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Novel synthesis of benzothiazole by self-redox tandem reaction of disulfide with aldehyde

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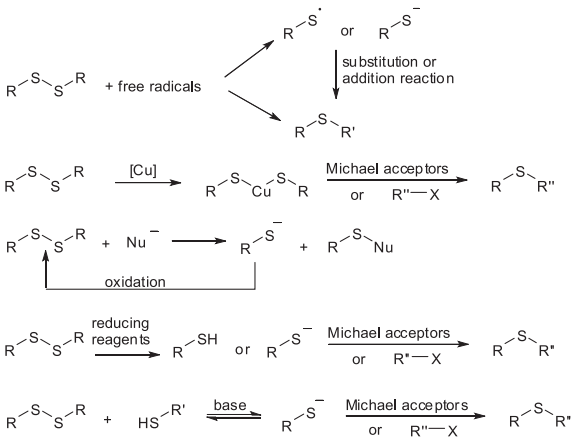
ABSTRACT

A novel methodology for the preparation of benzothiazole derivatives via the reaction of *ortho*-anilino disulfides with aryl and heteroaryl aldehydes catalyzed by $Na_2S \cdot 9H_2O$ has been developed. The reaction mechanism was investigated by LC–MS and ^1H NMR. The disulfide was cleaved firstly by the interchange reaction of the disulfide and metal sulfide, and the resulting thiol reacted in situ with the aldehyde to form the corresponding benzothiazoline. Subsequently, the intermediate benzothiazoline reduced the disulfide to thiol and it was oxidized to benzothiazole. The excess benzothiazoline was oxidized by air and both halves of the disulfide were ultimately converted to the desired benzothiazole.

1. Introduction

Organosulfur compounds are widely observed in natural products and used as drugs.[1] The synthesis of organosulfur compounds has received broad attention in recent years, with various methods developed to construct the C–S bonds.[2] Sulfur, metal sulfides, thiols, and other sulfur reagents have been widely used as sulfur-introducing reagents to prepare organic sulfur-containing molecules.[3] However, most thiols, especially aryl thiols, are readily oxidized to form disulfide.[4] Therefore, nowadays organic disulfides are often used to synthesize complex organosulfur compounds. To utilize the organic disulfide as a sulfur-containing starting material, S–S bond cleavage is the key to the construction of C–S bond. The S–S bond of disulfides is mainly cleaved by free radical reagents (such as *tert*-butyl hydroperoxide, $Na_2S_2O_4$, sodium formaldehyde sulfoxylate, and $K_2S_2O_8$),[5] copper catalysts,[6] nucleophilic reagents,[7] reducing reagents,[8] and thiol–disulfide dynamic interchange reactions.[9] The C–S bond can subsequently be constructed by the tandem substitution or addition reaction of sulfur radicals, thiolate anions, thiolate metal complexes, or thiols formed in situ from disulfides with halides or Michael acceptors (Scheme 1).



Scheme 1. C–S bond formation from disulfide.

Thiol–disulfide dynamic interchange reaction plays an important role in the biochemistry of almost all living organisms.[10] The thiol–disulfide dynamic interchange reaction was first used to prepare diverse benzofused nitrogen–sulfur heterocycles in our previous work.[9b] Recently, Lu prepared sulfides and sulfur heterocycles using this thiol–disulfide exchange reaction.[9c] However, the organic thiols and organic or inorganic bases used in these thiol–disulfide exchange reactions to cleave the S–S bond of disulfide have an unpleasant smell, and another disulfide was produced as

