

Supplementary Materials

Development of a reproducible and scalable method for the synthesis of biologically active pyrazolo[1,5-a]pyrimidine derivatives

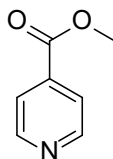
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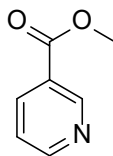
Characterization of intermediates

Methyl isonicotinate (**2a**)



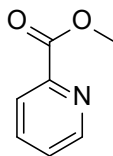
Yield 51 g (92%), colorless liquid, b.p. 145°C (20 mmHg). ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, *J* = 6.1 Hz, 2H), 7.73 (d, *J* = 6.1 Hz, 2H), 3.85 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 165.47, 150.54, 137.14, 122.73, 52.60; MS (ESI) *m/z*: 138.1 [M + H]⁺.

Methyl nicotinate (**2b**)



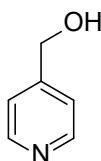
Yield 47 g (84%), colorless liquid, solidifies when distilled, b.p. 143°C (20 mmHg), m.p. 47°C. ¹H NMR (400 MHz, CDCl₃) δ 9.21 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.77 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.30 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.40 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1H), 3.94 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 165.77, 153.31, 150.82, 137.38, 126.23, 123.50, 52.58; MS (ESI) *m/z*: 138.1 [M + H]⁺.

Methyl picolinate (**2c**)



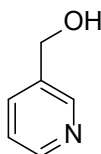
Yield 49 g (88%), colorless liquid, b.p. 142°C (20 mmHg). ¹H NMR (400 MHz, CDCl₃) δ 8.69 (dt, *J* = 4.8, 0.9 Hz, 1H), 8.08 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.80 (td, *J* = 7.8, 1.8 Hz, 1H), 7.44 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 3.95 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 165.62, 149.75, 147.80, 137.20, 127.04, 125.18, 52.94; MS (ESI) *m/z*: 138.1 [M + H]⁺.

Pyridin-4-ylmethanol (**3a**)



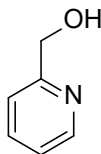
Yield 13 g (80%), colorless liquid, solidifies when distilled, b.p. 152°C (15 mmHg), m.p. 54°C. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, *J* = 6.1 Hz, 2H), 7.29 (d, *J* = 6.1 Hz, 2H), 5.48 (br s, 1H), 4.71 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 151.84, 149.03, 121.38, 62.74; MS (ESI) *m/z*: 110.1 [M + H]⁺.

Pyridin-3-ylmethanol (**3b**)



Yield 12.4 g (77%), colorless liquid, b.p. 144°C (15 mmHg). ¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, *J* = 2.2 Hz, 1H), 8.35 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.69 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.23 (dd, *J* = 7.8, 4.9 Hz, 1H), 5.22 (s, 1H), 4.65 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 148.04, 147.91, 137.35, 135.35, 123.72, 62.02; MS (ESI) *m/z*: 110.1 [M + H]⁺.

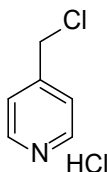
Pyridin-2-ylmethanol (**3c**)



Yield 13.2 g (82%), colorless liquid, b.p. 140°C (15 mmHg), solidifies at 12°C. ¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, *J* = 4.8 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H),

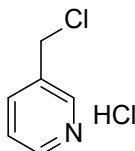
7.17 (dd, $J = 7.5, 5.0$ Hz, 1H), 4.80 (s, 1H), 4.74 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 159.60, 148.41, 137.04, 122.42, 120.87, 64.29; MS (ESI) m/z : 110.1 $[\text{M} + \text{H}]^+$.

4-(Chloromethyl)pyridine hydrochloride (**4a**)



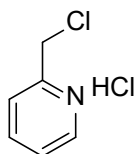
Yield 19.8 g (87%), colorless crystals, m.p. 170°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.95 (d, $J = 6.7$ Hz, 2H), 8.10 (d, $J = 6.6$ Hz, 2H), 5.10 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ 156.19, 142.18, 126.31, 43.22.

3-(Chloromethyl)pyridine hydrochloride (**4b**)



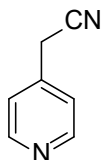
Yield 17.8 g (77%), colorless crystals, m.p. 146°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.06 (d, $J = 2.0$ Hz, 1H), 8.91 (dd, $J = 5.7, 1.4$ Hz, 1H), 8.64 (dt, $J = 8.2, 1.7$ Hz, 1H), 8.07 (dd, $J = 8.1, 5.6$ Hz, 1H), 5.01 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ 145.49, 141.98, 141.84, 137.52, 127.24, 41.38.

