Efficient synthesis of amino-pyridine derivatives by copper catalyzed amination reactions

Mohammed K. Elmkaddem,[a] Cédric Fischmeister,*[a] Christophe M. Thomas*[b] and Jean-Luc Renaud*[c]

Electronic supplementary data

Cu_2O was purchased from Strem Chemical and used as received. Bromo-derivativatives were of commercial grade and used as received. Ethylene glycol was purchased from Acros Organics and used as received. NH_3 (aq.) was purchased from Fluka as a 28% solution. Potassium carbonate (99+%) was purchased from Acros organics. DMEDA was purchased from Acros organics. NMR spectra were recorded on a Bruker Avance 200 dpx and a Bruker Avance 300P. GC/MS analyses were performed on a Shimadzu QP2010 fitted with a quadrupolar mass analyzer (EI, 70eV).

General procedure for the catalytic amination of bromopyridine derivatives

A Schlenck tube was loaded under an argon atmosphere with 3.6 mg of Cu_2O (0.025 mmol, 5 mol%), 0.05 ml of 2-bromopyridine (0.5 mmol), 0.62 ml of a 28% solution of $NH_3.H_20$ (10 mmol, 20 equiv.), 14 mg of K_2CO_3 (0.1 mmol, 20 mol%), 5.4 µl of DMEDA (0.05 mmol, 10 mol%) and 1 ml of ethylene glycol. The reaction was stirred for 16 h at 60°C. The reaction mixture was extracted with ethylacetate (4x5ml). Silica gel chromatography afforded **1** in 92% yield. All solvent evaporations and vacuum drying should be performed carefully as some products are volatile under high vaccum.

All the pure products were analysed by ^1H, ^{13}C NMR and subjected to low resolution mass spectrometry analysis using a GC/MS equipment.

2-aminopyridine **1**
NMR data were consistent with reported data[1]
^1H NMR (200 MHz, $CDCl_3$, δ ppm): 8.06 (d, J = 3.6 Hz, 1H), 7.41 (m, 1H), 6.63 (t, 1H), 6.48 (d, J = 8.2 Hz, 1H), 4.45 (bs, 2H, NH_2).
^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 158.3 (C), 148.1 (CH), 137.7 (CH), 114.0 (CH), 108,6 (CH).
LRMS : Th : m/z = 94 ; Exp : m/z (100%) = 94.

2-amino-6-methylpyridine **2**
NMR data were consistent with reported data[2]
^1H NMR (200 MHz, $CDCl_3$, δ ppm): 7.28 (m, 1H), 6.48 (d, J = 7.3Hz, 1H), 6.29 (d, J = 8.1 Hz, 1H), 4.48 (bs, 2H, NH_2), 2.36 (s, 3H, CH_3)
^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 157.8 (C), 156.7 (C), 137.9 (CH), 113 (CH), 105.3 (CH), 24.1 (CH_3).
LRMS : Th : m/z = 108 ; Exp : m/z (100%) = 108.

2-amino-3-methylpyridine **3**
NMR data were consistent with reported data[3]
^1H NMR (200 MHz, $CDCl_3$, δ ppm): 7.88 (d, *J* = 4.6 Hz, 1H), 7.17 (d, *J* = 7.1 Hz, 1H), 6.52 (m, 1H), 4.73 (bs, 2H, NH_2), 2.03 (s, 3H, CH_3).

^{13}C NMR (75 MHz, CDCl$_3$, δ ppm): 157.7 (C), 145.8 (CH) 137.9 (CH), 116.8 (C), 114.4 (CH), 17.4 (CH$_3$-C$_3$).
LRMS : Th : m/z = 108 ; Exp : m/z (100%) = 108.

2,6-bis-aminopyridine **4**
NMR data matched the data of the commercial compound.
^{1}H NMR (200 MHz, CDCl$_3$, δ ppm): 7.23 (t, J = 7.8 Hz, 1H), 5.89 (d, J = 7.8 Hz, 2H), 4.20 (bs, 4H, NH$_2$).
^{13}C NMR (75 MHz, CDCl$_3$, δ ppm): 158.1 (C), 140.1 (CH), 98.2 (CH).
LRMS : Th : m/z = 109 ; Exp : m/z (100%) = 109.

2-methoxy-6-aminopyridine **5**
^{1}H NMR (200 MHz, CDCl$_3$, δ ppm): 7.31 (m, 1H), 6.01-6.09 (m, 2H), 4.51 (s large, 2H, NH$_2$), 3.82 (s, 3H, OCH$_3$).
^{13}C NMR (75 MHz, CDCl$_3$, δ ppm): 162.8 (C), 156.6 (C), 139.4 (CH), 98.9 (CH), 97.4 (CH), 52.4 (CH$_3$).
LRMS : Th : m/z =124 ; Exp : m/z (100%) = 124.

5-(trifluoromethyl)-2-aminopyridine **6**
^{1}H NMR (200 MHz, CDCl$_3$, δ ppm): 8.28 (bs, 1H), 7.58 (dd, J = 2.1, 8.7 Hz, 1H), 6.49 (d, J = 8.7 Hz, 1H), 5.15 (bs, 2H, NH$_2$).
^{13}C NMR (75 MHz, CDCl$_3$, δ ppm): 106.6 (C), 145.8 (q, CH, J_{CF} = 8.7 Hz), 134.8 (q, CH, J_{CF} = 6.4 Hz), 124.3 (q, CF$_3$, J_{CF} = 267.2 Hz), 116.4 (q, C, J_{CF} = 33.0 Hz), 107.7 (CH).
LRMS : Th : m/z = 162; Exp : m/z (100%) = 162.

3-aminopyridine **7**
NMR data were consistent with reported data[1]
^{1}H NMR (200 MHz, CDCl$_3$, δ ppm): 8.07 (d, J = 2.1 Hz, 1H), 7.99 (d, J = 4.3Hz, 1H), 7.04-6.94 (m, 2H), 3.68 (bs, 2H, NH$_2$).
^{13}C NMR (75 MHz, CDCl$_3$, δ ppm): 142.5 (C), 139.8 (CH) 137.3 (CH), 123.6 (CH), 121.3 (CH).
LRMS : Th : m/z = 94; Exp : m/z (100%) = 94.

2-aminopyrimidine **8**
^{1}H NMR (200 MHz, CDCl$_3$, δ ppm): 8.28 (d, J = 4.8 Hz, 2H,), 6.59 (t, J = 4.9 Hz, 1H), 5.27 (bs, 2H, NH$_2$).
^{13}C NMR (75 MHz, CDCl$_3$, δ ppm): 162.5 (C), 157.7 (CH), 110.9 (CH)
LRMS : Th : m/z = 95 ; Exp : m/z (100%) = 95.

References

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