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Copper-Catalyzed Cascade Addition/Cyclization: An Efficient and Versatile Synthesis of *N*-Substituted 2-Heterobenzimidazoles

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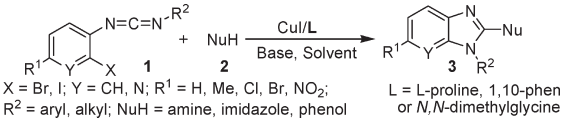

A novel and efficient one-pot synthesis of various *N*-substituted 2-heterobenzimidazoles has been developed. Through a Cu(I)-catalyzed cascade intermolecular addition/intramolecular C−N coupling process, a wide variety of 2-heterobenzimidazoles could be synthesized from *o*-haloarylcarbodiimides and *N*- or *O*-nucleophiles.

1,2-Disubstituted benzimidazole derivatives have shown their wide range of biological activities.[1] Among them, 2-heterobenzimidazoles such as 2-aminobenzimidazoles, 2-imidazylbenzimidazoles, and 2-phenoxylbenzimidazoles are important classes of heteroaromatics in biological chemistry and pharmaceutical areas.[2] For example, a number of 2-piperazinylbenzimidazoles (**A**) exhibit anti-inflammatory[3b] and antihistaminic activities;[3a] certain *N*-aryl 2-aminobenzimidazoles (**B**) were studied for their potential antistaphylococcal activity;[4] several 2-imidazylbenzimidazoles (**C**) possess fungicidal activity,[5b,5c] and might be employed as anti-ischemic agents;[5a] and some 2-phenoxylbenzimidazoles (**D**) are claimed to be antiviral active compounds[6] (Figure 1).

Although these *N*-substituted 2-heterobenzimidazoles play an important role in biological and pharmaceutical areas, efficient methods for the assembly of these molecules are limited. The classical approaches to 2-aminobenzimidazoles employ *o*-phenylenediamine as precursors. For example, Carpenter and co-workers recently synthesized 2-dimethylaminobenzimidazole from 2-amino-1-anilino-4-nitrobenzene and phosgene iminium chloride;[2d] Sun et al. reported *o*-phenylenediamines could react with isothiocynanates to give 2-aminobenzimidazoles.[7] Other approaches include the S_NAr reaction between 2-chlorobenzimidazoles and *N*-nucleophiles,[2b,2c,3a,8] Pd-catalyzed coupling of 2-halobenzimidazoles with amines,[9] etc. However, these methods might suffer from the limited availability of the starting materials, harsh conditions, poor yields, narrow scopes, and/or expensive catalysts. Recently, Batey and co-workers reported Cu- or Pd-catalyzed intramolecular aryl guanidinylation.[10] Although it provided an efficient approach to 2-aminobenzimidazoles, the precursors *o*-haloguanidines needed to be previously synthesized, and the diversity of the substituents on the 2-position was limited (only for certain aliphatic amino groups). The available methods that lead to 2-imidazylbenzimidazoles[5c,11] or 2-phenoxylbenzimidazoles[6,12] are much rarer. Therefore, more efficient and facile routes to these useful molecules under mild conditions are needed.

In the past decade, copper-mediated sp^2 C−X (X = N, O, S, etc.) bond formation reactions have drawn considerable attention for their efficiency and low cost.[13] And recently, these copper-catalyzed strategies have been successfully applied to the assembly of various heterocyclic compounds

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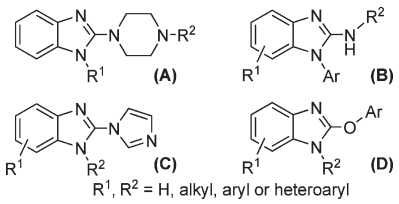
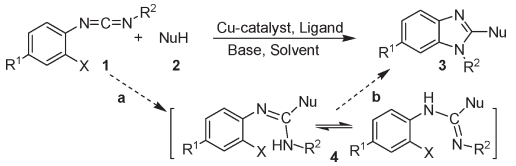


FIGURE 1. Structures of several biologically active and pharmaceutically useful 2-heterobenzimidazoles.

