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Synthesis of benzimidazoles by copper-catalyzed aerobic oxidative domino reaction of 1,2-diaminoarenes and arylmethyl halides

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Arylmethyl halides are readily synthesized via halogenation from the basic raw materials, even in green processes. They are used to replace their downstream products to prepare medicinally important 2-aryl benzimidazoles. CuBr-catalyzed synthesis of 2-aryl benzimidazoles from arylmethyl halides and 1,2-diaminoarenes via a one-pot domino reaction is developed. This new synthetic method is simple, practical and cost saving, and tolerates wide functional groups. A mechanism of CuBr-catalyzed aerobic oxidative domino reaction via a one-pot four-step process is proposed. Copyright © 2013 John Wiley & Sons, Ltd.

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Keywords: benzimidazoles; arylmethyl halides; 1,2-diaminoarenes; domino reaction; copper

Introduction

Benzimidazoles, an important class of nitrogen-containing heterocycles, widely occur in natural products,[1–4] and have extensively demonstrated important bioactivities and medical value.[5] Thus substantial efforts have been made in searching for new synthetic strategies to assemble this structure.

They are commonly synthesized via reactions of benzoic acids, acid anhydrides, esters and acid chlorides.[6–8] Benzimidazoles can also be prepared by the coupling of aldehydes with *o*-diaminoarene under oxidative conditions[9–12] or with 2-nitroanilines under reductive conditions.[13,14]

Ma and Buchwald developed copper- and palladium-catalyzed domino arylamination/condensation methods with *o*-haloacetanilides and amines as reagents, respectively.[15,16] Later, Buchwald further reported copper-catalyzed synthesis of benzimidazoles from *N*-arylbenzamidines.[17]

Punniyamurthy developed copper-catalyzed synthesis of substituted benzimidazoles via the intramolecular cyclization of *o*-haloarylamidines.[18] Recently Zhou reported Cu_2O-catalyzed domino reactions of *o*-haloaniline and amidine for synthesis of benzimidazoles.[19]

With *N*-benzylbenzene-1,2-diamines as substrate, Cho reported a ruthenium-catalyzed synthesis of benzimidazoles via alkyl group transfer.[20] While Fan reported an example of CuCl-catalyzed oxidative cyclization of N^1-benzyl-N^2-arylbenzene-1,2-diamine with 2 equiv. *t*-butyl hydroperoxide as oxidant afforded 1-aryl-2-phenylbenzimidazole.[21]

Using basic organic raw materials instead of their downstream products to synthesize 2-substituted benzimidazoles will shorten synthetic routes, and lower environmental damage, and also save production costs, which is valuable for industrial production and meaningful for academic research. As we know, arylmethyl halides are readily prepared via halogenation from the basic organic raw materials methylarenes,[22,23] even in green processes,[24,25] and thus a number of this type of chemical are readily available and inexpensive. While arylmethanols are commonly synthesized from arylmethyl halides, oxidation of arylmethanols is a classic production method of benzaldehydes. Oxidation of benzaldehydes to synthesize benzoic acids, especially for multi-substituted ones, is a general approach. Benzoic acid derivatives, such as acid anhydrides, esters, acid chlorides and benzamidines, are further prepared from these compounds.

N-Monobenzylation of 1,2-diaminoarenes with arylmethyl halides facilely affords *N*-benzyl-1,2-diaminoarenes.[26] We noted that CuCl-catalyzed oxidative cyclization of N^1-benzyl-N^2-arylbenzene-1,2-diamine with 2 equiv. *t*-butyl hydroperoxide as oxidant gave 1-aryl-2-phenylbenzimidazole,[21] and copper salts are good oxidation catalysts with air as the oxidant,[27,28] so we envisioned that in the presence of copper salt and under air and basic conditions 1,2-diaminoarenes and arylmethyl halides may be transformed firstly into *N*-benzyl-1,2-diaminoarenes, and then into 2-arylbenzimidazoles (Scheme 1). Our primary research supported our idea.

Recently Rangappa reported one-pot synthesis of benzimidazoles from gem-dibromomethylarenes using *o*-diaminoarenes,[29] but the superiority of our method is obvious. Rangappa's oxidation system needs anhydrous, toxic pyridine/DMF as mixture solvents, potassium *t*-butoxide as a strong base, and iodine and benzoyl peroxide as two oxidants. Compared with arylmethyl bromide, gem-dibromomethylarenes consume double the amount of bromine and double the amount of waste bromide salt. We used 5 mol% CuBr and a weak base, $NaHCO_3$, with air as only oxidant, and the greener solvent DMSO could be recycled.

