D-Glucosamine as an Efficient Ligand for Copper-Catalyzed Selective Synthesis of Aniline from Aryl Halides and NaN₃

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Supporting Information

Table of contents

- General information ........................................................................................................ S2
- General procedure for aniline formation of aryl halides ............................................. S2
- Spectral data for anilines .............................................................................................. S4
- Spectral data for 1-azido-4-methoxybenzene ............................................................. S8
- References .................................................................................................................... S8
- ICP mass analysis ........................................................................................................ S8
- NMR ............................................................................................................................ S9
Experimental Section:

All the reactions were carried out in reaction tube under normal atmospheric air. Commercially available monosaccharide ligands are purchased from Aldrich chemicals. Copper (I) iodide and other copper salts purchased from Alfa Aesar and Aldrich chemicals. Halobenzenes are purchased from Aldrich chemicals, Alfa Aesar, SRL (India) and Awra (India) chemicals. Potassium hydroxide purchased from Ranbaxy (India). N,N-dimethylformamide (DMF) was purchased from SRL india and all these reagents were used without further purification. Reaction temperatures were controlled by Varivolt temperature modulator, melting points were determined using a Guna 230 volts apparatus. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence lamp. Silica gel (particle size 100-200 mesh) purchased from SRL India, was used for chromatography. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker 400 MHz instrument. Spectra were reported relative to Me₄Si (δ 0.0 ppm) or residual peak (δ 7.26 ppm). ¹³C NMR were reported relative to CDCl₃ (δ 77.16 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer and are reported in frequency of absorption (cm⁻¹). High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer and GCMS.

General Procedure for Aniline Formation from Aryl Halides (0.5 mmol scale) Provided in Table 3.

2 mL of DMF/H₂O (1:1) mixture has taken in 15 mL reaction tube. Argon gas was passed gently for 5 minutes. Aryl halide (0.5 mmol), CuI (9.5 mg, .05 mmol), D-glucosamine (5.4 mg, 0.025 mmol), KI (83 mg, 0.5 mmol) and NaN₃ (97 mg, 1.5 mmol) were then transferred inside the tube along with a magnetic pallet of appropriate size. The reaction tube was then fitted over a preheated oil bath equipped with a magnetic stirrer at 120 °C. The neck of the reaction tube kept open for 1 minute to remove the pressure generated due to heating. After 1 minute of stirring, the reaction tube was fitted with a stopper and continued stirring for 10 minutes. Then KOH (28 mg, 0.5 mmol) was added either in solid or in water solution (0.5
mL. 1 M) form. The reaction tube was then fitted with a glass stopper properly shielded using Teflon tape and placed in the oil bath. Heating continued for 12 hours with the magnetic stirring (continuation of the reaction for extended time reduce the yield of product for few substrates). The reaction was monitored with TLC checking. After complete disappearance of aryl halide, the reaction mixture was allowed to cool to room temperature. After water/dichloromethane workup the organic phase was evaporated and further purification has done by column chromatography on nutral alumina using ethyl acetate/hexanes as the eluent to afford the aniline.

**General Procedure for Aniline synthesis from Aryl Halides (10 mmol scale) Provided in Table 3.**

In a 100 ml round bottom flask 10 mL each of DMF and H₂O has taken and argon gas was passed gently for 5 minutes. The reagents CuI (1 mmol, 190 mg) and D-glucosamine (0.5 mmol, 108 mg), KI (10 mmol, 1.67 gm), KOH (10 mmol, 560 mg) and NaN₃ (30 mmol, 2.01 gm) were transferred to the flask. Following this, 4-bromoacetophenone (10 mmol) was added to the reaction mixture. Then the reaction mixture with a condenser was placed in a preheated oil bath at 120 °C and stirring continued. The reaction was monitored using TLC. After the completion, the reaction was allowed to cool to room temperature. Then the aniline was extracted from water layer to organic layer by using dichloromethane as solvent. The further purification of aniline was done by column chromatography on silica gel using ethyl acetate/hexanes as the eluent.
**Characterization Data:**

