A New Synthesis of 2-Substituted Pyridines via Aluminum Chloride Induced Heteroarylation of Arenes and Heteroarenes

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Experimental Section

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. ^1H NMR and ^{13}C NMR spectra were determined in CDCl_3 , $\text{DMSO}-d_6$ or $\text{MeOH}-d_4$ solution on 200 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. Thermal analysis data [Differential Scanning Calorimetry (DSC)] was generated with the help of DSC-50 detector. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, retention times. Microanalyses were performed using a C H N S/O analyzer. Dry 1,2-dichloromethane was prepared by distilling it over phosphorous pentoxide.

Typical procedure for the synthesis of 3-nitro-2-{2,4,6-trimethoxyphenyl}pyridine (3d):

A mixture of 2-chloro-3-nitropyridine **1c** (0.20g, 1.26 mmol), 1,3,5-trimethoxybenzene (0.21g, 1.25 mmol) and AlCl_3 (0.20g, 1.51 mmol) in dichloroethane (10 mL) was stirred at 25 °C for 1h under a nitrogen atmosphere. The reaction mixture was then stirred at 75-80 °C for 24h. After completion the mixture was poured into ice-cold water (100 mL), stirred for 10 min and then extracted with chloroform (3 x 30 mL). The organic layers were collected, combined, washed with water (2 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography using ethyl acetate-petroleum ether to afford the expected product as a light yellow solid.

Spectral and analytical data for the 2-aryl and heteroaryl pyridine derivatives synthesized:

5-nitro-2-{2,4,6-trimethoxyphenyl}pyridine (3a): mp 162-164 °C; ^1H NMR (200 MHz, CDCl_3) δ 9.46 (s, 1H), 8.40 (d, $J = 8.7$ Hz, 1H), 7.50 (d, $J = 8.7$ Hz, 1H), 6.19 (s, 2H), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3); ν_{max} (KBr, cm^{-1}): 1592, 1348; Mass (CI method, *i*-butane): 291 ($\text{M}^+ + 1$, 100%); ^{13}C NMR (50 MHz, CDCl_3) 162.3 (2C), 160.8, 158.6, 144.3, 142.2, 130.3, 126.9, 110.1, 90.8 (2C), 55.8 (OCH_3), 55.3 (2C, OCH_3); HPLC 98.7%, Symmetry shield RP18 (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4

(pH=5.5): CH₃CN 0/50, 5/50, 20/80, 30/80, 35/50, 40/50, 1.0 mL/min, 210 nm, retention time 9.2 min.; UV (MeOH, nm) 385.5, 269.5, 207.5; Elemental analysis found C, 57.66; H, 4.80; N, 9.68; C₁₄H₁₄N₂O₅ requires C, 57.93; H, 4.86; N, 9.65.

2-{2,4-dimethoxyphenyl}-5-nitropyridine (3b): mp 116-118°C; ¹H NMR (200 MHz, CDCl₃) δ 9.44 (s, 1H), 8.43-8.39 (m, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 1H), 6.57 (d, *J* = 1.9 Hz, 1H), 3.90 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃); ν_{max} (KBr, cm⁻¹): 1511, 1346; Mass (CI method, *i*-butane): 261 (M⁺+1, 100%); ¹³C NMR (50 MHz, CDCl₃) 162.9, 160.9, 158.9, 144.5, 142.5, 132.9, 132.1, 123.9 (2C), 105.6, 98.8, 55.6 (OCH₃), 55.5 (OCH₃); HPLC 98.62%, Inertsil ODS 3V (250 x 4.6 mm), mobile phase 0.01M KH₂PO₄ (pH=5.5): CH₃CN 0/50, 5/50, 30/65, 40/80, 45/80, 50/50, 55/50, 1.0 mL/min, 210 nm, retention time 20.7 min.; UV (MeOH, nm) 359.5, 232.5, 205.0; Elemental analysis found C, 59.93; H, 4.79; N, 10.72; C₁₃H₁₂N₂O₄ requires C, 60.0; H, 4.65; N, 10.76.

