COPPER-CATALYZED AEROBIC OXIDATION FOR THE
AMINATION OF BENZOXAZOLE UNDER AIR

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GRAPHICAL ABSTRACT

Abstract A practical copper-catalyzed aerobic oxidation for the amination of benzoxazole with secondary amine has been discovered. This reaction has proved to be effective to a variety of amines with lower catalyst loading amount, and only oxygen in air is required to facilitate this transformation. A copper-catalyzed/amine-induced ring opening of the benzoxazole and recyclization mechanism was also proposed.

Keywords Aerobic oxidation; air; amination; benzoxazole; copper

INTRODUCTION

Amino-substituted benzoxazoles are important scaffolds in a large number of biologically active natural products and pharmaceutical compounds. To construct such motifs, transition-metal-catalyzed direct amination of benzoxazole with amine as nitrogen source represents the most atom-economic and highly efficient approach. Since pioneering work by Mori and Schreiber in 2009, this strategy has attracted interest from chemists and many efforts have been made to realize this transformation. However, there are still some drawbacks for this transformation, for example, the high reaction temperature, stoichiometric or substoichiometric metal reagents, and strong oxidants.

Recently, catalytic aerobic oxidation using oxygen as terminal oxidant has received much attention and has been used in the construction of C-C and C-N
bonds.\textsuperscript{[5]} In connection with our recent interest in constructing C-C and C-N bonds via transition-metal-catalyzed aerobic oxidation process\textsuperscript{[6]} we envisioned direct amination of benzoxazole with secondary amine as nitrogen source with low catalyst loading amount and mild temperature under O\textsubscript{2} or air atmosphere. In addition, Li and coworkers reported a similar strategy for this transformation under O\textsubscript{2} atmosphere.\textsuperscript{[4e]} However, the loading amount of catalyst is still high (20\%). Herein, we are pleased to report a very mild and efficient method to direct amination of benzoxazole with lower catalyst ratio under air atmosphere.

RESULTS AND DISCUSSION

To initiate our research, we choose benzoxazole and morpholine as model substrate to screen conditions and the results are summarized in Table 1. To our delight, with toluene as solvent, the amination can proceed at 70 \textdegree C in the presence of a catalytic amount of CuCl under air, and the desired coupling product was afforded with 15\% yield along with a large amount of side product 4 (Table 1, entry 1). Compound 4 was considered as the key intermediate for the subsequent cyclization to form the coupling product as proved by Chang and coworkers.\textsuperscript{[4d]} Compound 4 was the sole product when FeCl\textsubscript{3} was used (entry 2). Additionally, both CuBr\textsubscript{2} and Cu(OAc)\textsubscript{2} could not facilitate this coupling effectively (entries 3 and 4). When the reaction was carried out in CH\textsubscript{3}CN, the yields were improved obviously and the

\begin{table}[h]
\centering
\caption{Optimization of reaction conditions for direct amination of benzoxazole\textsuperscript{a}}
\begin{tabular}{lll}
\hline
Entry & Catalyst & Solvent/temp (\textdegree C)/time/atmos. & Yield (\%)\textsuperscript{b} \\
\hline
1 & CuCl & Toluene/70/12/air & 15 \\
2 & FeCl\textsubscript{3} & Toluene/70/12/air & — \\
3 & CuBr\textsubscript{2} & Toluene/110/12/air & 12 \\
4 & Cu(OAc)\textsubscript{2} & Toluene/110/12/air & 5 \\
5 & CuBr\textsubscript{2} & CH\textsubscript{3}CN/80/20/air & 37 \\
6 & CuBr\textsubscript{2} & CH\textsubscript{3}CN/80/20/O\textsubscript{2} & 30\textsuperscript{c,d} \\
7 & CuBr\textsubscript{2} & CH\textsubscript{3}CN/80/20/O\textsubscript{2} & 84\textsuperscript{c,e} \\
8 & CuBr\textsubscript{2} & CH\textsubscript{3}CN/50/12/O\textsubscript{2} & 82\textsuperscript{c,e} \\
9 & CuBr\textsubscript{2} & CH\textsubscript{3}CN/50/12/air & 81\textsuperscript{f} \\
10 & CuBr\textsubscript{2} & CH\textsubscript{3}CN/50/12/air & 43\textsuperscript{c,f} \\
11 & CuBr\textsubscript{2} & CH\textsubscript{3}CN/25/12/air & 52\textsuperscript{f} \\
\hline
\end{tabular}
\textsuperscript{a}Reaction condition: benzoxazole (0.5 mmol), morpholine (0.6 mmol), catalyst (0.05 mmol), and 2 mL of solvent under air atmosphere for 12 h.
\textsuperscript{b}Isolated yields based on benzoxazole.
\textsuperscript{c}O\textsubscript{2} balloon.
\textsuperscript{d}Added 1 mmol benzoic acid.
\textsuperscript{e}Added 1 mmol acetic acid.
\textsuperscript{f}With 5\% CuBr\textsubscript{2}.
\end{table}
desired product was obtained with 37% yield with CuBr$_2$ as catalyst (entry 5). When benzoic acid was added, this transformation still proceeded with low efficiency even under an O$_2$ atmosphere (entry 6). In contrast, the acetic acid promoted this coupling effectively and gave the desired product with 84% yield under 1 atm O$_2$ atmosphere (entry 7). The yield was slightly reduced when the reaction carried out at 50°C for 12 h (entry 8). It is worth noting that when the reaction was carried out under air atmosphere, the desired product was also obtained with 81% yield (entry 9). With 5% CuBr$_2$, the product also gave 43% yield (entry 10). The reaction also proceeded even at 25°C and gave the coupling product with 52% yield (entry 11). These results demonstrate the CuBr$_2$ displays much greater catalytic activity for the amination of benzoxazole with secondary amine than that of the reported catalysts. Meanwhile, the O$_2$ in air is sufficient for the subsequent oxidative dehydrogenation process.

