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Elemental Sulfur-Mediated Decarboxylative Redox Cyclization Reaction: Copper-Catalyzed Synthesis of 2-Substituted Benzothiazoles

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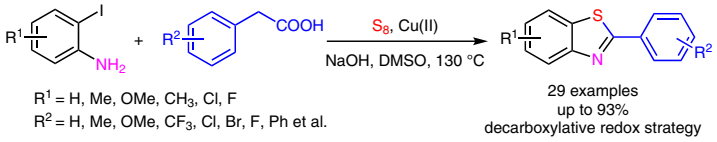

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Abstract A S_8-mediated directed decarboxylative redox-cyclization strategy for the synthesis of 2-substituted benzothiazoles from *o*-iodoanilines, arylacetic acids, and elemental sulfur catalyzed by cheap copper metal has been developed. This reaction is operationally simple, ligand-free, compatible with a wide range of functional groups, and provides the desired products in good to excellent yields. In addition, a gram-scale experiment was carried out to furnish PMX 610, an antitumor drug.

Key words benzothiazoles, decarboxylative cyclization, *o*-iodoanilines, arylacetic acids, elemental sulfur

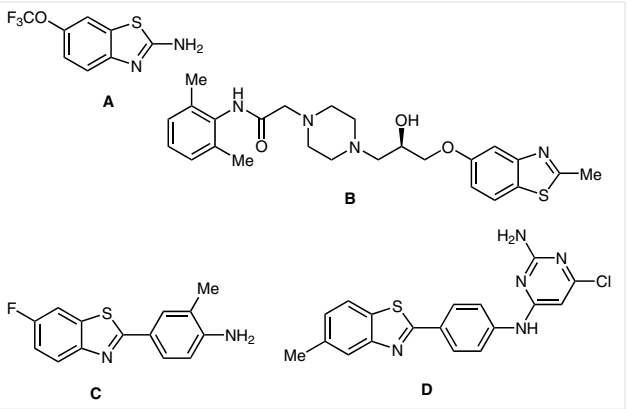
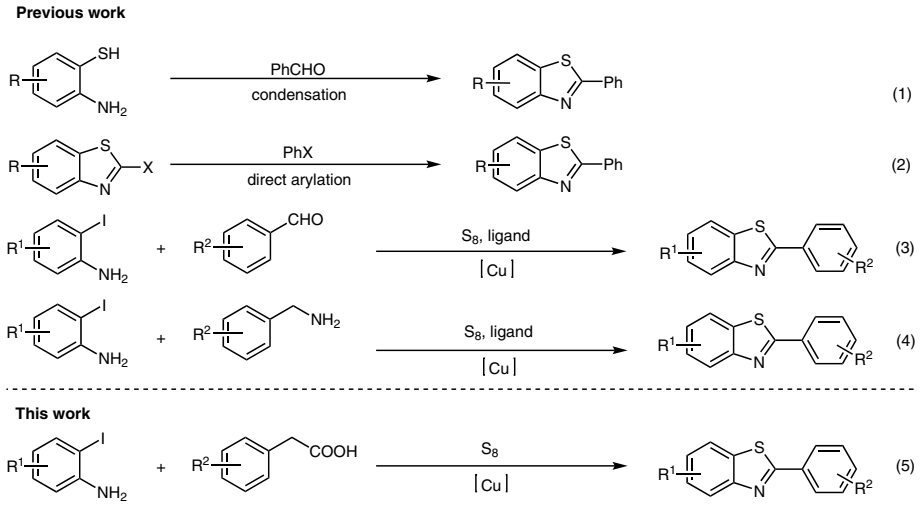


Figure 1 Biologically active benzothiazole derivatives

Among bioactive heterocyclic compounds, 2-substituted benzothiazoles and their corresponding derivatives are ubiquitous structural blocks in pharmaceuticals, agrochemicals, and functional materials due to their physical, chemical, and biological properties, which have captured much attention from organic chemists.[1] Most of them have been extensively studied for their potent biological activities and medicinal value (Figure 1),[2] such as a drug for amyotrophic lateral sclerosis (**A**, Riluzole®),[3a] a fatty acid oxidation inhibitor (**B**, (*R*)-CVT-3501),[3b] an antitumor drug (**C**, 5F203),[3c] and an antibacterial agent (**D**).[3d]

