

## Copper-Catalyzed Domino Synthesis of Nitrogen Heterocycle-Fused Benzoimidazole and 1,2,4-Benzothiadiazine 1,1-Dioxide Derivatives

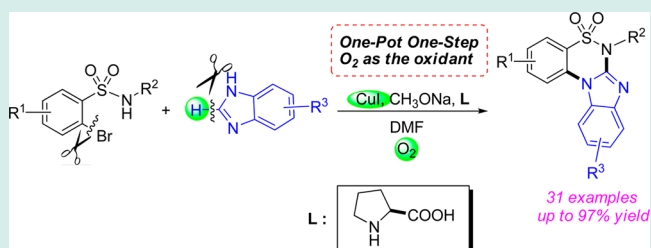
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## Supporting Information

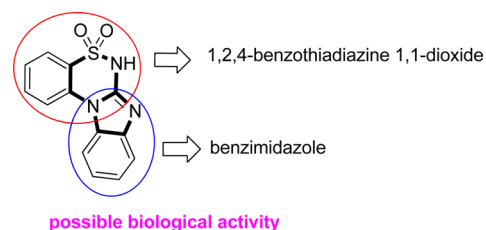
**ABSTRACT:** A convenient copper-catalyzed domino method for the synthesis of nitrogen heterocycle-fused benzoimidazole and 1,2,4-benzothiadiazine 1,1-dioxides has been developed using readily available 2-bromo-*N*-phenylbenzenesulfonamides and benzimidazole derivatives as the starting materials. The domino process comprises an Ullmann-type *N*-arylation and intramolecular C–H amination. The inexpensive and efficient copper-catalyzed method should provide a new and useful strategy for constructing novel, biologically interesting heterocycles containing benzoimidazole and 1,2,4-benzothiadiazine 1,1-dioxide motifs.

**KEYWORDS:** copper-catalyzed, *N*-heterocycle, domino reaction, benzimidazole, 1,2,4-benzothiadiazine 1,1-dioxide



**N**-heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, dyes, and particularly in biologically active molecules. Therefore, the development of novel, practical, and efficient methods for nitrogen-containing heterocyclic synthesis is an important goal in modern organic synthesis. The benzimidazole scaffold, broadly occurring in natural products, shows a variety of biological and medicinal activities. They also can be used as polymers,<sup>1</sup> dyes,<sup>2</sup> drugs<sup>3</sup> and enzyme inhibitors.<sup>4</sup> On the other hand, the 1,2,4-benzothiadiazine 1,1-dioxide ring is a key structure contained in some biologically active molecules.<sup>5</sup> For example, they have been used as potential anticancer agents,<sup>6</sup> and have been shown to possess antiviral activities including against human cytomegalovirus (H-CMV)<sup>7</sup> and human herpesvirus 6 (HHV-6).<sup>8</sup> In addition, some of the benzothiadiazine 1,1-dioxide derivatives have shown excellent biological activity in the treatment of early stages of Alzheimer disease,<sup>9</sup> and they have also been used as “potassium channel openers” (PCOs) that can activate KATP channels.<sup>10</sup> Recently, many methods have been developed for the synthesis of benzothiadiazines.<sup>11</sup> However, to the best of our knowledge, synthesis of the combined motifs of benzimidazole and 1,2,4-benzothiadiazine 1,1-dioxide frameworks (Figure 1) has not been reported thus far. Therefore, we seek to develop an efficient and practical method for the synthesis of this new kind of fused *N*-heterocycles which could possibly possess biological activity.

The C–N bond formation is of fundamental and immense importance in synthetic chemistry because of its wide existence in natural products, biologically active compounds, drug molecules, and materials. Palladium-catalyzed Buchwald–Hartwig coupling is a traditional method to construct aromatic C–N bonds.<sup>12</sup> Recently, considering the ready availability and low toxicity of copper catalysts and their ligands, great progress



**Figure 1.** Structure of fused heterocyclic compound containing benzimidazole and 1,2,4-benzothiadiazine 1,1-dioxide frameworks.

