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Cu-Catalyzed Three-Component Synthesis of Substituted Benzothiazoles in Water

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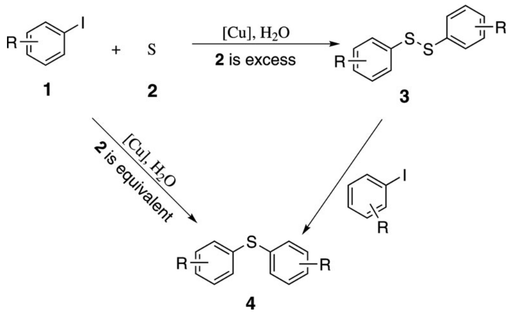
Multicomponent reactions (MCRs), by virtue of high selectivity, atom economy, and convergence,[1] have gained considerable and steadily increasing interest recently. Compared with the classical step-by-step formation of individual bonds for a given target molecule, the utmost attribute of MCRs is the inherent formation of several bonds in one operation, without isolating the intermediates, changing the reaction conditions, or adding further reagents.[2] Consequently, multicomponent reactions have served as a powerful tool in synthetic chemistry.

Substituted benzothiazoles have been widely known as prominent agents with a broad spectrum of pharmaceutical activities, namely as antitumor agents,[3] orexin receptor antagonists,[3,4] and as Gram-positive selective antibacterials.[5] Normally, the classical strategies to synthesize the benzothiazole framework are based on the condensation reaction of 2-aminothiophenols with carboxylic acids, nitriles, or aldehydes, which is limited by the difficulty to obtain the unstable 2-aminothiophenol substrates.[6] To overcome this drawback, some more sustainable cross-coupling reactions to prepare the target heterocycles under comparatively milder reaction conditions have recently been developed. For example, 2-substituted benzothiazoles was obtained by copper- or palladium-catalyzed intramolecular cross-coupling reactions starting from an amine.[7] In most cases such processes require the Lawesson reagent to convert the amides into the corresponding thioamides, which is generally not feasible for substrates containing functional groups such as ketone, ester, and amide moieties. Recently, Itoh and Ma et al. developed a novel and practical synthesis of benzothiazoles by using a cross-coupling reaction between 2-haloanilides and metal sulfides[8] and 2-ethylhexyl-3-mercaptopropionate.[9]

During our studies of copper-catalyzed reactions in water, we found that iodobenzene (**1**) reacted with an excess amount of elemental sulfur (**2**) to form diphenyldisulfide **3** or in the presence of a different molar ratio between iodobenzene and sulfur formed diphenylsulfide **4** (Scheme 1).[10]



Scheme 1. Reaction of iodobenzene with sulfur powder.

Moreover, diphenyldisulfide **3**, when treated with excess iodobenzene, formed the stable product **4**. In addition, Ma and Jiang have already reported that sulfur powder could be used as a coupling partner for copper-catalyzed arylation.[11c] On the basis of these results, we assumed that the nucleophilic reagent **3** could react with another component, leading to the formation of new compounds. Indeed, three-component reactions involving 2-iodoaniline, aldehydes, and sulfur powder work well to afford benzothiazoles in water and the results are reported herein.

Our initial efforts focused on searching for an efficient catalytic system based on 2-iodoaniline, benzaldehyde, and sulfur powder as model substrates. As shown in Table 1, among the different ligands examined, **L1** (1,10-phenanthroline) exhibited the highest catalytic activity in 81% yield (Table 1, entries 1–5). Control experiments indicated that the use of metal and ligand was essential, only 13% or trace amounts of product were obtained in the absence of a ligand or catalyst (Table 1, entries 6 and 7). Comparison of different copper sources indicated that $CuCl_2$ was superior to other sources, including $Cu(OAc)_2$, $CuSO_4$, CuI, and Cu_2O (Table 1, entries 8–11). The base screening suggested that K_2CO_3 was optimal (Table 1, entries 12–15). Reaction time was another important factor to affect the results. When the reaction time was decreased to 12 h, the yield of the desired product dropped to 80% (Table 1, entry 16).

