PAPER

Synthesis of benzimidazoles by CuI-catalyzed three-component reaction of 2-haloaniline, ammonia and aldehyde in water†

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An efficient copper-catalyzed three-component reaction of 2-haloaniline, ammonia and aldehyde for the synthesis of benzimidazoles with 1,10-phenanthroline as the ligand has been developed. A variety of substituted benzimidazole derivatives can be obtained in yields up to 95%.
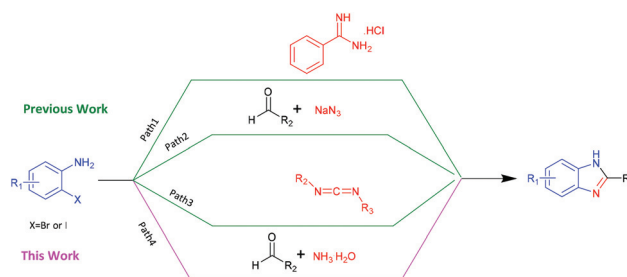
Introduction

Benzimidazole and its derivatives represent an important class of N-containing heterocyclic compounds, which have received considerable attention in recent years due to their potential applications as anticancer, antibacterial, antiulcer, antiviral and antihistamine agents.[1] In addition, they could also be applied in other fields, such as chemosensing, dyes, fluorescence and corrosion science.[2] Owing to the potential biological and other technical interest in benzimidazole compounds, a number of synthesis strategies have been developed.[3]

In general, the common synthesis methods include the reaction between *o*-phenylenediamine and carboxylic acid, nitrile, amidate or orthoester, but harsh dehydrating conditions are usually required.[4] Alternative approaches, such as the transition metal-catalyzed tandem carbonylation-cyclization reaction of *o*-phenylenediamine, the hydroformylation reaction of *N*-alkenyl phenylenediamines, *etc.* have also been developed to prepare functionalized benzimidazoles.[5] For instance, the efficacy of the *N*-arylation of amines was improved drastically by the use of a palladium catalyst.[6] Buchwald and co-workers reported an efficient approach of Cu(OAc)₂-catalyzed synthesis of benzimidazoles through a C–H functionalization/C–N bond forming process in the presence of O₂ from amidines.[7] The previous methods to synthesize benzimidazoles were very efficient, however there are very few general methods that convert commercially available or readily accessible materials in one step into benzimidazoles, and most of these procedures require expensive metal catalysts, specific additives or long reaction times. Therefore, developing new efficient and greener methods for the synthesis of benzimidazoles is an important task.[8]

In recent years, the synthesis of benzimidazoles from 2-iodoaniline and different nitrogen sources as a practical and efficient method has aroused great interest. In 2013, Qu *et al.* reported a method for the synthesis of benzimidazoles using amidine hydrochlorides as the nitrogen source and achieved good yields under mild conditions (Scheme 1 path 1).[9a] Furthermore, Kim and co-workers synthesized a benzimidazole scaffold from sodium azide (Scheme 1 path 2).[9b] In addition, Wang *et al.* developed an interesting protocol for the synthesis of benzimidazoles *via* a cascade reaction of *o*-haloanilines and carbodiimides (Scheme 1 path 3).[9c] However, most of the above reactions require harsh conditions, high temperature, a long reaction time and the use of expensive, air-sensitive, and toxic reagents. As we know, anilines can be prepared easily from iodobenzene by copper-catalyzed coupling reaction.[10a] In 2010, we synthesized *N*-arylamines from

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Scheme 1 Different pathways for the synthesis of benzimidazoles using different nitrogen sources.

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aryl halides with aqueous ammonia in water.[10b] The use of ammonia as a nitrogen nucleophile can make the synthesis of *N*-arylamines simple. But its application in the catalytic synthesis of heterocycles is limited. All of these facts stimulated us to explore the feasibility of using commercially available, nonhazardous, clean ammonia as the reaction partner instead of other nitrogen sources in the reaction to synthesize benzimidazoles (Scheme 1, path 4). In continuation of our efforts on transition-metal-catalyzed reactions in water,[11] herein we introduce a ligand-assisted copper-catalyzed direct synthesis of benzimidazoles by the reaction of 2-haloanilines, ammonia and aldehydes. A series of substrates were used in this catalytic system and afforded the products in good to excellent yields.