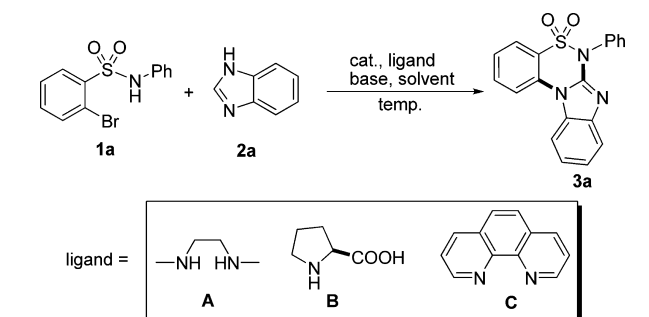
has been made in copper-catalyzed Ullmann-type C–X (X = N, O, and S) bond formation, and some *N*-heterocycles were made through such couplings.<sup>13–15</sup> Also, direct formation of various functional groups from inert C–H bonds meets the requirement of atom-economy and has emerged as a powerful tool for organic transformations.<sup>16</sup> Furthermore, for economical and environmental reasons, there is an increasing demand for the use of dioxygen as an ideal oxidant for many oxidation reactions because of its abundance, low cost, and nontoxicity.<sup>17</sup> Some elegant copper-catalyzed approaches have been developed for the synthesis of heterocycles via  $sp^2$  C–H activation/C–N bond-forming strategy using dioxygen as the green oxidant.<sup>18</sup> These works prompted us to seek more efficient methods to construct novel heterocycles with potential biological activity. Herein, we report an efficient copper-catalyzed “One-Pot, One-Step, approach” for the synthesis of benzoimidazo 1,2,4-benzothiadiazine 1,1-dioxide derivatives, a new class of *N*-heterocycles with potential biological activity.

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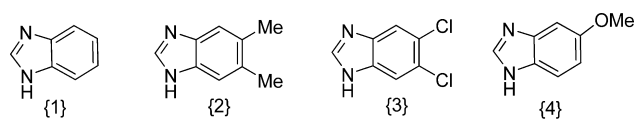
**Table 1. Copper-Catalyzed Coupling of 2-Bromo-*N*-phenylbenzenesulfonamide with 1*H*-benzo[*d*]imidazole: Optimization of Conditions<sup>a</sup>**



entry	cat.	ligand	base	solvent	temp. [°C]	yield [%] <sup>b</sup>
1	CuI	A	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	130	85
2	CuBr	A	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	130	81
3	CuCl <sub>2</sub>	A	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	130	78
4	Cu(OAc) <sub>2</sub>	A	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	130	70
5	CuSO <sub>4</sub>	A	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	130	75
6	CuI	B	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	130	87
7	CuI	C	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	130	80
8	CuI	B	K <sub>2</sub> CO <sub>3</sub>	DMSO	130	81
9	CuI	B	CH <sub>3</sub> ONa	DMSO	130	84
10	CuI	B	CH <sub>3</sub> ONa	DMF	130	89
11	CuI	B	CH <sub>3</sub> ONa	1,4-dioxane	130	45
12	CuI	B	CH <sub>3</sub> ONa	toluene	130	21
13	CuI	B	CH <sub>3</sub> ONa	DMF	110	67
14	CuI	B	CH <sub>3</sub> ONa	DMF	90	32
15	CuI	B	CH <sub>3</sub> ONa	DMF	130	74 <sup>c</sup>
16	CuI		CH <sub>3</sub> ONa	DMF	130	83

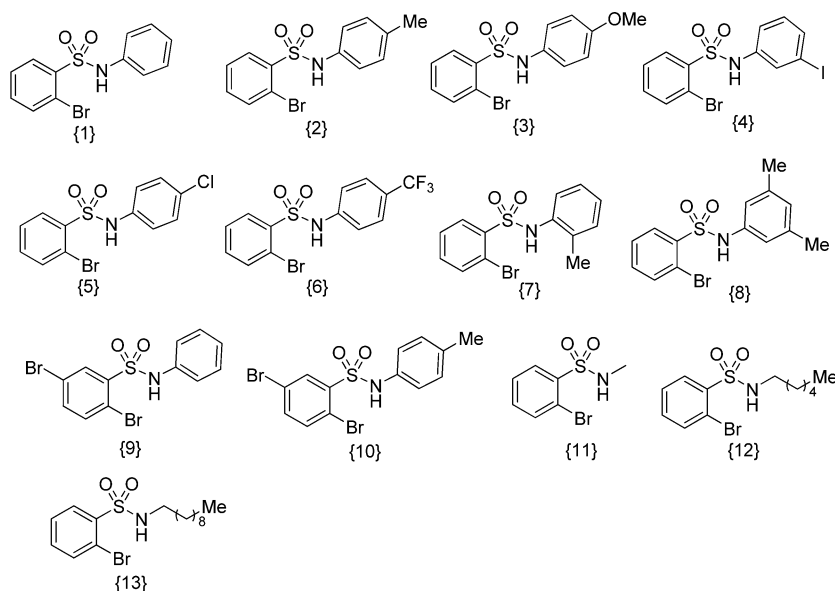
<sup>a</sup>Reaction conditions: 2-bromo-*N*-phenylbenzenesulfonamide **1a** (0.25 mmol), 1*H*-benzo[*d*]imidazole **2a** (0.3 mmol), catalyst (0.05 mmol), ligand (0.05 mmol), base (0.5 mmol), solvent (1 mL). <sup>b</sup>Isolated yield.

