



## Copper-catalyzed tandem reactions of 2-halobenzenamines with isothiocyanates under ligand- and base-free conditions

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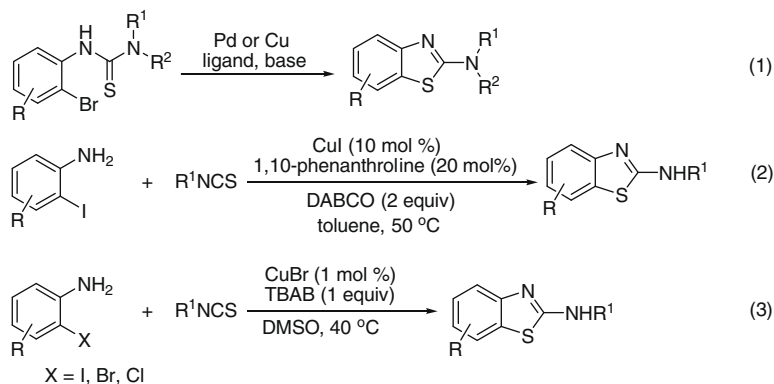
### ABSTRACT

A ligand-free copper-catalyzed reaction of 2-halobenzenamines with isothiocyanates has been developed for the synthesis of 2-aminobenzothiazoles. In the presence of CuBr and TBAB (tetra-*n*-butyl ammonium bromide, additive), a variety of 2-halobenzenamines underwent the reaction with isothiocyanates at 40 °C, affording 2-aminobenzothiazoles in moderate to excellent yields. It is noteworthy that the reaction is conducted under mild, relatively low catalyst loading, and ligand- and base-free conditions.

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Synthesis of 2-aminobenzothiazoles is a continuing hot topic because the 2-aminobenzothiazole moieties are privileged pharmacophores as well as valuable reactive intermediates.<sup>1–7</sup> The majority of efficient methods include transition metal-catalyzed cyclization of 2-bromobenzothioureas (often Pd or Cu catalysts, Eq. 1 in Scheme 1).<sup>5–7</sup> However, both a ligand and a base are required to promote the reaction, and the substrates are not readily available. For example,

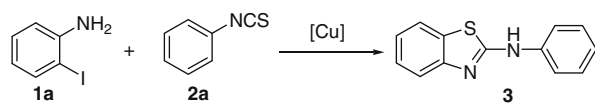
Pd-catalyzed cyclization of 2-bromophenylthioamides reported by Castellón and co-workers required *o*-biphenylP(*t*-Bu)<sub>2</sub> (ligand) and Cs<sub>2</sub>CO<sub>3</sub> (base).<sup>6a</sup> Very recently, Wu and co-workers developed a new copper-catalyzed tandem route to the construction of 2-aminobenzothiazole cores (Eq. 2).<sup>7</sup> In the presence of CuI, 1,10-phenanthroline, and DABCO, 2-iodobenzenamines underwent the reaction with isothiocyanates in moderate to excellent yields. Although the



Scheme 1.

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**Table 1**  
Screening optimal conditions<sup>a</sup>

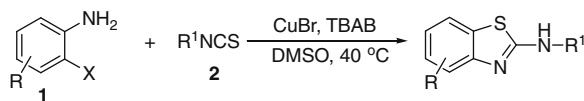
Entry	[Cu] (mol %)	TBAB (equiv)	Solvent	<i>t</i> (°C)	Yield <sup>b</sup> (%)
1	CuBr (5)	0	DMSO	80	60
2	CuBr (5)	0.1	DMSO	80	88
3	CuBr (5)	0.5	DMSO	80	92
4	CuBr (5)	1	DMSO	80	98
5	CuI (5)	1	DMSO	80	90
6	CuCl (5)	1	DMSO	80	98
7	Cu <sub>2</sub> O (5)	1	DMSO	80	90
8	CuBr (5)	1	DMF	80	73
9	CuBr (5)	1	Toluene	80	40
10	CuBr (5)	1	DMSO	40	98
11	CuBr (5)	1	DMSO	25	70
12	CuBr (1)	1	DMSO	40	98
13	CuCl (1)	1	DMSO	40	89

<sup>a</sup> Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), [Cu], TBAB (*n*-Bu<sub>4</sub>NBr), and solvent (2 mL) for 20 h.