via one-pot strategies.[14] For example, Ma et al. reported Cu-catalyzed coupling/condensation reactions for the synthesis of substituted indole or benzimidazole derivatives;[14k,14n,14q] Buchwald and co-workers developed a useful Cu-catalyzed cascade coupling/condensation process to assemble 1,2-disubstituted benzimidazoles;[14m] other groups also reported that benzimidazole derivatives could be efficiently syntheized via Cu-catalyzed one-pot[14a,14h] or stepwise reactions.[2a] However, to the best of our knowledge, there is no report about the versatile synthesis of 2-heterosubstituted benzimidazoles via a Cu-catalyzed one-pot process. Our group is interested in one-pot synthesis of heterocycles via Cu-catalyzed addition/cyclization reactions, which provide convenient and efficient approaches to potentially useful heterocyclic compounds.[15] Herein, as a part of our continuing effort, we report a novel Cu-catalyzed one-pot protocol to synthesize various *N*-substituted 2-heterobenzimidazoles from *o*-haloarylcarbodiimides and *N*-/*O*-nucleophiles.

We envisaged that *o*-haloarylcarbodiimide **1**[16] and proper nucleophile **2** would undergo a cascade process to afford 1,2-disubstituted benzimidazole derivative **3**. As shown in Scheme 1, the proposed reaction might proceed through an intermolecular addition of nucleophile **2** to *o*-halocarbodiimide **1** under proper conditions (step a, the plausible intermediate **4** would be formed),[17] followed by

SCHEME 1. Proposed One-Pot Synthesis of 1,2-Disubstituted Benzimidazoles via a Copper-Catalyzed Addition/Coupling Process



the formation of benzimidazole ring via an intramolecular C−N coupling (step b). The latter process might be analogous to those reported Cu-catalyzed intramolecular aminations to a certain extent.[10,18] With this idea in mind, we originally investigated the reaction of *o*-iodoarylcarbodiimide **1a** (X = I, R^1 = Me, R^2 = Ph) with piperidine **2a**. The first attempt was performed in toluene with CuI (10 mol %) as the catalyst and 1,10-phenanthroline (1,10-Phen, 20 mol %) as the ligand in the presence of Cs_2CO_3 (2 equiv) at 80 °C for 20 h.[19] Both the desired product **3a** and the additive product **4a** were obtained (53% and 31% yield, respectively), indicating the reaction occurred in the desired manner. Considering that the unsatisfying yield of **3a** might result from the incomplete conversion in the intramolecular coupling process, we then tried to optimize the conditions. It is found that solvent had a significant influence. The result was improved when DME or dioxane was used instead of other solvents (toluene, DMF, and CH_3CN), and dioxane was the best. After screening several ligands including 1,10-Phen, 2,2′-bipyridyl, DMEDA, *N*,*N*-dimethylglycine, L-proline, and ethyl 2-oxocyclohexanecarboxylate, both 1,10-Phen and L-proline emerged as suitable candidates, and L-proline was selected as the preferred ligand (1,10-Phen might be a second candidate). Other bases such as K_2CO_3 or K_3PO_4 provided lower yields. Among the Cu-catalysts examined (CuI, CuBr, CuCl, and Cu_2O), CuI acted as the optimal catalyst. When the reaction was performed in the absence of either catalyst or ligand, only **4a** was recovered and no desired product **3a** was detected, indicating that both Cu-catalyst and ligand were necessary for the cyclization process. Increasing the temperature to 90 °C did not give obvious improvement. Interestingly, the result remained almost the same upon lowering the temperature to 70 °C, while further lowering the temperature might lead to a poor yield. A two-step procedure was tried but the former one-step procedure is superior for its concise single-step manipulation and a bit better yield.[19]

Encouraged by these results, the scope of this Cu(I)-catalyzed cascade process was examined by employing different *o*-iodoarylcarbodiimides and amines (Table 1, entries 1−16). We were pleased to find that a variety of aliphatic amines were all viable *N*-nucleophiles. Both cyclic and *n*-alkyl secondary amines provided satisfying results at 70 °C (entries 1−3), while the reactions with β-amino alcohols required a higher temperature and gave relatively lower yields (entries 4 and 5). The electronic effect of the substituents on the aromatic rings of *o*-iododiarylcarbodiimides was investigated.