<sup>c</sup>Under air atmosphere.



**Figure 3.** 1*H*-benzo[*d*]imidazoles tested in the study (chemset 2).

In order to obtain optimal catalysis conditions, we screened various catalysts, ligands, bases and solvents under a dioxygen atmosphere using 2-bromo-*N*-phenylbenzenesulfonamide and 1*H*-benzo[*d*]imidazole as the model substrates. As shown in Table 1, the copper salts, CuI, CuBr, CuCl<sub>2</sub>, Cu(OAc)<sub>2</sub> and CuSO<sub>4</sub> (20 mol % amount relative to 2-bromo-*N*-phenylbenzenesulfonamide), were tested in DMSO (entries 1–5) using 20 mol % *N,N'*-dimethylethylenediamine as the ligand and 2 equiv of Cs<sub>2</sub>CO<sub>3</sub> as the base at 130 °C. CuI was found to be the most effective catalyst (entry 1). We attempted to use different ligands, and *L*-proline showed greater activity which had been widely used in many Ullmann-type couplings (compare entries 1, 6, and 7). The reason should be the chelation of Cu(I) with *L*-proline made Cu(I) species more reactive or stabilized the oxidative addition intermediates (see Scheme 2 formation mechanism) in the transformation based on its steric hindrance reported by Ma and co-workers.<sup>19</sup> The affect of bases was investigated, and CH<sub>3</sub>ONa provided the highest efficiency (compare entries 7–9). We screened two aprotic, polar solvents and DMF was slightly better than DMSO (compare entries 9–12). The reaction can also be performed under air atmosphere, and afforded the desired product in 74% yield. Interestingly, the target product (**3a**) was obtained in 83% yield in the absence of ligand (entry 16), which implied the existence of an *ortho*-substituent (see Scheme 2, formation mechanism, the nitrogen atom of NHSO<sub>2</sub>R group may coordinate to Cu, which can stabilize the intermediate **B**).<sup>21</sup> Reaction temperatures were also screened and the yield of the target product maximized at 130 °C (compare entries 10, 12–14). After the above optimization, a variety of heterocycles were synthesized under our standard conditions: 20 mol % CuI as the catalyst, 2 equiv



**Figure 2.** 2-Bromo-*N*-phenylbenzenesulfonamides tested in the study (chemset 1).

**Table 2. Copper-Catalyzed Synthesis of Benzoimidazo 1,2,4-Benzothiadiazine 1,1-Dioxides Derivatives via Cascade Reactions of Substituted 2-Bromo-*N*-phenylbenzenesulfonamides with 1*H*-Benzo[*d*]imidazoles<sup>ab</sup> (Chemset 3)**

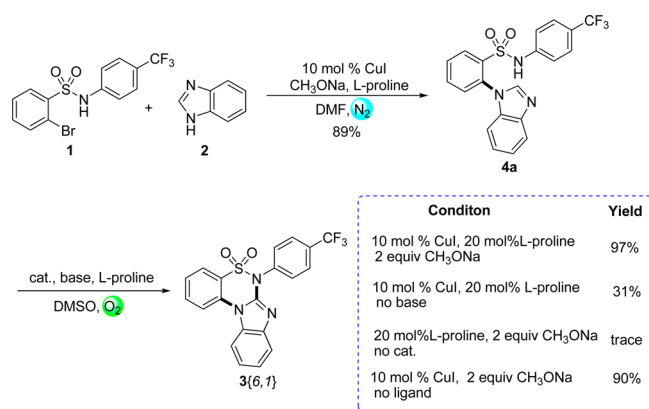
Entry	Product	Yield (%) <sup>b</sup>	Yield (%) <sup>bc</sup>	Entry	Product	Yield (%) <sup>b</sup>	Yield (%) <sup>bc</sup>
1		89	83	14		84	79
2		91	82	15		88	81
3		85	74	16		91	85
4		94	79	17		93	90
5		96	83	18		34	29
6		trace	trace	19		92	86
7		95	87	20		96	93
8		97	88	21		85	76
9		23	11	22		82	74
10		90	70	23		79	66
11		94	86	24		91	83
12		88	75	25		94	91
13		82	82	26		95 (1: 0.87)	92
				27		92 (1:1)	88