<sup>b</sup> Isolated yield.

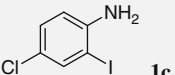
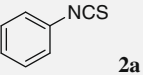
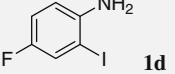
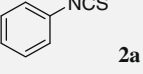
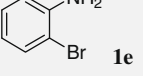
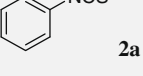
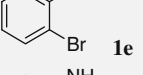
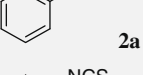
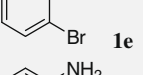
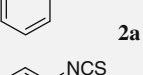
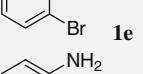
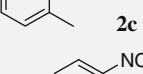
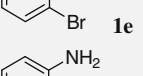
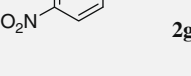
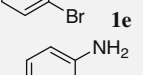
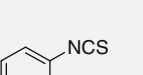
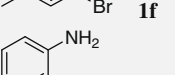
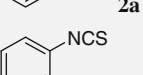
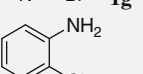
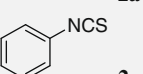
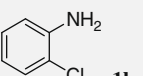

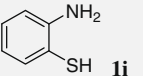
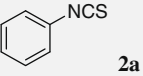
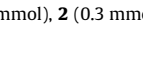
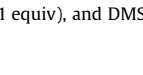
reaction partners, 2-iodobenzamines and isothiocyanates, are commercially available, both ligand and base are still necessary. Moreover, the scope is limited to 2-iodobenzamines. To overcome these drawbacks, herein we report a ligand- and base-free copper-catalyzed reaction of 2-halobenzamines with isothiocyanates using TBAB as the promoter<sup>8</sup> (Eq. 3).<sup>9,10</sup> Moreover, the reaction was conducted smoothly at 1 mol % loading of CuBr under mild conditions (Scheme 1).

As shown in Table 1, the reaction of 2-iodobenzamine (**1a**) with 1-isothiocyanatobenzene (**2a**) was investigated to optimize the reaction conditions. The results demonstrated that 2-iodobenzamine (**1a**) could undergo the reaction with 1-isothiocyanatobenzene (**2a**) and CuBr smoothly, affording the target product **3** in a 60% yield without the aid of both ligands and additives (entry 1). After a series of failures, we found that TBAB could improve the reaction, and the yield was enhanced by increasing the amount of TBAB (entries 2–4). For example, 88% yield of **3** was obtained using 0.1 equiv of TBAB (entry 2) and 98% yield in the presence of 1 equiv of TBAB (entry 4). Encouraged by these results, three other Cu salts, including CuI, CuCl, and Cu<sub>2</sub>O, were subsequently evaluated (entries 5–7). Results identical to those of CuBr were obtained using CuCl (entry 6). However, both CuI and Cu<sub>2</sub>O were less effective (entries 5 and 7). Among the effects of solvents and the reaction tem-

**Table 2**  
TBAB-promoted copper-catalyzed reactions of 2-halobenzamines (**1**) with isothiocyanates (**2**)<sup>a</sup>

Entry	Substrate <b>1</b>	Isothiocyanate <b>2</b>	Time (h)	Yield <sup>b</sup> (%)
1	<b>1a</b>	<b>2b</b>	20	91 ( <b>4</b> )
2	<b>1a</b>	<b>2c</b>	20	92 ( <b>5</b> )
3	<b>1a</b>	<b>2d</b>	20	95 ( <b>6</b> )
4 <sup>c</sup>	<b>1a</b>	<b>2e</b>	20	98 ( <b>7</b> )
5 <sup>c</sup>	<b>1a</b>	<b>2f</b>	20	98 ( <b>8</b> )
6	<b>1a</b>	<b>2g</b>	20	96 ( <b>9</b> )
7	<b>1a</b>	<b>2h</b>	20	70 ( <b>10</b> )
8	<b>1a</b>	MeNCS <b>2i</b>	48	57 ( <b>11</b> )
9	<b>1b</b>	<b>2a</b>	24	96 ( <b>12</b> )

