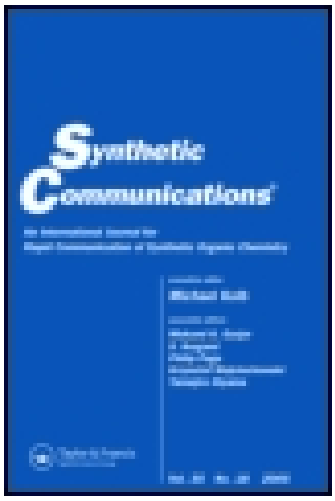

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A Practical Approach for Synthesis of 2-Amino-Benzoxazole in Water

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A practical approach for synthesis of 2-amino-benzoxazole in water

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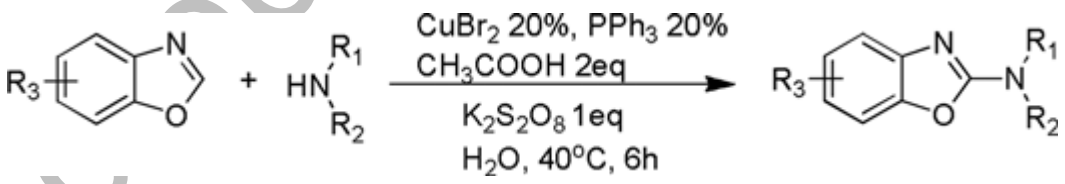
Abstract

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 re-cyclization /oxidation mechanism was also proposed.



KEYWORDS: amination ; benzoxazole; water; oxidation; copper

INTRODUCTION

The development of novel methodologies to construction of C-N bond is a very important and prosperous area due the nitrogen-containing compounds are a class of important motifs in biologically active natural products and materials science.[1] To facilitate this transformation, pioneering works focus on transition metal catalyzed C-H amination have been well developed, especially copper catalyzed aerobic oxidation to construction C-N bond represents the most economic and highly efficient strategy.[2]

For organic reactions, water would be an ideal medium due to 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 industry areas.[3] However, due the interaction (hydrogen bonding, polarity etc.) of water with substrates and the moisture sensitive characteristic of transition metal catalysts, which largely limited the application of water as reaction medium for construction of C-X bonds (X = N, O etc.). Therefore, development of novel method and further expand the substrate scope to construction of 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 2-position of benzoxazole has attracted many interests from chemists and has been well developed. Among them, the amination of benzoxazole displayed more challenge and still exist some drawbacks have not been addressed. Such as high reaction temperature,

stoichiometric or sub-stoichiometric metal reagents and strong oxidants etc..[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 proceeds in water with relatively mild conditions. Herein, we are pleased to represent our preliminary results.

RESULTS AND DISCUSSION

To initial our research, we choose benzoxazole and morpholine as substrate to screen conditions and the results were summarized in Table 1. To our delight, the amination could proceed at 60^{o}C with 10 mmol % of $CuBr_2$ and 2 equivalent of acetic acid under O_2 atmosphere, the desired coupling product was obtained only with 10% yield, and along with a large amount of decomposed product **4** (entry 1). When benzoic acid was used instead of acetic acid, the **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, when the reaction was conducted with I_2 at 25^{o}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 $Na_2S_2O_8$ and $K_2S_2O_8$, respectively (entries 5-6). The yield was further increased to 45% when $K_2S_2O_8$ 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 10-11). The yield was further increased to 75% when 20 mmol % of $CuBr_2$ was used (entry 12).

Following the optimized conditions (Table 1, entry12), we then examined the scope of the reaction, and the results were 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% yield, respectively, accompanied with large amount of **4**. Furthermore, when N-methylbenzylamine was used, the **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 have not obtained the desired coupling product, and only **4** can be isolated. We considered this result might arouse 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 under 40^{o}C for 1h, then H_2O, $CuBr_2$, PPh_3, AcOH and $K_2S_2O_8$ was sequentially added and continue stirred for 6h. With this method, the expected product **3e** could be isolated with 35% yield. Other amines such as phenylethylamine, diisopropylamine, N-methylaniline, tetrahydroisoquinoline, piperazine derivatives etc. are not compatible with this transformation, and only **4** were isolated as the sole product.

For benzoxazoles, both 5-methylbenzoxazole and 5-chlorobenzoxazole could facilitate this transformation and gave the desired product with 72% and 52% yield, respectively.

This result demonstrated the electronic effect has distinct influence on the reaction efficiency. However, when benzothiazole and benzimidazole was used, this reaction proceeded very sluggish, and could not give the expected products.