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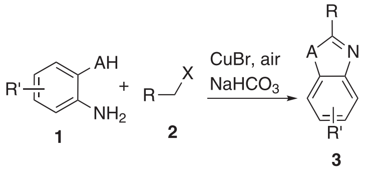


R = aryl, cinnamyl
R' = H, alkyl, aryl, halo, alkoxy, EtOCO-, CF_3
A = NH, S

Scheme 1. Copper-catalyzed domino synthesis of 2-arylbenzimidazoles from 1,2-diaminoarenes and arylmethyl halides.

Jiao developed a catalyst-free approach to synthesize 2-(aliphatic alkyl)benzimidazoles from 1,2-aminoarenes and aliphatic aldehydes using air as the oxidant at room temperature.[30] Unfortunately 2-arylbenzimidazoles cannot be obtained by this protocol. Interestingly, our method is mutually complementary to Jiao's approach.

As our ongoing research into transition metal-catalyzed reactions,[31–33] we report a new, efficient, simple synthetic method of copper-catalyzed domino synthesis of 2-aryl-benzimidazoles from arylmethyl halides, cinnamyl bromide, 1,2-diaminobenzenes and 2-aminothiophenol (Scheme 1).

Experimental

General

The purity of all the synthesized compounds was checked by thin-layer chromatography using various non-aqueous solvents. Melting points were measured on an Electrothermal digital melting point apparatus without corrections. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Advance 300 MHz NMR spectrometer in DMSO-d6 with tetramethylsilane as an internal standard. The chemicals were purchased from Aldrich, Alfa Aesar, Aladdin or Kelong chemical companies and used without further purification.

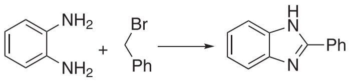
General Procedure

An oven-dried test tube with a stir bar was charged with CuBr (0.05 mmol), $NaHCO_3$ (1.2 mmol), arylmethyl halide (1.0 mmol), 1,2-phenylenediamines and DMSO (4 ml). The tube was placed in an oil bath pot pre-heated at 120 °C and kept stirred at that temperature for 24 h. The reaction mixture was then cooled to room temperature, quenched with water and extracted with ethyl acetate (20 ml) three times. The organic layers were combined, washed with water to remove DMSO, dried over anhydrous sodium sulfate and filtrated. The filtrate was condensed under reduced pressure. The residue was purified with silica gel column chromatography with a solution of petroleum ether and ethyl acetate (10/1 to 3/1 (v/v)) to afford 2-substituted benzimidazoles. All of the products are known and characterized by melting points, IR, ^{1}H NMR and ^{13}C NMR (see supporting information for their copies).

Results and Discussion

To begin, 1,2-diaminobenzene and benzyl bromide were used as model substrates to synthesize 2-phenylbenzimidazole under air and basic conditions (Table 1).

Table 1. Optimization of reaction conditions[a]



1a 2a 3a

Entry	Catalyst	Base	Solvent	Yield (%)
1	CuO	K_2CO_3	DMA	47
2	CuBr	K_2CO_3	DMA	60
3	CuI	K_2CO_3	DMA	56
4	Cu	K_2CO_3	DMA	57
5	N/A	K_2CO_3	DMA	Trace[b]
6	CuBr	K_2CO_3	DMA	Trace[c]
7	CuBr	K_2CO_3	DMF	65
8	CuBr	K_2CO_3	DMSO	65
9	CuBr	$KHCO_3$	DMSO	69
10	CuBr	$NaHCO_3$	DMSO	78
11	CuBr	$NaHCO_3$	DMSO	83[d]
12	CuBr	$NaHCO_3$	DMSO	75[e]

[a] Reaction conditions: *o*-phenylenediamine (3 mmol), benzyl bromide (1 mmol), catalyst (5% mmol), base (2 mmol), solvent (4 ml), under air, 120 °C,24 h, unless otherwise mentioned.

[b] The yield of *N*-benzyl *o*-phenylenediamine is 68%; N/A, not available.

[c] Under argon; the yield of *N*-benzyl *o*-phenylenediamine was 76%.

