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Synthesis of Pyrido[1,2-*a*]benzimidazoles through a Copper-Catalyzed Cascade C–N Coupling Process

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A simple and efficient method for the preparation of pyrido[1,2-*a*]benzimidazoles by a copper-catalyzed inter- and intramolecular C–N coupling cascade process was designed and carried out, and the products were obtained in moderate to excellent yields (up to 93 %).

Introduction

Pyrido[1,2-*a*]benzimidazoles are key core structures in a wide range of bioactive molecules such as antifungal **A**,[1] antitumor **B**,[2] and antiviral agent **C** (Figure 1).[3] Traditionally, these types of compounds are synthesized by the condensation of benzimidazole-2-acetonitrile with β-keto esters, which usually suffers from a tedious multistep sequence and limited variability in the precursor.[1] As an alternative approach, a one-pot, four-component procedure was developed recently, but its application was limited due to low selectivity and yield.[4] Very recently, Zhu and coworkers reported an elegant intramolecular C–H amination protocol.[5] However, it is still highly desirable to develop straightforward and general methods to further improve the synthetic efficiency.

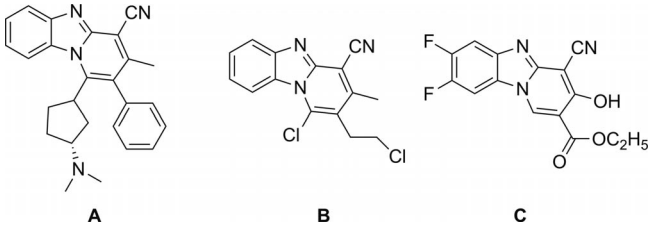
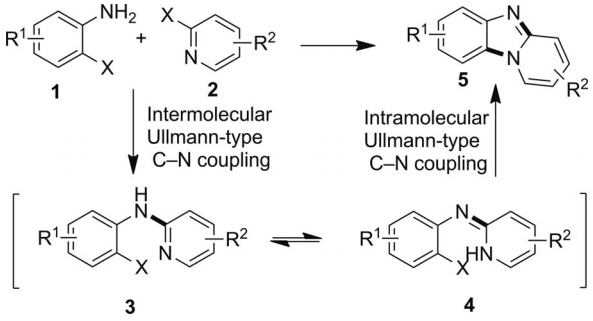


Figure 1. Biologically active pyrido[1,2-*a*]benzimidazoles.

Over the past decade, great progress has been made in copper-catalyzed Ullmann-type cross-coupling reactions, and this reaction has been successfully extended to the synthesis of various N-heterocycles through the use of tandem strategies.[6,7] In continuation of our efforts in copper-catalyzed Ullmann-type reactions,[8] herein is reported a simple, practical, and efficient strategy for the construction of pyrido[1,2-*a*]benzimidazole derivatives through a copper-catalyzed inter- and intramolecular C–N coupling cascade process starting from readily available 2-haloanilines and 2-halopyridines.

It is well known that aryl halides with electron-withdrawing groups usually react faster than those with electron-donating groups in Ullmann-type reactions. Thus, we surmise that 2-haloanilines **1** can couple exclusively with 2-halopyridines **2** due to the electron-deficient nature of the pyridine ring; subsequent isomerization of intermediate **3** into **4** followed by intramolecular C–N coupling would afford desired product **5** as show in Scheme 1.[9]



Scheme 1. Proposed procedure for the synthesis of pyrido[1,2-*a*]-benzimidazoles.

Results and Discussion

To verify this hypothesis, 2-iodoaniline and 2-iodopyridine were selected as the model substrates as indicated in Table 1. Gratifyingly, the substrates were transformed into the desired product in 27% yield in the presence of CuI (20 mol-%) at 120 °C (Table 1, Entry 1). Several ligands were then tested, and 1,10-phenanthroline proved to be the most effective, affording the product in 58% yield (Table 1, Entries 2–6). Screening of the bases suggested that Cs_2CO_3 was optimal (Table 1, Entries 6–8). Solvent is another im-

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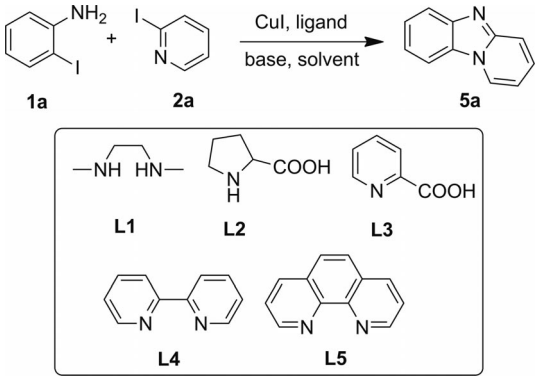
portant factor affecting catalysis. Both xylene and toluene were highly efficient for the catalysis, giving the product in 91% and 90% yield, respectively (Table 1, Entries 10 & 11). Further investigation revealed that 12 h was enough for the reaction to go to completion (Table 1, Entry 12). When the reaction time was decreased to 6 h, the yield dropped to 77% (Table 1, Entry 13). Furthermore, a low temperature slowed the reaction rate. Only 65% yield was obtained when the reaction was carried out at 100 °C (Table 1, Entry 14). Reducing the loading of the CuI catalyst to 10 mol-% caused the reaction yield to drop to 70% (Table 1, Entry 15).

