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An Efficient One-Pot Synthesis of Benzo[4,5]imidazo[1,2-*a*]quinoxalines *via* Copper-Catalyzed Process

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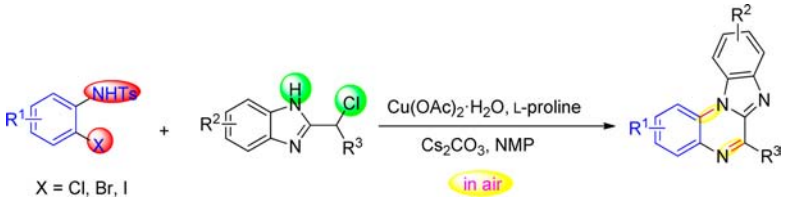
ABSTRACT



A copper-catalyzed one-pot process for the construction of benzo[4,5]imidazo[1,2-*a*]quinoxalines under air is described. Aryl chlorides, aryl bromides, and aryl iodides can be applied to the synthesis of these compounds.

Imidazo[1,2-*a*]quinoxaline derivatives have attracted considerable interest due to their outstanding biological and medicinal activities.[1] For example, EAPB0203 and its analogues exhibit high antitumor activities.[1a−d] Now, EAPB0203 is a promising candidate in the treatment of melanoma and T lymphomas.[1c] BMS-345541 is a highly selective inhibitor of IκB kinase.[1e] **3** And **4** act as an adenosine A_1 receptor antagonist.[1g,h] Many imidazo[1,2-*a*]-quinoxalines have been found to possess other biological activities, including antiallergic (**6**),[1i] antimicrobial,[1j] and cyclic nucleotide phosphordiesterase inhibitory (**5**)[1f] activities. In addition, some of them are also used as flurescent probes for Aβ_{1-42} fibrils (Figure 1).[1k] Benzimidazoles also

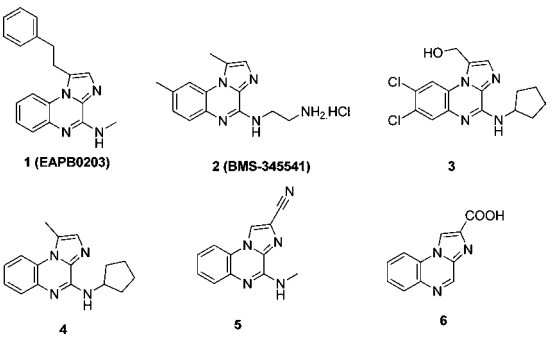


Figure 1. Some biologically active imidazo[1,2-*a*]quinoxalines.

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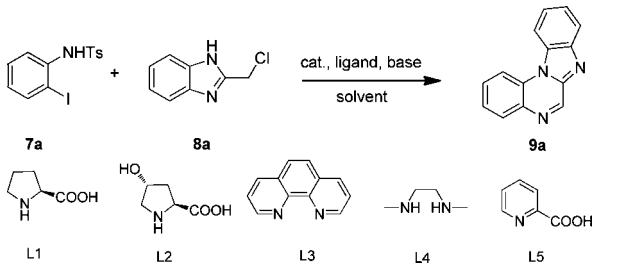
show various biological properties and are often used as enzyme inhibitors[2a−c] and drugs.[2d] We envision that the combined molecules of imidazo[1,2-*a*]quinoxaline and benzimidazole frameworks, benzo[4,5] imidazo[1,2-*a*]-quinoxaline derivatives, would be biologically active molecules and intermediates. However, the methods for preparation of benzo[4,5]imidazo[1,2-*a*]quinoxalines remain rare. The Maes group presented a Pd-catalyzed synthetic method to construct imidazo[1,2-*a*]quinoxalines from 2-chloro-3-iodopyridine or 2,3-dibromopyridine, but this method needs a multistep synthesis.[3a] Reeves et al. developed a Cu-catalyzed strategy from 2-formylpyrroles and *o*-aminoiodoarenes to assemble these compounds, but this approach needs a high temperature and very long reaction time.[3b] Shen et al. synthesized benzo[4,5]imidazo[1,2-*a*]-quinoxaline derivatives from 1-fluoro-2-nitrobenzene and 2-bromoanilines, but this method needs a multistep synthesis and high temperature.[4] Therefore, it is highly desirable to develop a convenient, efficient approach for the synthesis of these heterocycles.

