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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

An efficient and facile synthesis of benzimidazo[1,2-*a*]benzimidazoles via copper-catalyzed domino addition/double cyclization

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A copper-catalyzed synthesis of benzimidazo[1,2-*a*]benzimidazoles by domino addition/double cyclization of bis-(*o*-haloaryl)carbodiimides with primary amines was developed. A variety of the desired polycyclic benzimidazoles were efficiently and facilely assembled. Multibonds and polycyclic moieties were directly constructed in one pot. 2-Bromo-2'-iodo-diarylcarbodiimides gave good selectivity.

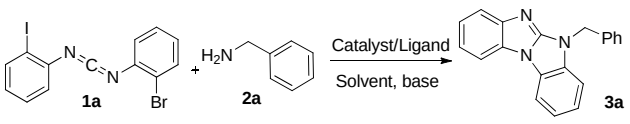
The benzimidazole skeleton is found in many biologically active natural products and pharmaceuticals.[1] Polycyclic benzimidzole derivatives are of significance in medicinal chemistry[2] and material science.[3] As a subclass of imidazobenzimidazoles,[2b, 4] benzimidazo[1,2-*a*]benzimidazoles may exhibit interesting pharmaceutical and biological activities. These polycyclic molecules have also attracted great interest in the field of electroluminescent devices.[5]

The common approaches to imidazobenzimidazoles usually suffer from the drawbacks such as the use of special reagents, tedious procedures, low efficiency, and/or the narrow application scopes.[2a-b, 5a, 6] Recently, Fu *et al.* found that the Cu-catalyzed oxidative intramolecular C-H amination lead to imidazobenzimidazoles.[7] The method was efficient and economical. However, substituted 2-(1*H*-imidazol-1-yl)-*N*–alkylbenzenamines should be prepared beforehand and high reaction temperature (155 °C) was required.

Catalytic domino transformation is an efficient and convenient strategy for the one-step assembly of molecular complexity and diversity from readily available starting materials.[8] Copper-catalyzed domino synthesis have received considerable attention because of their low cost, high efficiency and convenience.[9] To the best of our knowledge, there is no report about the copper-catalyzed one-pot multi-bond forming assembly of benzimidazo[1,2-*a*]benzimidazoles. In continuation of our efforts to synthesize heterocycles using domino methods,[10] we investigated the Cu-catalyzed domino approaches to benzimidazo[1,2-*a*]benzimidazoles from bis-(*o*-haloaryl)carbodiimides[11, 12] and primary amines.

Initially, 2-bromo-*N*-(((2-iodophenyl)imino)methylene)aniline **1a** and benzylamine **2a** were chosen as the model substrates. In a typical experiment, substrate **1a** (0.5 mmol, 1 equiv) was treated with **2a** (0.55 mmol, 1.1 equiv) in the presence of CuI (10 mol%), 1,10-phen (monohydrate, 20 mol%), and K_3PO_4 (2 mmol, 4 equiv) in dioxane at 100 ºC for 12 h. Encouragingly, the desired double-cyclized product **3a** was isolated in a good yield (Table 1, entry 1). Other copper catalysts such as CuBr, CuCl and Cu_2O were then screened, and the best result was obtained when CuCl was utilized as the catalyst (Table 1, entries 2-4). Trace amount of the product was observed in the absence of copper catalyst (Table 1, entry 5), showing that the catalyst was indispensable for this reaction. The effect of base was investigated (Table 1, entries 3 and 6-8), and K_3PO_4 turned out to be the optimal base (Table 1, entry 6). Different solvents were also examined for this domino transformation (Table 1, entries 6 and 9-11). Dioxane, DMF and toluene were found to be suitable solvents (Table 1, entries 6, 9 and 10), whereas dioxane showed to be superior to others (Table 1, entry 6). Among the ligands tested for the reaction, 1,10-phen exhibited the highest activity (Table 1, compare entry 6 with entries 12-14). Notably, 75% yield of the desired product was obtained in a control experiment without the addition of ligand (Table 1, entry 15), indicating that the addition intermediate itself might act as a ligand.