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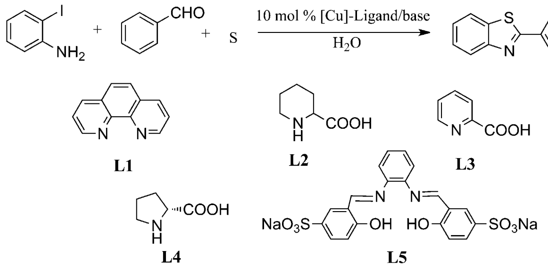
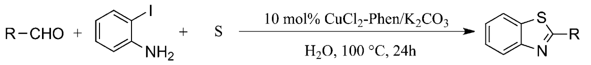
Table 1. Screening of catalysts and reaction conditions for the catalytic three-component reaction.[a]

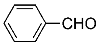
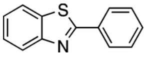
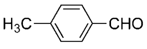
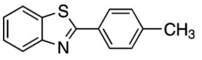
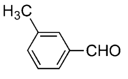
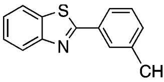
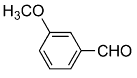
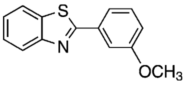
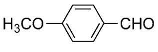
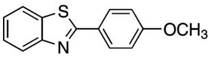
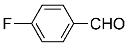
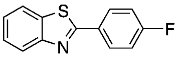
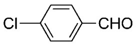
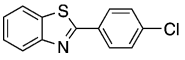
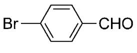
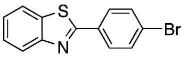
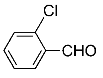
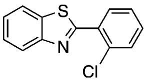
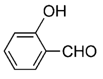
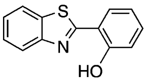
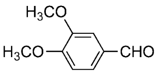
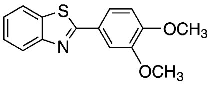
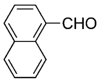
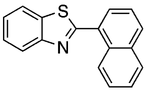
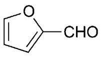
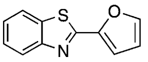
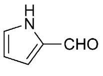
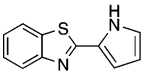
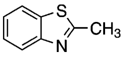
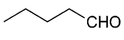
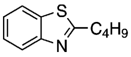


Entry	[Cu]	Ligand	Base	Yield [%][b]
1	CuI	**L1**	K_2CO_3	81
2	CuI	**L2**	K_2CO_3	58
3	CuI	**L3**	K_2CO_3	20
4	CuI	**L4**	K_2CO_3	19
5	CuI	**L5**	K_2CO_3	72
6	CuI	–	K_2CO_3	13
7	–	–	K_2CO_3	trace
8	$CuSO_4{\cdot}5H_2O$	**L1**	K_2CO_3	84
9	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	92
10	Cu_2O	**L1**	K_2CO_3	72
11	$Cu(OAc)_2{\cdot}H_2O$	**L1**	K_2CO_3	82
12	$CuCl_2{\cdot}2H_2O$	**L1**	Cs_2CO_3	75
13	$CuCl_2{\cdot}2H_2O$	**L1**	Na_2CO_3	88
14	$CuCl_2{\cdot}2H_2O$	**L1**	K_3PO_4	87
15	$CuCl_2{\cdot}2H_2O$	**L1**	NaOH	77
16[c]	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	80
17[d]	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	42

[a] All reactions were carried out using 2-iodoaniline (0.3 mmol), benzaldehyde (0.4 mmol), sulfur powder (0.9 mmol), Cu source and ligand (0.03 mmol), and base (0.6 mmol) in water (3 mL) at 100 °C for 24 h. [b] Isolated yield. [c] The reaction time was 12 h. [d] The reaction temperature was 80 °C.

Table 2. Catalytic three-component reaction by using different aldehydes.[a]



Entry	Aldehyde	Product		Yield [%][b]
1			**a**	92
2			**b**	84
3			**c**	82
4			**d**	85
5			**e**	92
6			**f**	86
7			**g**	96
8			**h**	89
9			**i**	94
10			**j**	90
11			**k**	93
12			**l**	83
13			**m**	72
14			**n**	63
15	H_3C-CHO		**o**	52
16			**p**	63

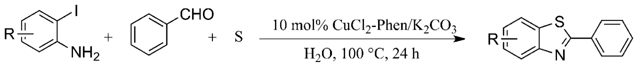
[a] All reactions were carried out using *o*-iodoaniline (0.3 mmol), aldehyde (0.4 mmol), sulfur powder(0.9 mmol), Cu source and ligand (0.03 mmol) and base(0.6 mmol) in water (3 mL). [b] Isolated yield.

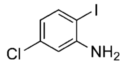
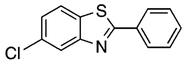
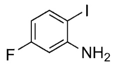
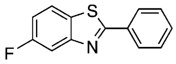
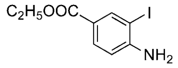
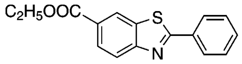
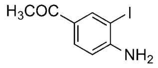
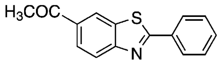
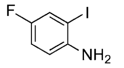
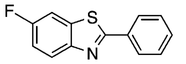
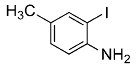
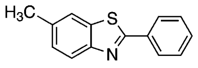
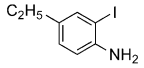
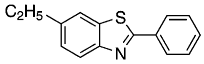
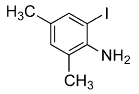
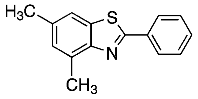
Furthermore, lower temperatures resulted in lower yields, and only a 42 % yield was obtained at 80 °C (Table 1, entry 17). Thus, the optimal catalytic conditions consist of $CuCl_2{\cdot}2H_2O$ (10 mol %), **L1** (10 mol %), and K_2CO_3 (2 equiv) in water at 100 °C for 24 h.

