove the THF, EtOH, and EtOAc. The resulting DMSO mixture was diluted with isopropyl alcohol (30 mL) followed by the dropwise addition

of H₂O (60 mL) over 1 h. The resulting precipitate was stirred at ambient temperature for 0.5 h and filtered. The solids were rinsed with H₂O (2 x 60 mL) followed by hexanes (2 x 50 mL), and then vacuum dried at 40 °C to afford 3.1 g of crude product. The material was further purified by treating with EtOAc (68 mL) and Darco (2 g). After stirring at ambient temperature for 30 min, this mixture was filtered across Hi-Flo and the pad rinsed with EtOAc (25 mL). After concentrating *in vacuo*, the resulting solids were treated with Et₂O (17 mL) and stirred at room temperature for 1 h. The solids were filtered, rinsed with Et₂O (10 mL), and vacuum dried at 40 °C. 2.6 g of pale yellow solids were recovered (37.6 % yield). mp 202.5 °C. IR 3310, 2977, 2218, 1656, 1518, 1483, 1425 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.34 (3H, t, *J* = 7.1 Hz), 1.36 (6H, d, *J* = 7.1 Hz), 3.23 (1H, sep, *J* = 7.1 Hz), 4.16 (2H, q, *J* = 7.1 Hz), 7.39 (2H, d, *J* = 8.2 Hz), 7.63 (2H, d, *J* = 8.2 Hz), 12.57 (1H, s). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 14.4, 21.9, 27.7, 60.7, 91.5, 116.1, 118.4, 121.8, 131.2, 131.8, 131.2, 132.4, 151.3, 160.0. Anal. Calcd for C₁₇H₁₇BrN₂O₂: C, 56.52; H, 4.74; Br, 22.12; N, 7.75. Found: C, 56.42; H, 4.76; Br, 22.00; N, 7.69.

3-(4-Bromo-phenyl)-5-tert-butyl-4-cyano-1H-pyrrole-2-carboxylic acid ethyl ester (**23**).

α-Isonitroso-β-ketoester **4** (1.9 g, 6.3 mmol) was dissolved in EtOH (17 mL) and cooled to 10 °C. Zinc dust (1.3 g, 20.2 mmol) was added and the resulting mixture stirred for 20 min, then further cooled to 5 °C. The 4,4-dimethyl-3-oxo-pentane-nitrile (2.0 g, 15.8 mmol) was added and the mixture stirred at 5 °C for 5 minutes. Acetic acid (3.8 g, 63.3 mmol) was added dropwise over 0.5 h, keeping the pot temperature below 10 °C. The resulting mixture was allowed to stir overnight while equilibrating to ambient temperature. The reaction mix was diluted with EtOAc (25 mL) and filtered to remove solids. The filtrate was concentrated *in vacuo* and the resulting residue was re-dissolved in EtOAc (50 mL) and transferred to a separatory funnel. After washing with H₂O (3 x 25 mL) and brine (25 mL), the solution was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Flash chromatography on silica gel using hexanes/EtOAc (4:1) provided the desired product as a white solid (0.21 g, 8.8% yield). mp 191.1 °C. IR 3313, 2969, 2223, 1672, 1517, 1485, 1469, 1431 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.09 (3H,

t, $J = 7.1$ Hz), 1.47 (9H, s), 4.14 (2H, q, $J = 7.1$ Hz), 7.37 (2H, d, $J = 8.2$ Hz), 7.63 (2H, d, $J = 8.2$ Hz), 12.11 (1H, s). ^{13}C NMR (100 MHz, DMSO- d_6) δ 14.3, 30.0, 33.8, 60.7, 91.3, 116.9, 118.9, 121.7, 131.1, 131.8, 132.6, 132.8, 152.6, 160.0. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}_2$: C, 57.61; H, 5.10; Br, 21.29; N, 7.46. Found: C, 56.08; H, 5.01; Br, 21.26; N, 7.12.

3-(4-Bromo-phenyl)-4-cyano-5-phenyl-1H-pyrrole-2-carboxylic acid ethyl ester (**24**).

