



## One-pot copper-catalyzed synthesis of 2-substituted benzothiazoles from 2-iodoanilines, benzyl chlorides and elemental sulfur



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### ABSTRACT

An efficient one-pot three-component reaction of 2-iodoanilines, benzyl chlorides and elemental sulfur to form 2-substituted benzothiazoles in satisfactory yields (up to 98%) has been described. The reaction tolerated a wide range of functional groups on the aromatic ring. And heterocycle methylene chlorides substrates were also found to be compatible.

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2-Substituted benzothiazoles are one important class of bicyclic privileged substructures present in a myriad of natural products and synthetic compounds,<sup>1</sup> and have attracted much attention due to their diverse biological and pharmacological properties, including antitumor,<sup>2</sup> antimicrobial,<sup>3</sup> anti-inflammatory<sup>4</sup> and anti-convulsant activities.<sup>5</sup> Thus, development of efficient methods for the synthesis of these compounds is valuable in drug discovery. Common methods involve the condensation reactions of 2-aminothiophenol with aldehydes, carboxylic acids or  $\alpha$ -ketone acids under oxidative conditions (Scheme 1a),<sup>6</sup> the transition-metal-catalyzed intramolecular cyclization of thiobenzanilides analogues (Scheme 1b),<sup>7</sup> Cu-catalyzed three-component reaction of 2-iodoanilines, aldehydes or benzylamine, and elemental sulfur to form benzothiazoles in a one-pot procedure (Scheme 1c),<sup>8</sup> the redox condensation of *o*-halonitrobenzenes, elemental sulfur and benzylamines, arylacetic acids or methylhetarene (Scheme 1d).<sup>9</sup> However, these methods have several shortcomings, such as pre-functionalization of the starting materials, employing expensive ligands or catalysts, unsatisfactory yields, harsh reaction conditions, etc.

Recently, our group successfully used benzyl chloride as the new carbon source, for the synthesis of 2-arylbenzothiazole derivatives via a three component reaction.<sup>10</sup> Inspired by this results, we wish to develop a one-pot synthetic approach for the synthesis of

2-substituted benzothiazoles from easily available 2-iodoanilines, benzyl chlorides and elemental sulfur (Scheme 1e).

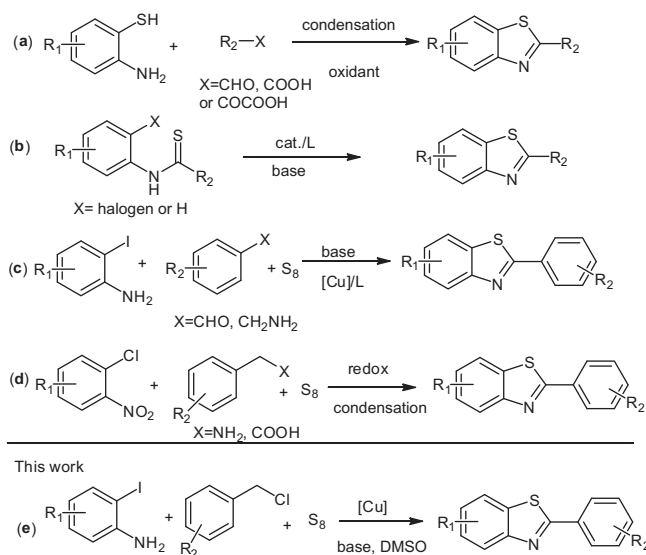
The reaction was optimized by varying different parameters using a model reaction of 2-iodoaniline (**1a**) and benzyl chloride (**2a**) in the presence of elemental sulfur (Table 1). The study was commenced using  $K_2CO_3$  in DMSO under nitrogen atmosphere at 100 °C for 24 h, which led to the formation of desired product 2-arylbenzothiazole (**3aa**) in 47% yield (Table 1, entry 1). Increasing the reaction temperature to 130 °C improved the product yield considerably (92%, entries 2–4). Comparison of different Cu(II) salts indicated that  $Cu(OAc)_2 \cdot H_2O$  was superior to other sources, including  $Cu(OAc)_2$ ,  $CuSO_4$  and  $CuO$  (Table 1, entries 4–7). However, the reaction did not take place with  $CuI$  and a lower yield was obtained when copper powder and  $FeCl_3 \cdot 6H_2O$  were chosen as catalysts (Table 1, entries 8–10). Subsequently, various bases were tested for this reaction, among them  $Na_2CO_3$  showed the best efficiency (Table 1, entries 11–14). Furthermore, reducing the amount of elemental sulfur (4 equiv. changed to 3 equiv.) resulted in a lower yield, and 89% yield was obtained (Table 1, entry 15). To our delight, the desired product **3aa** could be isolated in moderate yields when we replaced 2-iodoaniline with 2-bromoaniline, or benzyl chloride with benzyl bromide (Table 1, entries 16–17). Conducting the reaction under air atmosphere restrained the result (Table 1, entries 18). Finally, changing the equivalent of the base or catalyst didn't improve the reaction yield (Table 1, entries 19–22).

