

Supporting Information

Synthesis of C3-Substituted 4-Azaindoles : An Easy Access to 4-Azamelatonin and Protected 4-Azatryptophan.

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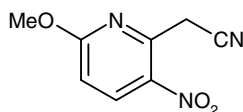
GENERAL EXPERIMENTAL DETAILS

The solvents used were ACS grade solvent, except for THF which were freshly distilled from Na/benzophenone.

Nuclear Magnetic Resonance (^1H and ^{13}C) spectra were recorded on a 250 MHz or a 400 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the reference tetramethylsilane. Coupling constants (J) are reported in hertz (Hz). The following symbol have been used to indicate multiplicities : s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), sex (sextet), m (multiplet).

All hydrogenation reactions were performed into hydrogenation bombs. The bomb was generally flushed with hydrogen twice to ensure a perfect hydrogen atmosphere.

EXPERIMENTAL PROCEDURES



2-Cyanomethyl-6-methoxy-3-nitropyridine (1a)

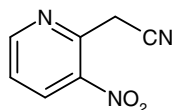
Under argon, the 2-methoxy-5-nitropyridine (41.8 g, 0.271 mol) and the 4-chlorophenoxyacetonitrile (50 g, 0.298 mol) were dissolved in 500 mL of anhydrous THF. This solution was added via cannula into a solution of potassium *tert*-butoxide (66.8 g, 0.597 mol) in 500 mL of anhydrous THF at $-20\text{ }^{\circ}\text{C}$. The resulting mixture was stirred for 35 hours at $-20\text{ }^{\circ}\text{C}$ then 500mL of aqueous solution of HCl (5%) was added dropwise, keeping the temperature below $-10\text{ }^{\circ}\text{C}$. The mixture was extracted twice with ethyl acetate. The organic layers were recombined then washed with water, dried over MgSO_4 and concentrated *in vacuo*. The brown residue was dissolved in a small volume of diethyl ether then two volumes of petroleum ether were added. The mixture was cooled to $-30\text{ }^{\circ}\text{C}$. A filtration gave the desired product (95%) as an orange solid.

mp = $116\text{ }^{\circ}\text{C}$ (lit.¹ mp = $116\text{--}117\text{ }^{\circ}\text{C}$).

IR (thin film, NaCl): 2963, 2259, 1580, 1506, 1337 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 4.13 (s, 3H), 4.43 (s, 2H), 6.87 (d, J = 9.0Hz, 1H), 8.42 (d, J = 9.0Hz, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 28.5, 56.4, 112.8, 116.4, 137.7, 139.5, 147.2, 166.7.



2-Cyanomethyl-3-nitropyridine (1b)

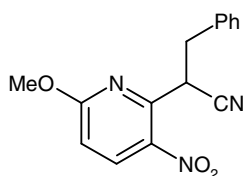
This compound was obtained from the procedure described by R.B. Katz and M. Voyle.²

^1H NMR (250 MHz, CDCl_3): δ = 4.46 (s, 2H), 7.60 (dd, J = 8.3Hz, J = 4.8Hz, 1H), 8.52 (dd, J = 8.3Hz, J = 1.5Hz, 1H), 8.92 (dd, J = 4.8Hz, J = 1.5Hz, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 27.1, 115.4, 124.5, 126.0, 133.8, 146.1, 153.9.

¹ Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1988**, 203.

² Katz, R. B.; Voyle, M. *Synthesis* **1988**, 314.



2-(6-Methoxy-3-nitro-pyridin-2-yl)-3-phenyl-propionitrile (3b)

The desired product was obtained according to the general procedure using 200 mg (1.03 mmol) of the compound **1a**, 285 mg (2.06 mmol) of potassium carbonate, 123 μ L (1.03 mmol) of benzyl bromide in 5 mL of acetonitrile. The solution was stirred for 3 hours at room temperature. The product was isolated with the eluent petroleum ether / ethyl acetate (9 / 1) as a white solid (85%).

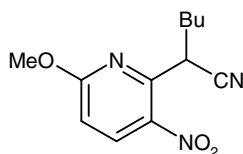
mp = 121 °C.

IR (thin film, NaCl): 3018, 2265, 1591, 1518, 1334 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 3.21-3.44 (m, 2H), 4.07 (s, 3H), 5.21 (dd, J = 8.8Hz, J = 5.3Hz, 1H), 6.82 (d, J = 8.9Hz, 1H), 7.25-7.32 (m, 5H), 6.32 (d, J = 8.9Hz, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 39.4, 40.0, 55.3, 111.8, 118.5, 127.7, 128.8, 129.3, 135.9, 136.7, 138.5, 149.7, 165.4.

HRMS calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 284.1035, found = 284.1024.



