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Synthetic Methods

S_8-Mediated Cyclization of 2-Aminophenols/thiophenols with Arylmethyl Chloride: Approach to Benzoxazoles and Benzothiazoles

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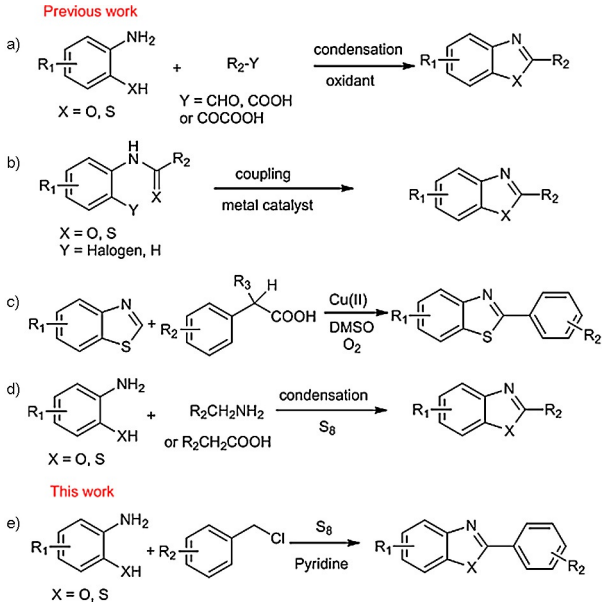
Abstract: A metal-free approach to benzazoles from arylmethyl chlorides and 2-mercaptan/2-hydroxyanilines using elemental sulfur as a traceless oxidizing agent has been developed. The reactions proceeded in good to excellent yields, exhibiting good functional groups tolerance and gram-scale ability. A key mechanistic investigation indicated that the key intermediate trisulfide **6**, which was characterized by NMR, HRMS and crystal X-ray crystallography, was separated in the reaction prior to the formation of the product.

2-Substituted benzazoles are important heterocyclic scaffolds in organic electronic materials, biologically active natural products, and particularly pharmaceutical compounds due to their high biological activities, such as antitumor, antimicrobial, and antiviral properties.[1,2] The development of a promising strategy for the synthesis of benzazoles has attracted much attention in the past decades. Common methods involve the condensation reactions of 2-aminophenols/thiophenols with aldehydes, carboxylic acids, or α-ketone acids under oxidative conditions (Scheme 1 a),[3] a transition-metal-catalyzed intramolecular cyclization of 2-haloanilides/analogues (Scheme 1 b),[4] and a copper-catalyzed oxidative decarboxylative intermolecular arylation of benzothiazoles with phenylacetic acids (Scheme 1 c).[5] However, these methods have one or more shortcomings, such as prefunctionalization of the starting materials, employing transition-metals or excess oxidants, harsh reaction conditions, and so forth.

Element sulfur is readily available, nontoxic, stable under normal conditions, and exists in numerous oxidation states, ranging from −2 to +6, and can form products with a homologous sulfur chain.[6] In recent years, sulfur-mediated/catalyzed/participated reactions have attracted a great deal of attention in organic synthesis for the construction of C–C and C–X bonds.[7] Nguyen[8] and Guntreddi[9] group independently developed S_8-catalyzed cyclization of 2-aminophenols/thiophenols with benzylamines or arylacetic acid (Scheme 1 d). Even so, to explore a new protocol for the synthesis of 2-substituted benzazoles from simple and readily available starting materials is highly urgent. As a continuation of our interest in sulfur-mediated reactions,[10] we disclose a simple and efficient approach to benzazoles by S_8-mediated cyclization of 2-aminophenols/thiophenols with arylmethyl chlorides under metal-free conditions (Scheme 1 e).



Scheme 1. Recent strategy for the synthesis of benzazoles.