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(17) Several references have described that *N*,*N*′-disubstituted carbodiimides could smoothly react with certain *N*- or *O*-nucleophiles to give the corresponding adducts under suitable conditions. For the addition with amine see: (a) Park, S. J.; Lee, M. J.; Rhim, H.; Kim, Y.; Lee, J.-H.; Chung, B. Y.; Lee, J. Y. *Bioorg. Med. Chem.* **2006**, *14*, 3502. (b) Heras, M.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Tetrahedron* **2001**, *57*, 4371. (c) Thomas, E. W.; Nishizawa, E. E.; Zimmermann, D. C.; Williams, D. J. *J. Med. Chem.* **1989**, *32*, 228. For the addition with imidazole see: (d) Ding, M.-W.; Tu, H.-Y.; Liu, Z.-J. *Synth. Commun.* **1997**, *27*, 3657.(e) Zinner, G.; Perner, M.; Gruenefeld, J.; Schecker, H. G. *Arch. Pharm.* **1986**, *319*, 1073. For the addition with phenol see: (f) Larksarp, C.; Alper, H. *J. Org. Chem.* **1999**, *64*, 9194.

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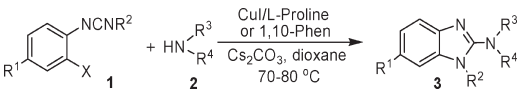
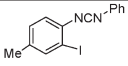
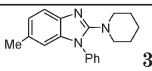
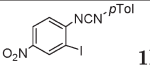
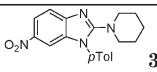
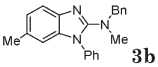
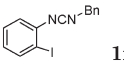
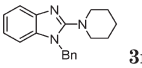
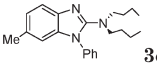
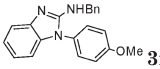
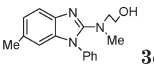
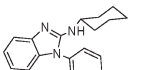
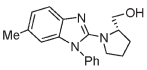
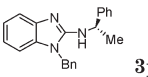
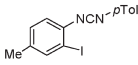
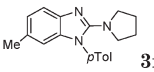
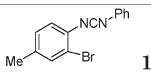
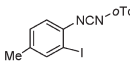
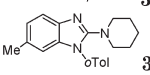
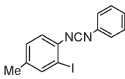
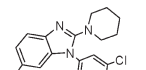
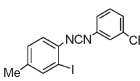
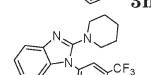
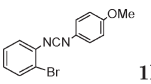
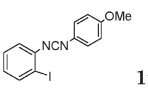
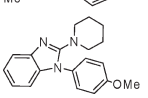
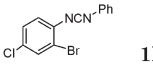
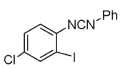
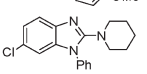
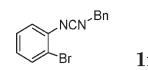
(19) For details, see the Supporting Information.

TABLE 1. One-Pot Synthesis of 2-Aminobenzimidazoles from *o*-Haloarylcarbodiimides and Amines[a]



entry	carbodiimide	product	yield (%)[b]	entry	carbodiimide	product	yield (%)[b]
1	 **1a**	 **3a**	95	12	 **1h**	 **3l**	59[d]
2	**1a**	 **3b**	90	13	 **1i**	 **3m**	72[c] 92[e]
3	**1a**	 **3c**	83[d]	14	**1f**	 **3n**	71[c] 88[e]
4	**1a**	 **3d**	61 78[c, d]	15	**1f**	 **3o**	86[e]
5	**1a**	 **3e**	75[c, d]	16	**1i**	 **3p**	91[e]
6	 **1b**	 **3f**	90	17	 **1j**	**3a**	87[f]
7	 **1c**	 **3g**	68[c, d]	18	**1j**	**3b**	85[e]
8	 **1d**	 **3h**	84	19	**1j**	**3c**	81[e]
9	 **1e**	 **3i**	70[c, d]	20	 **1k**	**3j**	87[e]
10	 **1f**	 **3j**	96[d]	21	 **1l**	**3k**	88[e]
11	 **1g**	 **3k**	93	22	 **1m**	**3m**	86[e]