2-(6-Methoxy-3-nitropyridin-2-yl)hexanenitrile (3c)

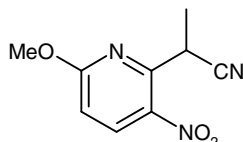
The desired product was obtained according to the general procedure using 800 mg (4.12 mmol) of the compound **1a**, 1.13 g (8.24 mmol) of potassium carbonate, 518 μ L (4.54 mmol) of *n*-butyl iodide in 15 mL of acetonitrile and 2 mL of dimethylformamide. The solution was stirred for 48 hours at room temperature. The product was isolated with the eluent petroleum ether / ethyl acetate (9 / 1) as a yellow oil (57%).

IR (thin film, NaCl): 2954, 2247, 1591, 1518, 1334, 1293 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 0.94 (t, J = 7.2Hz, 3H), 1.36-1.51 (m, 2H), 1.53-1.69 (m, 2H), 1.99-2.09 (m, 2H), 4.12 (s, 3H), 4.95 (t, J = 7.2Hz, 1H), 6.83 (d, J = 9.1Hz, 1H), 8.34 (d, J = 9.1Hz, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 13.8, 22.1, 29.5, 33.2, 37.7, 55.2, 111.6, 119.0, 136.8, 138.2, 150.7, 165.5.

HRMS calcd $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 250.1192, found = 250.1200.



2-(6-Methoxy-3-nitropyridin-2-yl)propanenitrile (3d)

The desired product was obtained according to the general procedure using 200 mg (1.03 mmol) of the compound **1a**, 284 mg (2.06 mmol) of potassium carbonate, 70 μ L (1.13 mmol) of methyl iodide in 5 mL of acetonitrile and 750 μ L of dimethylformamide. The solution was stirred for 3h30 at room temperature. The product was isolated with the eluent petroleum ether / ethyl acetate (9 / 1 then 8 / 2) as a yellow solid (80%).

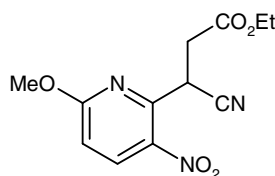
mp = 58 °C (lit.³ mp = 59-62.5 °C).

IR (thin film, NaCl): 3026, 2942, 2250, 1594, 1519, 1477, 1337, 1296, 1212 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 1.75 (d, *J* = 6.9 Hz, 3H), 4.12 (s, 3H), 5.01 (q, *J* = 6.9 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 8.37 (d, *J* = 9.0 Hz, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 18.8, 32.0, 55.2, 111.7, 119.7, 125.9, 136.8, 151.0, 165.6.

HRMS calcd for C₉H₉N₃O₃ [M+H]⁺: 208.0722, found = 208.0724.



3-Cyano-3-(6-methoxy-3-nitropyridin-2-yl)-ethyl propionate (3e)

The desired product was obtained according to the general procedure using 600 mg (3.09 mmol) of the compound **1a**, 855 mg (6.18 mmol) of potassium carbonate, 345 μL (3.09 mmol) of ethyl bromoacetate in 15 mL of acetonitrile. The solution was stirred for 3h30 at room temperature. The crude material was extracted with dichloromethane instead of ethyl acetate. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a yellow solid (88%).

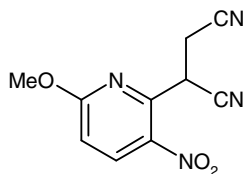
mp = 79 °C.

IR (thin film, NaCl): 2979, 2240, 1736, 1595, 1019 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 1.23 (t, *J* = 7.2 Hz, 3H), 3.10 (dd, *J* = 16.6 Hz, *J* = 6.6 Hz, 1H), 3.35 (dd, *J* = 16.9 Hz, *J* = 8.5 Hz, 1H), 4.07 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.31 (dd, *J* = 8.2 Hz, *J* = 6.6 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 8.38 (d, *J* = 9.1 Hz, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 14.0, 32.6, 35.8, 55.0, 61.4, 112.0, 117.7, 136.8, 138.9, 147.9, 165.4, 169.0.

HRMS calcd for C₁₂H₁₃N₃O₅ [M+H]⁺: 280.0933, found = 280.0923.



2-(6-Methoxy-3-nitropyridin-2-yl)acetonitrile (3f)

The desired product was obtained according to the general procedure using 200 mg (1.03 mmol) of the compound **1a**, 70 mg (0.5 mmol) of potassium carbonate, 75 μL (1.08 mmol) of bromoacetonitrile in 5 mL of dimethylformamide. The solution was stirred for 3 h at 0 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (7 / 3) as a yellow oil (54%).

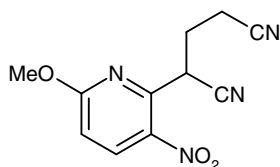
IR (thin film, NaCl): 2942, 2258, 1602, 1520, 1482, 1342, 1020 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 3.22 (dd, *J* = 16.7 Hz, *J* = 7.0 Hz, 1H), 3.33 (dd, *J* = 16.7 Hz, *J* = 6.0 Hz, 1H), 4.15 (s, 3H), 5.28 (t, *J* = 6.4 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 1H), 8.42 (d, *J* = 9.1 Hz, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 20.6, 33.6, 55.6, 113.0, 115.6, 116.0, 137.0, 138.5, 145.7, 165.7.