Table 1. Optimization of the reaction conditions[a]



Entry	Catalyst	Base	Solvent	Ligand	Yield[b]
1	CuI	Cs_2CO_3	dioxane	1,10-phen·H_2O	87%
2	CuBr	Cs_2CO_3	dioxane	1,10-phen·H_2O	70%
3	CuCl	Cs_2CO_3	dioxane	1,10-phen·H_2O	90%
4	Cu_2O	Cs_2CO_3	dioxane	1,10-phen·H_2O	81%
5	-	Cs_2CO_3	dioxane	1,10-phen·H_2O	trace
6	CuCl	K_3PO_4	dioxane	1,10-phen·H_2O	95%
7	CuCl	Na_2CO_3	dioxane	1,10-phen·H_2O	60%
8	CuCl	K_2CO_3	dioxane	1,10-phen·H_2O	73%
9	CuCl	K_3PO_4	DMF	1,10-phen·H_2O	91%
10	CuCl	K_3PO_4	toluene	1,10-phen·H_2O	88%
11	CuCl	K_3PO_4	MeCN	1,10-phen·H_2O	39%
12	CuCl	K_3PO_4	dioxane	L-proline	40%
13	CuCl	K_3PO_4	dioxane	2-piperidinecarboxylic acid	65%
14	CuCl	K_3PO_4	dioxane	2,2'-bipy	29%
15	CuCl	K_3PO_4	dioxane	-	75%

[a] Reaction conditions: 2-bromo-*N*-(((2-iodophenyl)imino)methylene)-aniline **1a** (0.5 mmol, 1 equiv), benzylamine **2a** (0.55 mmol, 1.1 equiv), Cu catalyst (0.05 mmol, 10 mol%), ligand (0.1 mmol, 20 mol%), and base (2 mmol, 4 equiv), in solvent (3 mL), under nitrogen atmosphere, at 100 ºC for 12 h. [b] Isolated yield.

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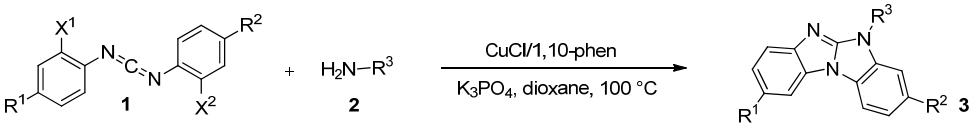
We next investigated the reaction scope by varying bis-(*o*-haloaryl)carbodiimides and *N*-nucleophiles. As summarized in Table 2, generally, both electron-donating and electron-withdrawing groups on the phenyl rings of bis-(*o*-haloaryl)carbodiimides were well tolerated, and the desired double cyclized products were efficiently generated (Table 2, entries 1-12 and 14-20). A range of the substrates including *o*-bromo-*o*'-iodo-diphenylcarbodiimides (Table 2, entries 1-12), bis-(*o*-iodophenyl)carbodiimides (Table 2, entries 14-17), and bis-(*o*-bromophenyl)carbodiimides (Table 2, entries 18-20) were compatible with the reaction conditions, delivering the corresponding benzimidazo[1,2-*a*]benzimidazoles in good to excellent yields, though the reactions of the dibromides usually required a longer reaction time (Table 2, entries 18-20). However,

Table 2. Cu-catalyzed domino synthesis of benzimidazo[1,2-*a*]benzimidazoles[a]



Entry	Carbodiimide **1**	Amine **2**	Product **3**	Yield[b]	Entry	Carbodiimide **1**	Amine **2**	Product **3**	Yield[b]
1	**1a**	**2a**	**3a**	95%	11	**1b**	**2a**	**3k**	93%
2	**1a**	**2b**	**3b**	90%	12	**1c**	**2d**	**3l**	84%[c]
3	**1a**	**2c**	**3c**	87%[c]	13	**1d**	**2a**	**3m**	55%[c]
4	**1a**	**2d**	**3d**	90%[c]	14	**1e**	**2a**	**3k**	96%
5	**1a**	**2e**	**3e**	88%[c]	15	**1e**	**2k**	**3n**	89%
6	**1a**	**2f**	**3f**	86%	16	**1f**	**2a**	**3o**	85%
7	**1a**	**2g**	**3g**	88%	17	**1f**	**2b**	**3p**	83%
8	**1a**	**2h**	**3h**	85%	18	**1g**	**2a**	**3a**	81%[d]
9	**1a**	**2i**	**3i**	86%	19	**1h**	**2a**	**3k**	84%[d]
10	**1a**	**2i**	**3i**	82%	20	**1i**	**2a**	**3o**	72%[d]