2-methoxyaniline (Table 3, entries 5 & 6) deep brown liquid; \( R_f = 0.73 \) (in 30% EtOAc/Hexane); IR 1038, 1160, 1207, 1297, 1465, 1492, 1601, 2927, 3368, 3463 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.82 (s, 2H), 3.88 (s, 3H), 6.72 - 6.81 (m, 2H), 6.81 - 6.88 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 55.4, 110.5, 115.0, 118.5, 121.1, 136.2, 147.3; HRMS [M\(^+\)+1] Calculated for C\(_7\)H\(_{10}\)NO: 124.0762; found: 124.0758.

3-methoxyaniline (Table 3, entries 7 & 8) dark brown liquid; \( R_f = 0.54 \) (in 30% EtOAc/Hexane); IR 1037, 1225, 1270, 1461, 1508, 2926, 3371, 3458 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.72 (s, 2H), 3.78 (s, 3H), 6.26 (t, \( J = 2.0 \) Hz, 1H), 6.31 (d, \( J = 8 \) Hz, 1.6 Hz, 1H), 6.29 (d, \( J = 8.4 \) Hz, 1H), 7.10 (t, \( J = 8 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 55.0, 101.0, 103.8, 107.9, 130.1, 148.0, 160.7; HRMS [M\(^+\)+1] Calculated for C\(_7\)H\(_{10}\)NO: 124.0762; found: 124.0760.

4-methoxyaniline (Table 3, entries 3 & 4) black solid; MP 56-59 °C. \( R_f = 0.43 \) (in 30% EtOAc/Hexane); IR 1031, 1125, 1234, 1458, 1506, 1630, 1858, 2053, 2960, 3345, 3420 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.35 (s, 2H), 3.75 (s, 3H), 6.62 - 6.68 (m, 2H), 6.72 - 6.79 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 55.8, 114.9, 116.5, 140.1, 152.8; HRMS [M\(^+\)+1] Calculated for C\(_7\)H\(_{10}\)NO: 124.0762; found: 124.0768.

4-nitroaniline (Table 3, entries 9, 10 & 20) yellow solid; mp 146-149 °C. \( R_f = 0.31 \) (in 30% EtOAc/Hexane); IR 1111, 1300, 1473, 1595, 1631, 2362, 3360, 3477 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD\(_3\)OD) \( \delta \) 4.85 (s, 2H), 6.58 - 6.64 (m, 2H), 7.94 - 8.00 (m, 2H); \(^{13}\)C
NMR (100 MHz, CD3OD) δ 1H 6.1, 127.3, 138.3, 156.7; HRMS [M+1] Calculated for C6H7N2O2: 139.0508; found: 139.0506.

3-nitroaniline (Table 3, entry 11) yellow solid; mp 111-114 °C; Rf = 0.21 (in 10% EtOAc/Hexane); IR 1084, 1265, 1342, 1482, 1521, 1619, 3327, 3431 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 3.97 (s, 2H), 6.87 (dd, J = 8 Hz, 2 Hz, 1H), 7.18 (t, J = 8 Hz, 1H), 7.40 (t, J = 2 Hz, 1H), 7.45 - 7.51 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 109.1, 113.2, 120.8, 130.0, 147.6, 149.3; HRMS [M+1] Calculated for C6H7N2O2: 139.0508; found: 139.0504.

4-aminoacetophenone (Table 3, entry 1 & 2) white solid; mp 103-107 °C Rf = 0.30 (in 30% EtOAc/Hexane); IR 1167, 1278, 1358, 1436, 1591, 1649, 3224, 3328 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 2.48 (s, 3H), 4.35 (d, J = 66.7 Hz, 2H), 6.57 - 6.69 (m, 2H), 7.73 - 7.84 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 26.2, 113.8, 127.6, 130.9, 151.6, 196.7; HRMS [M+1] Calculated for C8H10NO: 136.0762; found: 136.0759.