HRMS calcd for C₁₀H₈N₄O₃ [M+H]⁺: 233.0675, found = 233.0664.

³ Macor, J. E. ; Wehner, J. M. *Heterocycles* **1993**, 35, 349.



2-(6-Methoxy-3-nitropyridin-2-yl)pentanedinitrile (6b)

The desired product was obtained according to the general procedure using 1.0 g (5.15 mmol) of the compound **1a**, 1 mL (2.5 mmol) of benzyltrimethylammonium methoxide and 355 μ L (5.40 mmol) of acrylonitrile in 30 mL of methanol. The solution was stirred for 1h30 at 50 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a white solid (50%).

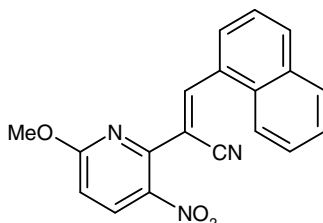
mp = 101 °C.

IR (thin film, NaCl): 2944, 2247, 1591, 1518, 1334, 1289 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 2.42-2.58 (m, 2H), 2.68-2.75 (m, 2H), 4.12 (s, 3H), 5.10 (dd, J = 6.0Hz, J = 7.8 Hz, 1H), 6.91 (d, J = 9.1Hz, 1H), 8.38 (d, J = 9.1Hz, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 15.2, 28.6, 36.6, 55.4, 112.6, 117.3, 117.8, 137.0, 138.6, 148.0, 165.6.

HRMS calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 247.0831, found = 247.0820.



(Z)-2-(6-Methoxy-3-nitropyridin-2-yl)-3-(naphthalen-1-yl)acrylonitrile (8b)

The desired product was obtained according to the general procedure for Knoevenagel condensations using 400 mg (2.06 mmol) of the 2-cyanomethyl-6-methoxy-3-nitropyridine **1a** and 322 μ L (2.06 mmol) of 1-naphthaldehyde. The product was obtained as a yellow solid (80%).

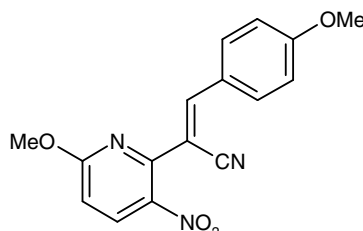
mp = 167 °C.

IR (thin film, NaCl): 2218, 1577, 1514, 1324 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 4.15 (s, 3H), 6.91 (d, J = 9.1Hz, 1H), 7.56-7.64 (m, 3H), 7.91-8.01 (m, 3H), 8.26 (d, J = 7.2Hz, 1H), 8.32 (d, J = 9.1Hz, 1H), 8.52 (s, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 55.2, 112.1, 112.2, 115.7, 123.3, 125.7, 126.7, 127.5, 127.8, 129.2, 130.0, 131.6, 132.0, 133.7, 136.6, 139.5, 146.8, 147.8, 165.1.

HRMS calcd for $\text{C}_{19}\text{H}_{13}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 332.1035, found = 332.1032.



(Z)-2-(6-Methoxy-3-nitropyridin-2-yl)-3-(4-methoxyphenyl)acrylonitrile (8c)

The desired product was obtained according to the general procedure for Knoevenagel condensations using 300 mg (1.54 mmol) of the 2-cyanomethyl-6-methoxy-3-nitropyridine **1a** and 196 μ L (1.62 mmol) of 4-methoxybenzaldehyde. The solution was stirred only 6 hours. The product was obtained as a yellow solid (85%).

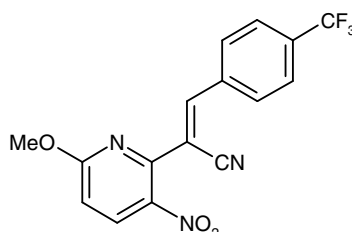
mp = 164 °C.

IR (thin film, NaCl): 2214, 1596, 1578, 1330, 1257, 1171, 1023 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 3.89 (s, 3H), 4.08 (s, 3H), 6.82 (d, *J* = 9.0Hz, 1H), 6.99 (d, *J* = 8.8Hz, 2H), 7.72 (s, 1H), 7.97 (d, *J* = 8.8Hz, 2H), 8.24 (d, *J* = 9.0Hz, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 55.0, 55.7, 105.4, 111.5, 114.7, 116.5, 125.7, 132.4, 136.5, 139.4, 147.3, 149.2, 162.7, 164.8.

HRMS calcd for C₁₆H₁₃N₃O₄ [M+H]⁺: 334.0804, found = 334.0815.