Results and discussion

Our initial efforts focused on searching for an efficient catalytic system based on 2-iodoaniline, benzaldehyde, and ammonia as model substrates. As shown in Table 1, first, various copper sources were tested, and the results revealed that CuI was better than other copper salts including CuCl$_2$, Cu(OAc)$_2$, CuSO$_4$ and Cu$_2$O (Table 1, entries 1–5). Among the different ligands examined, **L1** (1,10-phenanthroline) exhibited the highest catalytic activity in 85% yield (Table 1, entries 6–8). Control experiments indicated that the use of a metal and

Table 1 Optimization of reaction conditions[a]

Entry	Cu source	Ligand	Base	T/°C	t/h	Yield[b] (%)
1	CuCl$_2$	**L1**	K$_2$CO$_3$	100	12	64
2	Cu(OAc)$_2$	**L1**	K$_2$CO$_3$	100	12	76
3	CuSO$_4$	**L1**	K$_2$CO$_3$	100	12	50
4	CuI	**L1**	K$_2$CO$_3$	100	12	85
5	Cu$_2$O	**L1**	K$_2$CO$_3$	100	12	43
6	CuI	**L2**	K$_2$CO$_3$	100	12	44
7	CuI	**L3**	K$_2$CO$_3$	100	12	53
8	CuI	**L4**	K$_2$CO$_3$	100	12	40
9	—	**L1**	K$_2$CO$_3$	100	12	10
10	CuI	—	K$_2$CO$_3$	120	12	17
11	CuI	**L1**	NaOH	100	12	69
12	CuI	**L1**	K$_3$PO$_4$	100	12	38
13	CuI	**L1**	KOH	100	12	72
14	CuI	**L1**	Na$_2$CO$_3$	100	12	90
15	CuI	**L1**	Cs$_2$CO$_3$	100	12	84
16	CuI	**L1**	Na$_2$CO$_3$	90	12	60
17	CuI	**L1**	Na$_2$CO$_3$	100	8	80
18	**CuI**	**L1**	**Na$_2$CO$_3$**	**100**	**10**	**90**

[a] Reaction conditions: The reactions were carried out using 2-iodoaniline (0.5 mmol), benzaldehyde (0.6 mmol), 25%–28% aqueous ammonia (1 mL), Cu source (10 mol%), ligand (10 mol%), and base (1.0 mmol) in water (1 mL). [b] Determined by GC with 1,4-dichlorobenzene as the internal standard.
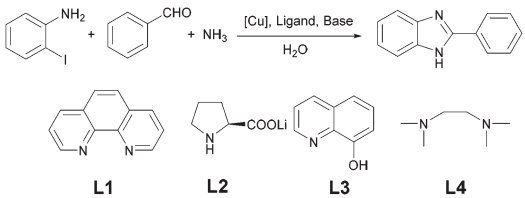
ligand was essential, only 10% or 17% of product were obtained in the absence of a ligand or catalyst (Table 1, entries 9 and 10). Of the bases tested, Na$_2$CO$_3$ gave the best results. The product was formed in a lower yield with K$_2$CO$_3$, NaOH, K$_3$PO$_4$, KOH, and Cs$_2$CO$_3$ (Table 1, entries 11–15). The effects of reaction time and temperature were also studied; 100 °C and 10 h were the optimal reaction conditions (Table 1, entries 11–20). Therefore, the optimal catalytic system involved the use of CuI (10 mol%), **L1** (10 mol%), 25%–28% aqueous ammonia (1 mL) and Na$_2$CO$_3$ (2 equiv.) in 1 mL water at 100 °C for 10 h.