Table 2. continued

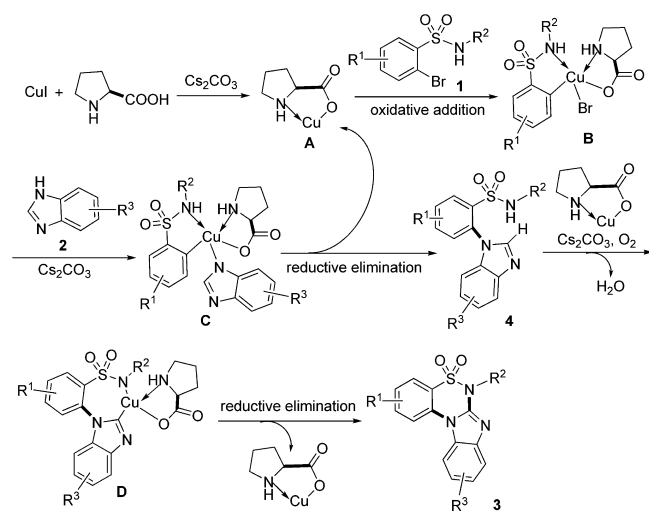
Entry	Product	Yield (%) <sup>b</sup>	Yield (%) <sup>bc</sup>	Entry	Product	Yield (%) <sup>b</sup>	Yield (%) <sup>bc</sup>
28		97 (1: 0.47)	91	31		76	66
29		81	75	32		83	73
30		79	67				

<sup>a</sup>Reaction conditions: under dioxygen atmosphere, 2-bromo-*N*-phenylbenzenesulfonamide derivative (0.25 mmol), benzimidazoles (0.3 mmol), CuI (0.05 mmol), *L*-proline (0.05 mmol), CH<sub>3</sub>ONa (0.5 mmol), DMF (1 mL). <sup>b</sup>Isolated yield. <sup>c</sup>Without ligand.

### Scheme 1. Investigation on Effect of Catalyst, Base, and Ligand for Oxidative Cyclization Reaction



### Scheme 2. Possible Formation Mechanism of Benzoimidazole 1,2,4-Benzothiadiazine 1,1-Dioxides



of CH<sub>3</sub>ONa as the base, 20 mol % *L*-proline as the ligand and DMF as the solvent under O<sub>2</sub> atmosphere.

We selected 13 2-bromo-*N*-phenylbenzenesulfonamides (Figure 2) and 4 1*H*-benzo[*d*]imidazoles (Figure 3) from our internal database to test the proposed combination. As shown in Table 2, the scope of substrates was investigated, most of the examined substrates provided the corresponding target