(Z)-3-(4-(Trifluoromethyl)phenyl)-2-(6-methoxy-3-nitropyridin-2-yl)acrylonitrile (8d)

The desired product was obtained according to the general procedure for Knoevenagel condensations using 400 mg (2.06 mmol) of the 2-cyanomethyl-6-methoxy-3-nitropyridine **1a** and 282 μL (2.06 mmol) of 4-trifluoromethylbenzaldehyde. The crude had to be purified by flash column chromatography with the eluent petroleum ether / ethyl acetate (8 / 2). After a wash with a small amount of ethanol, the product was obtained as a white solid (41%).

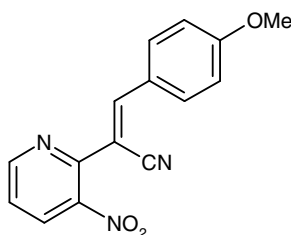
mp = 164 °C.

IR (thin film, NaCl): 2220, 1583, 1474, 1317, 1116 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 4.10 (s, 3H), 6.91 (d, *J* = 8.8Hz, 1H), 7.72 (s, 1H), 7.76 (d, *J* = 8.2Hz, 2H); 8.05 (d, *J* = 8.2Hz, 2H), 8.32 (d, *J* = 8.8Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 52.1, 111.8, 112.6, 115.3, 123.7 (*J* = 270.9Hz), 126.2 (*J* = 3.7Hz), 130.1, 133.0 (*J* = 32.7Hz), 136.1, 136.6, 139.5, 146.4, 147.2, 165.2.

HRMS calcd for C₁₆H₁₀F₃N₃O₃ [M+H]⁺: 350.0753, found = 350.0755.



(Z)-3-(4-Methoxyphenyl)-2-(3-nitropyridin-2-yl)acrylonitrile (8e)

The desired product was obtained according to the general procedure for Knoevenagel condensations using 300 mg (1.93 mmol) of the 2-cyanomethyl-3-nitropyridine **1b** and 234 μL (1.93 mmol) of 4-methoxybenzaldehyde. The crude had to be purified by flash column chromatography with the eluent petroleum ether / ethyl acetate (7 / 3 then 1 / 1). The product was obtained as a yellow solid (97%).

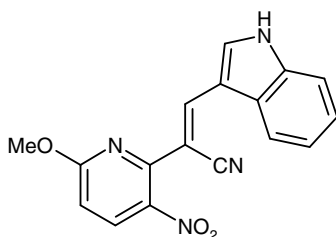
mp = 96 °C.

IR (thin film, NaCl): 3026, 2212, 1586, 1514, 1355, 1271, 1180, 1027 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 3.89 (s, 3H), 7.00 (d, *J* = 8.8Hz, 2H), 7.50 (dd, *J* = 8.2Hz, *J* = 4.7Hz, 1H), 7.87 (s, 1H), 7.98 (d, *J* = 8.8Hz, 2H), 8.29 (dd, *J* = 8.2Hz, *J* = 1.5Hz, 1H), 8.84 (dd, *J* = 4.7Hz, *J* = 1.5Hz, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 55.7, 104.5, 114.7, 116.5, 123.7, 125.7, 132.5, 133.4, 145.1, 147.6, 149.8, 152.6, 162.8.

HRMS calcd for C₁₅H₁₁N₃O₃ [M+H]⁺: 282.0879, found = 282.0890.



(Z)-3-(1H-Indol-3-yl)-2-(6-methoxy-3-nitropyridin-2-yl)acrylonitrile (8f)

The desired product was obtained according to the general procedure for Knoevenagel condensations using 200 mg (1.03 mmol) of the 2-cyanomethyl-6-methoxy-3-nitropyridine **1a** and 148 mg (1.03 mmol) of indole-3-carboxaldehyde. The product was obtained as an orange solid (84%).

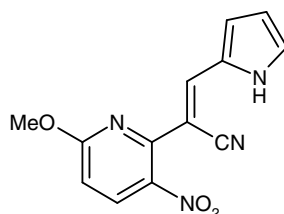
mp = 230 °C.

IR (thin film, NaCl) : 3010, 2193, 1592, 1503, 1314 cm⁻¹.

¹H NMR (250 MHz, DMSO): δ = 4.09 (s, 3H), 6.99 (d, *J* = 9.0Hz, 1H), 7.21-7.32 (m, 2H), 7.57 (d, *J* = 7.2Hz, 1H), 7.94 (d, *J* = 6.9Hz, 1H), 8.38 (d, *J* = 9.0Hz, 1H), 8.51 (s, 1H), 8.56 (s, 1H), 12.34 (bs, 1H).

¹³C NMR (62.5 MHz, DMSO): δ = 54.7, 98.4, 110.5, 110.5, 112.7, 117.8, 118.3, 121.5, 123.3, 127.2, 129.6, 136.0, 137.2, 138.6, 142.6, 146.0, 164.0.

HRMS calcd for C₁₇H₁₂N₄O₃ [M+H]⁺: 343.0807, found = 343.0810.