With their superior properties considered, many efforts have been made to develop greener and user-friendly protocols. Over the years, these compounds are synthesized by the condensation of 2-aminothiophenols (Scheme 1, eq. 1),[4] direct arylation via C–H bond functionalization catalyzed by transition metal between benzothiazoles and aryl halides or 2-halide-substituted benzothiazoles with aryl metals (Scheme 1, eq. 2).[5] In 2012, a three-component reaction of 2-iodoanilines, aldehydes, and sulfur powder to form benzothiazoles was reported by Zhou group (Scheme 1, eq. 3).[6] Then later, the Wang group described an efficient method for the 2-substituted benzothiazoles from 2-iodoanilines, benzylamines, and sulfur powder (Scheme 1, eq. 4).[7] However, most of these methods required prefunctionalization of the starting materials, ligand, or drastic reaction conditions. It is highly desirable to develop a simple, mild, and green approach for the synthesis of valuable 2-substituted benzothiazoles.

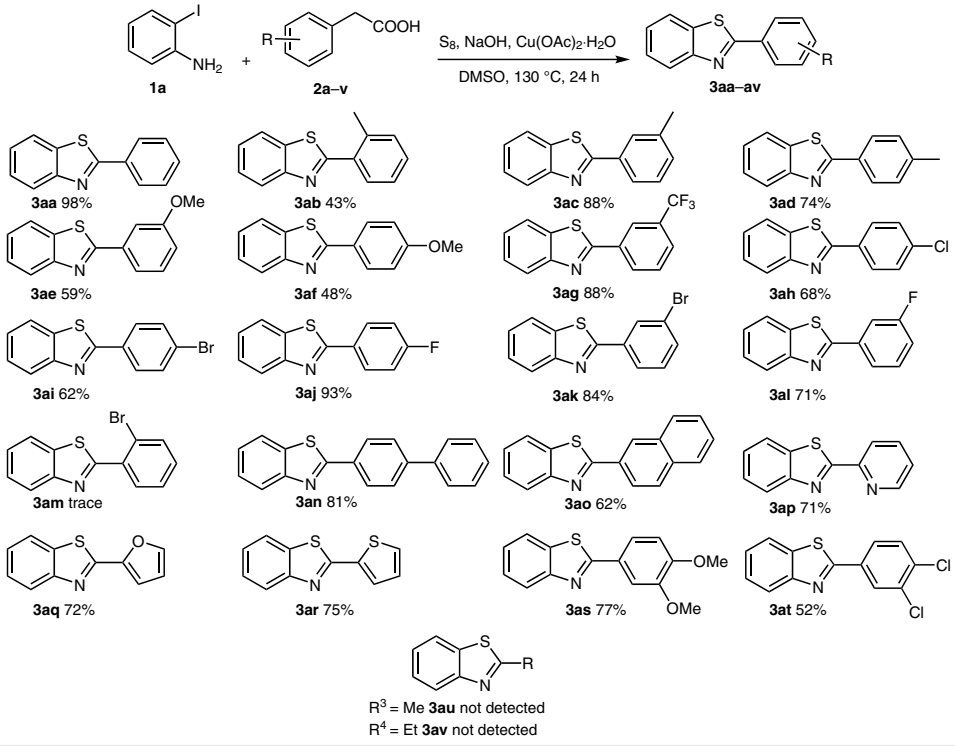
As we all know, decarboxylative reactions have attracted much attention in organic synthesis due to arylacetic acids are common, stable, and nontoxic, which can serve as versatile arylation reagents through metal-mediated decarboxylation to generate aryl-metal intermediates.[8] They have been highlighted by their occurrence in a myriad of



Scheme 1 Different routes for the synthesis of 2-substituted benzothiazoles

natural products and wide applications in pharmaceutical chemistry. Moreover, it is a well-known fact that elemental sulfur can promote the electron transfer in a redox reaction depending on its numerous oxidation states, ranging from –2 to +6. With advances in sulfur-mediated/-catalyzed/-participated reactions, the formation for the construction of C–C and C–X bonds has become a hot spot.[9] As a case study, we disclose herein the development of novel and user-friendly S_8-mediated decarboxylative redox cyclization of *o*-iodoanilines, arylacetic acids, and elemental sulfur to synthesize 2-substituted benzothiazoles (Scheme 1, eq. 5).

