Supplementary Information

Green and efficient methods for one pot aerobic oxidative synthesis of benzimidazoles from alcohols with TEMPO-PEG₄₀₀₀-NHC-Cu(II) complex in water

Zhao-gang Wang, Xiao-hua Cao, Yao Yang and Ming Lu*

School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China.

General information

All starting materials were purchased from commercial sources and used without further treatment. Analytical thin layer chromatography (TLC) was performed on precoated silica plates. Yields of the products refer to purification by silica-gel column chromatography. All starting chemicals are commercially available. Melting points were determined on a Perkin-Elmer differential scanning calorimeter. Elemental analysis were performed on Elementar Vario Micro spectrometer. ¹HNMR were recorded on a Bruker Advance III (500MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. High performance liquid chromatography experiments were performed on a liquid chromatograph (Shimadzu LC-20AT).

General procedure for preparation of catalyst:

To a solution of PEG-4000 (0.06 mol) in toluene (150 mL), pyridine(0.12 mol) was added, followed by the addition of thionyl chloride (0.12 mol) within 30 min under N₂ atmosphere at 0 °C. The resulting slurry was stirred for 24 h at room temperature and filtered. The toluene was then removed by rotator evaporation under reduced pressure to give intermediate **1** as a gray viscous liquid. 4-hydroxy-TEMPO (0.05mol) was added to a suspension of Na (0.05 mol) in benzene (100 mL) and the resulting slurry was stirred for 8 h at room temperature. Intermediate **1** (0.025 mol) was then added and stirring for 24 h at room temperature. The suspension was then filtered and the filtrate concentrated under reduced pressure. This solution was then added to ether (100 mL) that was stirred vigorously and the precipitate collected by filtration, washed twice with ether (50 mL) and dried under vacuum. The product **2** was obtained as orange red viscous solid. In the next step, intermediate **2** (0.025 mol) was added to N-methylimidazole (0.025 mol) solution which was dissolved in toluene(100 mL) and the mixture was stirred at 80 °C for 20 h. The reaction was determined by HPLC and evaporated under reduced pressure to give intermediate **3** as an orange red oil. In the last step, the intermediate **3** (0.05 mol) and CuCl₂ (0.05 mmol) was mixed with *t*-BuONa(0.01 mol) in dry THF at room temperature under N₂ atmosphere for 12 h. The obtained viscous brown solid was washed with ether and dried in vacuum successively.

General procedure for synthesis of benzimidazoles:

To a 10 mL round-bottom flask *O*-phenylenediamine 1.08g (10 mmol), benzyl alcohol (10 mmol), TEMPO-PEG₄₀₀₀-NHC-Cu(II) complex (0.5 mmol), *t*-BuONa(0.5 mmol), H₂O(1.0 ml) was successively added under a constant vigorous stirring. The reaction

temperature was raised to 75°C and monitored by TLC analysis. Upon completion, the reaction mixture was extracted by adding ether. The organic phase was dried over anhydrous MgSO₄, evaporated under reduced pressure. The residue was purified by column chromatograph on a silica gel using petrel ether/ethyl acetate (10:1) as eluent to afford the pure product in 96% yield; mp 292-294°C. The catalyst left was dried to remove small amount of water by vacuum and fresh substrates were then recharged to react once again. The next run was performed under identical reaction conditions.

Characterization of 2-substituted benzimidazoles

2-phenyl-1H-Benzimidazole (Table 2, entry 1)

Yellow solid; m.p. 292-294°C (lit.¹, 292-293°C); ¹H NMR (500MHz, DMSO-d₆): δ12.89 (s, 1H, N-H), 8.17-8.16(d, 2H, Ar-H), 7.64(s, 1H, Ar-H), 7.55-7.45(m, 4H, Ar-H), 7.18(s, 2H, Ar-H). Elemental analysis % Calcd for C₁₃H₁₀N₂: C 80.38; H 5.19; N 14.43. Found: C 80.32; H 5.21; N 14.47.

2-(4-hydroxyphenyl)-1H-benzimidazole (Table 2, entry 2)

White solid; m.p. 294-295 °C (lit.² m.p. 294-296 °C); ¹H NMR (DMSO-d₆, 500 MHz): δ12.65 (s, 1H, N-H), 9.98(s, 1H, O-H), 7.99-8.02(d, 2H, Ar-H), 7.16-7.14(d, 2H, Ar-H), 7.57-7.53(d, 2H, Ar-H), 6.93-6.91(d, 2H, Ar-H). Elemental analysis % Calcd for C₁₃H₁₀N₂O: C 74.27; H 4.79; N 13.33; O 7.61. Found: C 74.38; H 4.75; N 13.30; O 7.57.

2-(4-Dimethylaminophenyl)-1H-benzimidazole (Table 2, entry 3)

Pale yellow solid; m.p. 293-295°C (lit.³ m.p. 294-296 °C); ¹H NMR (DMSO-d₆, 500 MHz): δ12.54 (s, 1H, N-H), 7.99-7.98(d, 2H, Ar-H), 7.49(s, 2H, Ar-H), 7.10-7.13(m, 2H, Ar-H), 6.83-6.82(d, 2H, Ar-H), 2.99(s, 6H, CH₃-H). Elemental analysis % Calcd for C₁₅H₁₅N₃: C 75.92; H 6.37; N 17.71. Found: C 75.84; H 6.42; N 17.74.