Copper-catalyzed Ullmann coupling reactions have made significant progress,[5−9] and the *N*-arylation strategy has been extensively explored to construct nitrogen heterocycles.[10−13] Many pharmaceutical molecules have been synthesized by the use of Cu-catalyzed coupling strategy.[14] However, most of these reactions were performed under a nitrogen or argon atmosphere, which could prevent oxidation of the catalysts. In particular, the use of inexpensive but less reactive aryl chlorides in Cu-catalyzed coupling is still a challenge compared to the commonly used aryl bromides and aryl iodides. In addition, the application of Cu-catalyzed transformation for benzo[4,5]imidazo[1,2-*a*]-quinoxalines is rarely reported. On the basis of base-catalyzed elimination of the sulfinate group from *N*-tosyl derivatives to afford imines,[15] we used *N*-tosyl-2-haloanilines

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	ligand	base	solvent	yield (%)[b]
1	**$Cu(OAc)_2 \cdot H_2O$**	**L1**	**Cs_2CO_3**	**NMP**	**96**
2	$Cu(OAc)_2 \cdot H_2O$	L1	K_2CO_3	NMP	90
3	$Cu(OAc)_2 \cdot H_2O$	L1	K_3PO_4	NMP	53
4	$Cu(OAc)_2 \cdot H_2O$	L1	KOH	NMP	67
5	$Cu(OAc)_2 \cdot H_2O$	L1	NaOt-Bu	NMP	21
6	$Cu(OAc)_2 \cdot H_2O$	L1	KOt-Bu	NMP	19
7	CuI	L1	Cs_2CO_3	NMP	74
8	CuBr	L1	Cs_2CO_3	NMP	67
9	CuCl	L1	Cs_2CO_3	NMP	92
10	$CuBr_2$	L1	Cs_2CO_3	NMP	64
11	$CuCl_2 \cdot 2H_2O$	L1	Cs_2CO_3	NMP	59
12	–	L1	Cs_2CO_3	NMP	trace
13	$Cu(OAc)_2 \cdot H_2O$	L2	Cs_2CO_3	NMP	82
14	$Cu(OAc)_2 \cdot H_2O$	L3	Cs_2CO_3	NMP	73
15	$Cu(OAc)_2 \cdot H_2O$	L4	Cs_2CO_3	NMP	47
16	$Cu(OAc)_2 \cdot H_2O$	L5	Cs_2CO_3	NMP	72
17	$Cu(OAc)_2 \cdot H_2O$	-	Cs_2CO_3	NMP	84
18[c]	$Cu(OAc)_2 \cdot H_2O$	L1	Cs_2CO_3	THF	trace
19	$Cu(OAc)_2 \cdot H_2O$	L1	Cs_2CO_3	DMSO	65
20	$Cu(OAc)_2 \cdot H_2O$	L1	Cs_2CO_3	DMF	84
21	$Cu(OAc)_2 \cdot H_2O$	L1	Cs_2CO_3	dioxane	93
22	$Cu(OAc)_2 \cdot H_2O$	L1	Cs_2CO_3	toluene	83
23[d]	$Cu(OAc)_2 \cdot H_2O$	L1	Cs_2CO_3	NMP	95

[a] Reaction conditions: *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **7a** (0.5 mmol), 2-(chloromethyl)-1*H*-benzo[*d*]imidazole **8a** (0.5 mmol), Cu (10 mol %), ligand (20 mol %), base (3.5 equiv), solvent (3 mL), 80 °C, in air. [b] Isolated yield. [c] Reaction was refluxed. [d] Reaction was carried out under N_2.

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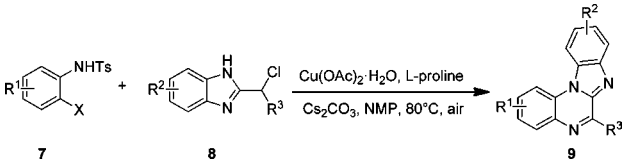
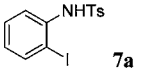
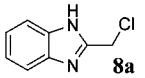
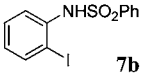
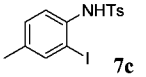
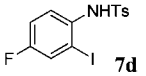
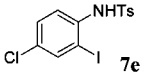
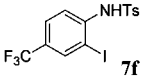
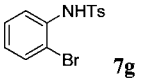
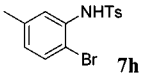
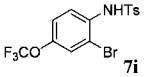
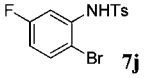
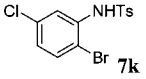
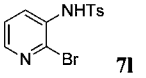
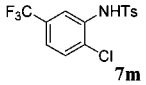
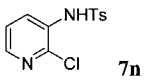
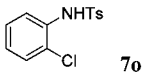
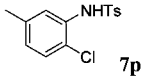
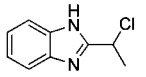
Table 2. Synthesis of Benzo[4,5]imidazo[1,2-*a*]quinoxalines[a]