We initiated our investigation by using 2-aminothiophenol (**1 a**) with benzyl chloride (**2 a**) as model substrates (Table 1). Different parameters were screened. The use of inorganic bases, such as $NaHCO_3$, Na_2CO_3, and K_2CO_3, in DMSO gave less product (entries 1–3), and other organic bases, such as trimethylamine (TEA), *N*-methylmorpholine, and *N*-methylpiperidine, also performed poorly (entries 4–6). Then, we used pyridine as

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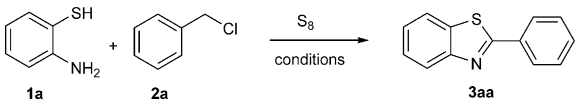
Table 1. Optimization of conditions.[a]



1a 2a 3aa

Entry	Base	Solvent	*T* [°C]	Yield [%][b]
1	$NaHCO_3$ (3 equiv)	DMSO	130	84
2	Na_2CO_3 (3 equiv)	DMSO	130	69
3	K_2CO_3 (3 equiv)	DMSO	130	41
4	TEA	–	130	31
5	NMM	–	130	79
6	*N*-methyl piperidine	–	130	75
7	**Pyridine**	–	**130**	**92**
8	Pyridine	–	150	92
9	Pyridine	–	110	35
10	Pyridine	–	130	92[c]
11	Pyridine	–	130	81[d]
12	Pyridine	–	130	85[e]
13	Pyridine	–	130	90[f]
14	Pyridine	–	130	92[g]
15	Pyridine	–	130	43[h]
16	K_2S	Pyridine	130	74
17	$Na_2S_2O_3$	Pyridine	130	14
18	Na_2SO_3	Pyridine	130	trace

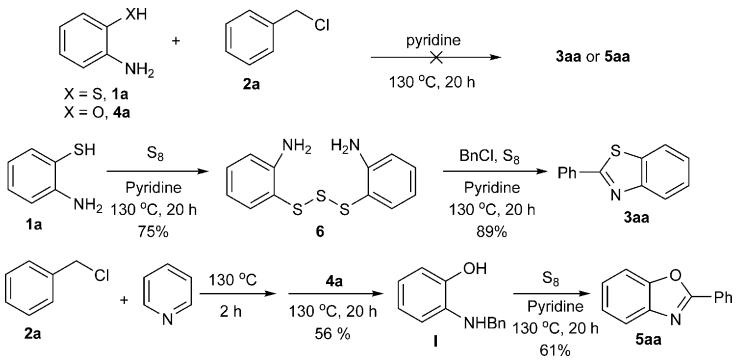
[a] Conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), sulfur (3.0 mmol), solvent (2.0 mL), 130 °C, 20 h under nitrogen atmosphere. [b] Isolated yield. [c] BnCl (1.5 mmol). [d] BnCl (1.0 mmol). [e] Sulfur (2.0 mmol). [f] Sulfur (4.0 mmol). [g] BnBr (1.2 mmol). [h] Under air atmosphere. NMM = *N*-methylmorpholine. Bn = benzyl chloride

base and solvent to explore the reaction. To our delight, the product was obtained in 92% yield at 130 °C for 20 h (entry 7). Increasing the reaction temperature to 150 °C did not enhance the yield of the product (entry 8), whereas decreasing the temperature to 110 °C decreased the yield dramatically (entry 9). Furthermore, changing the equivalent of BnCl and sulfur did not improve the reaction (entries 10–13). In addition, replacing BnCl with BnBr performed equally (entry 14). Conducting the reaction under air restrained the result (entry 15). Finally, different sulfurating reagents, such as K_2S, $Na_2S_2O_3$, and Na_2SO_3, gave less product too (entries 16–18). The optimal reaction conditions were obtained with 2-aminothiophenol (1.0 equiv), BnCl (1.2 equiv), and element sulfur (3.0 equiv) in pyridine (2 mL) at 130 °C for 20 h.

With the optimized conditions in hand, the scope and versatility of substituted benzyl chlorides and 2-aminothiophenols was then examined. The results are summarized in Table 2. Benzyl chlorides possessing electron-donating or weak to moderate electron-withdrawing groups on the aromatic rings gave the desired products **3ab**–**3ao** in 84–96% yields. Notably, the position of the substituents on aromatic rings of benzyl chlorides had little effect (**3ab**–**3ao**), with only *o*-substitution giving slightly inferior yields to *m*- and *p*-substitution (**3ak**, **3ap**), probably as a result of steric hindrance. Besides, 1-naphthylmethyl chloride reacted well to give **3aq** in 73% yield. Heteroaromatic methyl chlorides also worked well under the standard conditions and offered **3ar**–**3au** in moderate to good isolated yield, especially **3as**, a dinitrogen donor, was obtained in 90% yield. 3,4-Dimethoxylbenzyl chloride gave the desired product **3av** in good yield. Furthermore, we have explored different substituted aminothiophenol **1b**–**1e** and found that they were tolerated in the present reaction conditions. Methylbenzothiazole **3be**, a precursor of an imaging agent for amyloid plaques in Alzheimer disease,[1c] was obtained in 81% yield, and fluorinated benzothiazole **3ew** (**PMX 610**), which has a potent and selective inhibitory activity against lung, colon, and breast cancer cell lines,[11] was obtained in 54% yield. Both **3be** and **3ew** could be obtained in a single step from commercially available starting materials. To explore the efficiency of our reaction, a gram-scale experiment was also carried out. **3af** could still be achieved at 5 mmol scale in 80% isolated yield (1.16 g).

