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# Copper-catalyzed synthesis of 2-aminobenzimidazoles from carbonimidoyl dichlorides and amines

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ABSTRACT

A new protocol for the synthesis of a variety of 2-aminobenzimidazole derivatives has been developed. *O*-haloaryl carbonimidoyl dichloride reacted with anilines to generate an *o*-haloaryl guanidine intermediate, which underwent copper catalyzed ring closure to afford 2-aminobenzimidazole derivative in moderate yields



## Introduction

2-Aminobenzoimidazoles play an important role in biological and pharmaceutical areas for their significant and potential biological activities.[1] 2-Aminobenzoimidazoles' core structure can be widely found in commercial drugs such as Vermox, Fenbendazole, oncodazole, and mizolastine. Chiral 2-aminobenzoimidazoles can serve as efficient organocatalyst in asymmetric chemistry, especially for enantioselective Michael addition.[2] Therefore, 2-aminobenzimidazole has been a target molecule of medicinal chemistry and organic chemistry. The conventional methods for the preparation of 2-aminobenzimidazoles involved the nucleophilic aromatic substitution reaction ($S_NAr$) of 2-halobenzimidazole.[3] Though this transformation was widely used in the construction of 2-aminobenzimidazole motif, there still remained some drawbacks such as harsh reaction conditions and low yields.

Over the past ten years, copper-catalyzed Ullmann type C–N bond formation provided new choices for the assembly of 2-aminobenzimidazoles, such as intramolecular *N*-arylation of *ortho*-halophenyl guanidines (path a),[4] or intermolecular coupling of 1,2-dihalobenzene and guanidines (path b).[5] Anyway, these methods suffered from the multi-step synthesis of the requisite guanidines precursor. Recently, more convenient approach to 2-aminobenzimidazoles was developed by Bao and Xi independently. 2-Haloaryl guanidines' intermediate was generated *in situ* by amination of 2-haloaryl carbodiimides[6] (path c) or addition of 2-haloanilines to carbodiimides[7] (path d, $R_3$ = H), and then underwent condensation cyclization catalyzed by copper to give the products. Herein, as a part of our efforts on copper-catalyzed synthesis of heterocycles, we wish to report a new protocol for the preparation of 2-aminobenzimidazoles from carbonimidoyl dichlorides and amines (Fig. 1).

## Results and discussion

In our previous work, we reported the synthesis of substituted guanidines from carbonimidoyl dihalides and amines.[8] By the combination of this guanylation process and copper-catalyzed cyclization, we envisioned that 2-aminobenzimidazoles could be obtained from *N*-(2-halophenyl) carbonimidoyl dihalides and amines.

*N*-(2-bromophenyl) carbonimidoyl dichloride **1a,** easily prepared from *N*-(2-bromophenyl) formamide **2** by treatment with $SOCl_2$ and $SO_2Cl_2$,[9] was selected as the model substrate to react with aniline **3a** for this copper-catalyzed process. To optimize the reaction conditions, we examined different solvents, bases, and ligands. The results are listed in Table 1. Firstly the reaction was carried out in DMF with CuI (5 mol%), 1,10-phenthroline (10 mol%) as the catalyst, $Cs_2CO_3$ (3.5 equiv) as the base at 100 °C under $N_2$. To our delight, 16 h later, the desired product **4a** was

