A mild method for Ullmann coupling reaction of amines and aryl halides

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Supporting information

General procedure for the coupling reaction of iodobenzene with benzylamine catalyzed by CuI and amino acid:

A mixture of iodobenzene (5 mmol), BnNH₂ (5 mmol), K₂CO₃ (10 mmol), CuI (0.5 mmol) and a suitable amino acid (1 mmol) in 3 mL of DMSO was heated at 40 °C for 12 h. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with 1/10 to 1/8 ethyl acetate/petroleum ether to afford *N*-benzyl aniline. ¹H NMR (CDCl₃, 300 MHz) δ 4.0 (br, 1H), 4.34 (s, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 7.71-7.40 (m, 7H); MS *m/z* 183 (M⁺), 91, 77, 65, 51, 41.

General procedure for the coupling reaction of aryl halides with benzylamine catalyzed by CuI and N-methyl glycine or L-proline:

A mixture of aryl halide (5 mmol), BnNH₂ (7.5 mmol), K₂CO₃ (10 mmol), CuI (0.5 mmol) and a suitable amino acid (1 mmol) in 3 mL of DMSO was heated at the indicated temperature. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with 1/10 to 1/8 ethyl acetate/petroleum ether to afford the corresponding aniline.

***N*-Benzyl-4-iodoaniline:** ¹H NMR (CDCl₃, 300 MHz) δ 4.12 (br, 1H), 4.30 (s, 2H),

6.40 (d, $J = 8.7$ Hz, 2H), 7.34-7.40 (m, 5H), 7.42 (d, $J = 8.7$ Hz, 2H); MS m/z 309 (M^+), 92, 91, 77, 65, 51, 41.

2-[(Phenylmethyl)amino]benzoic acid¹: ^1H NMR (CDCl_3 , 300 MHz) δ 4.50 (s, 2H), 6.61-6.66 (m, 2H), 7.26-7.37 (m, 6H), 7.99-8.01 (m, 2H); MS m/z 227 (M^+), 208, 180, 132, 106, 91, 77, 65, 51, 43.

N-Benzyl-3-nitroaniline²: ^1H NMR (CDCl_3 , 300 MHz) δ 4.40 (br, 3H), 6.88 (d, $J = 8.1$ Hz, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.44-7.45 (m, 1H), 7.53-7.55 (m, 1H), 7.25-7.38 (m, 5H); MS m/z 228 (M^+), 91, 65, 51, 41.

N-(4-Methylphenyl)benzylamine³: ^1H NMR (CDCl_3 , 300 MHz) δ 2.23 (s, 3H), 3.90 (br, 1H), 4.30 (s, 2H), 6.54 (d, $J = 8.7$ Hz, 2H), 6.97 (d, $J = 7.8$ Hz, 2H), 7.32-7.35 (m, 5H); MS m/z 197 (M^+), 120, 91, 77, 65, 51, 41.

N-Phenyl-*p*-anisidine¹: ^1H NMR (CDCl_3 , 300 MHz) δ 3.74 (s, 3H), 4.28 (s, 2H), 6.55 (d, $J = 8.7$ Hz, 2H), 6.76 (d, $J = 8.7$ Hz, 2H), 7.25-7.20 (m, 5H); MS m/z 213 (M^+), 122, 107, 91, 77, 65, 52, 41.

N-Benzyl-4-bromoaniline⁴: ^1H NMR (CDCl_3 , 300 MHz) δ 4.08 (br, 1H), 4.30 (s, 2H), 6.49 (d, $J = 9.0$ Hz, 2H), 7.22 (d, $J = 9.0$ Hz, 2H), 7.26-7.35 (m, 5H); MS m/z 263, 261, 91, 77, 65, 63, 51, 41.

N-Benzyl-3-fluoroaniline⁶: ^1H NMR (CDCl_3 , 300 MHz) δ 4.18 (br, 1H), 4.30 (s, 2H), 6.20-6.34 (m, 1H), 6.38-6.43 (m, 2H), 7.05-7.11 (m, 1H), 7.25-7.37 (m, 5H); MS m/z 201 (M^+), 91, 65, 51, 41.

N-Benzyl-biphenyl-4-yl-amine: ^1H NMR (CDCl_3 , 300 MHz) δ 4.1 (br, 1H), 4.37 (s, 2H), 6.69 (d, $J = 8.1$ Hz, 2H), 7.35-7.45 (m, 10H), 7.51 (d, $J = 8.1$ Hz, 2H); MS m/z

257 (M⁺), 182, 168, 152, 141, 115, 91, 77, 65, 63, 51.

***N*-Benzyl-4-chloroaniline⁵**: ¹H NMR (CDCl₃, 300 MHz) δ 4.06 (br, 1H), 4.30 (s, 2H), 5.22 (d, *J* = 6.6 Hz, 2H), 7.09 (d, *J* = 6.6 Hz, 2H), 7.25-7.35 (m, 5H); MS *m/z* 217 (M⁺), 91, 65, 51, 41.

General procedure for the coupling reaction of aryl iodides with amines catalyzed by CuI and L-proline:

A mixture of aryl iodide (2 mmol), amine (3 mmol), K₂CO₃ (4 mmol), CuI (0.2 mmol) and L-proline (0.4 mmol) in 4 mL of DMSO was heated at the indicated temperature. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with 1/10 to 1/8 ethyl acetate/petroleum ether to afford the corresponding product.