With the optimized reaction conditions in hand, we then examined the scope of the reaction. The results of 2-iodoaniline **1a** with

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**Scheme 1.** Different routes for the synthesis of 2-substituted benzothiazoles.**Table 1**  
Reaction conditions optimization.<sup>a</sup>

Entry	Catalyst (mol %)	Base	Temperature (°C)	Yield <sup>b</sup> (%)
1	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	100	47
2	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	110	80
3	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	120	86
4	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	130	92
5	Cu(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	130	90
6	CuSO <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	130	50
7	CuO	K <sub>2</sub> CO <sub>3</sub>	130	68
8	CuI	K <sub>2</sub> CO <sub>3</sub>	130	0
9	Cu	K <sub>2</sub> CO <sub>3</sub>	130	60
10	FeCl <sub>3</sub> ·6H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	130	43
11	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	NaOH	130	38
<b>12</b>	<b>Cu(OAc)<sub>2</sub>·H<sub>2</sub>O</b>	<b>Na<sub>2</sub>CO<sub>3</sub></b>	<b>130</b>	<b>97</b>
13	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	NaHCO <sub>3</sub>	130	Trace
14	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	KHCO <sub>3</sub>	130	Trace
15 <sup>c</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	130	89
16 <sup>d</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	130	67
17 <sup>e</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	130	77
18 <sup>f</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	130	80
19 <sup>g</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	130	83
20 <sup>h</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	130	86
21 <sup>i</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	130	52
22 <sup>j</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	130	96

<sup>a</sup> Reaction conditions: 2-iodoaniline **1a** (0.5 mmol), benzyl chloride **2a** (1 mmol), elemental sulfur (2 mmol), catalyst (20 mol%) and base (1 mmol) in DMSO (3 mL) under nitrogen atmosphere at 130 °C for 24 h.

<sup>b</sup> Isolated yields.

<sup>c</sup> S<sub>8</sub> 3 equiv.

<sup>d</sup> **1a** = 2-bromoaniline.

<sup>e</sup> **2a** = benzyl bromide.

<sup>f</sup> Air atmosphere.

<sup>g</sup> Base 1.5 equiv.

<sup>h</sup> Base 2.5 equiv.

<sup>i</sup> Catalyst (15 mol%).