[d] $NaHCO_3$ (1.2 mmol) was used.

[e] $NaHCO_3$ (1.2 mmol) and *o*-phenylenediamine (1.5 mmol) were used.

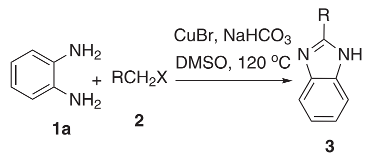
Considering cheap and less toxic copper salts with air as oxidants having good oxidation catalysis,[34,35] and our former study on CuO-catalyzed synthesis of 4(3*H*)-quinazolinones under air,[11] CuO was first chosen as catalyst to explore this new protocol. Fortunately, CuO afforded the desired 2-pheylbenzimidazole with 47% yield (Table 1, entry 1). When CuBr and CuI were used as catalysts for this transformation, the yields increased obviously (entries 2 and 3). Even metallic copper could promote this reaction and gave a similar yield to that of CuBr (entry 4); metallic copper was dissolved during the reaction and perhaps turned into CuBr *in situ*. Without metallic copper and copper salt, however, or operated under argon, the starting materials 1, 2-diaminobenzene and benzyl bromide gave no desired 2-phenylbenzimidazole product but the *N*-benzylated product *N*-benzyl *o*-phenylenediamine (entries 5 and 6).

Screening of solvents demonstrated that DMF and DMSO gave the same yield of 65% (entries 7 and 8), which is better than DMA. Because DMSO is a greener solvent than DMF,[36] DMSO was used for the subsequent reactions.

Interestingly, weaker bases $KHCO_3$ and $NaHCO_3$ dramatically increased the yields up to 78% (entries 9 and 10). To our delight, a decrease in the amount of $NaHCO_3$ to 1.2 equiv. increased the yield to 83% (entry 11). But a decrease in the amount of *o*-phenylenediamine to 1.5 equiv. resulted in a lower yield (entry 12 vs. entry 11), probably because excess *o*-phenylenediamine (3 equiv.) efficiently inhibited dialkylation.

With the optimized conditions in hand, various arylmethyl halides as well as cinnamyl bromide were examined to react with *o*-phenylenediamine for the synthesis of 2-arylbenzimidazoles (Table 2). Besides 2,6-difluorobenzyl bromide and cinnamyl

Table 2. Reactions of arylmethyl halides and *o*-phenylenediamine[a]

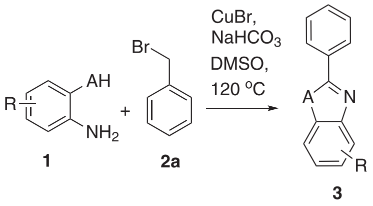


Entry	R	X	Product	Yield (%)	Ref.
1	Ph	Br	**3a**	83	[38]
2	2-CH_3Ph	Br	**3b**	85	[39]
3	3-CH_3Ph	Br	**3c**	80	[39]
4	4-CH_3Ph	Br	**3d**	74	[40]
5	4-CH_3OPh	Br	**3e**	86	[39]
6	4-CF_3Ph	Br	**3f**	70	[41]
7	3-FPh	Br	**3g**	76	[42]
8	2-FPh	Br	**3h**	76	[43]
9	2,6-F_2Ph	Br	**3i**	53	[44]
10	3,4-Cl_2Ph	Br	**3j**	70	[45]
11	4-NO_2Ph	Br	**3k**	71	[45]
12	4-EtOCOPh	Br	**3l**	74	[46]
13	3-CNPh	Br	**3m**	82	[47]
14	3-CF_3Ph	Cl	**3n**	83	[48]
15	4-ClPh	Cl	**3o**	76	[48]
16	PhCH=CH	Br	**3p**	46	[49]

[a]Reaction conditions: arylmethyl halide (1 mmol), *o*-phenylenediamine (3 mmol), $NaHCO_3$ (1.2 mmol), DMSO (4 ml), 24 h under air.