α -Isonitroso- β -ketoester **4** (5.7 g, 18.9 mmol) was dissolved in EtOH (50 mL) and cooled to 10 °C. Zinc dust (3.9 g, 60.1 mmol) was added and the resulting mixture stirred for 20 min, then further cooled to 5 °C. A mixture of AcOH (9.4 g, 156 mmol) and H_2O (6 mL) was charged to an addition funnel, then added in 10 drop portions (30 drops total) until initiation is noted (exotherm to 10 °C). The remaining AcOH/ H_2O was added dropwise over 30 minutes while controlling the pot temperature in the 5-10 °C range. The resulting mixture was stirred at 0-5 °C for 0.5 h. Benzoylacetonitrile (4.1 g, 28.5 mmol) was added in one portion and the resulting mixture was allowed to stir overnight (15 h) while equilibrating to ambient temperature. AcOH (17.1 g, 285 mmol) was added followed by EtOAc (150 mL). After stirring for 0.5 h, the mixture was filtered to remove solids and the filtrate was heated to 50 °C and stirred for 1 h. The solution was cooled to ambient temperature, transferred to a separatory funnel and washed with H_2O (50 mL). The aqueous wash was back-extracted with EtOAc (50 mL) and the combined organics were washed with brine (50 mL) and saturated NaHCO_3 (2 x 50 mL). The solution was then dried over Na_2SO_4 , treated with Darco (2 g), and filtered across Hi-Flo. Concentration *in vacuo* afforded 7.5 g of light orange colored solids. The crude material was purified by stirring in EtOAc (75 mL) for 1 h, filtering, and finally rinsing with Et_2O (25 mL). After vacuum drying at 40 °C, 4.1 g (54.0 % yield) of white solids were recovered. mp 232.5 °C. IR 3274, 2976, 2219, 1668, 1525, 1466, 1434 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6) δ 1.57 (3H, t, $J = 7.1$ Hz), 4.20 (2H, q, $J = 7.1$ Hz), 7.48 (2H, d, $J = 8.2$ Hz), 7.51-7.62 (3H, m), 7.68 (2H, d, $J = 8.2$ Hz), 7.86 (2H, d, $J = 7.1$ Hz), 13.10 (1H, s). ^{13}C NMR (100 MHz, DMSO- d_6) δ 14.4, 60.9, 93.2, 116.5, 120.7, 122.0,

128.1, 128.9, 129.3, 130.2, 131.3, 131.6, 132.5, 133.3, 142.3, 159.9. Anal. Calcd for $C_{20}H_{15}BrN_2O_2$: C, 60.78; H, 3.83; Br, 20.22; N, 7.09. Found: C, 60.88; H, 3.94; Br, 20.11; N, 7.06.

3-(4-Bromo-phenyl)-4-cyano-5-furan-2-yl-1H-pyrrole-2-carboxylic acid ethyl ester (**25**).