[a] Reaction conditions: **1** (0.5 mmol, 1 equiv), primary amine **2** (0.55 mmol, 1.1 equiv), CuCl (0.05 mmol, 10 mol%), 1,10-phen·H_2O (0.1 mmol, 20 mol%), and K_3PO_4 (2 mmol, 4 equiv), in dioxane (3 mL), under nitrogen atmosphere, at 100 ºC for 12 h. [b] Isolated yield. [c] For 24 h. [d] For 18 h.

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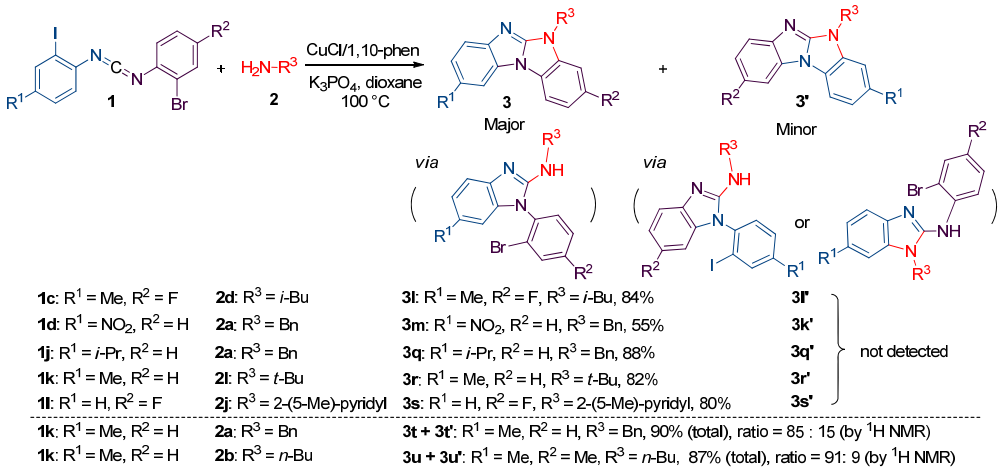
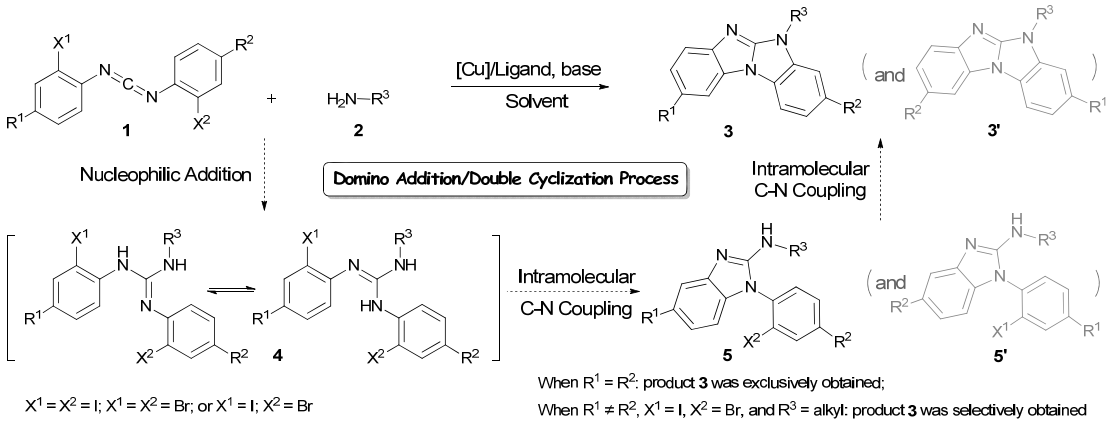
the 2-bromo-*N*-(((2-iodophenyl)imino)methylene)aniline with a strong electron-withdrawing group (NO_2) on the aromatic ring showed less reactive and furnished the product only in a moderate yield (Table 2, entry 13). A variety of primary amines were also employed. Either aliphatic (including the benzylamines; Table 2, entries 1-6 and 11-20) or aromatic primary amines (Table 2, entries 7-10) efficiently reacted with bis-(*o*-haloaryl)carbodiimides to afford the corresponding polycyclic benzimidazole derivatives. The anilines bearing electron-poor aromatic rings (Table 2, entries 8 and 10) performed as well as those with electron-rich phenyl rings (Table 2, entry 9). Notably, a heteroaromatic aniline could also be successfully employed as the *N*-nucleophile (Table 2, entry 10).