Table 2 (continued)

Entry	Substrate <b>1</b>	Isothiocyanate <b>2</b>	Time (h)	Yield <sup>b</sup> (%)
10	 <b>1c</b>	 <b>2a</b>	24	98 ( <b>13</b> )
11	 <b>1d</b>	 <b>2a</b>	24	90 ( <b>14</b> )
12	 <b>1e</b>	 <b>2a</b>	24	66 ( <b>3</b> )
13 <sup>c</sup>	 <b>1e</b>	 <b>2a</b>	24	68 ( <b>3</b> )
14 <sup>d</sup>	 <b>1e</b>	 <b>2a</b>	16	63 ( <b>3</b> )
15	 <b>1e</b>	 <b>2c</b>	20	62 ( <b>5</b> )
16	 <b>1e</b>	 <b>2g</b>	20	68 ( <b>9</b> )
17	 <b>1e</b>	 <b>2i</b>	48	45 ( <b>11</b> )
18	 <b>1f</b>	 <b>2a</b>	24	70 ( <b>12</b> )
19	 <b>1g</b>	 <b>2a</b>	24	trace ( <b>15</b> )
20	 <b>1h</b>	 <b>2a</b>	36	67 ( <b>3</b> )
21	 <b>1h</b>	 <b>2i</b>	48	41 ( <b>11</b> )
22	 <b>1i</b>	 <b>2a</b>	24	76 ( <b>3</b> )

<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), CuBr (1 mol %), TBABr (1 equiv), and DMSO (2 mL) at 40 °C.

<sup>b</sup> Isolated yield.

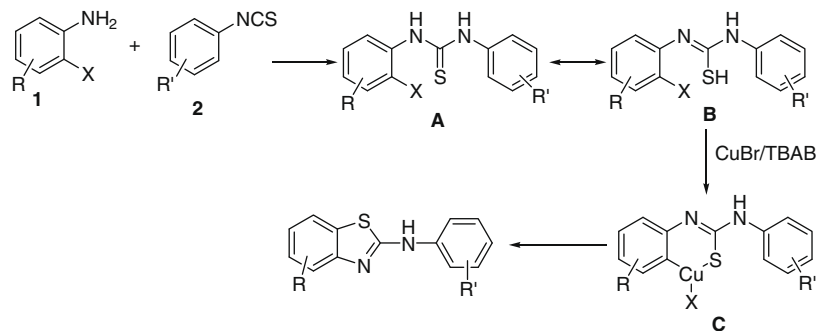
<sup>c</sup> CuBr (10 mol %).

<sup>d</sup> At 80 °C.

perature examination (entries 8–11), it turned out that DMSO combined with 40 °C afforded the best results (entry 10). It is noteworthy that excellent yield is still achieved using 1 mol % of CuBr (entry 12), but 1 mol % of CuCl reduces the yield to some extent (entry 13).

The scopes of both 2-halobenzenamines and isothiocyanates were explored under the optimized conditions, and the results are summarized in Table 2.<sup>11</sup> Our initial investigation was focused on the scope of isothiocyanates (entries 1–8). It was found that several functional groups, including methyl, methoxy, chloro, and nitro groups, on the aryl moiety were tolerated (entries 1–6). For example, methyl-substituted aryl isothiocyanates **2b** and **2c** reacted with **1a**, CuBr, and TBAB, furnishing benzothiazoles **4** and **5** in 91% and 92% yields, respectively (entries 1 and 2). Substrates **2e–2g**, bearing a chloro group or a nitro group, were also suitable for the reaction with **1a** under the same conditions (entries 4–6).