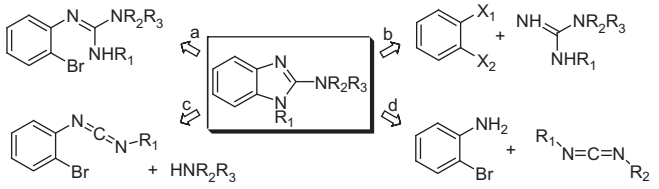


**Figure 1.** Reported copper-catalyzed synthesis of 2-aminobenzimidazoles.

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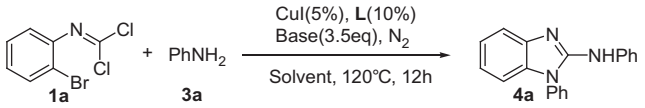
**Table 1**
Optimization of the reaction conditions[a]




| Entry | Base (3.5eq) | Solvent | Catalyst/Ligand[b] | Yield[c] (%) |
|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | DMF | CuI/**L1** | 60 |
| 2 | $Cs_2CO_3$ | Dioxane | CuI/**L1** | 50 |
| 3 | $Cs_2CO_3$ | DMSO | CuI/**L1** | 46 |
| 4 | $Cs_2CO_3$ | DMA | CuI/**L1** | 42 |
| 5 | $Cs_2CO_3$ | toluene | CuI/**L1** | 38 |
| 6 | $Cs_2CO_3$ | NMP | CuI/**L1** | 72 |
| 7 | $K_2CO_3$ | NMP | CuI/**L1** | 10 |
| 8 | *t*-BuONa | NMP | CuI/**L1** | 16 |
| 9 | DBU | NMP | CuI/**L1** | 8 |
| 10 | $K_3PO_4$ | NMP | CuI/**L1** | 27 |
| 11 | KOH | NMP | CuI/**L1** | 19 |
| 12 | $Cs_2CO_3$ | NMP | CuI/— | 0 |
| 13 | $Cs_2CO_3$ | NMP | CuI/**L2** | 41 |
| 14 | $Cs_2CO_3$ | NMP | CuI/**L3** | 53 |
| 15 | $Cs_2CO_3$ | NMP | CuI/**L4** | 67 |
| 16 | $Cs_2CO_3$ | NMP | CuBr/**L1** | 32 |
| 17 | $Cs_2CO_3$ | NMP | $Cu_2O$/**L1** | 59 |

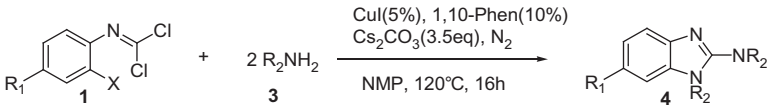
[a] The reactions were performed in a schlenk tube with **1a** (0.5 mmol), aniline (1.25 mmol), base (1.75 mmol), catalyst (5 mol%), and ligand (10 mol%) in solvent (2 mL) for 12 h.
[b] **L1**:1,10-Phenthroline; **L2**: 2-2′dipirydine; **L3**: L-proline; **L4**: TMEDA.
[c] Isolated yield after flash chromatography based on **1a**.

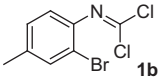
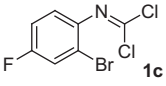
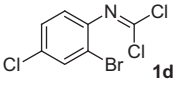
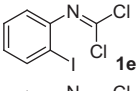
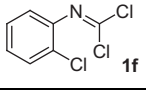
isolated in 60% yield (Table 1, entry 1). Various solvents were screened and NMP (*N*-Methyl- 2-pirrolidone) was found to be the best one (Table 1, entries 2–6). Different bases including *t*-BuONa, DBU, $K_3PO_4$, and KOH were evaluated and $Cs_2CO_3$ remained as the best one (Table 1, entries 7–11). The product cannot be obtained without ligand, and other ligands gave lower yield compared to 1,10-Phenthroline (Table 1, entries 12–15). Some other copper salts were also tested but lead to low yields (Table 1, entries 16–17). On the basis of these results, the entry 6 undoubtedly represents the best conditions.

Under the optimized conditions,[10] we employed a variety of carbonimidoyl dichlorides and substituted amines to examine the scope of the reaction, and the results are summarized in Table 2. Here the reaction time was prolonged to 16 h to purchase higher yields.