4-{5-nitropyridin-2-yl}benzene-1,3-diol (3c): mp 216-218 °C; ¹H NMR (200 MHz, DMSO-*d*₆) δ 13.5 (bs, 1H), 9.78 (bs, 1H), 9.27 (d, *J* = 2.5 Hz, 1H), 8.54-8.48 (dd, *J* = 9.3 & 6.7 Hz, 1H), 7.94 (d, *J* = 9.3 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 1H), 6.46 (s, 1H); ν_{max} (KBr, cm⁻¹): 1572, 1342; Mass (CI method, *i*-butane): 233 (M⁺+1, 100%); ¹³C NMR (50 MHz, CDCl₃) 162.4, 161.5, 158.5, 142.9, 140.9, 132.5, 130.3, 129.7, 119.4, 108.5, 103.5; HPLC 95.51%, Symmetry shield RP18 (250 x 4.6 mm), mobile phase 0.01M KH₂PO₄ (pH=5.5): CH₃CN 0/50, 5/50, 20/80, 30/80, 35/50, 40/50, 1.0 mL/min, 210 nm, retention time 9.3 min.; UV (MeOH, nm) 354.0, 210.0; Elemental analysis found C, 56.84; H, 3.59; N, 12.05; C₁₁H₈N₂O₄ requires C, 56.90; H, 3.48; N, 12.06.

3-nitro-2-{2,4,6-trimethoxyphenyl}pyridine (3d): mp 170-172 °C; ¹H NMR (200 MHz, CDCl₃) δ 8.90-8.87 (dd, *J* = 1.4 & 1.4 Hz, 1H), 8.28-8.23 (dd, *J* = 1.4 & 1.7 Hz, 1H), 7.43-7.37 (m, 1H), 6.20 (s, 2H), 3.85

(s, 6H, 2 OCH₃), 3.70 (s, 3H, OCH₃); $\nu_{\max}$ (KBr, cm⁻¹): 1526, 1418, 1355; Mass (CI method, *i*-butane): 291 (M⁺+1), 261(M⁺-30, 100%); ¹³C NMR (50 MHz, CDCl₃) 162.3 (2C), 158.2, 152.3, 148.9, 147.3, 131.7, 122.0, 107.9, 90.9 (2C), 55.7 (OCH₃), 55.3 (2C, OCH₃); HPLC 99.10%, Inertsil ODS 3V (250 x 4.6mm), mobile phase 0.01M KH₂PO₄: CH₃CN 0/40, 5/40, 30/70, 40/70, 45/40, 50/40, 1.0 mL/min, 210 nm, retention time 11.1 min.; UV (MeOH, nm) 284.0, 208.0; Elemental analysis found C, 57.83; H, 4.84; N, 9.87; C₁₄H₁₄N₂O₅ requires C, 57.93; H, 4.86; N, 9.65.

2-{2,4-dimethoxyphenyl}-3-nitropyridine (3e): mp 86-88 °C; ¹H NMR (200 MHz, CDCl₃) δ 8.87-8.81 (dd, J = 1.4 & 1.4 Hz, 1H), 8.19-8.14 (dd, J = 1.4 & 1.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.39-7.32 (m, 1H), 6.70-6.64 (dd, J = 2.2 & 2.3 Hz, 1H), 6.65 (s, 1H), 3.86 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃); $\nu_{\max}$ (KBr, cm⁻¹): 1510, 1462, 1359; Mass (CI method, *i*-butane): 261(M⁺+1, 100%); ¹³C NMR (50 MHz, CDCl₃) 162.5, 159.6, 152.2, 146.7, 133.3, 131.7, 131.5, 129.7, 121.5, 105.6, 98.2, 55.4 (OCH₃), 54.8 (OCH₃); HPLC 91.42%, SYMMETRY SHIELD RP18 (250 x 4.6 mm) mobile phase 0.01M KH₂PO₄: CH₃CN 0/40, 5/40, 30/80, 40/80, 45/40, 50/40; 1.0 mL/min, 210 nm, retention time 13.9 min.; UV (MeOH, nm) 290.0, 207.5; Elemental analysis found C, 59.80; H, 4.53; N, 10.52; C₁₃H₁₂N₂O₄ requires C, 60.0; H, 4.65; N, 10.76.