Having optimized the reaction conditions, we examined a series of 2-haloanilides to establish the scope and limits of this process. As summarized in Table 2, by using the present method, all the examined substrates provided the corresponding benzimidazoles in good to excellent yields. In general, 2-iodoanilides were more reactive than 2-bromoanilides and gave the corresponding products in higher yields. It is noteworthy that the reaction is absolutely clean producing solely 2-substituted benzimidazoles and no other side products were detected. These studies clearly reveal that the substrates having electron-donating and electron-withdrawing groups are compatible with this process to afford the substituted benzimidazoles in high yield. The substrates with electron-donating *o*-haloanilines seemed to be more suitable for the catalysis (Table 2, entries 2 and 6). Then, we examined the general applicability of this methodology by using a variety of aldehydes. It is noteworthy that aldehydes bearing electron-donating groups were found to give better results than those with electron withdrawing groups (Table 2, entries 10–19). The reason may be that strong electron-donating groups (OCH$_3$) enhance the reaction rate (Table 2, entry 11). Several functional groups, such as fluoro, chloro, bromo, nitro, cyanide, methyl, methoxy, and hydroxyl groups, are well-tolerated under these reaction conditions. These functional groups would allow additional transformations to give more complex benzothiazoles (Table 2, entries 14 and 20). Both 3-substituted and 3,4-disubstituted aldehydes could be elaborated from the corresponding 2-haloanilides. Moreover, heterocyclic aldehydes and aliphatic aldehydes were also investigated and found to form the desired products in high yields (Table 2, entries 21–24).

Finally, mebendazole, which is a potential antihelminthic agent, could also be prepared by this method starting from (3-amino-4-bromophenyl)(phenyl)methanone and formamide in a good yield of 83% (Scheme 2). It was formerly obtained by a more complicated multiple step procedure.
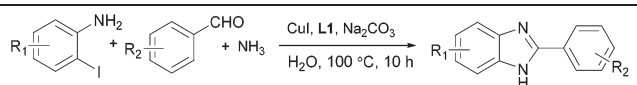
To explore the catalytic mechanism, the following experiments were performed as shown in Scheme 3, the aldehyde reacted well with ammonia to provide an imide in 85% yield using a Cu source and ligand. Only 34% yield of *o*-phenylenediamine and 12% yield of *N*-phenylmethanimine were observed under the catalyzed conditions. Furthermore, when 2-iodoaniline and benzaldehyde were directly subjected under the reaction conditions, the imine was obtained in moderate yield. This experiment proved that the three-component reaction proceeds mainly through imine (**I**), and not through com-

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Table 2 Synthesis of benzimidazoles from 2-haloanilines, aldehydes and aqueous ammonia[a]

Entry	2-Haloanilide	Aldehyde	Product	Yield[b] (%)
1				90 (X = I) / 82 (X = Br)
2				94 (X = I) / 85 (X = Br)
3				95 (X = I) / 84 (X = Br)
4				88 (X = I) / 76 (X = Br)
5				87 (X = I) / 75 (X = Br)
6				86 (X = I) / 76 (X = Br)
7				84 (X = I) / 71 (X = Br)
8				81 (X = I) / 63 (X = Br)
9				78 (X = I) / 63 (X = Br)
10				88 (X = I) / 73 (X = Br)
11				94 (X = I) / 81 (X = Br)
12				80 (X = I) / 66 (X = Br)
13				83 (X = I) / 82 (X = Br)
14				89 (X = I) / 85 (X = Br)
15				86 (X = I) / 73 (X = Br)
16				83 (X = I) / 79 (X = Br)
17				78 (X = I) / 63 (X = Br)
18				81 (X = I) / 78 (X = Br)
19				82 (X = I) / 76 (X = Br)
20				86 (X = I) / 78 (X = Br)
21				85 (X = I) / 79 (X = Br)

Table 2 (Contd.)