***N*-Hexylaniline**: ¹H NMR (CDCl₃, 300 MHz) δ 0.91 (t, 3H), 1.30-1.44 (m, 6H), 1.60-1.65 (m, 2H), 3.11 (t, 2H), 3.60 (br, 1H), 6.60 (d, 2H), 6.70 (t, 1H), 7.18-7.26 (t, 2H); MS *m/z* 177 (M⁺), 106, 93, 79, 77, 65, 55, 51, 41.

***N*-Allylaniline⁸**: ¹H NMR (CDCl₃, 300 MHz) δ 3.80 (brs, 3H), 5.17 (dd, 1H), 5.27 (dd, 1H), 5.92-6.03 (m, 1H), 6.64 (d, 2H), 6.73 (t, 1H), 7.17-7.27 (t, 2H); MS *m/z* 133 (M⁺), 106, 91, 77, 65, 57, 51, 39.

***N*-Cyclohexylaniline⁷**: ¹H NMR (CDCl₃, 300 MHz) δ 1.09-1.46 (m, 5H), 1.64-1.69 (m, 1H), 1.75-1.81 (m, 2H), 2.05-2.10 (m, 2H), 3.22-3.30 (m, 1H), 3.50 (br s, 1H), 6.59-6.70 (m, 3H), 7.14-7.26 (m, 2H); MS *m/z* 175 (M⁺), 132, 118, 106, 93, 77, 65, 51,

43, 41.

4-Phenylmorpholine⁹: ¹H NMR (CDCl₃, 300 MHz) δ 3.15-3.19 (t, 4H), 3.86-3.90 (t, 4H), 6.88-6.95 (m, 3H), 7.27-7.33 (m, 2H); MS *m/z* 163 (M⁺), 105, 77, 71, 57, 55, 51, 43, 41.

1-Phenylpiperidine: ¹H NMR (CDCl₃, 300 MHz) δ 1.57-1.61 (m, 2H), 1.68-1.76 (m, 4H), 3.16 (t, 4H), 6.83 (t, 1H), 6.94 (d, 2H), 7.23-7.29 (t, 1H); MS *m/z* 161 (M⁺), 160, 146, 132, 120, 105, 91, 77, 55, 51, 41.

Diphenylamine: ¹H NMR (CDCl₃, 300 MHz) δ 5.70 (br, 1H), 6.90-6.95 (m, 2H), 7.04-7.08 (m, 4H), 7.23-7.29 (m, 4H); MS *m/z* 169 (M⁺), 77, 65, 51, 41.

(4-Methoxyphenyl)phenylamine¹: ¹H NMR (CDCl₃, 300 MHz) δ 3.80 (s, 3H), 5.49 (br, 1H), 6.81-6.92 (m, 5H), 7.06-7.09 (m, 2H), 7.19-7.27 (m, 2H); MS *m/z* 199 (M⁺), 184, 154, 128, 77, 63, 51, 41.

Bis-(4-methoxyphenyl)amine: ¹H NMR (CDCl₃, 300 MHz) δ 3.80 (s, 6H), 5.40 (br, 1H), 6.83-7.00 (m, 8H); MS *m/z* 229 (M⁺), 214, 199, 182, 171, 154, 143, 127, 122, 115, 107, 92, 77, 64, 52, 41.

N-(4-Methoxyphenyl)-cyclohexylamine⁹: ¹H NMR (CDCl₃, 300 MHz) δ 1.08-1.38 (m, 5H), 1.62-1.66 (m, 1H), 1.72-1.78 (m, 2H), 2.90 (brs, 1H), 3.13-3.19 (m, 1H), 3.75 (s, 3H), 6.56 (d, 2H), 6.76 (d, 2H); MS *m/z* 205 (M⁺), 190, 176, 162, 149, 134, 123, 118, 108, 95, 92, 83, 80, 77, 65, 55, 41.

N-Hexyl-*p*-anisidin: ¹H NMR (CDCl₃, 300 MHz) δ 0.90 (t, 3H), 1.30-1.33 (m, 6H), 1.50-1.70 (m, 2H), 3.05 (t, 2H), 3.74 (s, 3H), 6.60 (d, 2H), 6.80 (d, 2H); MS *m/z* 207 (M⁺), 136, 121, 108, 93, 77, 65, 53, 41.

N-Hexyl-4-iodoaniline: ^1H NMR (CDCl_3 , 300 MHz) δ 0.92 (t, 3H), 1.31-1.46 (m, 6H), 1.57-1.70 (m, 2H), 3.08 (t, 2H), 3.70 (brs, 1H), 6.39-6.42 (m, 2H), 7.29-7.44 (m, 2H); MS m/z 303 (M^+), 232, 105, 91, 76, 65, 50, 41.

References

1. Nonnenmacher, E.; Hever, A.; Mahamoud, A.; Aubert, C.; Molnar, J.; Barbe, J. *Org.Prep.Proced.Int.*; **1997**, 29, 711-715.
2. Safdar, H.; Atta-ur-Rahman; Iqbal, C. M.; Mohammed, K. K.; Wilhelm, S.; Ernst, B. *Tetrahedron* **2001**, 57, 9951-9958.
3. Tanaka, M.; Kobayashi, T. *Synthesis* **1985**, 967-969.
4. Carboni, B.; Vaultier, M.; Courgeon, T.; Carrie, R. *Bull. Soc. Chim. Fr.* **1989**, 844-849.
5. Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* **2000**, 789-800.
6. Leyva, E.; Munoz, D.; Platz, M. S. *J. Org. Chem.* **1989**, 54, 5938-5945.
7. Kawakami, T.; Sugimoto, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1995**, 60, 2677-2682.
8. Nakanishi, S.; Okamoto, K.; Yamaguchi, H.; Takata, T. *Synthesis* **1998**, 1735-1741.
9. Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, 55, 12829-12842.