7 8 9

entry	substrate 7	substrate 8	time (h)	9	yield (%)[b]
1	 **7a**	 **8a**	6	**9a**	96
2	 **7b**	**8a**	6	**9a**	93
3	 **7c**	**8a**	7	**9b**	90
4	 **7d**	**8a**	3	**9c**	88
5	 **7e**	**8a**	3	**9d**	78
6	 **7f**	**8a**	2	**9e**	85
7	 **7g**	**8a**	6	**9a**	95
8	 **7h**	**8a**	6	**9f**	94
9	 **7i**	**8a**	5	**9g**	88
10	 **7j**	**8a**	3	**9h**	84
11	 **7k**	**8a**	3	**9i**	81
12	 **7l**	**8a**	5	**9j**	92
13	 **7m**	**8a**	2	**9k**	72
14	 **7n**	**8a**	5	**9j**	91
15[c]	 **7o**	**8a**	15	**9a**	46
16[c]	 **7p**	**8a**	15	**9f**	42
17	**7a**	 **8b**	6	**9l**	71
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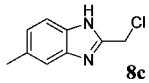
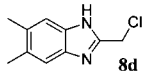
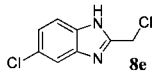
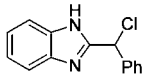
19	**7g**	**8b**	5	**9l**	70
20	**7a**	 **8c**	4	**9n**	78
21	**7e**	**8c**	3	**9o**	77
22	**7g**	**8c**	5	**9n**	70
23	**7a**	 **8d**	4	**9p**	85
24	**7e**	**8d**	3	**9q**	89
25	**7a**	 **8e**	3	**9r**	81
26	**7a**	 **8f**	6	**9s**	74

[a] Reaction conditions: *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **7** (0.5 mmol), 2-(chloromethyl)-1*H*-benzo[*d*]imidazole **8** (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mol %), L-proline (20 mol %), Cs_2CO_3 (3.5 equiv), NMP (3 mL), 80 °C, in air. [b] Isolated yield. [c] Reaction performed at 120 °C.

as starting material. Herein, we report a convenient, efficient Cu-catalyzed one-pot reaction of *N*-tosyl-2-haloanilines and 2-(chloromethyl)-1*H*-benzo[d]imidazoles for the construction of benzo[4,5]imidazo[1,2-*a*]quinoxalines in air. Aryl chlorides, aryl bromides, and aryl iodides can be applied to the synthesis of these compounds.

First, we examined the reaction of *N*-tosyl-2-iodoaniline **7a**[16] and 2-(chloromethyl)-1*H*-benzo[*d*]imidazole **8a** with $Cu(OAc)_2 \cdot H_2O$ as the catalyst, L-proline (L1) as the ligand, Cs_2CO_3 as the base, and NMP as the solvent at 80 °C under air. We collected the product of benzo-[4,5]imidazo[1,2-*a*]quinoxaline **9a** in 96% yield (Table 1, entry 1). As shown in Table 1, we investigated the effect of bases, and Cs_2CO_3 showed the best activity (entry 1). K_2CO_3, K_3PO_4, and KOH gave moderate to good yields (entries 2−4). Only 21% and 19% isolated yields were obtained by the use of NaOt-Bu and KOt-Bu (entries 5 and 6). The efficiency of six Cu catalysts were tested (entries 1 and 7−11). It was found that CuI, CuBr, CuCl, $CuBr_2$, and $CuCl_2 \cdot 2H_2O$ were active, but $Cu(OAc)_2 \cdot H_2O$ afforded the highest yield. A Cu catalyst was absolutely required in this reaction; only a trace amount of target product was observed in the absence of copper salt (entry 12). Different ligands were screened (L1−L5); 4-hydro-L-proline,

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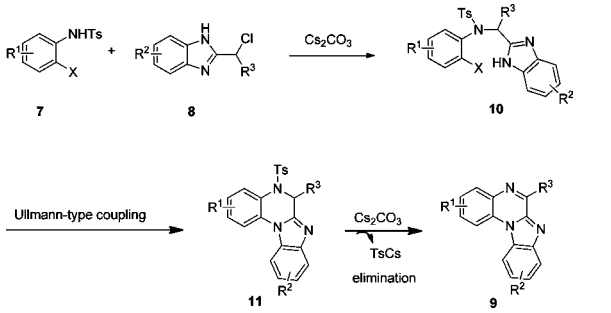
1,10-phenanthronine, *N*,*N*′-dimethylethylenediamine (DMEDA), and picolinic acid were not suitable for this reaction (entries 13−16). Ligands play an important role in the reaction. $Cu(OAc)_2 \cdot H_2O$ alone gave the product in a lower yield (entry 17). Finally, the effect of solvents on the reaction was examined under the same reaction conditions (entries 18−22). NMP proved to be the most effective solvent (entry 1). DMSO, DMF, dioxane, and toluene also gave the product in good yields (entries 19−22). Only a trace amount of product were observed in THF (entry 18). We attempted the reaction under a nitrogen atmosphere, and a 95% yield was obtained (entry 23). The result indicated that oxygen in air did not affect the reaction.