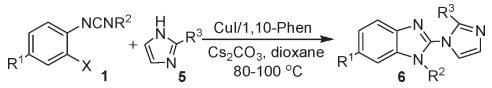
[a] Reaction conditions: *o*-haloarylcarbodiimide **1** (0.5 mmol), amine **2** (0.55 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), and Cs_2CO_3 (1.0 mmol) in dioxane (3 mL) under N_2 at 70 °C for 20 h. [b] Isolated yield. [c] At 80 °C. [d] For 30 h. [e] 1,10-Phen (0.1 mmol) as the ligand, at 80 °C. [f] At 100 °C.

The presence of either a weak electron-donating group (*p*-Me) or a weak electron-withdrawing group (*m*-Cl, *p*-Cl) on the aromatic ring of **1** provided good yield (entries 6, 8, and 11). Increasing the electron density on the nonhalogenated ring might favor the intramolecular C−N coupling process. The reaction of the *o*-iododiarylcarbodiimide bearing a methoxy group afforded the desired product in excellent yield (entry 10). However, the carbodiimides bearing strong electron-withdrawing groups (*m*-CF_3, *p*-NO_2) were unfavorable for the reaction (entries 9 and 12). An ortho-substituted diarylcarbodiimide was tested and only gave moderate yields, which might result from the ortho-steric hindrance (entry 7). *N*-Aryl-*N*′-benzylcarbodiimide **1i** could smoothly react with piperidine (entry 13), too. Primary amines were also utilized as the nucleophiles (entries 14−16), and 1,10-Phen was a superior ligand for these cases. Interestingly, the reactions might have good regioselectivities. The *NH*-aryl group would take priority over the *NH*-alkyl group in the intramolecular couping process (entries 14 and 15). When α-phenylethanamine was used, its *NH*-group would be inferior to the *NH*-benzyl group in the cyclization process (entry 16). Bromides are more accessible and economical than iodides. Therefore, further investigation of the one-pot reaction between *o*-bromoarylcarbodiimide and amine was pursued (entries 17−22). Although L-proline could also successfully promote these reactions, it required a much higher temperature (entry 17). Switching the ligand to 1,10-Phen led to a milder condition. Therefore, 1,10-Phen was chosen as the ligand for these reactions. The results were similar to those obtained with *o*-iodoarylcarbodiimides, and the desired products were delivered in good to excellent yields.

We then attempted to extend this method to the synthesis of 2-imidazylbenzimidazoles. And we were pleased to find that our protocol was also efficient when imidazoles were employed as the *N*-nucleophiles (Table 2). And 1,10-Phen seemed to be a suitable ligand for these reactions. Generally, good to execellent yields could be obtained. Both electron-donating groups (*p*-Me, *p*-MeO) and electron-withdrawing groups (*m*-Cl, *p*-Cl) on the aromatic rings of carbodiimides were tolerated (entries 1−8). The reaction with 2-methylimidazole required a higher temperature and longer reaction time, indicating that the ortho-steric hindrance on the nucleophile was unfavorable for the reaction (entries 9 and 10).

We also explored whether our protocol was viable for the reaction between *o*-iodoarylcarbodiimides and phenols. By using **1a** and phenol as the model substrates under the

TABLE 2. One-Pot Synthesis of 2-Imidazylbenzimidazoles[a]



entry	carbodiimide	product	yield (%)[b]
1	**1a**	**6a**	91
2	**1j**	**6a**	86[c]
3	**1n**	**6b**	90[c]
4	**1o**	**6c**	92
5	**1b**	**6d**	86
6	**1d**	**6e**	87
7	**1f**	**6f**	85
8	**1g**	**6g**	82
9	**1o**	**6h**	73[c, d]
10	**1g**	**6i**	75[c, d]
11	**1i**	**6j**	92

[a] Reaction conditions: *o*-haloarylcarbodiimide **1** (0.5 mmol), imidazole **5** (0.6 mmol), CuI (0.05 mmol), 1,10-Phen (0.10 mmol), and Cs_2CO_3 (1.0 mmol) in dioxane (3 mL) under N_2 at 80 °C for 24 h. [b] Isolated yield. [c] At 100 °C. [d] For 36 h.

above optimized conditions, the desired product 2-phenoxylbenzimidazole **8a** was obtained only in poor yield (< 40%). Shifting the ligand to *N*,*N*-dimethylglycine afforded **8a** in moderate yield (57%). Further investigation revealed DMSO was the best solvent and K_3PO_4 was the optimal base, and good yield (76%) could be obtained under these improved conditions. The scope was explored by varying different substrates. Moderate to good yields were obtained (Table 3).