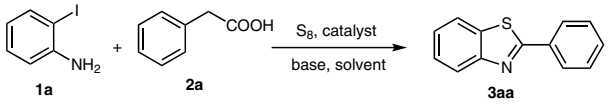
Our initial efforts commenced with the treatment of *o*-iodoaniline (**1a**), arylacetic acid (**2a**), and elemental sulfur using $Cu(OAc)_2{\cdot}H_2O$ as catalyst and K_2CO_3 as base in DMSO



Scheme 2 ·Scope of substituted arylacetic acids. *Reagents and conditions*: **1a** (0.5 mmol, 1 equiv), **2a–v** (0.6 mmol), S_8 (3 equiv), $Cu(OAc)_2{\cdot}H_2O$ (20 mmol%), and NaOH (2 equiv) in DMSO (3 mL) under a nitrogen atmosphere at 130 °C for 24 h. All reported yields are isolated yields.

at 130 ℃ for 24 hours under a nitrogen atmosphere (Table 1). To our delight, the reaction afforded the expected product **3aa** in 61% (Table 1, entry 1). Encouraged by this result, we explored the effect of temperature (Table 1, entry 2), and 130 ℃ was better. To determine the most efficient base for this reaction, various bases were examined (Table 1, entries 3–5), and the results indicated that NaOH is the best one for this redox reaction (Table 1, entry 4). Then a variety of copper salts were screened including Cu(I), Cu(II), and Cu powder. We found that the Cu(II) salts were all excellent (Table 1, entries 6–12), and we chose $Cu(OAc)_2{\cdot}H_2O$ as the best base. Besides, the amount of **2a** was investigated, and it was inferred that 1.2 equivalents of **2a** were more efficient for the reaction (Table 1, entries 13 and 14). When a lower amount of elemental sulfur was tested, three equivalents of elemental sulfur was found to be the best choice (Table 1, entries 15 and 16).

Table 1 Optimization of the Reaction Conditions[a]



1a 2a 3aa

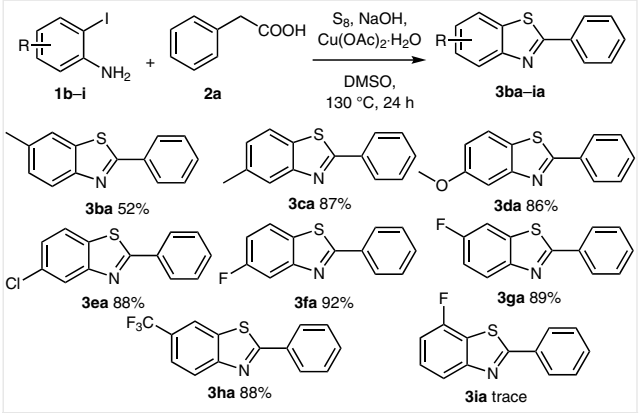
Entry	Catalyst	Temp (°C)	Solvent	Base	Yield (%)[b]
1	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	K_2CO_3	61
2	$Cu(OAc)_2{\cdot}H_2O$	120	DMSO	K_2CO_3	51
3	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	CS_2CO_3	52
4	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	NaOH	95
5	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	KOH	91
6	$CuCl_2{\cdot}H_2O$	130	DMSO	NaOH	93
7	$Cu(OH)_2$	130	DMSO	NaOH	92
8	CuO	130	DMSO	NaOH	92
9	Cu_2O	130	DMSO	NaOH	80
10	CuCl	130	DMSO	NaOH	90
11	CuI	130	DMSO	NaOH	85
12	Cu powder	130	DMSO	NaOH	76
13[c]	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	NaOH	96
14[d]	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	NaOH	92
15[c,e]	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	NaOH	88
16[c,f]	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	NaOH	65
17[c,e]	$Cu(OAc)_2{\cdot}H_2O$	130	DMF	NaOH	23
18[c,e]	$Cu(OAc)_2{\cdot}H_2O$	130	toluene	NaOH	trace
19[c,e]	$Cu(OAc)_2{\cdot}H_2O$	130	NMP	NaOH	36
20[c,e,g]	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	NaOH	84
21[c,e,h]	$Cu(OAc)_2{\cdot}H_2O$	130	DMSO	NaOH	54

[a] The reaction was carried out with **1a** (0.5 mmol, 1 equiv), **2a** (2 equiv), S_8 (4 equiv), base (2 equiv), and Cu source (20 mmol%) in 3 mL solvent under a nitrogen atmosphere for 24 h.
[b] Isolated yields.
[c] **2a** (1.2 equiv).
[d] **2a** (1.0 equiv).
[e] S_8(3 equiv).
[f] S_8 (2 equiv).
[g] 12 h.
[h] The reaction was carried out under an air atmosphere.