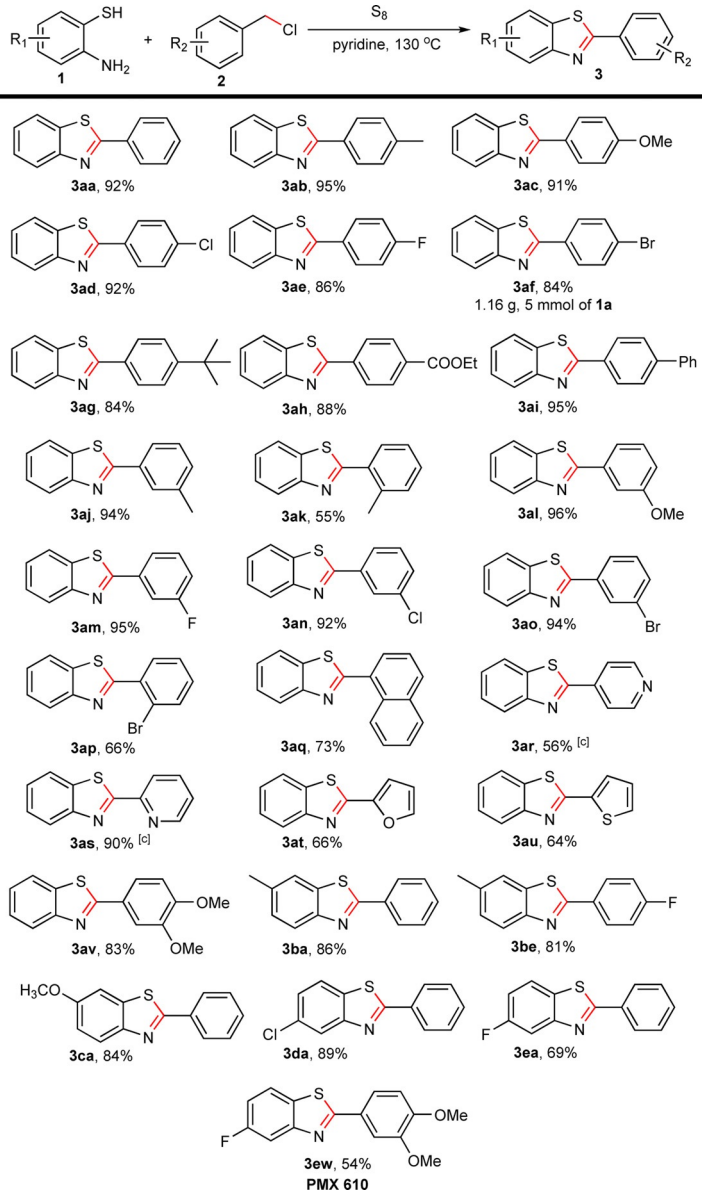
To further establish the general utility of these transformations, 2-aminothiophenol was replaced with 2-aminophenol for the synthesis of benzoxazoles (Table 3). To our delight, 2-phenylbenzoxazole (**5aa**) was obtained in 56% isolated yield under the standard conditions. Benzyl chlorides with an electron-donating group in the *para*-position afforded **5ab**–**5ad**, and **5ai** in moderate to good yields, whereas halogen-substituted benzyl chlorides (**2e**–**2g**) offered relatively low yield (**5ae**–**5ag**). Benzyl chlorides with *meta*-position substituents, such as methyl group (**2j**), methoxy group (**2k**), and halogens group (**2e**–**2g**), provided **5aj**–**5an** in 54–60% yields. Moderate electron-withdrawing substituents at the *para*-position (**2h**) gave **5ah** in 52% yield. Besides, different substituted aminophenols **4b**–**4e** were tolerated in the present reaction conditions. 5-Methyl-2-aminophenol (**4b**) afforded **5ba** in 75% yield, whereas 4-methyl-2-aminophenol (**4c**) afforded **5ca** in 51% yield. Halogen-substituted aminophenols **4d** and **4e** provided **5da** and **5ea**, respectively, in moderate yields.