As shown in Scheme 1, excellent selectivity was achieved during our research. It was noticeable that the reaction of unsymmetrical 2-bromo-2'-iodo-diphenylcarbodiimide gave the polycyclic products with good to exclusive selectivity .



Scheme 1. The selective domino reactions of unsymmetrical bis-(*o*-haloaryl)carbodiimides with primary aliphatic amines

A possible pathway to the benzimidazo[1,2-*a*]benzimidazole from the reaction of bis-(*o*-haloaryl)carbodiimide with primary amine was shown in Scheme 2. The nucleophilic addition of primary amine **2** to carbodiimide **1** initiated the reaction, and addition intermediate **4** was generated; then **4** might give intermediate **5** (or **5'**) through an intramolecular C-N coupling; finally, product **3** (or **3'**) formed *via* another intramolecular C-N coupling process. It was worthy noting that **3** was selectively obtained when unsymmetrical substituted 2-bromo-2'-iodo-diphenylcarbodiimide and aliphatic primary amine were utilized as the materials, probably due to the different reactivity of the C-I bond and C-Br bond, as well as the NH-aryl group's better activity than the NH-alkyl group's in the intramolecular coupling process.



Scheme 2. The proposed mechanism for the domino reaction of bis-(*o*-haloaryl)carbodiimide with primary amine

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Conclusions

In conclusion, a novel, concise and efficient method for the synthesis of benzimidazo[1,2-*a*]benzimidazoles has been developed. A wide range of the polycyclic benzimidazole derivatives, which might be useful in medicinal chemistry and material fields, were facilely generated in good to excellent yields through copper-catalyzed domino addition/double cyclization process. The starting materials are readily available, the application scope is broad, and the procedure is convenient. Notably, multibonds and polycyclic moieties were directly constructed in one pot. Furthermore, good selectivity was observed when unsymmetrical 2-bromo-2'-iodo-diphenylcarbodiimides were utilized. The domino transformation would be useful and practical for the synthesis of various polycyclic *N*-heterocycles of medicinal and material interests.

Acknowledgment

This work was financially supported by the National Natural Science Foundation of China (No. 21202152) and the Zhejiang Provincial Natural Science Foundation (No. Y4110044).

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization and copies of NMR for all the key products. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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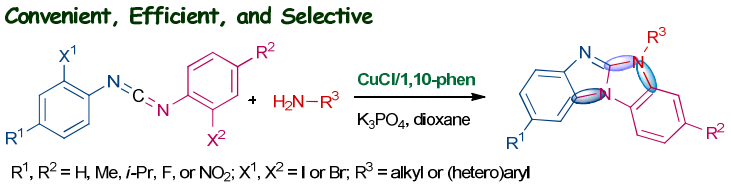
An efficient and facile synthesis of benzimidazo[1,2-*a*]benzimidazoles via copper-catalyzed domino addition/double cyclization

Graphical Abstract (for Table of Content)

A variety of benzimidazo[1,2-*a*]benzimidazole derivatives were efficiently and facilely assembled from bis-(*o*-haloaryl)carbodiimides and primary amines through a Cu-catalyzed domino addition/double cyclization process.



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