1-Methyl-3-{3-nitropyridin-2-yl}-1H-indole (3f): mp 109.8 °C; ¹H NMR (200 MHz, CDCl₃) δ 8.81 (d, J = 4.5 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.53 (s, 1H), 7.38-7.18 (m, 4H), 3.84 (s, 3H, CH₃); $\nu_{\max}$ (KBr, cm⁻¹): 1517, 1378; Mass (CI method, *i*-butane): 254 (M⁺+1, 100%); ¹³C NMR (50 MHz, CDCl₃) 151.8, 147.5, 144.9, 137.1, 131.7, 130.5, 126.2, 122.6, 121.1, 120.5, 119.7, 111.1, 109.7, 33.1 (CH₃); HPLC 98.91%, Inertsil ODS 3V (250 x 4.6mm), mobile phase 0.01M KH₂PO₄: CH₃CN 0/40, 5/40, 25/80, 30/80, 35/40, 40/40, 1.0 mL/min, 220 nm, retention time 18.6 min.; UV (MeOH, nm) 318.5, 259.5, 220.0; Elemental analysis found C, 65.45; H, 4.31; N, 16.39; C₁₄H₁₁N₃O₂ requires C, 66.40; H, 4.38; N, 16.59.

1-Ethyl-3-{3-nitropyridin-2-yl}-1H-indole (3g): ^1H NMR (200 MHz, CDCl_3) δ 8.80 (d, $J = 4.2$ Hz, 1H), 8.04 (d, $J = 7.9$ Hz, 1H), 7.86 (d, $J = 7.3$ Hz, 1H), 7.60 (s, 1H), 7.38 (d, $J = 7.6$ Hz, 1H), 7.31-7.21 (m, 3H), 4.26-4.09 (m, 2H, CH_2), 1.47 (t, $J = 8.9$ Hz, 3H, CH_3); ν_{max} (KBr, cm^{-1}): 1523, 1395; Mass (CI method, *i*-butane): 268 ($\text{M}^+ + 1$, 100%); ^{13}C NMR (50 MHz, CDCl_3) 151.7, 147.4, 144.7, 136.0, 131.6, 128.7, 126.2, 122.3, 120.9, 120.5, 119.6, 110.9, 109.7, 41.1 (CH_2), 14.9 (CH_3); HPLC 98.89%, SYMMETRY SHIELD RP18 (250 x 4.6mm), 0.01M KH_2PO_4 , CH_3CN 0/50, 5/50, 25/80, 30/80, 35/50, 40/50; 1.0 mL/min, 223 nm, retention time 13.8 min. UV (MeOH, nm) 318.5, 260.5, 221.5; Elemental analysis found C, 67.35; H, 4.91; N, 16.01; $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$ requires C, 67.40; H, 4.90; N, 15.72.

2-{2,4,6-Trimethoxyphenyl}nicotinonitrile (3h): mp 158-160 °C; ^1H NMR (200 MHz, CDCl_3) δ 8.87 (d, $J = 5.9$ Hz, 1H), 7.99 (d, $J = 7.8$ Hz, 1H), 7.35-7.28 (m, 1H), 6.21 (s, 2H), 3.86 (s, 3H, OCH_3), 3.75 (s, 6H, 2 OCH_3); ν_{max} (KBr, cm^{-1}): 2981, 2221 ($\text{C}\equiv\text{N}$); Mass (CI method, *i*-butane): 271 ($\text{M}^+ + 1$, 100%); ^{13}C NMR (50 MHz, $\text{DMSO}-d_6$) 162.6 (2C), 158.7, 157.9, 152.1, 139.9, 121.1, 117.2, 112.3, 108.6, 90.8 (2C), 55.7 (OCH_3), 55.3 (2C, OCH_3); HPLC 99.5%, Inertsil ODS 3V (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4 (pH = 7.0): CH_3CN , 0/30, 5/30, 30/70, 40/70, 45/30, 50/30, 1.0 mL/min, 210 nm, retention time 18.5 min; UV (MeOH, nm) 280.0, 207.5; Elemental analysis found C, 66.74; H, 5.20; N, 10.48; $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$ requires C, 66.66; H, 5.22; N, 10.36.