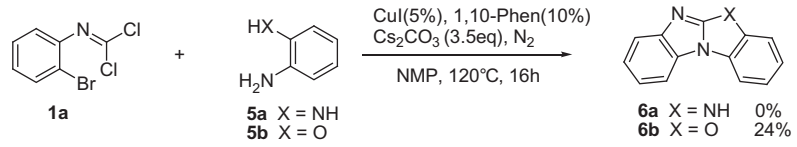
A family of anilines was used to react with **1a**. The position of the substituent group on the benzene ring had an influence on the yields, for different MeO substituted anilines, the yields were *p* > *m* > *o*, indicating the effect of steric hindrance in the reaction (Table 2, entries 2–4). When sterically more hindered 2, 4, 6-trimethylaniline was applied under the optimized condition, no product was obtained (Table 2, entry 5). Generally, the presence of electron-withdrawing group on the phenyl ring of aniline gave lower yields than ones containing electron-donating groups (Table 2, entries 6–9). For anilines with strong electron-withdrawing group on the benzene ring such as $NO_2$, no product could be found and all the 4-nitroaniline was recovered (Table 2, entry 10). To our delight, aliphatic amines such as $BnNH_2$ and n-butyl amine could

**Table 2**
Synthesis of 2-aminobenzimidazoles from carbonimidoyl dichlorides and amines

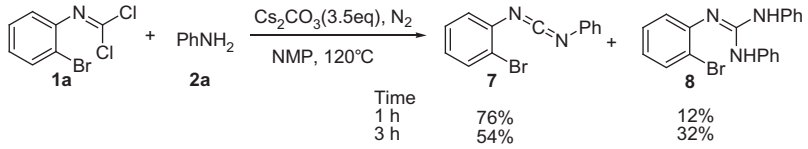



| Entry | Substrate 1 | Substrate 3 | Product | Yield[a] (%) |
|---|---|---|---|---|
| 1 | 1a | $C_6H_5NH_2$ | 4a | 73 |
| 2 | 1a | 2-$MeOC_6H_4NH_2$ | 4b | 42 |
| 3 | 1a | 3-$MeOC_6H_4NH_2$ | 4c | 56 |
| 4 | 1a | 4-$MeOC_6H_4NH_2$ | 4d | 64 |
| 5 | 1a | 2,4,6-$Me_3C_6H_2NH_2$ | 4e | — |
| 6 | 1a | 4-$MeC_6H_4NH_2$ | 4f | 75 |
| 7 | 1a | 4-$FC_6H_4NH_2$ | 4g | 62 |
| 8 | 1a | 4-$ClC_6H_4NH_2$ | 4h | 54 |
| 9 | 1a | 4-$BrC_6H_4NH_2$ | 4i | 38 |
| 10 | 1a | 4-$NO_2C_6H_4NH_2$ | 4j | — |
| 11 | 1a | BnNH2 | 4k | 70 |
| 12 | 1a | n -$BuNH_2$ | 4l | 46 |
| 13 | 1a | i-$PrNH_2$ | 4m | – |
| 14 |  1b | $C_6H_5NH_2$ | 4n | 52 |
| 15 |  1c | $C_6H_5NH_2$ | 4o | 58 |
| 16 |  1d | $C_6H_5NH_2$ | 4p | 49 |
| 17 |  1e | $C_6H_5NH_2$ | 4a | 67 |
| 18 |  1f | $C_6H_5NH_2$ | 4a | 41 |

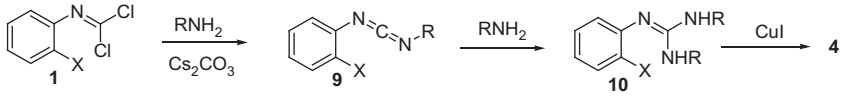
[a] Isolated yield. Reaction conditions unless otherwise stated: CuI (5 mol%, 5 mg), 1, 10-phenanthroline (10 mol%, 9 mg), **1a** (0.5 mmol), $Cs_2CO_3$ (1.5 mmol, 0.49 g), and aniline (1.25 mmol) in NMP (2 mL).