α -Isonitroso- β -ketoester **4** (5.7 g, 18.9 mmol) was dissolved in EtOH (50 mL) and cooled to 10 °C. Zinc dust (3.9 g, 60.1 mmol) was added and the resulting mixture stirred for 20 min, then further cooled to 5 °C. A mixture of AcOH (13.7 g, 228.0 mmol) and H₂O (6 mL) was charged to an addition funnel, then added in 10 drop portions (30 drops total) until initiation is noted (exotherm to 10 °C). The remaining AcOH/H₂O was added dropwise over 30 minutes while controlling the pot temperature in the 5-10 °C range. The resulting mixture was stirred at 5 °C for 0.5 h. 2-furoylacetonitrile (3.9 g, 28.5 mmol) was added in one portion and the resulting mixture was allowed to stir overnight (15 h) while equilibrating to ambient temperature. EtOAc (100 mL) was added and stirring was continued for 1 h. The mixture was filtered and the resulting solids were rinsed with EtOAc (50 mL). The filtrate was concentrated in vacuo. The resulting residue was triturated with Et₂O (50 mL), stirred for 4 h, and filtered. The solids were treated with EtOH (35 mL) and TFA (2.1 mL, 22.1 mmol) and stirred for 3 h. Concentration in vacuo afforded 5.8 g of light brown solids. Purification was affected by flash chromatography on silica gel using hexanes/EtOAc (4/1 to 2.3/1 gradient). 2.3 g of white solids were recovered (31.7% yield). mp 208.0 °C. IR 3247, 2983, 2219, 1672, 1519, 1489, 1421 cm^{-1} . ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.14 (3H, t, *J* = 7.1 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 6.74 (1H, dd, *J* = 1.7, 3.8 Hz), 7.32 (1H, d, *J* = 3.8 Hz), 7.45 (2H, d, *J* = 8.2 Hz), 7.67 (2H, d, *J* = 8.2 Hz), 7.95 (1H, d, *J* = 1.7 Hz), 13.21 (1H, s). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 13.8, 60.5, 91.0, 110.4, 112.2, 115.1, 119.9, 121.5, 130.6, 130.7, 132.0, 132.1, 132.5, 143.5, 144.4, 159.3. Anal. Calcd for $C_{18}H_{13}BrN_2O_3$: C, 56.12; H, 3.40; Br, 20.74; N, 7.27. Found: C, 56.50; H, 3.48; Br, 20.96; N, 7.25.

3-(4-Bromo-phenyl)-4-cyano-5-thiophen-2-yl-1H-pyrrole-2-carboxylic acid ethyl ester (**26**). α -Isonitroso- β -ketoester **4** (5.7 g, 18.9 mmol) was dissolved in EtOH (50 mL) and cooled to 10 °C. Zinc

dust (3.9 g, 60.1 mmol) was added and the resulting mixture stirred for 20 min, then further cooled to 5 °C. A mixture of AcOH (9.4 g, 156 mmol) and H₂O (6 mL) was charged to an addition funnel, then added in 10 drop portions (30 drops total) until initiation is noted (exotherm to 10 °C). The remaining AcOH/H₂O was added dropwise over 30 minutes while controlling the pot temperature in the 5-10 °C range. The resulting mixture was stirred at 0-5 °C for 0.5 h. 3-Oxo-3-thiophene-2-yl-propionitrile¹⁴ (4.3 g, 28.5 mmol) was dissolved in DMSO (12 mL) and added via syringe, keeping the pot temperature below 5 °C. The resulting mixture was allowed to stir overnight (15 h) while equilibrating to ambient temperature. EtOAc (100 mL) was added, and after stirring for 0.5 h, the mixture was filtered to remove solids. The filtrate was washed with H₂O (3 x 100 mL) and brine 100 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The resulting solids was triturated with Et₂O (100 mL), filtered and the solids rinsed with Et₂O (2 x 25 mL). The crude solids were treated with EtOH (40 mL) and TFA (1.5 mL, 20.2 mmol), stirred at 40 °C for 1 h, and concentrated *in vacuo*. Purification of the crude residue was affected by flash chromatography on silica gel using hexanes/EtOAc (9/1 to 3/1 gradient). 0.40 g of off-white solids were recovered (5.2% yield). mp 232.7 °C. IR 3280, 3220, 3106, 2979, 2222, 1655, 1534, 1478, 1438 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.14 (3H, t, *J* = 7.1 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 7.27 (1H, dd, *J* = 4.9, 3.8 Hz), 7.46 (2H, d, *J* = 8.2 Hz), 7.67 (2H, d, *J* = 8.2 Hz), 7.80 (1H, d, *J* = 4.9 Hz), 7.91 (1H, d, *J* = 3.8 Hz), 13.18 (1H, s). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 14.3, 61.0, 92.6, 116.1, 120.4, 122.1, 128.5, 128.8, 129.1, 130.1, 131.2, 131.3, 132.5, 133.1, 136.3, 159.8. Anal. Calcd for C₁₈H₁₃BrN₂O₃: C, 53.88; H, 3.27; Br, 19.91; N, 6.98. Found: C, 55.41; H, 3.93; Br, 20.40; N, 6.70.