2-(2-chlorophenyl)-1H-benzimidazole (Table 2, entry 4)

White solid; m.p. 231-233 °C (lit.⁵ m.p. 233-234 °C); ¹H NMR (DMSO-d₆, 500 MHz): δ12.69 (s, 1H, N-H), 7.89-7.88(d, 1H, Ar-H), 7.88-7.62(d, 2H, Ar-H), 7.55-7.48(m, 3H, Ar-H), 7.25-7.19(m, 2H, Ar-H). Elemental analysis % Calcd for C₁₃H₉N₂Cl: C 68.28; H 3.97; N 12.25; Cl 15.50. Found: C 68.35; H 3.95; N 12.22; Cl 15.48.

2-(4-chlorophenyl)-1H-benzimidazole (Table 2, entry 5)

White solid; m.p. 293-294 °C (lit.⁶ m.p. 292-294°C); ¹H NMR (DMSO-d₆, 500 MHz): δ12.96 (s, 1H, N-H), 8.18-8.15(d, 2H, Ar-H), 7.65-7.51(m, 4H, Ar-H), 7.21-7.26(m, 2H, Ar-H). Elemental analysis % Calcd for C₁₃H₉N₂Cl: C 68.28; H 3.97; N 12.25; Cl 15.50. Found: C 68.22; H 3.96; N 12.28; Cl 15.54.

2-(2,4-dichlorophenyl)-1H-benzimidazole (Table 2, entry 6)

White solid; m.p. 217-219 °C (lit.⁹ m.p. 218-220 °C); ¹H NMR (DMSO-d₆, 500 MHz): δ12.76 (s, 1H, N-H), 7.92-7.91(d, 1H, Ar-H), 7.83(s, 1H, Ar-H), 7.69-7.54(m,

3H, Ar-H), 7.26-7.19(m, 2H, Ar-H). Elemental analysis % Calcd for $C_{13}H_8N_2Cl_2$: C 59.34; H 3.06; N 10.65; Cl 26.95. Found: C 59.27; H 3.09; N 10.71; Cl 26.93.

2-(4-bromophenyl)-1H-benzimidazole (Table 2, entry 7)

Yellow solid; m.p. 297-298 °C (lit.⁸ m.p. 299-300 °C); 1H NMR (DMSO- d_6 , 500 MHz): δ 12.96 (s, 1H, N-H), 8.10-8.08(d, 2H, Ar-H), 7.75-7.74(d, 2H, Ar-H), 7.65-7.64(d, 1H, Ar-H), 7.52-7.50(d, 1H, Ar-H), 7.21-7.17(m, 2H, Ar-H). Elemental analysis % Calcd for $C_{13}H_9N_2Br$: C 57.17; H 3.32; N 10.26; Br 29.25. Found: C 57.20; H 3.35; N 10.21; Br 29.24.

2-(3-nitrophenyl)-1H-benzimidazole (Table 2, entry 8)

Yellow solid; m.p. 206-210 °C (lit.⁷ m.p. 206-207 °C); 1H NMR (DMSO- d_6 , 500 MHz): δ 13.29 (s, 1H, N-H), 9.00-8.99(s, 1H), 8.60-8.58(d, 1H, Ar-H), 8.32-8.30(d, 1H, Ar-H), 7.85-7.82(t, 1H, Ar-H), 7.68-7.56(d, 2H, Ar-H), 7.24(m, 2H, Ar-H). Elemental analysis % Calcd for $C_{13}H_9N_3O_2$: C 65.26; H 3.79; N 17.57; O 13.38. Found: $C_{13}H_9N_3O_2$: C 65.17; H 3.82; N 17.61; O 13.40.

1H-Benzimidazole (Table 2, entry 9)

White flaky solid; mp 171-172 °C (lit.¹⁰, 171 °C-173 °C); 1H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H, Ar-H), 7.71-7.69(m, 2H, Ar-H), 7.34-7.28(m, 2H, Ar-H). Elemental analysis % Calcd for $C_7H_6N_2$: C 71.16; H 5.12; N 23.72. Found: C 71.12; H 5.13; N 23.75.

Fig 1. 1H NMR of 2-phenyl-1H-Benzimidazole

Fig 2. ¹H NMR of 2-(4-hydroxyphenyl)-1H-benzimidazole

Fig 3. ¹H NMR of 2-(4-Dimethylaminophenyl)-1H-benzimidazole

Fig 4. ¹H NMR of 2-(2-chlorophenyl)-1H-benzimidazole

Fig 5. ¹H NMR of 2-(4-chlorophenyl)-1H-benzimidazole

Fig 6. ¹H NMR of 2-(2,4-dichlorophenyl)-1H-benzimidazole

Fig 7. ¹H NMR of 2-(4-bromophenyl)-1H-benzimidazole

Fig 8. ^1H NMR of 2-(3-nitrophenyl)-1H-benzimidazole

Fig 9. ^1H NMR of 1H-benzimidazole

References

- [1] A. A. Ben, K. Bougrin, M. Soufiaoui. *Tetrahedron Lett.* **2003**, 44, 5935.

- [2] J. C. Lewis. *J. Am. Chem. Soc.* **2008**, 130, 8, 2493
- [3] G. Navarrete, D. H. Moreno, S. S. Estrada, P. M. Torres. *Synth. Commun.* **2007**, 37, 2815.
- [4] H. Sharghi, O. Asemani, R. Khalifeh. *Synth. Commun.* **2008**, 38, 1128.
- [5] C. J. Zhu, Y. Y. Wei. *ChemSusChem*, **2011**, 4, 1082
- [6] S. Hashem. *Eur. J. Org. Chem.* **2008**, 24, 4126
- [7] B. Das, B. S. Kanth, K. R. Reddy, A. S. Kumar. *J. Heterocycl. Chem.* **2008**, 45, 1499.
- [8] L. H. Du, Y. G. Wang. *Synthesis*. **2007**, 675.
- [9] Petrow, V.; Sape, J. *J. Chem. Soc.* **1948**, 282, 1389.