In order to gain an opinion on the reaction mechanism, we conducted some control experiments as following: Treatment of **1a** or **4a** with **2a** in pyridine (2 mL) at 130 °C for 20 h did not give the desired product **3aa** or **5aa** (Scheme 2). Element sulfur with **4a** in pyridine (2 mL) at 130 °C for 20 h provided trisulfide **6**, which was confirmed by crystal X-ray crystallography[12] (Figure 1), in 75% isolated yield and was subsequently subjected to the standard conditions to afford **3aa** in 89% isolated yield. Furthermore, **2a** was reacted with pyridine (2 mL) at 130 °C for 4 h, and then **4a** was added and reacted for another 20 h to afford intermediate **I** in 56% isolated yield. Final-



Scheme 2. Control experiments.

Table 2. Substrate scope I.[a,b]



[a] Conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), sulfur (3.0 mmol), solvent (2.0 mL), 130 °C, 20 h under nitrogen atmosphere. [b] Isolated yield. [c] The starting material are 4-(chloromethyl)pyridine hydrochloride and 2-(chloromethyl)pyridine hydrochloride, respectively.

ly, intermediate **I** was treated with sulfur in pyridine (2 mL) at 130 °C for 20 h to provide **5aa** in 61% yield.

Based on the above experiments and related literatures,[8,13] a plausible mechanism is outlined in Scheme 3. In the presence of elemental sulfur and a base, **1a** is oxidized to form trisulfide **6** because of its propensity to form polysulfur chain. Meanwhile, **2a** can easily react with pyridine to give 1-benzylpyridinium chloride **7**. Then, trisulfide **6** can oxidize **7** to afford disulfide **8** and thiobenzaldehyde **9**, which undergoes a nucleophilic addition/elimination reaction to give intermediate **10** followed by an intramolecular cyclization to afford **11**. Finally, dehydrogenation of **11** forms the desired product **3aa**.[14] Indeed, when **1a** was mixed with elemental sulfur, evolution of H_2S was observed even at room temperature. Compound **4a** is alkylated with 1-benzylpyridinium chloride **7** to generate intermediate **I**, which is oxidized by elemental sulfur to give thioamide **II** followed by the cyclization to afford the desired product **5aa**. Related data are showed in the Supporting Information. Notably, the hydroxy group in **4a** renders the *o*-amino group less nucleophilic, and thus less effective for the trans-thioamidation step, which results in lower yield of benzoxazole **5aa** compared to its thio analogues (**3aa**).

In summary, a metal-free approach to benzazoles from arylmethyl chlorides and 2-mercaptan/2-hydroxyanilines using elemental sulfur as a traceless oxidizing agent has been developed. The reactions proceeded in good to excellent yields, exhibiting good functional groups tolerance and gram-scale ability. Primary mechanistic investigations indicated that the key intermediate trisulfide **6**, which was characterized by NMR, HRMS, and crystal X-ray crystallography, was separated in the reaction prior to the formation of the product. The reaction is free from the use of metal and external oxidant, which makes the process attractive and practical. A research on the scope, detailed reaction mechanism, extension to other heteroaromatic substrates of this protocol is currently underway in our laboratory.

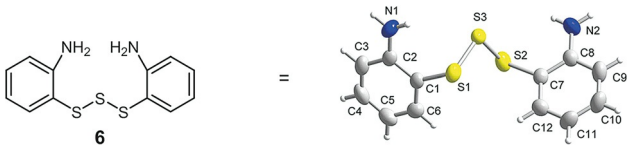


Figure 1. X-ray crystallography of **6**. The probability of atoms is 50%.

Experimental Section

Typical procedure for the synthesis of benzazoles

A mixture of 2-aminothiophenol **1a** (1.0 mmol), benzyl chloride **2a** (1.2 mmol), elemental sulfur (3.0 mmol), and pyridine (2 mL) was placed in a sealed pressure vessel (25 mL) containing a magnetic stirring bar and then capped and stirred at 130 °C for 20 h under nitrogen atmosphere. After the reaction was completed (TLC), the mixture was cooled to room temperature, diluted with methanol (2 mL) and ethyl acetate (10 mL), evaporated in vacuum and purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluent (200:1) to afford the related product **3aa** as a light yellow solid (194 mg, 92% yield).