products in good to excellent yields. It should be not that, The substrates **1** in which the aromatic amines bearing an electron-donating group showed higher reactivities than those in which it was an electron-withdrawing group (products 3{1,1}, 3{2,1}, 3{3,1}, and 3{6,1}), and the substrates **1** containing aryl substituent showed higher reactivity than aliphatic ones (compare entries 3{1,1}–3{8,4} and 3{11,2}–3{13,2}). The electron-effect of the substituted groups in 1*H*-benzo[*d*]imidazoles including electron-rich, -deficient, and -neutral groups did not display evidently difference of reactivity. Although this transformation was efficient, unfortunately, not all the benzimidazole derivatives **2** were compatible with 2-bromo-*N*-phenylbenzenesulfonamides **1**. For example, if 5, 6-dichloro-1*H*-benzo[*d*]imidazole chemset 2{3} and 2-bromo-*N*-*p*-tolylbenzenesulfonamide chemset 1{2} were used as the substrates under the optimal reaction conditions, only a trace of product was obtained (Table 2, 3{2,3}). The reason might be the electronic effect of the substrates influenced the stability of the transition state. Thus, further investigations to explore more powerful catalyst and ligands was required. Notably, reactions of 2,5-dibromo-*N*-phenylbenzenesulfonamides with 1*H*-benzo[*d*]imidazoles only took place on the *ortho*-site C–Br bond of the sulfonamide group, the 5-site C–Br bond remained intact, and the result showed the *ortho*-substituent effect of the sulfonamide group during *N*-arylations<sup>19</sup> (products 3{9,1}–3{10,2}). As expected, unsymmetrical substituted 1*H*-benzo[*d*]imidazole gave a mixture of two regioselective products 3{4,1}/3{4,1}' (or 3{4,1}'/3{4,1}) and 3{8,4}/3{8,4}' (or 3{8,4}'/3{8,4}) in ratios of 1:0.87 and 1:0.47, respectively. Interestingly, when 2-bromo-*N*-*p*-tolylbenzenesulfonamide chemset 1{2} and 6-methoxy-1*H*-benzo[*d*]imidazole chemset 2{4} were used as the substrates, giving a mixture of two regioselective products 3{7,4}/3{7,4}' in ratios of 1:1 demonstrating slight steric effects in this transformation. In addition, the cascade reactions could tolerate some functional groups such as methyl ether (products 3{3,1}, 3{3,2}, and 3{3,3}), CF<sub>3</sub> group (products 3{6,1} and 3{6,2}), C–Cl bond (products 3{1,3}, 3{3,3}, 3{5,2}, and 3{5,3}), C–Br bond (products 3{9,1}–3{10,2}) and C–I bond (products 3{4,1} and 3{4,2}), which could be used for further modifications at the substituted positions. This reaction was also performed under ligand-free conditions, and it provided the target product in slightly lower yields. However, the experimental procedure of ligand-free conditions was more convenient. Three representative examples are shown in ref 20.

To understand the mechanism further, we performed some control experiments, with results shown in Scheme 1. First, Copper-catalyzed coupling of **1** with **2** under nitrogen atmosphere provided *N*-arylation product **4a** in 89% yield. Then, intramolecular aerobic oxidative cyclization of **4a** under various conditions were investigated. Treatment of **4a** provided **3{6,1}** in 97% yield in the presence of 0.1 equiv of CuI, 0.2 equiv of *L*-proline and 1 equiv of CH<sub>3</sub>ONa, while product **3{6,1}** was obtained in 31% yield in the absence of CH<sub>3</sub>ONa. Yields greatly decreased with reduction of CuI, however, the amount of ligand showed insensitivity.

On the basis of these results above, together with literature reports,<sup>21</sup> we proposed the mechanism in Scheme 2. Reaction of CuI with *L*-proline produced a five-membered chelate **A**. Oxidative addition of the chelated Cu(I) with substituted 2-bromo-*N*-phenylbenzenesulfonamide (**1**) led to the intermediate **B** stabilized by the NHSO<sub>2</sub>R group in which the nitrogen atom may coordinate to Cu. Treatment of 1*H*-benzo[*d*]-imidazole (**2**) in the presence of the base Cs<sub>2</sub>CO<sub>3</sub> provided the complex **C**, and then reductive elimination of **C** afforded the *N*-arylation product **4a** and regenerate the chelate **A**. Treatment of **4a** with chelate **A** provided intermediate **D** in the presence of base and dioxygen. Reductive elimination of **D** afforded the target product **3** leaving the catalyst, chelate **A**.

In conclusion, we have developed a simple, practical and efficient copper-catalyzed domino method for the synthesis of the nitrogen heterocycle-fused benzoimidazole and 1,2,4-benzothiadiazine 1,1-dioxide derivatives with potentially biological activities. Some advantages of the protocol involve the use of inexpensive CuI/*L*-proline as the catalyst/ligand system, readily available substituted 2-bromo-*N*-phenylbenzenesulfonamides and benzimidazole derivatives as the starting materials, and environmentally friendly dioxygen as the sole oxidant. Importantly, the corresponding benzoimidazo 1,2,4-benzothiadiazine 1,1-dioxides were obtained in good to excellent yields. The process is of tolerance toward various functional groups in the substrates, and it should attract much attention in organic chemistry and medicinal chemistry and combinatorial chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

Figures giving <sup>1</sup>H and <sup>13</sup>C NMR spectra for all compounds is prepared. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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118.5, 113.2, 45.3, 31.0, 28.5, 26.0, 22.4, 14.2. HRMS calc. for  $C_{16}H_{15}N_3O_2S$  ( $M + H$ )<sup>+</sup>, 355.1354; found, 355.1354.

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