Then, a variety of aldehydes were examined under the optimized reaction conditions to explore the scope of the substrates. As shown in Table 2, benzaldehydes containing electron-donating and withdrawing groups were employed to afford the corresponding benzothiazoles in good to excellent yields ranging from 82 to 94 %. No significant substituent effect was observed (Table 2, entries 2–12). Furthermore, some heterocyclic aldehydes such as pyrrole-2-carboxaldehyde, furfuraldehyde, and aliphatic aldehydes such as acetaldehyde and pentaldehyde were also investigated and found to form the desired products in moderate yields ranging from 52 to 72 % (Table 2, entries 13–16).

To expand the scope of this the methodology, we also examined a series of substituted 2-iodoanilines. As summarized in Table 3, several functional groups, such as fluoro, chloro, bromo, ketone, and ester groups, are well-tolerated under the reaction conditions and give the corresponding benzothiazoles in moderate to excellent yields (Table 3). Furthermore, substitution at the 4-position showed more influence than substitution at the 5-position. For example, when 2-iodo-4-fluoroaniline or 2-iodo-4-methylaniline were used in place of 2-iodoaniline, the yields changed dramatically from 92 to 60 or 91 %, respectively, which indicated that electron-donating groups that were *para* to the amino group benefited the catalysis (Table 2, entry 1 and Table 3, entries 5 and 6). Furthermore, electron-withdrawing groups in the 4-position promote the intermolecular coupling reaction of 2-iodoaniline, which forms the main side product of this reaction, phenazines (Table 3, entries 3–5). Meanwhile, when 2-iodo-5-fluoroaniline was used in place of 2-iodoani-

Table 3. Catalytic three-component reaction by using different 2-iodoanilines.[a]

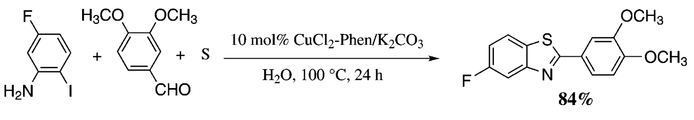


Entry	2-Iodoaniline	Product		Yield [%][b]
1			**q**	86
2			**r**	90
3			**s**	64
4			**t**	51
5			**u**	60
6			**v**	91
7			**w**	90
8			**x**	91

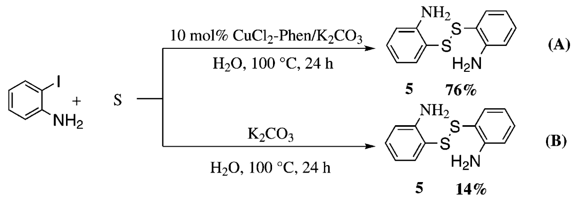
[a] All reactions were carried out using *o*-iodoaniline (0.3 mmol), benzaldehyde (0.4 mmol), sulfur powder (0.9 mmol), Cu source and ligand (0.03 mmol), and base (0.6 mmol) in water (3 mL). [b] Isolated yield.

line, the yields remained quite stable at around 90% (Table 2, entry 1 and Table 3, entry 2). These phenomena might be caused by the fact that the 4-substituted electron-donating groups could stabilize the intermediate radical **III** in Scheme 6 to form benzothiazole products.

Finally, PMX 610, which is a potential antitumor agent, could also be prepared by this method starting from 5-fluoro-2-iodobenzenamine and 3,4-dimethoxybenzaldehyde in a good yield of 84% (Scheme 2).[3] It was formerly obtained by a more complicated multiple step procedure.[6g,j]

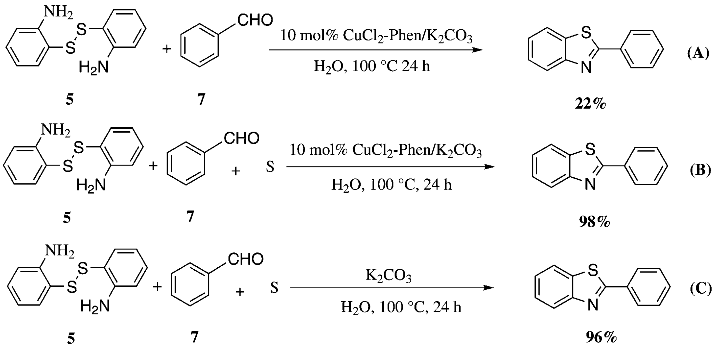


Scheme 2. Synthesis of PMX 610 in water.