2-(Chloromethyl)pyridine hydrochloride (**4c**)



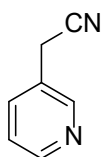
Yield 18.6 g (82%), colorless crystals, m.p. 131°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.83 (dd, $J = 5.5, 1.0$ Hz, 1H), 8.42 (td, $J = 7.8, 1.7$ Hz, 1H), 8.02 (d, $J = 7.9$ Hz, 1H), 7.87 (ddd, $J = 7.6, 5.5, 1.2$ Hz, 1H), 5.08 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ 152.33, 144.44, 144.08, 126.45, 126.04, 41.84.

2-(Pyridin-4-yl)acetonitrile (**5a**)



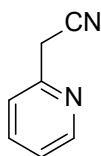
Yield 19.3 g (86%), colorless liquid, b.p. 145°C (15 mmHg), solidifies, m.p. 45°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.59 (d, *J* = 6.1 Hz, 2H), 7.38 (d, *J* = 6.1 Hz, 2H), 4.15 (s, 2H); ¹³C NMR (101 MHz, DMSO) δ 150.11, 140.44, 123.22, 118.13, 22.12; MS (ESI) *m/z*: 119.1 [M + H]⁺.

2-(Pyridin-3-yl)acetonitrile (**5b**)



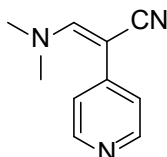
Yield 18.2 g (81%), colorless liquid, b.p. 135°C (10 mmHg). ¹H NMR (400 MHz, CDCl₃) δ 8.50 (d, *J* = 2.2 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.82 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.38 (dd, *J* = 7.8, 4.9 Hz, 1H), 4.11 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 149.47, 146.25, 137.77, 135.69, 123.94, 118.25, 25.34; MS (ESI) *m/z*: 119.1 [M + H]⁺.

2-(Pyridin-2-yl)acetonitrile (**5c**)



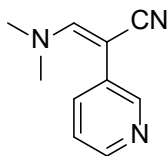
Yield 19 g (85%), colorless liquid, b.p. 130°C (10 mmHg), solidifies, m.p. 27°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.56 (ddd, *J* = 4.8, 1.5, 0.8 Hz, 1H), 7.82 (td, *J* = 7.7, 1.1 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.35 (dd, *J* = 7.5, 4.9 Hz, 1H), 4.21 (s, 1H); ¹³C NMR (101 MHz, DMSO) δ 151.33, 149.56, 137.47, 122.93, 122.76, 118.34, 25.67; MS (ESI) *m/z*: 119.1 [M + H]⁺.

3-(Dimethylamino)-2-(pyridin-4-yl)acrylonitrile (**6a**)



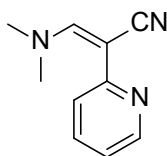
Yield 25 g (85%), light yellow crystals, m.p. 182°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (d, *J* = 6.3 Hz, 2H), 7.79 (s, 1H), 7.26 (d, *J* = 6.3 Hz, 2H), 3.25 (s, 6H); ¹³C NMR (101 MHz, DMSO) δ 152.01, 149.45, 144.83, 119.84, 116.61, 71.74; MS (ESI) *m/z*: 174.1 [M + H]⁺.

3-(Dimethylamino)-2-(pyridin-3-yl)acrylonitrile (**6b**)



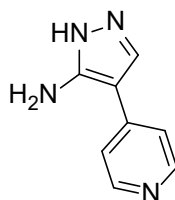
Yield 24.4 g (63%), light yellow crystals, m.p. 174°C. ^1H NMR (400 MHz, DMSO- d_6) δ 8.55 (d, $J = 2.2$ Hz, 1H), 8.26 (dd, $J = 4.7, 1.5$ Hz, 1H), 7.66 (ddd, $J = 8.1, 2.6, 1.5$ Hz, 1H), 7.56 (s, 1H), 7.29 (ddd, $J = 8.2, 4.6, 0.7$ Hz, 1H), 3.21 (s, 6H); ^{13}C NMR (101 MHz, DMSO) δ 151.23, 145.14, 144.21, 132.81, 129.86, 123.43, 120.42, 70.22; MS (ESI) m/z : 174.1 $[\text{M} + \text{H}]^+$.