Table 1. Copper-catalyzed coupling of 2-iodoaniline with 2-iodopyridine under different reaction conditions.[a]

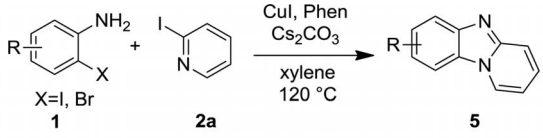


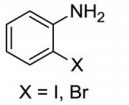
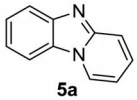
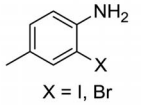
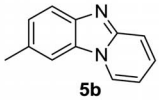
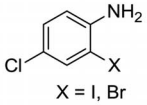
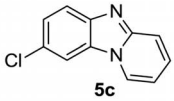
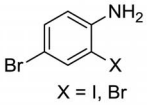
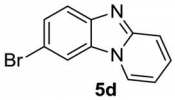
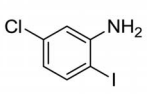
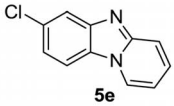
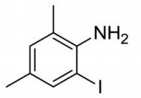
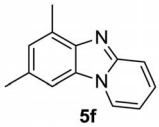
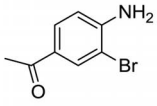
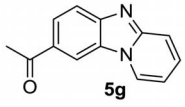
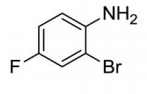
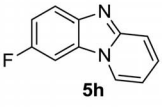
Entry	Ligand	Base	Solvent	Time [h]	% Yield[b]
1	–	K_2CO_3	DMF	24	27
2	**L1**	K_2CO_3	DMF	24	10
3	**L2**	K_2CO_3	DMF	24	12
4	**L3**	K_2CO_3	DMF	24	13
5	**L4**	K_2CO_3	DMF	24	48
6	**L5**	K_2CO_3	DMF	24	58
7	**L5**	Na_2CO_3	DMF	24	24
8	**L5**	Cs_2CO_3	DMF	24	66
9	**L5**	Cs_2CO_3	DMSO	24	60
10	**L5**	Cs_2CO_3	toluene	24	90
11	**L5**	Cs_2CO_3	xylene	24	91
12	**L5**	Cs_2CO_3	xylene	12	90
13	**L5**	Cs_2CO_3	xylene	6	77
14	**L5**	Cs_2CO_3	xylene	12	65[c]
15	**L5**	Cs_2CO_3	xylene	12	70[d]

[a] Reaction conditions: 2-iodoaniline (0.25 mmol), 2-iodopyridine (0.3 mmol), base (0.75 mmol), CuI (0.05 mmol), ligand (0.1 mmol), solvent (0.5 mL), N_2 atmosphere, 120 °C. [b] Isolated yield. [c] 100 °C. [d] CuI (0.025 mmol), ligand (0.05 mmol).

With the optimal reaction conditions established, we tried to investigate the scope of this new protocol. First, differently substituted 2-iodoanilines were examined and treated with 2-iodopyridine. As shown in Table 2, steric hindrance of the substituents on the phenyl ring exhibited a greater effect than the electronic properties. For example, *para*-substituted 2-iodoanilines containing either electron-rich or electron-deficient substituents worked well to give the corresponding products in good to excellent yields ranging from 85 to 91%. *meta*-Chloroiodoaniline also reacted to form the desired product in 89% yield (Table 2, Entry 5). Meanwhile, sterically hindered 4,6-dimethyl-2-iodoaniline afforded the product in a much lower yield of 39% (Table 2, Entry 6). Furthermore, 2-bromoanilines were also found to be applicable to this reaction, although a longer reaction time of 24 h was required to give the products in moderate to good yields ranging from 53 to 93% (Table 2, Entries 1–4, 7, 8).