(Z)-2-(6-Methoxy-3-nitropyridin-2-yl)-3-(1H-pyrrol-2-yl)acrylonitrile (8g)

The desired product was obtained according to the general procedure for Knoevenagel condensations using 200 mg (1.03 mmol) of the 2-cyanomethyl-6-methoxy-3-nitropyridine **1a** and 98 mg (1.03 mmol) of pyrrole-2-carboxaldehyde. The product was obtained as an orange solid (95%).

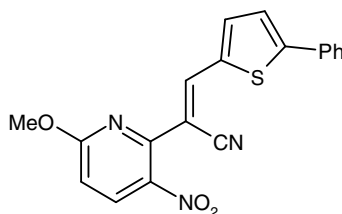
mp = 191 °C.

IR (thin film, NaCl): 2206, 1569, 1500, 1318, 1278, 1055 cm⁻¹.

¹H NMR (250 MHz, DMSO): δ = 4.04 (s, 3H), 6.44 (bs, 1H), 6.96 (d, *J* = 9.0Hz, 1H), 7.35 (bs, 2H), 8.15 (s, 1H), 8.34 (d, *J* = 9.0Hz, 1H), 11.95 (bs, 1H).

¹³C NMR (62.5 MHz, DMSO): δ = 54.6, 96.8, 110.4, 112.6, 114.9, 116.9, 126.2, 127.2, 137.3, 138.6, 139.3, 145.5, 164.5.

HRMS calcd for C₁₃H₁₀N₄O₃ [M+H]⁺: 271.0831, found = 271.0845.



(Z)-2-(6-Methoxy-3-nitropyridin-2-yl)-3-(5-phenylthiophen-2-yl)acrylonitrile (8h)

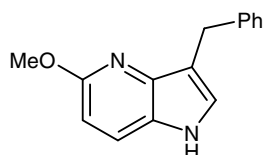
The desired product was obtained according to the general procedure for Knoevenagel condensations using 250 mg (1.29 mmol) of the 2-cyanomethyl-6-methoxy-3-nitropyridine **1a** and 244 mg (1.29 mmol) of 5-phenylthiophene-2-carboxaldehyde. The product was obtained as a yellow solid (82%).

mp = 175 °C.

IR (thin film, NaCl): 3017, 1589, 1435 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 4.09 (s, 3H), 6.80 (d, J = 9.0Hz, 1H), 7.25-7.43 (m, 4H), 7.68-7.72 (m, 3H), 7.98 (s, 1H), 8.23 (d, J = 9.0Hz, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 55.0, 104.1, 111.5, 116.2, 124.1, 126.5, 129.3, 133.2, 136.2, 136.6, 136.8, 139.3, 142.0, 146.4, 152.1, 164.7.



3-Benzyl-5-methoxy-1H-pyrrolo[3,2-b]pyridine (4b) or (9a)

The desired product was obtained according to the general procedure for hydrogenation using 200 mg (0.70 mmol) of the compound (**3b**), in 100 mL of the mixture ethanol / acetic acid. Methanol (10 mL) was added to ensure the complete solubility. The solution was hydrogenated for 48 h at 50 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (1 / 1) as a brown solid (43%).

The desired product was also obtained according to the general procedure for hydrogenation using 400 mg (1.42 mmol) of the compound (**8a**), in 100 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 12 h at 45 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (1 / 1) as a brown solid (55%).

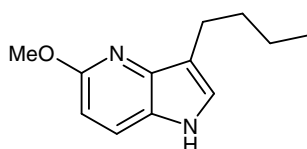
mp = 97 °C.

IR (thin film, NaCl): 1619, 1573, 1409, 1216, 1032 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 3.99 (s, 3H), 4.11 (s, 2H), 6.55 (d, J = 8.8Hz, 1H), 6.90 (d, J = 2.5Hz, 1H), 7.16-7.25 (m, 3H), 7.36-7.40 (m, 2H), 7.42 (d, J = 8.8Hz, 1H), 7.92 (bs, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 30.5, 53.4, 105.3, 116.5, 121.7, 124.6, 124.8, 125.8, 128.3, 129.0, 141.6, 142.0, 159.9.

HRMS calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 239.1184, found = 239.1174.



3-Butyl-5-methoxy-1H-pyrrolo[3,2-b]pyridine (4c)

The desired product was obtained according to the general procedure for hydrogenation using 570 mg (2.28 mmol) of the compound **3c**, in 50 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 12 h at room temperature. The product was isolated with the eluent petroleum ether / ethyl acetate (9 / 1) as a white solid (40%).

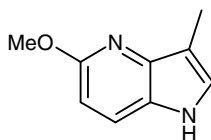
mp = 68 °C.

IR (thin film, NaCl): 3017, 2927, 1615, 1577, 1403 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 0.94 (t, J = 7.3Hz, 3H), 1.42 (sex, J = 7.3Hz, 2H), 1.73 (ddt, J = 7.3Hz, J = 7.5Hz, 2H), 2.78 (t, J = 7.5Hz, 2H), 4.00 (s, 3H), 6.56 (d, J = 8.6Hz, 1H), 7.05 (d, J = 2.5Hz, 1H), 7.46 (d, J = 8.6Hz, 1H), 8.04 (bs, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 14.1, 22.7, 23.7, 32.2, 53.4, 104.9, 117.3, 121.6, 123.9, 124.9, 142.0, 159.7.

HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 205.1341, found = 205.1338.



5-Methoxy-3-methyl-1H-pyrrolo[3,2-b]pyridine (4d)

The desired product was obtained according to the general procedure for hydrogenation using 550 mg (2.64 mmol) of the compound **3d**, in 50 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 18 h at 35 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a white solid (35%).

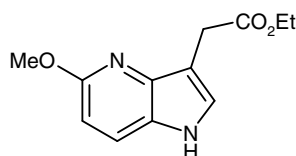
mp = 88 °C.

IR (thin film, NaCl): 2944, 1573, 1449, 1284, 1238, 1087 cm⁻¹.

¹H NMR (250 MHz, CDCl₃, in accordance with the literature data⁴): δ = 2.31 (s, 3H), 4.00 (s, 3H), 6.56 (d, *J* = 8.8Hz, 1H), 7.03 (d, *J* = 1.25Hz, 1H), 7.41 (d, *J* = 8.8Hz, 1H); 8.46 (bs, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 8.7, 53.5, 104.7, 111.5, 121.8, 124.8, 124.9, 142.3, 159.8.

HRMS calcd for C₉H₁₀N₂O [M+H]⁺: 163.0871, found = 163.0862.



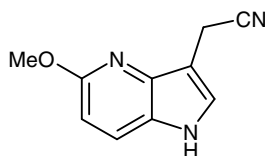
Ethyl 2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetate (4e)

The desired product was obtained according to the general procedure for hydrogenation using 450 mg (1.61 mmol) of the compound **3e**, in 100 mL of ethanol. The solution was hydrogenated for 3 days at 45 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a green oil (63%).

IR (thin film, NaCl): 2945, 1715, 1270, 1078 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 1.27 (t, *J* = 7.1Hz, 3H), 3.83 (s, 2H), 3.96 (s, 3H), 4.19 (q, *J* = 7.1Hz, 2H), 6.50 (d, *J* = 8.8Hz, 1H), 7.10 (d, *J* = 2.5Hz, 1H), 7.33 (d, *J* = 8.8Hz, 1H), 8.66 (bs, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 14.3, 29.6, 53.3, 60.9, 105.2, 108.0, 121.9, 124.5, 125.6, 141.4, 159.9, 173.1.



2-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetonitrile (4f)

The desired product was obtained according to the general procedure for hydrogenation using 400 mg (1.71 mmol) of the compound **3f**, in 50 mL of ethanol. The solution was hydrogenated for 7 hours at 45 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (7 / 3) as a white solid (46%).

mp = 92 °C.

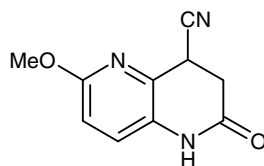
IR (thin film, NaCl): 3020, 2254, 1616, 1581, 1409, 1216, 1027 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 3.89 (s, 2H), 3.99 (s, 3H), 6.62 (d, *J* = 8.8Hz, 1H), 7.30 (d, *J* = 2.2Hz, 1H), 7.54 (d, *J* = 8.8Hz, 1H), 8.46 (bs, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 13.1, 53.5, 105.0, 106.5, 118.9, 122.2, 124.6, 124.7, 140.4, 160.3.

⁴ Macor, J. E. ; Wehner, J. M. *Heterocycles* **1993**, 35, 349.

HRMS calcd for $C_{10}H_9N_3O$ $[M+H]^+$: 188.0824, found = 188.0837.



10-Methoxy-5-oxo-3,4,5,6-tetrahydro-[1,6]naphthyridine-3-carbonitrile (5)

In a hydrogenation bomb, 580 mg (2.07 mmol) of the compound **3e** was dissolved in a 50 mL of ethyl acetate and 200 μ L of acetic acid. Palladium on carbon (15% wt.) was added and the mixture was hydrogenated for 12 hours under 75 psi of hydrogen at 40 °C. The crude material was then filtered through a plug of celite and concentrated. The product was obtained after recrystallisation in chloroform as a yellow solid (95%).

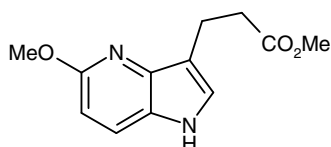
mp > 250 °C.

IR (thin film, NaCl): 3017, 2290, 1669, 1480, 1381, 1272, 1214 cm^{-1} .

1H NMR (250 MHz, DMSO): δ = 2.95 (d, J = 7.8Hz, 2H), 3.84 (s, 3H), 4.74 (t, J = 7.8Hz, 1H), 6.81 (d, J = 8.5Hz, 1H); 7.29 (d, J = 8.5Hz, 1H), 10.29 (bs, 1H).

