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# Copper-catalyzed synthesis of 1,2-disubstituted benzimidazoles from imidoyl chlorides

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**Abstract**

A strategy for the synthesis of 1,2-disubstituted benzimidazoles has been developed and a variety of 1,2-disubstituted benzimidazoles were obtained from imidoyl chlorides and *o*-haloanilines *via* copper(I)-catalyzed reaction in moderate yields.


*Keywords:* 1,2-Disubstituted benzimidazole; Copper(I)-catalysis; Imidoyl chloride

Due to their versatile biological activities, benzimidazoles attract much attention as important organic compounds to pharmaceutical chemistry [1]. They can be used as anti-inflammatory, antibacterial, and antiviral agents [2]. Thus, development of general methods for the synthesis of benzimidazoles is highly valuable for drug discovery. The traditional preparation of benzimidazoles starts from *o*-aminoaniline, and often involved harsh conditions such as strong acids and high temperature [3]. Recently, the development of copper catalyzed cross-coupling reactions, which allow the efficient formation of C–N bonds under comparatively milder reaction conditions [4], provides a straightforward route to the synthesis of benzimidazoles *via* intramolecular cyclization with wide substrate scope in good yield [5]. As a progress on the construction of heterocyclic compounds in our lab, here we describe a new method for the synthesis of 1,2-disubstituted benzimidazoles *via* copper catalyzed intramolecular cross-coupling reaction.

We envisaged that *o*-bromoaniline **1a** and imidoyl chloride **2a** would undergo a cascade process to afford 1,2-disubstituted benzimidazole **3a**. The first attempt was performed in DMF with CuI (5 mol%) as catalyst, and $Cs_2CO_3$ (3.0 equiv.) as base at 100 °C for 12 h. Encouragingly, the product **3a** was isolated in 22% yield without ligand (Table 1, entry 1). The yield could be improved significantly by the addition of ligands, and among the ligands examined in the reaction, 1,10-phenanthroline gave higher yield than *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) and L-proline (Table 1, entries 2–4). Then different solvents such as 1,4-dioxane, *N*-methyl-2-pyrrolidone (NMP), dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were screened. To our delight, the yield greatly increased to 82% when NMP was employed as solvent (Table 1, entries 5–8). Next, the bases were evaluated in the reaction. Clearly, $Cs_2CO_3$ was superior to $K_3PO_4$, DBU, and DABCO (Table 1, entries 9–12). On the other hand, when CuBr or $Cu_2O$ was used instead of CuI, the reaction proceeded to lower yield (Table 1, entries 13–14).

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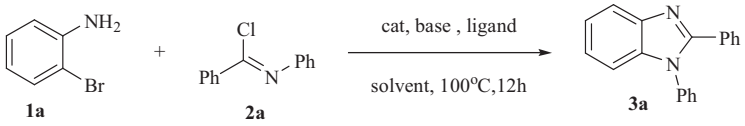
Table 1
Optimization between *o*-bromoaniline **1a** and imidoyl chloride **2a**.

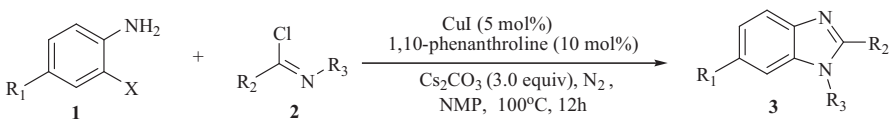



| Entry | Cat. (5 mol%) | Base (2 equiv.) | Ligand (10 mol%) | Solvent | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | CuI | $Cs_2CO_3$ | No ligand | DMF | 22 |
| 2 | CuI | $Cs_2CO_3$ | L-Proline | DMF | 55 |
| 3 | CuI | $Cs_2CO_3$ | TMEDA | DMF | 60 |
| 4 | CuI | $Cs_2CO_3$ | 1,10-Phenanthroline | DMF | 72 |
| 5 | CuI | $Cs_2CO_3$ | 1,10-Phenanthroline | DMA | 64 |
| 6 | CuI | $Cs_2CO_3$ | 1,10-Phenanthroline | DMSO | 40 |
| 7 | CuI | $Cs_2CO_3$ | 1,10-Phenanthroline | Dioxane | 61 |
| 8 | CuI | $Cs_2CO_3$ | 1,10-Phenanthroline | NMP | 82 |
| 9 | CuI | $K_2CO_3$ | 1,10-Phenanthroline | NMP | 48 |
| 10 | CuI | DBU | 1,10-Phenanthroline | NMP | 30 |
| 11 | CuI | $^t$BuONa | 1,10-Phenanthroline | NMP | 59 |
| 12 | CuI | KOH | 1,10-Phenanthroline | NMP | 53 |
| 13 | CuBr | $Cs_2CO_3$ | 1,10-Phenanthroline | NMP | 34 |
| 14 | $Cu_2O$ | $Cs_2CO_3$ | 1,10-Phenanthroline | NMP | 56 |

[a] Isolated yields.