Based on these optimized conditions (Table 1, entry 9), the scope of the reaction was then examined and the results are summarized in Table 2. Employing cyclic amines, the reaction proceeded well and gave the corresponding products 3b–3d with moderate to good yields. On the other hand, the acyclic amines such as diethylamine

| Table 2. Copper-catalyzed amination of benzoxazole with secondary amine$^{a,b,c,d,e}$ |
|---------------------------------|
| $\text{N}+\text{HN}$ $\text{R}_1$ $\text{R}_2$ | $\text{CuBr}_2$ 10% $\implies$ R$_3$ $\text{N}^{-}\text{N}$ $\text{R}_1$ $\text{R}_2$ |
| CH$_3$COOH 2eq | CH$_3$CN, 50°C, Air, 12h |
| 3a (81%) | 3b (95%) | 3c (31%)$^e$ |
| 3d (92%) | 3e (65%) | 3f (65%) |
| 3g (37%)$^d$ | 3h (0%)$^e$ | 3i (0%)$^e$ |

$^a$Reaction conditions: benzoxazole (0.5 mmol), amine (0.6 mmol), CuBr$_2$ (0.05 mmol), CH$_3$CN (2 mL), 50°C, air.
$^b$Isolated yield.
$^c$With 2eq amine at 50°C for 30 h.
$^d$With 2eq amine at 70°C for 48 h.
$^e$With DMF as nitrogen source.
and N-methylbenzylamine displayed lower reactivity and the desired products 3e and 3f were formed with moderate yields. It is noteworthy that the diisopropylamine with high steric hindrance also accommodated this catalytic system and the corresponding product 3g was obtained with 37% yield after 30 h at 70°C. In contrast to the reported results, this is the first example for the direct amination of benzoxazole with bulky hindrance amine. However, when primary amine and amide such as phenylethylamine and dimethylformamide (DMF) were used as nitrogen sources, the desired amination did not proceed at all (3h–3i).

Next, the substituted benzoxazole and other heteroarenes were also investigated and the results are summarized in Table 3. When 5-methyl benzoxazole was subject to the standard conditions, the desired product 3j was obtained with 95% yield. However, when other heteroarenes such as benzothiazole, thiazole, and N-methyl benzoimidazole were used, we did not isolate the desired amination products and recovered the substrates.

![Scheme 1. Proposed mechanism for the CuBr₂-catalyzed amination of benzoxazole.](image-url)
Based on the experiment results, the mechanism for the amination is proposed as shown in Scheme 1. First, the copper would coordinate with nitrogen of benzoxazole to form A. Then o-hydroxyamidine B was formed via the ring opening of benzoxazole by morpholine, which was isolated and confirmed by $^1$H NMR. Subsequently, the intermediate C was formed via intramolecular cyclization promoted by acetic acid. At last, the oxidative dehydrogenation of C by O$_2$ in air gave the product 3a and released the copper to the next cycle.

**EXPERIMENTAL**

The materials were used as purchased, and the CH$_3$CN was dried and distilled over P$_2$O$_5$ before use. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. The silica gel (200–300 mesh) is used for column chromatography, and the distillation range of petroleum ether is 60–90 °C. $^1$H and $^{13}$C NMR spectra were recorded on 600-MHz or 400-MHz instruments, and spectral data are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were measured on a spectrometer by direct inlet at 70 eV, and signals were given in m/z with relative intensity (%) in brackets.

**General Procedure for Synthesis of 3a–3j**

CH$_3$CN (2 mL), benzoxazole (60 mg, 0.5 mmol), amine (0.6 mmol), CuBr$_2$ (11.2 mg, 0.05 mmol), and 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 50 °C until the substrate was consumed completely (12 h), the reaction mixture was cooled to room temperature and filtered through a short silica-gel column using AcOEt as eluent. After evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/AcOEt = 4:1). Compounds 3a–3j have been reported in Ref. 4.

**CONCLUSION**

In summary, we have developed a copper-catalyzed amination of benzoxazole with secondary amine as nitrogen source under air atmosphere. This mild condition facilitated the amination of benzoxazole with kinds of secondary amines including bulky hindrance disisopropylamine, and a series of amino-substituted benzoxazole have been synthesized from simple and readily available starting materials. Further studies toward the insight into the reaction mechanism and the synthetic application are currently ongoing in our group.

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SUPPORTING INFORMATION

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

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