^{13}C NMR (62.5 MHz, DMSO): δ = 30.2, 33.0, 53.4, 110.9, 118.7, 127.7, 128.1, 133.6, 158.8, 166.0.

HRMS calcd for $C_{10}H_9N_3O_2$ $[M+H]^+$: 204.0773, found = 204.0776.



Methyl 3-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)propanoate (7a)

The desired product was obtained according to the general procedure for hydrogenation using 400 mg (1.42 mmol) of the compound **6a**, in 100 mL of ethanol. The solution was hydrogenated for 5 hours at 40 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (1 / 1) as a yellow solid (42%).

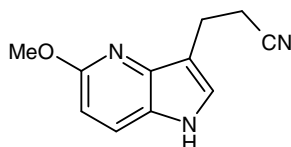
mp = 104 °C.

IR (thin film, NaCl): 2944, 1724, 1573, 1454, 1220, 1027 cm^{-1} .

1H NMR (250 MHz, $CDCl_3$): δ = 2.85 (t, J = 7.5Hz, 2H), 3.12 (t, J = 7.5Hz, 2H), 3.66 (s, 3H), 3.98 (s, 3H); 6.57 (d, J = 8.5Hz, 1H), 7.09 (d, J = 1.8Hz, 1H), 7.48 (d, J = 8.5Hz, 1H), 8.08 (bs, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.0, 34.3, 51.6, 53.3, 105.4, 114.9, 121.7, 124.1, 124.8, 141.7, 159.7, 174.4.

HRMS calcd for $C_{12}H_{14}N_2O_3$ $[M+H]^+$: 235.1083, found = 235.1091.

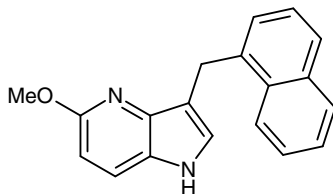


3-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)-propionitrile (7b)

The desired product was obtained according to the general procedure for hydrogenation using 550 mg (2.23 mmol) of the compound **6b**, in 50 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 3 hours at 45 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a yellow solid (36%).

mp = 74 °C.

IR (thin film, NaCl): 2935, 2238, 1614, 1577, 1486, 1243, 1027 cm^{-1} ;
 ^1H NMR (250 MHz, CDCl_3): δ = 2.91 (t, J = 6.9Hz, 2H), 3.11 (t, J = 6.9Hz, 2H), 3.97 (s, 3H), 6.58 (d, J = 8.7Hz, 1H), 7.16 (d, J = 2.5Hz, 1H), 7.48 (d, J = 8.7Hz, 1H), 8.39 (bs, 1H).
 ^{13}C NMR (62.5 MHz, CDCl_3): δ = 18.0, 21.1, 53.3, 105.5, 112.1, 120.5, 122.0, 124.6, 124.9, 141.2, 159.8.
 HRMS calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 202.0980, found = 202.0974.



5-Methoxy-3-((naphthalen-1-yl)methyl)-1H-pyrrolo[3,2-b]pyridine (9b)

The desired product was obtained according to the general procedure for hydrogenation using 500 mg (1.51 mmol) of the compound **8b**, in 50 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 6 hours at 35 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a white solid (48%).

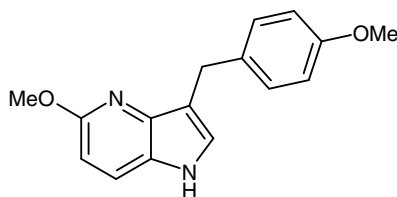
mp = 85 °C.

IR (thin film, NaCl): 1573, 1400, 1283, 1222, 1035 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 4.03 (s, 3H), 4.55 (s, 2H), 6.56 (d, J = 8.8Hz, 1H), 6.64 (bs, 1H), 7.34-7.48 (m, 5H), 7.71 (d, J = 8.2Hz, 1H), 7.79-7.83 (m, 2H), 8.20 (d, J = 9.4Hz, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 27.7, 53.5, 105.4, 116.0, 121.7, 124.6, 124.9, 125.1, 125.5, 125.7, 125.8, 126.8, 126.9, 128.6, 132.2, 134.0, 137.8, 141.5, 159.9.

HRMS calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 289.1341, found = 289.1353.



3-(4-Methoxybenzyl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine (9c)

The desired product was obtained according to the general procedure for hydrogenation using 200 mg (0.64 mmol) of the compound **8c**, in 50 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 18 hours at 45 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a white solid (41%).

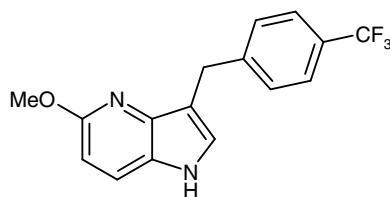
mp = 124 °C.