3-(Dimethylamino)-2-(pyridin-2-yl)acrylonitrile (**6c**)



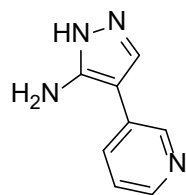
Yield 23.8 g (80%), light yellow crystals, m.p. 169°C. ^1H NMR (400 MHz, DMSO- d_6) δ 8.34 (ddd, $J = 4.8, 1.9, 0.9$ Hz, 1H), 8.07 (s, 1H), 7.65 (ddd, $J = 8.2, 7.4, 1.9$ Hz, 1H), 7.23 (dt, $J = 8.1, 1.1$ Hz, 1H), 6.99 (ddd, $J = 7.4, 4.8, 1.1$ Hz, 1H), 3.24 (s, 6H); ^{13}C NMR (101 MHz, DMSO) δ 154.60, 152.17, 148.55, 137.03, 137.01, 120.63, 118.83, 116.60, 74.35; MS (ESI) m/z : 174.1 $[\text{M} + \text{H}]^+$.

4-(Pyridin-4-yl)-1H-pyrazol-5-amine (**7a**)



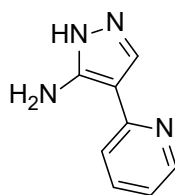
Yield 17.4 g (92%), light brown crystals, m.p. 185°C. ^1H NMR (400 MHz, DMSO- d_6) δ 11.94 (br s, 1H), 8.42 (d, $J = 6.3$ Hz, 1H), 7.90 (br s, 1H), 7.49 (d, $J = 6.3$ Hz, 1H), 5.18 (br s, 2H); MS (ESI) m/z : 161.1 $[\text{M} + \text{H}]^+$.

4-(Pyridin-3-yl)-1*H*-pyrazol-5-amine (**7b**)



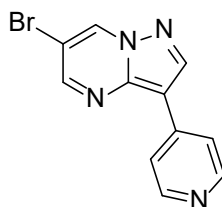
Yield 16.8 g (88%), light brown crystals, m.p. 182°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.88 (br s, 1H), 8.75 (dd, *J* = 2.6, 0.8 Hz, 1H), 8.31 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.91–7.84 (m, 2H), 7.32 (ddd, *J* = 8.2, 4.6, 0.7 Hz, 1H), 5.30 (br s, 2H); MS (ESI) *m/z*: 161.1 [*M* + *H*]⁺.

4-(Pyridin-2-yl)-1*H*-pyrazol-5-amine (**7c**)



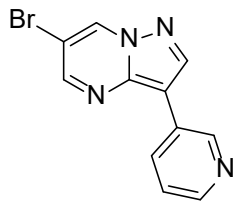
Yield 17.4 g (92%), light brown crystals, m.p. 190°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.86 (br s, 1H), 8.82 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 8.11 (br s, 1H), 7.65 (td, *J* = 7.7, 1.9 Hz, 1H), 7.54 (dt, *J* = 7.9, 1.0 Hz, 1H), 6.99 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H), 5.70 (br s, 2H); MS (ESI) *m/z*: 161.1 [*M* + *H*]⁺.

6-Bromo-3-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine (**9a**)



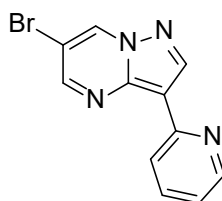
Yield 24.7 g (90%), bright yellow crystals, m.p. 223°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.74 (d, *J* = 2.2 Hz, 1H), 8.96 (s, 1H), 8.84 (d, *J* = 2.2 Hz, 1H), 8.60 (d, *J* = 6.2 Hz, 2H), 8.10 (d, *J* = 6.2 Hz, 2H); ¹³C NMR (101 MHz, DMSO) δ 151.86, 150.00, 144.09, 143.39, 138.84, 137.05, 119.81, 106.89, 104.59; MS (ESI) *m/z*: 275.0 [*M* + *H*]⁺.