2-{1-Methyl-1H-indol-3-yl}nicotinonitrile (3i): mp 139.51°C; ^1H NMR (200 MHz, CDCl_3) δ 8.84 (d, $J = 3.0$ Hz, 1H), 8.53 (d, $J = 6.8$ Hz, 1H), 8.17 (s, 1H), 7.95 (d, $J = 7.6$ Hz, 1H), 7.39-7.10 (m, 4H), 3.89 (s, 3H, CH_3); ν_{max} (KBr, cm^{-1}): 2215 ($\text{C}\equiv\text{N}$), 1533, 1378; Mass (CI method, *i*-butane): 234 ($\text{M}^+ + 1$, 100%); ^{13}C NMR (50 MHz, CDCl_3) 156.6, 152.4, 141.6, 137.2, 131.3 (2C), 126.7, 122.9, 121.4, 119.1, 118.5, 112.6, 109.5, 103.9, 33.3 (CH_3); HPLC 99.7%, symmetry shield RP18 (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4 : CH_3CN 0/50, 5/50, 20/80, 30/80, 35/50, 40/50, 1.0 mL/min, 220 nm, retention time 13.2 min.; UV (MeOH, nm) 318.5, 267.5, 212.5; Elemental analysis found C, 77.26; H, 4.72; N, 18.05; $\text{C}_{15}\text{H}_{11}\text{N}_3$ requires C, 77.23; H, 4.75; N, 18.01.

2-{1-Ethyl-1H-indol-3-yl}nicotinonitrile (3j): mp 60.65 °C; ^1H NMR (200 MHz, CDCl_3) δ 8.85 (d, $J = 6.4$ Hz, 1H), 8.55-8.51 (m, 1H), 8.24 (s, 1H), 7.96 (d, $J = 7.8$ Hz, 1H), 7.94-7.11 (m, 4H), 4.33-4.22 (m, 2H, CH_2), 1.56 (t, $J = 5.6$ Hz, 3H, CH_3); ν_{max} (KBr, cm^{-1}): 2214 ($\text{C}\equiv\text{N}$), 1529, 1315; Mass (CI method, *i*-butane) 248 (M^++1 , 100%); ^{13}C NMR (50 MHz, CDCl_3) 156.8, 152.4, 141.6, 136.2, 129.7, 126.9, 122.7, 122.6, 121.3, 119.1, 118.5, 112.6, 109.5, 104.1, 41.5 (CH_2), 15.2 (CH_3); HPLC 98.74%, HICHROM RPB (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4 : CH_3CN 0/40, 5/40, 25/80, 30/80, 35/40, 40/40, 1.0 mL/min, 210 nm, retention time 18.9 min.; UV (MeOH, nm) 319.5, 267.5, 222.0, 213.5; Elemental analysis found C, 77.75; H, 5.28; N, 16.93; $\text{C}_{16}\text{H}_{13}\text{N}_3$ requires C, 77.71; H, 5.30; N, 16.99.

2-{1H-indol-3-yl}nicotinonitrile (3k): mp 198-200 °C; ^1H NMR (200 MHz, CDCl_3) δ 11.81 (bs, 1H), 8.90 (d, $J = 4.6$ Hz, 1H), 8.37-8.29 (m, 3H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.37 (t, $J = 4.8$ Hz, 1H), 7.33-7.12 (m, 2H); ν_{max} (KBr, cm^{-1}): 3422, 2227 ($\text{C}\equiv\text{N}$); Mass (CI method, *i*-butane): 220 (M^++1 , 100%); HPLC 90.7%, Inertsil ODS 3V (250 x 4.6 mm), mobile phase 0.01M KH_2PO_4 (pH = 7.0): MeOH, 0/50, 40/60, 60/80, 70/80, 75/50, 80/50, 1.0 mL/min, 210 nm, retention time 28.8 min.; UV (MeOH, nm) 316.0, 270.0, 218.0, 210.5; Elemental analysis found C, 76.74; H, 4.13; N, 19.09; $\text{C}_{14}\text{H}_9\text{N}_3$ requires C, 76.70; H, 4.14; N, 19.17.