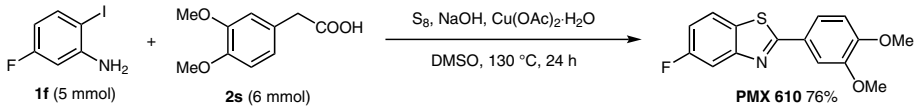
Different solvents were checked, which suggested DMSO performed better as solvent for this reaction (Table 1, entries 17–19). In addition, the yield of **3aa** decreased to 84% when the reaction time was shortened to 12 hours (entry 20). Finally, the product **3aa** was obtained in 54% yield under an air atmosphere (Table 1, entry 21).

With the optimal reaction conditions in hand, the generality of this copper-catalyzed decarboxylative reaction was examined. At first, we investigated the substrate scope of arylacetic acids (Scheme 2). The results showed that arylacetic acids containing not only electron-donating but also electron-withdrawing functional groups can be employed to afford the corresponding benzothiazoles in moderate to excellent yields. Furthermore, in contrast with the yields of methyl-substituted (**3ab**, **3ac,** and **3ad**) and bromo-substituted benzothiazoles (**3ai, 3ak**, and **3am**), we speculated the position of the substituent has some effect on the yield of this coupling reaction. Both 4-biphenylacetic acid and 2-naphthylacetic acid reacted well and gave **3an** and **3ao** in 81% and 62%, respectively. In addition, heteroaromatic arylacetic acids also worked well under standard conditions and offered **3ap–ar** in good isolated yields. Besides, disubstituted arylacetic acids also led to the corresponding 2-substituted benzothiazoles smoothly in moderate to good yields (**3as** and **3at**). The expected products were not detected when alkyl carboxylic acids were used as substrates (**3au** and **3av**).

To extend the potential of this transformation further, a library of *o*-iodoanilines was investigated under the optimized conditions (Scheme 3). The results demonstrated that *o*-iodoanilines bearing electron-rich functional groups could smoothly undergo the transformation in moderate to



Scheme 3 Scope of substituted *o*-iodoanilines. *Reagents and conditions*: **1b–i** (0.5 mmol, 1 equiv), **2a** (0.6 mmol), S_8 (3 equiv), $Cu(OAc)_2{\cdot}H_2O$ (20 mmol%), and NaOH (2 equiv) in DMSO (3 mL) under a nitrogen atmosphere at 130 °C for 24 h. All reported yields are isolated yields.