IR (thin film, NaCl): 3262, 1578, 1509, 1407, 1303, 1239, 1026 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 3.77 (s, 3H), 4.01 (s, 3H), 4.07 (s, 2H), 6.58 (d, J = 8.8Hz, 1H), 6.82 (d, J = 8.5Hz, 2H), 6.94 (d, J = 2.5Hz, 1H), 7.32 (J = 8.5Hz, 2H), 7.48 (d, J = 8.8Hz, 1H), 7.87 (bs, 1H).

^{13}C NMR (62.5 MHz, CDCl_3): δ = 29.6, 53.4, 55.4, 105.5, 113.8, 117.2, 121.6, 124.4, 124.8, 130.0, 134.1, 141.7, 157.8, 159.9.

HRMS calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 269.1290, found = 269.1285.



3-(4-(Trifluoromethyl)benzyl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine (9d)

The desired product was obtained according to the general procedure for hydrogenation using 200 mg (0.57 mmol) of the compound **8d**, in 50 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 18 hours at 35 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a white solid (45%).

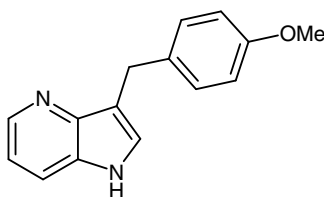
mp = 119 °C.

IR (thin film, NaCl): 3266, 1574, 1407, 1322, 1256, 1170, 1110, 1065, 1021 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 3.98 (s, 3H), 4.17 (s, 2H), 6.59 (d, *J* = 8.8Hz, 1H), 6.99 (d, *J* = 2.5Hz, 1H), 7.46-7.50 (m, 5H), 7.99 (bs, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 30.5, 53.4, 105.8, 115.5, 121.8, 124.4, 124.6 (*J* = 270.0Hz), 124.8, 125.2 (*J* = 3.8Hz), 128.2 (*J* = 32.0Hz), 129.3, 141.6, 146.1, 160.0.

HRMS calcd for C₁₆H₁₃F₃N₂O [M+H]⁺: 307.1058, found = 307.1055.



3-(4-méthoxybenzyl)-1H-pyrrolo[3,2-b]pyridine (9e)

The desired product was obtained according to the general procedure for hydrogenation using 650 mg (2.31 mmol) of the compound **8e**, in 50 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 18 hours at 45 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (1 / 1 then 1 / 2) as a white solid (42%).

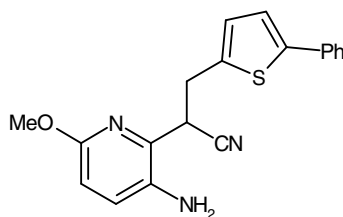
mp = 167 °C.

IR (thin film, NaCl): 3022, 1608, 1505, 1215, 1029 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 3.77 (s, 3H), 4.17 (s, 2H), 6.82 (d, *J* = 8.5Hz, 2H), 7.03 (d, *J* = 2.2Hz, 1H), 7.10 (dd, *J* = 8.2Hz, *J* = 4.7Hz, 1H), 7.25 (d, *J* = 8.5Hz, 2H), 7.60 (dd, *J* = 8.2Hz, *J* = 1.5Hz, 1H), 8.49 (dd, *J* = 4.7Hz, *J* = 1.5Hz, 1H), 8.55 (bs, 1H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 29.4, 55.4, 113.9, 117.0, 117.5, 118.3, 126.0, 129.3, 129.9, 133.4, 143.0, 145.2, 157.9.

HRMS calcd for C₁₅H₁₄N₂O [M+H]⁺: 239.1184, found = 239.1191.



(Z)-2-(3-Amino-6-methoxypyridin-2-yl)-3-(5-phenylthiophen-2-yl)acrylonitrile (9h)

The desired product was obtained according to the general procedure for hydrogenation using 300 mg (1.51 mmol) of the compound **8h**, in 50 mL of the mixture ethanol / acetic acid. The solution was hydrogenated for 18 hours at 40 °C. The product was isolated with the eluent petroleum ether / ethyl acetate (8 / 2) as a yellow solid (72%).

mp = 119 °C.

IR (thin film, NaCl): 1482, 1426, 1265, 1029 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 3.22 (bs, 2H), 3.60-3.64 (m, 2H), 3.91 (s, 3H), 4.20 (t, *J* = 7.5Hz, 1H), 6.59 (d, *J* = 8.8Hz, 1H), 6.84 (d, *J* = 3.6Hz, 1H), 7.01 (d, *J* = 8.5Hz, 1H), 7.11 (d, *J* = 3.6Hz, 1H), 7.22-7.37 (m, 3H), 7.50-7.54 (m, 2H).

¹³C NMR (62.5 MHz, CDCl₃): δ = 31.9, 36.8, 53.7, 111.5, 119.3, 123.1, 125.7, 127.6, 127.8, 129.0, 130.5, 134.1, 134.2, 135.1, 138.6, 144.0, 157.9.

HRMS calcd for C₁₉H₁₇N₃OS [M+H]⁺: 336.1171, found = 336.1180.