Table 2. Copper-catalyzed coupling of various substituted 2-haloanilines with 2-iodopyridine.[a]



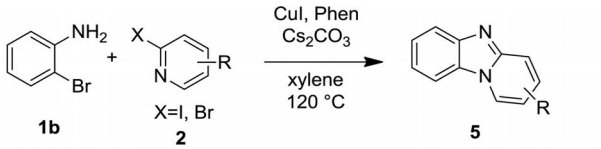
Entry	2-Haloanilines	Products	% Yield[b]
1			90 (X=I) 77 (X=Br)
2			84 (X=I) 53 (X=Br)
3			85 (X=I) 64 (X=Br)
4			91 (X=I) 67 (X=Br)
5			89
6			39
7			93
8			73

[a] Reaction conditions: 2-haloaniline (0.25 mmol), 2-iodopyridine (0.3 mmol), base (0.75 mmol), CuI (0.05 mmol), 1,10-phenanthroline (0.1 mmol), solvent (0.5 mL), N_2 atmosphere, 12 h for 2-iodoaniline and 24 h for 2-bromoaniline, 120 °C. [b] Isolated yield.

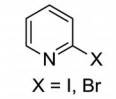
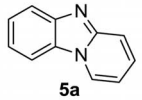
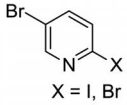
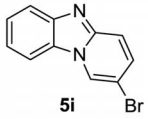
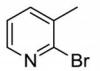
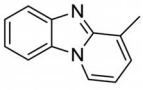
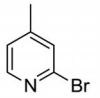
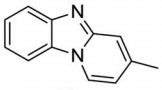
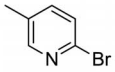
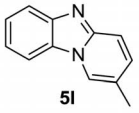
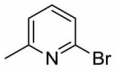
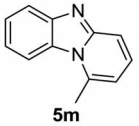
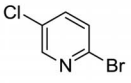
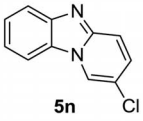
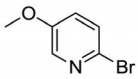
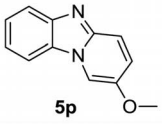
Then, various substituted 2-halopyridines were tested in this copper-catalyzed tandem process as shown in Table 3. To our delight, almost of the 2-bromopyridines and 2-iodopyridines bearing electron-withdrawing or electron-donating groups were able to react with 2-bromoaniline smoothly to afford the corresponding products (Table 3, Entries 2–8). Generally, 2-bromopyridines gave lower yields than 2-

iodopyridines, which might be caused by the low reactivity of 2-bromopyridines in this catalytic system. Sterically hindered 6-methyl-2-bromopyridine was also coupled with 2-bromoaniline, though only 25% yield was obtained (Table 3, Entry 6).

Table 3. Copper-catalyzed coupling of various substituted 2-halopyridines with 2-bromoaniline.[a]

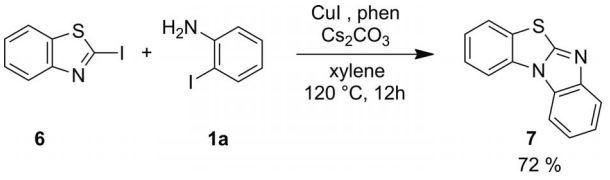


1b 2 5

Entry	2-Halopyridines	Products	% Yield[b]
1	 X = I, Br	 5a	77 (X=I) 58 (X=Br)
2	 X = I, Br	 5i	69 (X=I) 61 (X=Br)
3		 5j	55
4		 5k	53
5		 5l	50
6		 5m	25
7		 5n	53
8		 5p	61

[a] Reaction conditions: 2-bromoaniline (0.25 mmol), 2-halopyridine (0.3 mmol), base (0.75 mmol), CuI (0.05 mmol), 1,10-phenanthroline (0.1 mmol), solvent (0.5 mL), N_2 atmosphere, 24 h, 120 °C. [b] Isolated yield.

This catalytic system was further applied to the coupling reaction of 2-iodobenzothiazole with 2-iodoaniline to afford imidazo[2,1-*b*]benzothiazole, which is an important chemical building block in organic and biological chemistry.[10] As shown in Scheme 2, 72% yield of the corresponding product could be obtained.



6 1a 7
72 %

Scheme 2. Synthesis of benzimidazo[2,1-*b*]benzothiazole.

Conclusions

In summary, we have designed a simple and efficient method for the preparation of pyrido[1,2-*a*]benzimidazoles through a copper-catalyzed inter- and intramolecular C–N coupling cascade process. A wide range of functional groups were well tolerated under the reaction conditions, and a series of pyrido[1,2-*a*]benzimidazoles with substituents at different positions were generated in moderate to excellent yields. Considering the low cost of the catalytic system and the starting materials, this strategy will thus be highly useful in organic and medicinal chemistry.