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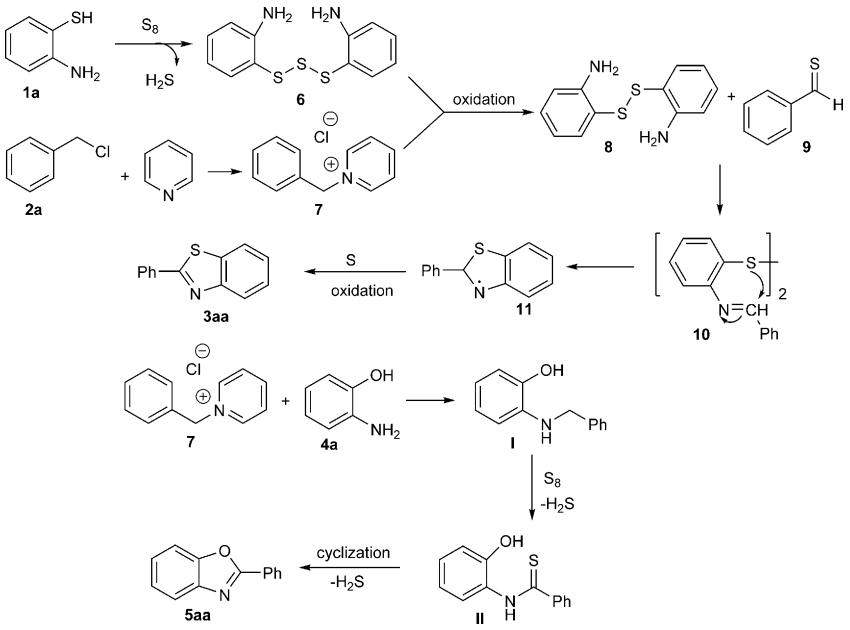
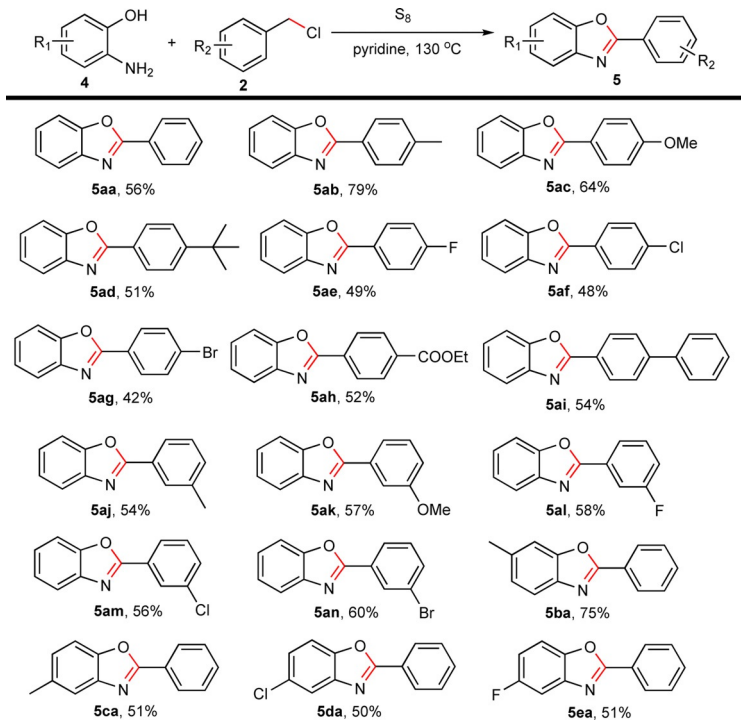


Scheme 3. Proposed mechanisms.

Table 3. Substrate scope II.[a,b]



[a] Conditions: **4a** (1.0 mmol), **2a** (1.2 mmol), sulfur (3.0 mmol), solvent (2.0 mL), 130 °C, 20 h under nitrogen atmosphere. [b] Isolated yield.

Keywords: arylmethyl chlorides · benzothiazoles · benzoxazoles · cyclization · sulfur

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[12] CCDC 1450794 (**6**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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