Scheme 4 A grame-scale experiment of **PMX 610**

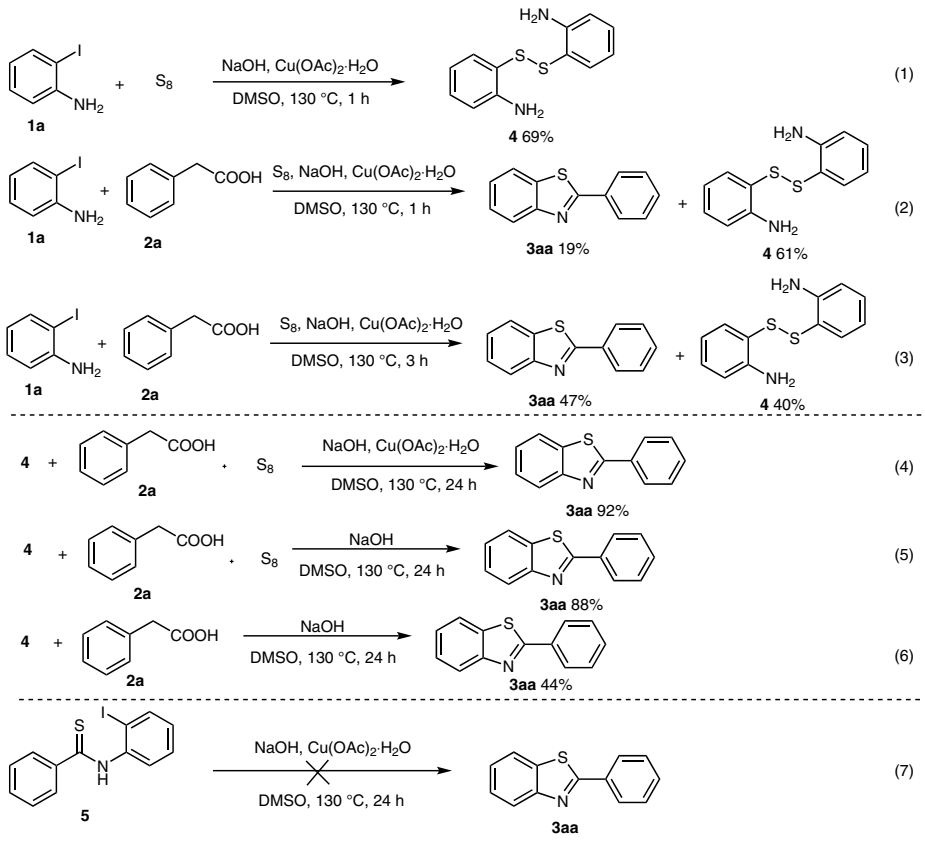
excellent yields (**3ba–da**). Moreover, electron-deficient groups on the aromatic ring also furnished the desired products in 88–92% yields (**3ea–ha**).

Exceptionally, only a trace amount of product **3ia** was obtained when 3-fluoro-2-iodoaniline was used as the substrate, which indicates that the reaction might be affected by steric hindrance.[10]

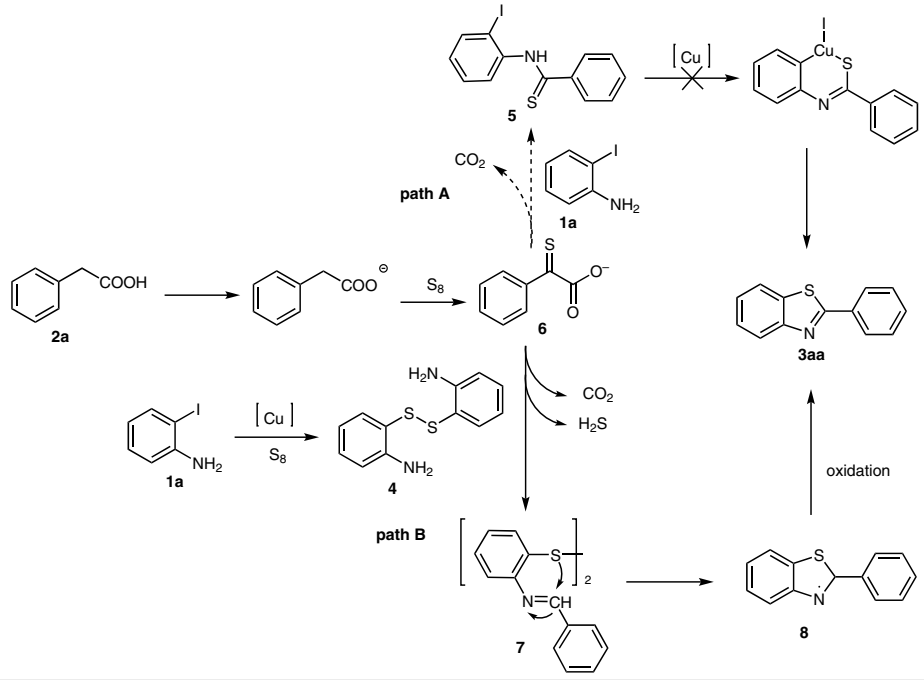
With the consideration of the efficiency of this reaction, a gram-scale experiment was carried out under the standard reaction conditions (Scheme 4). Compound **PMX610** (**3fs**), which shows potent and selective inhibitory activity against lung, colon, and breast cancer cell lines, could be achieved on a 5 mmol scale in 76% isolated yield.[6,10]

Several control experiments were carried out in order to shed light on the possible mechanism of the reaction, as shown in Scheme 5. First of all, *o*-iodoaniline (**1a**) was subjected to elemental sulfur, and diaryl disulfide **4** was formed (Scheme 5, eq. 1). When the mixture of all substrates was reacted for one hour under standard conditions, **3aa** and diaryl disulfide **4** were obtained in 19% and 61%, respectively (Scheme 5, eq. 2).