Entry	2-Haloanilide	Aldehyde	Product	Yield[b] (%)
22				88 (X = I) / 80 (X = Br)
23		HCHO		88 (X = I) / 75 (X = Br)
24				86 (X = I) / 78 (X = Br)

[a] Reaction conditions: 2-Haloanilide (0.5 mmol), aldehyde (0.6 mmol), 25%–28% aqueous ammonia (1 mL), CuI (10 mol%), **L1** (10 mol%), Na_2CO_3 (1 mmol), H_2O (1 mL), 100 °C, 10 h. [b] Isolated yield.
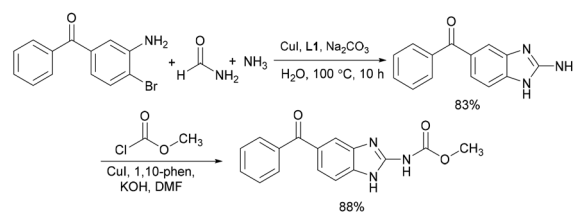
Scheme 2 Synthesis of mebendazole.
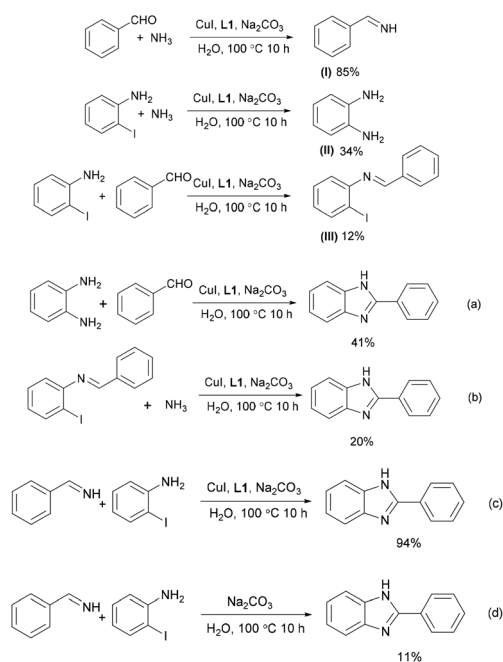
Scheme 3 Reaction of intermediates.

pounds (**II**) and (**III**). Moreover, the reaction cannot proceed well in the absence of a catalyst (Schemes 3c and d). Thus, the copper catalyst promotes the tandem reaction of 2-iodoaniline with ammonia and an aldehyde.

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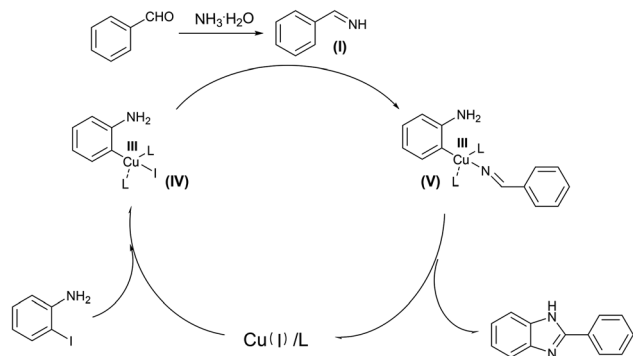
Scheme 4 Proposed reaction mechanism.

According to the above observations, the possible routes might exist as shown in Scheme 4 based on the previous reports in the literature.[12] Firstly, ammonia is reacted with the aldehyde to form an *N*-substituted imine, and the following step is copper catalyzed with 2-iodoaniline to form the metallic intermediates (**IV**). Then, the copper-catalyzed reaction of *N*-substituted imine (**I**) with intermediates (**IV**) affords intermediates (**V**), and the subsequent intramolecular nucleophilic cyclization affords the final product.

Conclusions

In summary, we have developed an efficient and promising three-component reaction of 2-haloaniline including aryl iodides and bromides, various aldehydes, and ammonia to form benzimidazoles in a simple one-pot procedure. In this copper catalytic system, a new reaction mechanism was developed, and neat water was used as the solvent. The tolerance of diverse functional groups makes the present system attractive. To the best of our knowledge, this is the first example of using ammonia as the nitrogen source in the synthesis of substituted benzimidazoles in water. Considering the inexpensive catalytic system and the readily available starting materials, this strategy would thus be highly useful in the synthesis of biologically important compounds containing a benzimidazole framework.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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