3-aminoacetophenone (Table 3, entry 19) white solid; mp 94-98 °C; Rf = 0.32 (in 30% EtOAc/Hexane); IR 1015, 1238, 1289, 1323, 1355, 1459, 1491, 1599, 1669, 3369, 3466 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 2.59 (s, 3H), 3.86 (s, 2H), 6.90 (dd, J = 8 Hz, 1.6 Hz, 1H), 7.23 - 7.33 (m, 2H), 7.37 (d, J = 7.6 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 26.8, 114.1, 119.0, 119.8, 129.6, 138.3, 146.8, 198.6; HRMS [M+1] Calculated for C8H10NO: 136.0762; found: 136.0757.

2-aminoacetophenone (Table 3, entry 18) yellow liquid, Rf = 0.56 (in 20% EtOAc/Hexane); IR 1020, 1162, 1246, 1367, 1447, 1484, 1550, 1632, 2820, 2945, 3340,
3443 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.61 (s, 3H), 6.32 (s, 2H), 6.64 - 6.73 (m, 2H), 7.30 (dt, \(J = 8.4\) Hz, 1.2 Hz, 1H), 7.74 (d, \(J = 8.0\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 27.9, 115.8, 117.3, 118.3, 132.1, 134.5, 150.4, 200.9; HRMS [M\(^{+}\)+1] Calculated for C\(_8\)H\(_{10}\)NO: 136.0762; found: 136.0761.

4-aminobenzaldehyde (Table 3, entry 12) yellow solid, \(R_f = 0.15\) (in 20% EtOAc/Hexane); IR 1046, 1103, 1163, 1250, 1390, 1440, 1597, 1664, 2935, 3447 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-D\(_6\)) \(\delta\) 4.85 (s, 2H), 6.68 (d, \(J = 8.4\) Hz, 2H), 7.61 (d, \(J = 8.4\) Hz, 2H), 9.55 (s, 1H); \(^{13}\)C NMR (100 MHz, DMSO-D\(_6\)) \(\delta\) 114.5, 127.0, 133.7, 156.9, 192.3; HRMS [M\(^{+}\)+1] Calculated for C\(_7\)H\(_8\)NO: 122.0606; found: 122.0601.

4-aminobenzophenone (Table 3, entry 13) yellow solid, mp 121-124 °C; \(R_f = 0.20\) (in 20% EtOAc/Hexane); IR 1020, 1287, 1321, 1415, 1445, 1593, 1637, 2827, 2945, 3360 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.18 (s, 2H), 6.66 (dd, \(J = 8.4\) Hz, 2.0 Hz, 2H), 7.41 - 7.50 (m, 2H), 7.50 - 7.58 (m, 1H), 7.23 (d, \(J = 8.0\) Hz, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 113.7, 127.5, 128.2, 129.6, 131.5, 133.1, 139.0, 151.1, 195.5; HRMS [M\(^{+}\)+1] Calculated for C\(_{13}\)H\(_{12}\)NO: 198.0919; found: 198.0926.

2-aminobenzophenone (Table 3, entry 15) yellow solid, mp 103-107 °C; \(R_f = 0.57\) (in 20% EtOAc/Hexane); IR 1023, 1114, 1245, 1413, 1450, 1552, 1628, 2524, 2830, 2946, 3367 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.14 (s, 2H), 6.65 (t, \(J = 7.6\) Hz, 1H), 6.80 (d, \(J = 8.4\) Hz, 1H), 7.29 - 7.38 (m, 1H), 7.45 - 7.53 (m, 3H), 7.54 - 7.61 (m, 1H), 7.65 - 7.73 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 115.6, 117.1, 118.3, 128.2, 129.2, 131.2, 134.4, 134.7, 140.2, 151.1, 199.2; HRMS [M\(^{+}\)+1] Calculated for C\(_{13}\)H\(_{12}\)NO: 198.0919; found: 198.0910.