Experimental Section

Typical Procedure for the Catalysis: An oven-dried Schlenk tube was charged with 2-iodoaniline (0.25 mmol, 54.8 mg), Cs_2CO_3 (0.75 mmol, 244.4 mg), CuI (0.05 mmol, 9.5 mg), and 1,10-phenanthroline (0.1 mmol, 18 mg). The tube was evacuated and backfilled with N_2, and then 2-iodopyridine (0.3 mmol, 61.5 mg) and xylene (0.5 mL) was added. The reaction mixture was stirred at 120 °C for 12 h and then allowed to cool to room temperature. The mixture was diluted with water and extracted with ethyl acetate. The extracts were combined and then dried with anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography to afford the corresponding product (37.8 mg).

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures, characterization data, and copies of the NMR spectra.

Acknowledgments

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[1] H. Takeshita, J. Watanabe, Y. Kimura, K. Kawakami, H. Takahashi, M. Takemura, A. Kitamura, K. Someya, R. Nakajima, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3893.
[2] E. Badaway, T. Kappe, *Eur. J. Med. Chem.* **1995**, *30*, 327.
[3] S. K. Kotovskaya, Z. M. Baskakova, V. N. Charushin, O. N. Chupakhin, E. F. Belanov, N. I. Bormotov, S. M. Balakhnin, O. A. Serova, *Pharm. Chem. J.* **2005**, *39*, 574.
[4] a) N. C. Fletcher, D. Abeln, A. V. Zelewsky, *J. Org. Chem.* **1997**, *62*, 8577; b) C. G. Yan, Q. F. Wang, X. K. Song, J. Sun, *J. Org. Chem.* **2009**, *74*, 710; c) M. R. Cargill, K. E. Linton, G. Sandford, D. S. Yufit, J. A. K. Howard, *Tetrahedron* **2010**, *66*, 2356.
[5] H. Wang, Y. Wang, C. Peng, J. Zhang, Q. Zhu, *J. Am. Chem. Soc.* **2010**, *132*, 13217.

[6] For recent reviews, see: a) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054; b) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450; c) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2008**, *47*, 3096; d) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954; e) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13.

[7] For some recent studies on the syntheses of N-heterocycles by using Ullmann-type couplings, see: a) B. Zou, Q. Yuan, D. Ma, *Angew. Chem. Int. Ed.* **2007**, *46*, 2598; b) C. Huang, Y. Fu, H. Fu, Y. Jiang, Y. Zhao, *Chem. Commun.* **2008**, 6333; c) Q. Cai, Z. Li, J. Wei, C. Ha, D. Pei, K. Ding, *Chem. Commun.* **2009**, 7581; d) X. Liu, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem. Int. Ed.* **2009**, *48*, 348; e) A. K. Verma, T. Kesharwani, J. Singh, V. Tandon, R. C. Larock, *Angew. Chem. Int. Ed.* **2009**, *48*, 1138; f) D. Chen, W. Bao, *Adv. Synth. Catal.* **2010**, *352*, 955; g) D. Ma, Q. Geng, H. Zhang, Y. Jiang, *Angew. Chem. Int. Ed.* **2010**, *49*, 1291; h) Q. Cai, Z. Li, J. Wei, L. Fu, C. Ha, D. Pei, K. Ding, *Org. Lett.* **2010**, *12*,1500.

[8] a) F. Ke, Y. Qu, Z. Jiang, Z. Li, D. Wu, X. Zhou, *Org. Lett.* **2011**, *13*, 454; b) L. Jing, J. Wei, L. Zhou, Z. Huang, Z. Li, X. Zhou, *Chem. Commun.* **2010**, 4767; c) Y. Wang, Z. Wu, L. Wang, Z. Li, X. Zhou, *Chem. Eur. J.* **2009**, *15*, 8971; d) L. Liang, Z. Li, X. Zhou, *Org. Lett.* **2009**, *11*, 3294.

[9] Palladium-catalyzed intramolecular Buchwald–Harwtig aryl amination of 2-(2-bromoanilino)quinolines: a) C. Venkatesh, G. S. M. Sundaram, H. Ila, H. Junjappa, *J. Org. Chem.* **2006**, *71*, 1280; palladium-catalyzed synthesis of dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogues: b) K. T. J. Loones, B. U. W. Maes, R. A. Dommisse, G. L. F. Lemiere, *Chem. Commun.* **2004**, 2466; c) K. T. J. Loones, B. U. W. Maes, C. Meyers, J. Deruytter, *J. Org. Chem.* **2006**, *71*, 260.

[10] B. H. Yousefi, A. Manook, A. Drzezga, B. Reutern, M. Schwarger, H. J. Wester, G. Henriksen, *J. Med. Chem.* **2011**, *54*, 949.

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