To our delight, the standard conditions were also compatible with aliphatic isothiocyanates **2h** and **2i** (entries 7 and 8). Subsequently, a variety of 2-halobenzenamines **1b–1i** were examined for the reaction with isothiocyanates **2** (entries 9–22). The results demonstrated that 2-iodobenzenamines **1b–1d**, bearing methyl, chloro, or fluoro groups, displayed high activity (entries 9–11). 2-Iodo-4-methylbenzenamine (**1b**), for instance, reacted with 1-isothiocyanatobenzene, affording the target product **12** in 96% yield (entry 9). Gratifyingly, the standard conditions were successfully applied in the reactions of both 2-bromobenzenamines and 2-chlorobenzenamine (entries 12–18 and 20–21). For example, 2-bromobenzamide (**1e**) underwent the reactions with isothiocyanates **2a**, **2c**, **2g**, or **2i**; CuBr; and TBAB smoothly in 66%, 62%, 68%, and 45% yields, respectively (entries 12 and 15–17). We found that increasing either CuBr loading or reaction temperature affected the yield slightly (entries 13 and 14). However, an attempt to cyclize sub-



Scheme 2. A possible mechanism.

strate **1g**, a heteroarylamine, with isothiocyanate **2a** failed (entry 19). We were pleased to disclose that moderate yields were still achieved from the reaction of 2-chlorobenzamine (**1i**) with isothiocyanates **2a** or **2i** under the optimized conditions (entries 20 and 21). Notably, 2-aminobenzethiol (**1i**) was a suitable substrate, affording the target product **3** in 76% yield (entry 22).

A possible mechanism was proposed as outlined in Scheme 2 on the basis of the earlier proposed mechanism.<sup>6–10</sup> Intermediate **A** can be generated readily in situ from the reaction between 2-halobenzenamines **1** and isothiocyanates **2**,<sup>6b</sup> followed by cross-coupling to afford the target product with the aid of CuBr and TBAB.<sup>6–10</sup> Among the process, 2-halobenzenamines, 2-aminobenzothiazoles, and DMSO (a Lewis base) may play the role as bases. We also deduced that TBAB might play two roles in the present reaction: (i) a promoter or/and a ligand to activate and stabilize the active Cu species; and (ii) phase-transfer catalyst for the inorganic catalyst/solvent/substrate/product phases.<sup>8</sup> Study on the detailed mechanism is in progress.

In summary, a mild and efficient tandem method for the synthesis of 2-aminobenzothiazoles has been demonstrated. The results showed that TBAB could improve the reaction. In the presence of CuBr and TBAB, a variety of 2-halobenzenamines underwent the tandem reaction with isothiocyanates smoothly in moderate to excellent yields. It is noteworthy that the reaction is conducted under mild, relatively low catalyst loading, and ligand- and base-free conditions. Further application of the present system in organic synthesis and study of the detailed mechanism are underway.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.086.

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- Typical procedure*: A mixture of 2-halobenzenamine **1** (0.3 mmol), isothiocyanates **2** (0.3 mmol), CuBr (1 mol %), and TBABr (1 equiv) was stirred in DMSO (2 mL) at 40 °C for the indicated time (Tables 1 and 2) until the complete consumption of starting material as monitored by TLC. After the reaction was complete, the mixture was washed with saturated brine and extracted with diethyl ether. The organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum, the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the pure product. *N*-Phenylbenzo[d]thiazol-2-amine (**3**): White solid, mp 158.1–159.3 °C (lit.<sup>12</sup> mp 157.2–159.4 °C); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 10.47 (s, 1H), 7.82–7.78 (m, 3H), 7.59 (s, 1H), 7.39–7.33 (m, 3H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 161.9, 152.4, 141.0, 130.3, 129.3, 126.2, 122.6, 122.4, 121.3, 119.5, 118.1; LRMS (EI, 70 eV) *m/z* (%): 226 (M<sup>+</sup>, 74), 225 (100), 96 (13).
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