With the optimal reaction conditions in hand, the scope of Cu-catalyzed domino reactions of various substituted *N*-tosyl-2-haloanilines **7** with 2-(chloromethyl)-1*H*-benzo[*d*]imidazoles **8**[17] was examined as shown in Table 2. We initially investigated reactions of *N*-tosyl-2-iodoanilines with 2-(chlorome-thyl)-1*H*-benzo[*d*]imidazole **8a**. All the tested substrates worked well giving the corresponding products in good to excellent yields. It is noteworthy that the substrates *N*-tosyl-2-iodoanilines with no substituted group (entry 1) and electron-donating groups (entry 3) afforded higher yields than the others with electron-withdrawing groups (entries 4−6), but the substrates with electron-withdrawing groups reacted faster. Moreover, the optimized conditions could also be applied to *N*-(2-iodophenyl)benzenesulfonamide **7b** to obtain the corresponding product **9a** (entry 2). We next studied reactions of *N*-tosyl-2-bromoanilines. To our delight, the desired products were also obtained in good to excellent yields (entries 7−12). In general, no significant difference of reactivity was observed between *N*-tosyl-2-iodoanilines and *N*-tosyl-2-bromoanilines. We investigated the reaction of *N*-tosyl-2-chloroaniline, and only a trace amount of the product was observed. However, when the reaction was examined at 120 °C, the desired product was obtained in moderate yield (entry 15). The conditions were also applied to *N*-tosyl-2-chloro-5-methylaniline **7p** to obtain the corresponding product **9f** (entry 16). *N*-Tosyl-2-chloroanilines with electron-withdrawing groups could proceed easily to give the products in good yields (entries 13 and 14).

We next examined substituted 2-(chloromethyl)-1*H*-benzo[*d*]imidazoles. All substrates provided the products in moderate to good yields. Reactions of 2-(1-chloroethyl)-1*H*-benzo[*d*]imidazole **8b** with *N*-tosyl-2-iodoaniline **7a**, *N*-tosyl-4-chloro-2-iodoamide **7e**, and *N*-tosyl-2-bromoaniline **7g** proceeded smoothly to afford the products in good yields (entries 17−19). 2-(Chloromethyl)-1*H*-benzo[*d*]imidazoles **8c**, **8d**, **8e**, and **8f** also worked well under the same reaction conditions (entries 20−26). Notably, reactions of 2-(chloromethyl)-1*H*-benzo[*d*]imidazole **8c** and **8e** provided two regioisomers. In addition, several interesting functional groups, such as fluoro, chloro, and trifluoromethoxy, were well tolerated in this process (entries 4, 5, 9−11, 18, 21, 24, and 25). These functionalities in the products might be useful for further synthetic modifications.

A possible pathway for the formation of imidazo[1,2-*a*]-quinoxaline derivatives is proposed in Scheme 1. First, the intermolecular nucleophilic substitution of *N*-(2-halophenyl)-4-methylbenzenesulfonamide **7** with 2-(chloromethyl)-1*H*-benzo[*d*]imidazole **8** provided **10** in the presence of Cs_2CO_3. The next step was the formation of **11** via the Cu-catalyzed intramolecular Ullmann-type coupling reaction of **10**. Finally, elimination of cesium *p*-toluenesulfinate provided the target product **9**.

Scheme 1. Proposed Reaction Pathway for Synthesis of Benzo[4,5]imidazo[1,2-*a*]quinoxalines



In summary, we have developed a convenient, efficient Cu-catalyzed domino process for the construction of benzo[4,5]imidazo[1,2-*a*]quinoxalines from *N*-tosyl-2-haloanilines and 2-(chloromethyl)-1*H*-benzo[*d*]imidazoles under mild conditions. A variety of benzo[4,5]imidazo-[1,2-*a*]quinoxaline derivatives were obtained in good to excellent yields. Notably, *N*-tosyl-2-chloroanilines were compatible with this process, giving the corresponding products in good yields. This Cu-catalyzed one-pot process has potential applications in the synthesis of biologically and medicinally relevant compounds.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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