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3-aminobenzophenone (Table 3, entry 14) yellow solid, mp 81-84 °C; $R_f = 0.29$ (in 20% EtOAc/Hexane); IR 1024, 1113, 1321, 1414, 1450, 1649, 2830, 2951, 3390 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.87 (s, 2H), 6.30 (dd, $J = 7.6$ Hz, 1.2 Hz, 1H), 7.17 (d, $J = 7.2$ Hz, 2H), 7.28 (t, $J = 8.0$ Hz, 1H), 7.50 (t, $J = 7.2$ Hz, 2H), 7.61 (dt, $J = 7.2$ Hz, 1.2 Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 116.0, 119.1, 120.8, 128.3, 129.2, 130.2, 132.6, 137.9, 138.8, 146.6, 197.1; HRMS [M$^+$+1] Calculated for C$_{13}$H$_{12}$NO: 198.0919; found: 198.0916.

(2-amino-5-nitrophenyl)(phenyl)methanone (Table 3, entry 16) yellow solid, mp 166-168 °C; $R_f = 0.31$ (in 20% EtOAc/Hexane); IR 1028, 1112, 1262, 1330, 1416, 1452, 1637, 2527, 2834, 2947, 3370 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.76 (d, $J = 8.4$ Hz, 1H), 6.90 (s, 2H), 7.52 (s, 2H), 7.57 - 7.83 (m, 3H), 8.16 (d, $J = 7.6$ Hz, 1H), 8.48 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 116.1, 116.9, 128.8, 129.2, 129.4, 131.7, 132.3, 136.8, 138.6, 155.4, 198.0; HRMS [M$^+$+1] Calculated for C$_{13}$H$_{11}$N$_2$O$_3$: 243.0770; found: 243.0760.

2-Amino-2',5-dichlorobenzophenone (Table 3, entry 17) yellow solid, mp 87-89 °C; $R_f = 0.29$ (in 20% EtOAc/Hexane); IR 1018, 1043, 1232, 1372, 1414, 1452, 1631, 1644, 1708, 2521, 2833, 2941, 2969, 3455 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.46 (s, 2H), 6.68 (d, $J = 8.8$ Hz, 1H), 7.11 (d, $J = 2.4$ Hz, 1H), 7.23 (dd, $J = 8.8$ Hz, 2.4Hz, 1H), 7.30 (dd, $J = 7.6$Hz, 1.6Hz, 1H), 7.36 (dt, $J = 7.2$Hz, 1.2Hz, 1H), 7.42 (dt, $J = 8.0$Hz, 1.6Hz, 1H), 7.46 (d, $J = 7.6$Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 118.1, 118.6, 120.2, 126.9, 128.5, 130.2, 130.81, 130.84, 133.3, 135.4, 139.1, 150.0, 196.5; HRMS [M$^+$+1] Calculated for C$_{13}$H$_{10}$Cl$_2$NO: 266.0139; found: 266.0134.
1-azido-4-methoxybenzene (Scheme 1, compound 1); Yellow liquid; \( R_f = 0.4 \) (in 100% hexane); IR 1029, 1104, 1178, 1245, 1289, 1503, 1636, 2947, 3428 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 3.70 \) (s, 3H), 6.80 (t, \( J = 4.4 \) Hz, 2H), 6.84-6.94 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta 55.7, 115.3, 120.1, 132.5, 157.2 \); GC-MS \( \text{EI}^+ \) : m/z calculated for \( \text{C}_7\text{H}_7\text{N}_3\text{O} \): 149.

References


ICP mass analysis for the copper content in the organic phase after aqueous work up.

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<th>SampleID</th>
<th>Analyte</th>
<th>Mean</th>
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<tbody>
<tr>
<td>KG-6-81</td>
<td>Cu 327.393</td>
<td>0.736 mg/L</td>
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</table>

[Sample volume 25 mL. Copper content = 0.736x 25/1000 mg = 0.0184 mg]
2-Methoxyaniline
4-Methoxyanisole
4-Nitroaniline
3-Nitroaniline
4-Aminoacetophenone

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4-Aminobezophenone
2-Aminobenzophenone
3-Aminobenzophenone
(2-Amino-5-nitrophenyl)(phenyl)methanone
(2-Amino-5-chlorophenyl)(2-chlorophenyl)methanone
1-Azido-4-methoxybenzene