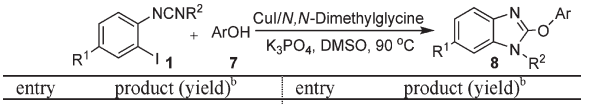
Our one-pot method was also successfully applied to the assembly of *N*-aryl-2-aminopyridoimidazoles (Scheme 2).[19]

Simplified procedures were also tried (for the synthesis of **3a** and **6a**), and the results remained almost the same (94% and 89% yield, respectively).[20]

In summary, a novel, efficient, and versatile strategy for the synthesis of various 2-heterobenzimidazoles has been developed. A number of *N*-substituted 2-aminobenzimidazoles (or 2-aminopyridoimidazoles), 2-imidazylbenzimidazoles, and 2-phenoxylbenzimidazoles, which might possess biological and pharmaceutical activities, were smoothly synthesized via the Cu-catalyzed one-pot addition/C−N coupling process. Our protocol allows the introduction of different kinds of *hetero*-substituents in the 2-position of the benzimidazole ring. The efficient and versatile one-pot transformation of the readily available starting materials into 2-heterobenzimidazoles would make this protocol valuable to synthetic chemists.

(20) The reactions were carried out in a simple oven-dried round-bottomed flask with a septum and under positive N_2 pressure. See the Supporting Information.

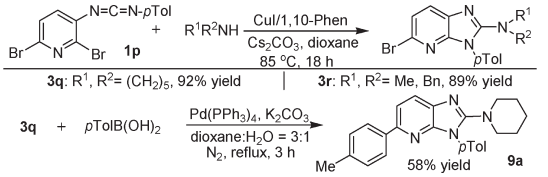
TABLE 3. One-Pot Synthesis of 2-Phenoxylbenzimidazoles[a]



entry	product (yield)[b]	entry	product (yield)[b]
1	**8a** (76%)	3	**8c** (68%)
2	**8b** (72%)	4	**8d** (71%)

[a] Reaction conditions: *o*-iodoarylcarbodiimide **1** (0.5 mmol), phenol **7** (0.6 mmol), CuI (0.05 mmol), *N*,*N*-dimethylglycine (0.10 mmol), and K_3PO_4 (1.5 mmol) in DMSO (2 mL) under N_2 at 90 °C for 24 h. [b] Isolated yield.

SCHEME 2. Synthesis of 2-Aminopyridoimidazole Derivatives



Experimental Section

General Experimental Procedures for the Cu(I)-Catalyzed One-Pot Synthesis of 2-Aminobenzimidazoles. An oven-dried Schlenk tube was charged with a magnetic stir bar, CuI (0.05 mmol), ligand (0.1 mmol), and Cs_2CO_3 (1.0 mmol). The Schlenk tube was capped, and then evacuated and backfilled with N_2 (3 times). Under a positive pressure of N_2, a solution of amine **2** (0.55 mmol) in dioxane (1.5 mL) was added via syringe and the mixture was prestirred at 60 °C in a preheated oil bath for 10 min. Then a solution of *o*-haloarylcarbodiimide **1** (0.5 mmol) in dioxane (1.5 mL) was added dropwise via syringe (for about 0.5 h). The tube was sealed and allowed to stir at the indicated temperature for 20−30 h. The reaction was stopped and cooled to room temperature. The reaction mixture was directly passed through Celite and rinsed with an additional 30 mL of AcOEt. The combined filtrate was concentrated and purified by column chromatography to give the corresponding product **3**.

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Supporting Information Available: Optimization procedure, experimental procedures, experimental data, and copies of ^1H and ^{13}C NMR spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.