6-Bromo-3-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidine (**9b**)



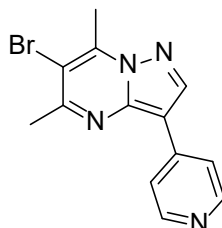
Yield 23.7 g (86%), bright yellow crystals, m.p. 218°C. ^1H NMR (400 MHz, DMSO- d_6) δ 9.79 (d, $J = 2.2$ Hz, 1H), 9.50 (dd, $J = 2.3, 0.8$, 1H), 9.12 (ddd, $J = 8.0, 2.3, 1.7$, 1H), 9.06 (s, 1H), 8.89 (d, $J = 2.2$ Hz, 1H), 8.78 (dd, $J = 4.7, 1.6$ Hz, 1H), 8.08 (ddd, $J = 8.0, 4.8, 0.9$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 152.40, 143.99, 143.22, 140.05, 139.66, 139.13, 137.27, 130.73, 126.87, 105.01, 103.93; MS (ESI) m/z : 275.0 $[\text{M} + \text{H}]^+$.

6-Bromo-3-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (**9c**)



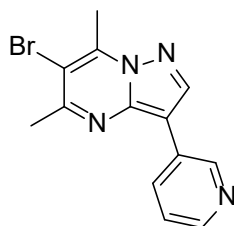
Yield 25.3 g (92%), bright yellow crystals, m.p. 215°C. ^1H NMR (400 MHz, DMSO- d_6) δ 9.70 (d, $J = 2.2$ Hz, 1H), 8.80 (d, $J = 2.3$ Hz, 1H), 8.79 (s, 1H), 8.60 (ddd, $J = 4.7, 1.9, 0.9$ Hz, 1H), 8.36 (dt, $J = 7.9, 1.1$ Hz, 1H), 7.87 (td, $J = 7.7, 1.9$ Hz, 1H), 7.25 (ddd, $J = 7.5, 4.9, 1.2$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 151.44, 150.40, 149.43, 144.33, 143.05, 136.92, 136.82, 121.43, 120.47, 110.40, 104.12; MS (ESI) m/z : 275.0 $[\text{M} + \text{H}]^+$.

6-Bromo-5,7-dimethyl-3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (**9d**)



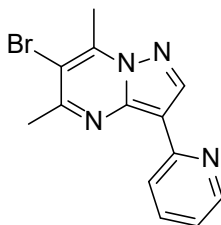
Yield 24.8 g (82%), light yellow crystals, m.p. 212°C. ^1H NMR (400 MHz, DMSO- d_6) δ 8.88 (s, 1H), 8.56 (d, $J = 6.2$ Hz, 2H), 8.11 (d, $J = 6.2$ Hz, 2H), 2.89 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 158.30, 149.92, 145.71, 143.25, 143.05, 139.22, 119.49, 107.47, 105.75, 26.36, 17.19; MS (ESI) m/z : 303.0 $[\text{M} + \text{H}]^+$.

6-Bromo-5,7-dimethyl-3-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidine (**9e**)



Yield 24.2 g (80%), light yellow crystals, m.p. 202°C. ^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 9.36 (dd, $J = 2.3, 0.8$, 1H), 8.50 (ddd, $J = 8.0, 2.3, 1.6$, 1H), 8.46 (dd, $J = 4.7, 1.6$ Hz, 1H), 7.50 (ddd, $J = 8.0, 4.7, 0.9$ Hz, 1H), 2.89 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 158.74, 145.66, 143.54, 142.10, 141.34, 140.15, 139.74, 130.66, 126.23, 106.25, 104.73, 26.36, 17.19; MS (ESI) m/z : 303.0 $[\text{M} + \text{H}]^+$.

6-Bromo-5,7-dimethyl-3-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (**9f**)



Yield 22.7 g (75%), light yellow crystals, m.p. 194°C. ^1H NMR (400 MHz, DMSO- d_6) δ 8.72 (s, 1H), 8.58 (ddd, $J = 4.8, 1.9, 0.9$ Hz, 1H), 8.33 (dt, $J = 7.9, 1.1$ Hz, 1H), 7.89 (td, $J = 7.7, 1.9$ Hz, 1H), 7.26 (ddd, $J = 7.5, 4.8, 1.2$ Hz, 1H), 2.89 (s, 3H), 2.74 (s, 3H); 158.24, 150.20, 149.61, 145.87, 144.49, 142.95, 137.38, 122.13, 120.97, 112.04, 105.57, 26.36, 17.19; MS (ESI) m/z : 303.0 $[\text{M} + \text{H}]^+$.