PRACTICAL APPROACH FOR SYNTHESIS OF 2-AMINO-BENZOXAZOLE IN WATER

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GRAPHICAL ABSTRACT

Abstract A practical copper-catalyzed amination of benzoxazole with secondary amine in water has been developed. This reaction has proved to be effective to some cyclic amines, and the substituted group of nitrogen has a great impact on the amination reaction. A copper-catalyzed/amine-induced ring opening of the benzoxazole and recyclization/oxidation mechanism was also proposed.

Keywords Amination; benzoxazole; copper; oxidation; water

INTRODUCTION

The development of novel methodologies to construct a C-N bond is a very important and lucrative area because the nitrogen-containing compounds are a class of important motifs in biologically active natural products and materials science.\(^\text{[1]}\) To facilitate this transformation, pioneering works that focus on transition-metal-catalyzed C-H amination have been well developed, and copper-catalyzed aerobic oxidation for construction of the C-N bond is the most economical and highly efficient strategy.\(^\text{[2]}\)

For organic reactions, water would be an ideal medium because of its safety and environmentally friendly character. Therefore, the development of organic transformation in water has been attracting many research interests from chemists in academic as well as industrial areas.\(^\text{[3]}\) However, the interaction (hydrogen bonding, polarity etc.) of water with substrates and the moisture-sensitive characteristics of transition-metal catalysts have largely limited the application of water as...
reaction medium for construction of C-X bonds (X=N, O etc.). Therefore, development of a novel method and further expansion of the substrate scope for the construction of a C-X bond in water medium is desired and still a challenge.

The benzoxazole moiety is the key structure feature of a large number of biologically active natural products and pharmaceutical compounds.[4] The functionalization of the 2-position of benzoxazole has attracted much interest from chemists and has been well developed. Among them, the amination of benzoxazole displayed more challenges and still some drawbacks have not been addressed, such as high reaction temperature, stoichiometric or substoichiometric metal reagents, and strong oxidants.[5] In connection with our continued interest in construction of C-C and C-N bonds,[6] we recently found the amination of benzoxazole could proceed in water with relatively mild conditions. Herein, we are pleased to represent our preliminary results.

RESULTS AND DISCUSSION

For our initial research, we choose benzoxazole and morpholine as substrates to screen conditions, and the results are summarized in Table 1. To our delight, the amination could proceed at 60 °C with 10 mmol% of CuBr₂ and 2 equivalents of acetic acid under an O₂ atmosphere, but the desired coupling product was obtained only with 10% yield and along with a large amount of decomposed product.

Table 1. Optimization of reaction conditions for amination of benzoxazole in water

| Entry | Catalyst | Acid/oxidant/temp. (°C) | Yield (%) |
|-------|----------|-------------------------|-----------|
| 1     | CuBr₂    | AcOH/O₂/60              | 10        |
| 2     | CuBr₂    | PhCOOH/O₂/60            | Trace     |
| 3     | Cu(OAc)₂ | AcOH/O₂/60              | Trace     |
| 4     | CuBr₂    | AcOH/I₂/25              | 13        |
| 5     | CuBr₂    | AcOH/Na₂S₂O₈/25         | 30        |
| 6     | CuBr₂    | AcOH/K₂S₂O₈/25          | 35        |
| 7     | CuBr₂    | AcOH/K₂S₂O₈/25          | 45        |
| 8     | CuSO₄·5H₂O | AcOH/K₂S₂O₈/40       | 41        |
| 9     | CuBr₂    | AcOH/K₂S₂O₈/40          | 55        |
| 10    | CuBr₂    | AcOH/K₂S₂O₈/40          | Trace     |
| 11    | CuBr₂    | AcOH/K₂S₂O₈/40          | 45        |
| 12    | CuBr₂    | AcOH/K₂S₂O₈/40          | 75        |

*aReaction condition: benzoxazole (0.5 mmol), morpholine (0.6 mmol), catalyst (0.05 mmol), acid (1 mmol), oxidant (1 mmol except entries 1–3), and 1 mL of water under air atmosphere for 6 h.
*bIsolated yields based on benzoxazole.
*cWith 0.5 mmol K₂S₂O₈.
*dAdded 0.1 mmol PPh₃.
*eAdded 0.1 mmol bipyridine.
*fAdded 0.1 mmol tetrabutylammonium bromide.
*gWith 0.1 mmol of CuBr₂.
4 (entry 1). When benzoic acid was used instead of acetic acid, 4 was afforded as major product and only gave trace amount of the expected amination product (entry 2). With Cu(OAc)$_2$ as catalyst, the result was similar to that of entry 2 (entry 3). Next, we intended to examine the effect of oxidant, and when the reaction was conducted with I$_2$ at 25 °C, the corresponding product was afforded with 13% yield (entry 4). Furthermore, the yields were enhanced to 30% and 35% when the reaction was carried with 2 equivalents of Na$_2$S$_2$O$_8$ and K$_2$S$_2$O$_8$, respectively (entries 5 and 6). The yield was further increased to 45% when K$_2$S$_2$O$_8$ was reduced to 1 equivalent (entry 7). Fortunately, when 20 mmol% of PPh$_3$ was added, the expected product was given in 55% yield (entry 9). Other additive such as bipyridine and tetrabutylammonium bromide could not facilitate the transformation effectively (entries 10 and 11). The yield was further increased to 75% when 20 mmol% of CuBr$_2$ was used (entry 12).