<sup>j</sup> Catalyst (25 mol%).

various benzyl chlorides under standard reaction conditions were shown in Table 2. A variety of benzyl chlorides with both electron-donating and electron-withdrawing groups afforded the corresponding 2-substituted benzothiazole derivatives in moderate to excellent yields (53–98%) (**3ab–3ao**). For example, benzyl chloride containing electron-donating groups such as 2-methyl, 3-methyl, 4-methyl, 3-methoxy, 4-methoxy, 3,4-dimethoxy, and 4-*tert*-butyl groups provided the desired products in 55–98% yields (**3ab–3ah**). It is worthy to note that *meta*-methyl or *meta*-methoxy benzyl chloride could provide the corresponding products with higher yields than *para*-methyl or *para*-methoxy benzyl chloride (**3ac, 3ae** vs **3ad, 3af**). On the other hand, 2-iodoaniline with electron-withdrawing benzyl chloride generated the corresponding products in 53–96% yields (**3ai–3ao**). It is particularly noteworthy that the use of the *meta*-bromo benzyl chloride proved to be more effective compared with *ortho*- and *para*-bromo benzyl chloride, resulting in the formation of the corresponding 2-substituted benzothiazoles derivatives in excellent yields (**3am–3ao**). Heteroaromatic methyl chlorides also worked well under standard conditions and offered **3ap–3au** in satisfactory yields, especially **3ar**, a dinitrogen donor, was obtained in 90% yield.

To expand the scope of this methodology, we also examined a series of substituted 2-haloanilines. As summarized in Table 3, several functional groups, such as trifluoromethyl, fluoro, chloro, and methyl groups, were well-tolerated under the standard reaction conditions and gave the corresponding benzothiazoles in moderate to excellent yields ranging from 59% to 98% (**3ba–3ha**). When the substituted 2-haloanilines were substituted 2-iodoaniline (**3ba–3fa**), the yield of target products were above 90%. In addition, substituted 2-bromoaniline (**3ga, 3ha**) could also be converted into the corresponding products in spite of lower efficiency.

To further clarify the mechanism, some control experiments were carried out as shown in Scheme 2. According to the results of this transformation, first of all, the reaction was carried out using benzyl chloride and Na<sub>2</sub>CO<sub>3</sub> in DMSO for 5 h to provide benzaldehyde in 94% yield (Scheme 2A). Subsequently, the reaction was carried out using 2-iodoaniline, benzyl chloride and Na<sub>2</sub>CO<sub>3</sub> in DMSO to provide *N*-benzyl-2-iodoaniline **4** in 78% yield and a small amount of benzaldehyde (Scheme 2B). It showed that benzyl chloride first reacted with 2-iodoaniline to generate **4**, then excessive benzyl chloride was oxidized to benzaldehyde. Subsequently, the reaction of **4** with elemental sulfur afforded 2-substituted benzothiazoles and *N*-(2-iodophenyl)benzothioamide in a trace amount (Scheme 2C). Whereas, in the presence of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O, a significant increase in yield of target product was observed, which demonstrated that a copper catalytic cycle was involved in this reaction (Scheme 2D). In addition, the reaction was carried out using 2-iodoaniline, benzaldehyde and elemental sulfur under the standard reaction conditions to provide **3aa** in 96% yield (Scheme 2E).

On the basis of the above observations and previous literature, an outline mechanism is proposed and shown in Scheme 3. Firstly, 2-iodoaniline **1a** reacts with benzyl chloride **2a** to form *N*-benzyl-2-iodoaniline **4**.<sup>11</sup> Then the copper-catalyzed coupling of *N*-benzyl-2-iodoaniline **4** with sulfur powder provides a disulfide product **5**.<sup>12</sup> The disulfide product **5** is unstable and will fracture to produce intermediate **6** in alkaline conditions.<sup>13</sup> Subsequently, intermediate **6** undergoes an intramolecular nucleophilic attack as well as addition to produce intermediate **7**.<sup>14</sup> Finally, an oxidative dehydrogenation sequence affords the desired product benzothiazole **3aa**.<sup>15</sup> Considering the fact in control experiments Scheme 2A, B and E, an alternative approach to the product **3aa** is also possible: First of all, benzyl chloride was generated benzaldehyde under the action of base and DMSO, then reacted with 2-iodoaniline **1a** and elemental sulfur to generated the target product under the copper salt catalyst.<sup>8</sup>

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