**Scheme 1.** Reaction between **1a** and o-diaminobenzene **5a**/o-hydroxyaniline **5b**.




**Scheme 2.** Reaction between **1a** and aniline in the absence of copper.




**Scheme 3.** Proposed reaction mechanism.

also be successfully applied to the reaction, and the products were obtained in 70% and 40% yields, respectively (Table 2, entries 11–12). In case of isopropyl amine, the reaction lead to complex mixture and no desired product was found (Table 2, entry 13). When substituted *N*-(2-bromophenyl) carbonimidoyl dichloride such as **1b, 1c**, and **1d** were used to react with aniline, the reaction proceeded well and the products were isolated in moderate yields (Table 2, entries 14-16). *N*-(2-iodophenyl) carbonimidoyl dichloride **1e** gave the same product **4a** in lower yield than its bromo analogues possibly for its instability[11] (Table 2, entry 17). As anticipated, *N*-(2-chloroophenyl) carbonimidoyl dichloride **1f** gave only 41% yield for its less reactivity (Table 2, entry 18).

The reaction between **1a** and *o*-diaminobenzene **5a** was also tested, but no desired product bicyclic guanidine was detected. Interestingly, when *o*-hydroxyaniline **5b** was employed to the reaction instead of *o*-diaminobenzene, a fused ring compound **6b** could be obtained in 24% yield[12] (Scheme 1).

To disclose the details of the reaction process, **1a** was heated with 2 equiv aniline in the presence of 3.5 equiv $Cs_2CO_3$ at 120 °C in NMP. 1 h later, TLC showed the consumption of **1a**, then the main product was carefully isolated and identified as 2-bromophenyl carbodiimides **7** (76%), accompanied with a small amount of 2-bromophenylguanidines **8** (12%). If the reaction time was prolonged to 3 h, the yield of 7 decreased to 54% and the yield of **8** increased to 32% (Scheme 2). This result suggested that **8** was not generated directly from **1a** and aniline as expected, while 7 was involved as an intermediate. When **8** was subjected to the standard condition, **4a** was obtained in yield of 89%.

Based on the experimental results, a proposed reaction mechanism is shown in Scheme 3. Reaction of *N*-(2-halophenyl) carbonimidoyl dihalides **1** and amine formed 2-haloaryl carbodiimides **9**, which was attacked by excess amine to create 2-haloaryl guanidine **10**.[13] **10** was the key intermediate which could undergo ring closure to product 4 under copper-catalyzed conditions.[7,14]

## Conclusion

In summary, we have developed a one-pot method for the synthesis of 2-aminobenzimidazoles from carbonimidoyl dichloride and anilines under copper-catalyzed condition. The procedure was easy to handle and various 2-aminobenzimidazoles have been synthesized by such a strategy.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.072.

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10. *Typical experimental procedure for synthesis of 2-amino- benzimidazoles:* Under $N_2$ atmosphere, a schlenk tube was filled with the mixture of **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 aniline (1.25 mmol) then stirred in NMP (2 mL) at 120 °C for 16 h. After completion of the reaction, the mixture was cooled to room temperature, then $H_2O$ (5 mL) was added. 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/EtOAc = 4/1) provided the corresponding product. *N*,1-Diphenyl-1H-2-aminobenzimidazole **4a**: white solid, m.p.164–166 °C, $_1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.65–7.62 (m, 6H), 7.55–7.48 (m, 2H), 7.33–7.31 (m,2H), 7.22–7.19 (m, 1H), 7.10–7.01 (m, 3H), 6.32 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 148.9, 142.3, 139.2, 134.6, 134.4, 130.7, 130.0, 129.3, 127.3, 122.6, 122.3, 121.0, 118.3, 117.6, 108.2.

11. Freshly distilled 1e is a yellow oil but turn to red and brown within 24 hours at room temperature.
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