Following the optimized conditions (Table 1, entry 12), we then examined the scope of the reaction, and the results are summarized in Table 2. Surprisingly, when piperidine and pyrrole were subjected to the standard conditions, the desired product was afforded with only 34% and 41% yields, respectively, accompanied with large amount of 4. Furthermore, when N-methylbenzylamine was used, 4 was isolated as the main product, and the corresponding coupling product 3d was only given with 15% yield. However, when diethylamine was used, we did not obtain the desired coupling product, and only 4 can be isolated. We considered that this result might arise from the hydrolysis of the ring-opening product of benzoxazole with diethylamine (see B in Scheme 1). So, we first mixed benzoxazole and diethylamine and stirred them at 40 °C for 1 h, and then H$_2$O, CuBr$_2$, PPh$_3$, AcOH, and K$_2$S$_2$O$_8$ were sequentially added. Stirring continued for 6 h. With this method, the expected product 3e could be isolated with 35% yield. Other amines such as phenylethylamine, diisopropylamine, N-methylaniline, tetrahydroisoquinoline, and piperazine derivatives are not compatible with this transformation, and only 4 was isolated as the sole product.

| Table 2. Copper-catalyzed amination of benzoxazole with secondary amine in water$^{a,b}$ |
|----------------------------------|------------------|
| R$_1$ | R$_2$ |
| 3a (75%) | 3b (34%) |
| 3c (41%) | 3d (15%) |
| 3e (35%) | 3f (72%) |
| 3g (52%) |

$^a$Reaction conditions: benzoxazole (0.5 mmol), amine (0.6 mmol), CuBr$_2$ (0.1 mmol), PPh$_3$ (0.1 mmol), K$_2$S$_2$O$_8$ (0.5 mmol), AcOH (1 mmol), H$_2$O (1 mL), 40 °C.

$^b$Isolated yield.
For benzoxazoles, both 5-methylbenzoxazole and 5-chlorobenzoxazole could facilitate this transformation and gave the desired product with 72% and 52% yields, respectively. This result demonstrated the electronic effect has distinct influence on the reaction efficiency. However, when benzothiazole and benzimidazole were used, this reaction proceeded very sluggishly and could not give the expected products.

Based on the experiment results, the mechanism for the amination is proposed and shown in Scheme 1. First, coordinating copper with nitrogen of benzoxazole forms A. Then, $\sigma$-hydroxyamidine B was formed via the ring opening of benzoxazole by morpholine. Subsequently, acetic acid promoted intramolecular cyclization to give the intermediate C. Meanwhile, if the B is not stable enough, it would hydrolyze to 4; that is to say, the formation of C and 4 is a competed process, and the substituted group of nitrogen has an important influence in this stage. At last, the oxidative dehydrogenation of C gave the product 3a and released the copper to the next cycle.

**EXPERIMENTAL**

**General Procedure for Syntheses of 3a–3d and 3f–3g**

Benzoxazole (60 mg, 0.5 mmol), amine (0.6 mmol), $\text{H}_2\text{O}$ (1 mL), $\text{CuBr}_2$ (22.4 mg, 0.1 mmol), $\text{PPh}_3$ (26.2 mg, 0.1 mmol), $\text{K}_2\text{S}_2\text{O}_8$ (135 mg, 0.5 mmol), and $\text{AcOH}$ (0.057 mL, 1 mmol) were sequentially added to a 10-mL flask under an air atmosphere. After the reaction mixture was stirred at 40 °C until the substrate was consumed completely (about 6 h), the reaction mixture was quenched with $\text{NaHSO}_3$(aqueous) and cooled to room temperature. The product was extracted with $\text{AcOEt}$ (3 × 15 mL), washed with $\text{NaHCO}_3$(aqueous) (3 × 5 mL) and brine.
(3 × 10 mL), and dried over anhydrous sodium sulfate. After evaporation of the solvent under vacuum, the residue was purified by column chromatography.

CONCLUSION

In summary, we have developed a copper-catalyzed amination of benzoxazole with secondary amine as nitrogen source in water for the first time. This method facilitated the amination of benzoxazole with mild and green conditions, and a series of amino-substituted benzoxazole have been synthesized from simple and readily available starting materials. Further studies toward synthetic application are currently ongoing in our group.

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SUPPORTING INFORMATION

Full experimental details, ¹H and ¹³C NMR spectra, and MS data for this article can be accessed on the publisher’s website.

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