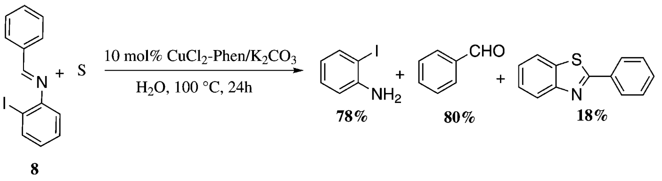


Scheme 3. Reaction of 2-iodoaniline with sulfur powder.

To explore the catalytic mechanism, the following experiments were performed as shown in Scheme 3. 2-Iodoaniline reacted well with sulfur powder to provide diaryl disulfide (**5**) in 76% yield (Scheme 3A), whereas only a small amount of **5** was observed in the absence of the Cu source and ligand (Scheme 3B). This experiment demonstrates the essential role of the copper catalyst for this reaction. Next, the reaction of **5** with benzaldehyde afforded the desired product in a lower yield of 22% (Scheme 4A). Whereas, in the presence of sulfur powder (2 equiv), a significant increase in yield was observed (Scheme 4B). This result suggested that the sulfur powder serves as both the sulfur source and reaction promoter. Astoundingly, the reaction can proceed well in the absence of catalyst (Scheme 4C). Thus, the copper catalyst only promotes the coupling reaction of 2-iodoaniline with sulfur powder. Ultimately, a control experiment was performed as shown in Scheme 5, the reaction of imine **8** with sulfur powder provided hydrolyzed product as the main product and a small amount of the desired product 2-phenylbenzothiazole after 24 h. This experiment proved that the three-component reaction of 2-iodoaniline, aldehydes, and sulfur powder proceeds mainly through compound **5**, not imine **8**.

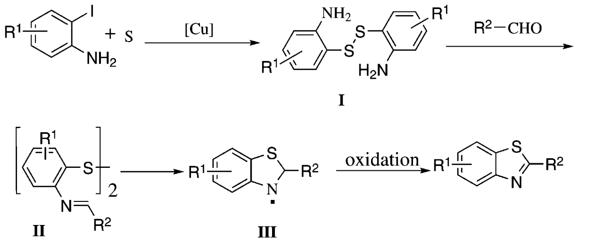


Scheme 4. Reaction of diaryl disulfides with benzaldehyde.



Scheme 5. Reaction of sulfur powder with *N*-benzylidene-2-iodoaniline **8**.

According to the above observations, a tentative mechanism for the formation of 2-arylbenzothiazoles was proposed based on previous reports in the literature.[11] As shown in Scheme 6, the copper-catalyzed coupling of 2-iodoaniline with sulfur powder first provides a diaryl disulfide product **I**. Then, a nucleophilic addition–elimination reaction of **I** with an aldehyde affords intermediate **II**, and intramolecular nucleophilic addition of the disulfides to the $C{=}N$ bond in **II** gives **III.** Finally, further oxidation of **III** provides the target product.



Scheme 6. Possible mechanism for Cu-catalyzed three-component synthesis of substituted benzothiazoles.

In summary, we have developed an efficient, simple, and environmentally friendly three-component reaction of *o*-iodoaniline, aldehydes, and sulfur powder to form benzothiazoles in a simple one-pot procedure. In this catalytic system, neat water is used as the solvent. The tolerance of diverse functional groups makes the present system attractive. To the best of our knowledge, this is the first example to use sulfur powder as the sulfur source in the synthesis of substituted benzothiazoles in water. Considering the inexpensive catalytic system, and the readily available starting materials, this strategy would thus be highly useful in the synthesis of biologically important compounds containing a benzothiazole framework.

Experimental Section

General procedure: 2-Iodoaniline (0.3 mmol), benzaldehyde (0.4 mmol), sulfur powder (0.9 mmol), $CuCl_2 \cdot 2H_2O$ (0.03 mmol), 1,10-Phen **L1** (0.03 mmol), and K_2CO_3 (0.6 mmol) in water (3 mL) were put into a Teflon septum screw-capped tube. The reaction mixture was stirred at 100 °C for 24 h without an inert gas atmosphere and then cooled to room temperature and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography to afford the corresponding product.

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Keywords: catalysis · copper · heterocycles · multicomponent reactions · sulfur

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