We then investigated the scope of this reaction under the optimized conditions, and the results were shown in Table 2. *o*-Iodoaniline and *o*-chloroaniline were also examined and the reactions could proceed smoothly to give **3a** with 65% and 55% yield (Table 2, entries 2–3). The 2-bromoanilines containing halogen and electron-withdrawing group $NO_2$ provided lower yields than the one containing electron-donating group Me (Table 2, entries 4–7). For imidoyl chlorides with substituted groups on the benzene ring, **2b**–**2d** were employed to the reaction but the corresponding benzimidazoles were obtained with low yields, and most of the imidoyl chlorides converted to imides during the reaction (entries 8–10).

Table 2
Synthesis of 1,2-disubstituted benzimidazoles.




| Entry | $R_1$ | X | $R_2$ | $R_3$ | Product | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | H | Br **1a** | $C_6H_5$ | $C_6H_5$ **2a** | **3a** | 82 |
| 2 | H | I **1b** | $C_6H_5$ | $C_6H_5$ **2a** | **3a** | 65 |
| 3 | H | Cl **1c** | $C_6H_5$ | $C_6H_5$ **2a** | **3a** | 45 |
| 4 | Me | Br **1d** | $C_6H_5$ | $C_6H_5$ **2a** | **3b** | 73 |
| 5 | Cl | Br **1e** | $C_6H_5$ | $C_6H_5$ **2a** | **3c** | 54 |
| 6 | Br | Br **1f** | $C_6H_5$ | $C_6H_5$ **2a** | **3d** | 45 |
| 7 | $NO_2$ | Br **1g** | $C_6H_5$ | $C_6H_5$ **2a** | **3e** | 31 |
| 8 | H | Br **1a** | 4-$MeC_6H_4$ | $C_6H_5$ **2b** | **3f** | 25 |
| 9 | H | Br **1a** | 4-$NO_2C_6H_4$ | $C_6H_5$ **2c** | **3g** | 27 |
| 10 | H | Br **1a** | $C_6H_5$ | 4-$MeC_6H_4$ **2d** | **3h** | 18 |

[a] Isolated yields.

## 1. Experimental

A mixture of thionyl chloride (50 mL) and *N*-phenyl benzamide (25 mmol) was refluxed for 2 h in a 100 mL round bottom flask protected with a calcium chloride guard tube. The reaction mixture was cooled, the condenser was set for downward distillation and the excess thionyl chloride was removed by distillation. The residue was further purified by distillation under reduced pressure to give the pure imidoyl chlorides **1a** in nearly quantitative yield [6].

A schlenk tube was charged with the mixture of *o*-bromoaniline **1a** (0.5 mmol), $Cs_2CO_3$ (1.5 mmol, 0.49 g), CuI (5 mol%, 5 mg), 1,10-phenanthroline (10 mol%, 9 mg) and imidoyl chloride **2a** (0.5 mmol) then stirred in NMP (2 mL) at 100 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature, then $H_2O$ (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL) and dried by anhydrous $Na_2SO_4$. Evaporation of the solvent followed by purification on silica gel (petroleum ether/dichloromethane = 2/1) provided the corresponding product. **3a** [7]: White solid, mp 109 °C (lit. [7b] 110 °C) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.86 (d, 1H, $J$ = 7.8 Hz), 7.55–7.43 (m, 5H), 7.32–7.24 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 152.8, 143.5, 137.6, 137.4, 130.3, 130.0, 129.0, 128.8, 127.7, 123.6, 123.3, 120.2, 116.7, 110.9. **3b** [8]: White solid, mp 93 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.98 (d, 1H, $J$ = 1.1 Hz), 7.61–7.53 (m, 2H), 7.56–7.54 (m, 1H), 7.42 (dd, 1H, $J$ = 8.7, 1.1 Hz), 7.38–7.33 (m, 2H), 7.16 (d, 1H, $J$ = 8.7 Hz), 2.55 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 153.4, 142.0, 138.5, 135.4, 130.3, 129.2, 126.8, 125.1, 124.8, 119.3, 116.2.

In conclusion, we have developed a concise method to synthesize 1,2-disubstituted benzimidazoles using CuI as catalyst and various 1,2-disubstituted benzimidazole were obtained.

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