Then the reaction time was prolonged to three hours and the yield of **3aa** was increased to 47%, accordingly the yield of **4** was decreased to 40% (Scheme 5, eq. 3). Thus it showed that diaryl disulfide **4** may be the key intermediate for the reaction. In addition, we conducted the cross-coupling reaction involving diaryl disulfide **4** with arylacetic acid **2a** (Scheme 5, eq. 4–6): **3aa** was obtained in 92% in the presence of elemental sulfur and $Cu(OAc)_2{\cdot}H_2O$ (Scheme 5, eq. 4). By treatment of **4** with **2a**, **4** was transformed into **3aa** in 88% yield mediated by elemental sulfur (Scheme 5, eq. 5). The yield of **3aa** decreased to 44% in the absence of elemental sulfur and $Cu(OAc)_2{\cdot}H_2O$ (Scheme 5, eq. 6). It proved that elemental sulfur served not only as sulfur source but also as reaction promoter.[5,6,11] According to previous literature,[12] an approach to 2-substituted benzo-



Scheme 5 Control experiments



Scheme 6 Plausible mechanism

thiazoles by the intramolecular coupling reaction of *o*-iodothiobenzanilide **5** was reported, therefore we put forward another hypothesis (Scheme 6, **Path A**). However, the reaction of *o*-iodothiobenzanilide **5** catalyzed by a copper salt failed to afford the target product **3aa** under standard conditions (Scheme 5, eq. 7). This result indicates that compound **5** may not be the intermediate.

On the basis of above-mentioned observations and previous work,[10,13] a tentative mechanism for the product formation is proposed (Scheme 6, **Path B**). At first, arylacetic acid **2a** was deprotonated under alkaline conditions and then reacted with elemental sulfur to sulfide **6**,[14] and at the same time the copper-catalyzed coupling of *o*-iodoaniline (**1a**) with elemental sulfur provided diaryl disulfide product **4**. Then, compound **6** reacted with **4** to yield intermediate **7** by a decarboxylative nucleophilic addition–elimination reaction. Subsequently, intermediate **8** was generated by intramolecular nucleophilic addition, which followed by oxidation reaction to furnish the target product **3aa**.[15]

To sum up, we have developed a novel and efficient copper-catalyzed decarboxylative redox cyclization of readily available *o*-iodoanilines, arylacetic acids, and elemental sulfur to synthesize 2-substituted benzothiazoles without the addition of a ligand or additive.[16] This methodology provides a three-component reaction to afford the corresponding benzothiazoles in moderate to excellent yields. In addition, the approach exhibited good functional-group tolerance. Further study and extension of the present results are underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589112.

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(16) **General Procedure for the Synthesis of Benzothiazoles**

A mixture of *o*-iodoaniline (0.5 mmol, 1 equiv), arylacetic acid (0.6 mmol), elemental sulfur (1.5 mmol), $Cu(OAc)_2·H_2O$ (20 mmol%), and NaOH (1.0 mmol) in DMSO (3 mL) was put into a sealed pressure vessel (25 mL) containing a magnetic stirring bar. The tube was purged with nitrogen three times, and then capped and stirred in a preheated oil bath at 130 °C for 24 h. The reaction mixture then cooled to r.t. and extracted with EtOAc (3 × 10 mL), the organic layer was washed with sat. NaCl (2 × 10 mL), dried over anhydrous Na_2SO_4, evaporated under vacumm, and then purified by silica gel column chromatography (PE–EtOAc 200:1) to give pure compound **3aa** in 98% yield.

Selected Spectral Data for 2-Phenylbenzothiazole (3aa)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.11 (m, 3 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 7.48–7.52 (m, 4 H), 7.38 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0, 154.1, 135.1, 133.6, 130.9, 129.0, 127.5, 126.2, 125.1, 123.2, 121.6.