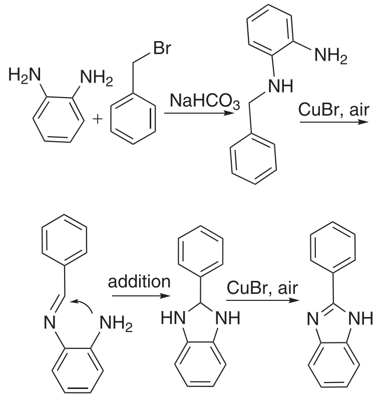
bromide, various arylmethyl halides afforded the desired products with good yields (Table 2, entries 1–15). Substituted benzyl bromides both with electron-donating groups and with electron-withdrawing groups were suitable for this reaction (entries 2–15). Also, a wide range of functional groups including fluoro, chloro, trifluoromethyl, nitro, ester, cyano and alkenyl were tolerated in this reaction (Table 2, entries 5–16).

Table 3. Reactions of 1,2-diaminoarenes and benzyl bromide[a]



Entry	R	A	Product	Yield (%)	Ref.
1	H	NH	**3a**	83	[38]
2	4,5-$(CH_3)_2$	NH	**3q**	82	[39]
3	4-CH_3O	NH	**3r**	87	[39]
4	4-NO_2	NH	**3s**	88	[50]
5	4-CF_3	NH	**3t**	90	[51]
6	4-Cl	NH	**3u**	88	[39]
7	H	S	**3w**	87	[40]

[a]Reaction conditions: 1 mmol arylmethyl halide, 3 mmol substituted *o*-phenylenediamine, 1.2 mmol $NaHCO_3$, 4 ml DMSO, 24 h under air.



Scheme 2. A plausible mechanism for the domino reaction.

Commonly, steric hindrance at the *ortho* position to the reaction site on an aromatic ring will decrease the yield.[33] Contrary to the general rule, 2-methylbenzyl bromide afforded a slightly better yield than that of 3-methyl- and 4-methylbenzyl bromide (entries 2–4). The reason perhaps is the lower steric effect of the 2-aryl group during the formation of 2-arylbenzimidazoles. Fazlinia and co-workers found a similar effect in the synthesis of benzimidazoles.[37] It seems that this rule is also suitable for substrates with electron-withdrawing groups. 4-Trifluoromethylbenzyl bromide afforded a lower yield than that of 3-trifluoromethylbenzyl chloride (entry 6 vs. entry 14); and *m*- and 2-fluorobenzyl bromides had the same yield of 76% (entry 7 vs. entry 8).

It seems that halo types of arylmethyl halides with electron-withdrawing groups did not obviously influence the yields (Table 2, entries 14–15 vs. entries 6–13). Cinnamyl bromide also gave the desired product but with moderate yield (entry 16).

Next we investigated various 1,2-diaminoarenes to react with benzyl bromide to synthesize substituted 2-phenylbenzimidazoles (Table 3). To our delight, all of the 1,2-diaminoarenes afforded good to excellent yields (Table 3, entries 1–6). It seems that electron-withdrawing substitutes on the 1,2-diaminoarenes benefit from this domino cyclization (entries 2 and 3 vs. entries 4–6). Also, the functional groups including methoxy, halo, nitro and trifluoromethyl were tolerated under the reaction conditions (entries 3–6).

In order to expand the substrate, 2-aminothiophenol, with a similar structure to 1,2-diaminobenzene, was also investigated. 2-Aminothiophenol gave 2-phenylbenzthiazole with a better yield than that of 1,2-diaminobenzene (entry 7 vs. entry 1).

To explain the reaction, we propose a mechanism of a four-step domino reaction, namely weak base-promoted S_N2 substitution of benzyl halides, CuBr-catalyzed aerobic oxidation of *N*-benzyl 1,2-diaminobenzenes into *N*-benzylidene 1,2-diaminobenzenes, intramolecular addition, and CuBr-catalyzed aerobic oxidation of 2-aryl-2,3-dihydrobenzimidazoles into 2-arylbenzimidazoles. A plausible mechanism is depicted in Scheme 2.

Conclusion

CuBr-catalyzed synthesis of 2-aryl benzimidazoles, a class of heterocycles with extensive pharmacological effects, from arylmethyl halides and 1,2-diaminobenzenes via a one-pot domino reaction, is developed. All arylmethyl bromides and 1,2-diaminoarenes afforded good to excellent yields. This process is highly efficient, cost saving and simple. A mechanism of copper-catalyzed synthesis of 2-arylbenzimidazoles via a four-step domino reaction containing S_N2 substitution, aerobic oxidation, addition and aerobic oxidation was proposed.

Acknowledgments

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