Based on the experiment results, the mechanism for the amination was also proposed and showed in Scheme 1. First, coordinating of copper with nitrogen of benzoxazole to form **A**. Then, *o*-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, which would hydrolysis to **4**, that is to say, the forming 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 releases the copper to the next cycle.

EXPERIMENTAL

General Procedure For Synthesis Of 3a-3d And 3f-3g

To a 10mL flask were sequentially added benzoxazole (60mg, 0.5mmol), amine (0.6mmol), H_2O (1mL), $CuBr_2$ (22.4mg, 0.1mmol), PPh_3 (26.2mg, 0.1mmol), $K_2S_2O_8$ (135mg, 0.5mmol) and AcOH (0.057mL, 1mmol) under air atmosphere. After the reaction mixture was stirred at 40^{o}C until the substrate was consumed completely (about 6h), the reaction mixture was quenched with $NaHSO_3$(aq.) and cooled to room temperature. Then extracted with AcOEt (3x15mL), washed with $NaHCO_3$ (aq.) (3x5mL), brine (3x10mL) and dried

over anhydrous sodium sulfate. After evaporation of the solvent under vaccum, 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.

SUPPORTING INFORMATION

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

ACKNOWLEDGEMENT

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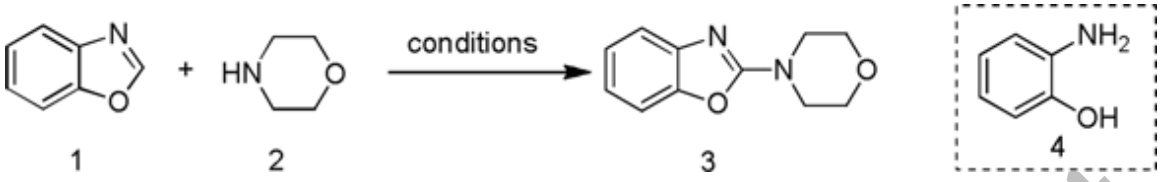
Table 1 Optimization of reaction conditions for amination of benzoxazole in water[a]



1 2 3 4

entry	catalyst	acid/oxidant/temp(^{o}C)	% yield[b]
1	$CuBr_2$	AcOH/O_2/60	10
2	$CuBr_2$	PhCOOH/O_2/60	trace
3	$Cu(OAc)_2$	AcOH/O_2/60	trace
4	$CuBr_2$	AcOH/I_2/25	13
5	$CuBr_2$	AcOH/$Na_2S_2O_8$/25	30
6	$CuBr_2$	AcOH/$K_2S_2O_8$/25	35
7	$CuBr_2$	AcOH/$K_2S_2O_8$/25	45[c]
8	$CuSO_4{\cdot}5H_2O$	AcOH/$K_2S_2O_8$/40	41[c]
9	$CuBr_2$	AcOH/$K_2S_2O_8$/40	55[c,d]
10	$CuBr_2$	AcOH/$K_2S_2O_8$/40	trace[c,e,g]
11	$CuBr_2$	AcOH/$K_2S_2O_8$/40	45[c,f,g]
12	$CuBr_2$	AcOH/$K_2S_2O_8$/40	75[c,d,g]

[a]Reaction 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 6h.

[b]Isolated yields based on benzoxazole.

[c]with 0.5 mmol $K_2S_2O_8$,

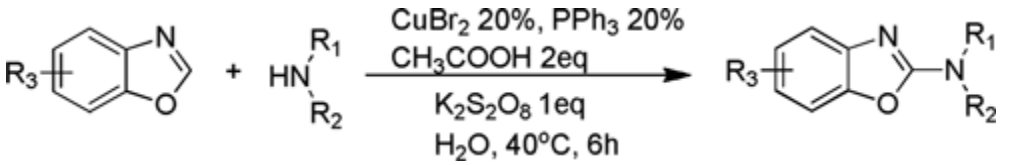
[d]added 0.1mmol PPh_3.

[e] added 0.1mmol bipyridine.

[f] added 0.1mmol tetrabutylammonium bromide.

[g]with 0.1 mmol of $CuBr_2$

Table 2. The copper-catalyzed amination of benzoxazole with secondary amine in water[a,b]



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), $K_2S_2O_8$ (0.5 mmol), AcOH (1 mmol), H_2O (1 mL), 40°C.

[b] Isolated yield.

Scheme 1. Proposed mechanism for the amination of benzoxazole in water