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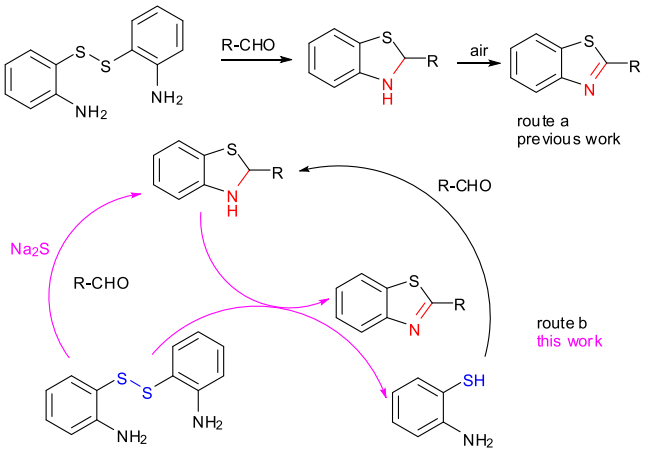
a byproduct.[9b,9c] To overcome these drawbacks, new reagents need to be developed to replace the organic thiols. Metal sulfides are inexpensive, odorless inorganic reagents and are basic. If the interchange reaction between metal sulfide and disulfide could take place, it would be a novel green strategy to break the disulfide bond.

Benzothiazole derivatives exhibit various bioactivities and are used as drugs.[11] Benzothiazole is usually prepared by the condensation of 2-aminobenzenethiols or 2,2′-disulfanediyldianilines, the cyclization of thioformanilides, or the sulfurization of 2-haloanilides.[12] Furthermore, in the reaction of 2,2′-disulfanediyldianilines with aldehydes to prepare benzothiazole, the important intermediate benzothiazoline could be formed, followed by the spontaneous generation of benzothiazole via air oxidation of the benzothiazoline[5b,6b] (Scheme 2, route a). During the process of benzothiazole formation from disulfide, the intermediate benzothiazoline needs to be oxidized, and the starting material disulfide needs to be reduced to 2-aminobenzenethiol through the S–S bond breakage. We postulated whether the oxidation process and reduction process can be coupled in one reaction process under inert atmosphere (Scheme 2, route b). Our experimental results confirmed the plausibility of this methodology. To the best of our knowledge, this is the first successful example of using a metal sulfide as the S–S bond cleaving reagent to catalyze the reaction of a disulfide and an aldehyde, where the intermediate benzothiazoline formed in situ acts as a reducing agent to break the S–S bond of disulfide. Herein we disclose the details of our results.

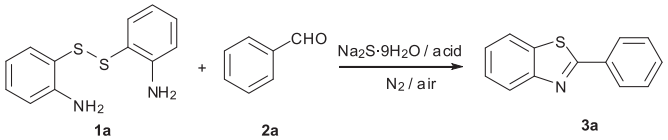


Scheme 2. The process of benzothiazole formation from disulphide.

2. Results and discussion

The reaction of 2,2′-disulfanediyldianiline (**1a**) with benzaldehyde (**2a**) was conducted to screen the optimal reaction conditions, and the results are summarized in Table 1. Initially, the target product 2-phenylbenzothiazole (**3a**) was obtained with only a 21% yield in the presence of catalytic amount of $Na_2S·9H_2O$ in DMF at 100 °C (Entry 1). When $Na_2S·9H_2O$ and $NaHCO_3$ were added to the reaction system, the yield of **3a** was enhanced to 89% (Entry 2). However, when the reaction was conducted in the absence of $Na_2S·9H_2O$ and $NaHCO_3$, the reaction did not take place and no target product could be detected (Entry 3). The target product **3a** could be obtained with only 20% yield solely in the presence of 20 mol% $NaHCO_3$ (Entry 4). These experimental results (Entries 1–4) indicate that $Na_2S·9H_2O$ and $NaHCO_3$ can effectively catalyze the reaction of **1a** and **2a** to afford the target product **3a**. When other solvents such as dioxane, DMSO and NMP were investigated, the results showed that DMF gave the highest yield of **3a** in the reaction process of **1a** and **2a** (Entries 2, 5–7). In the next step, the reaction temperature was examined. The results showed that 100 °C was the most efficient temperature for the reactions of **1a** and **2a** (Entries 2, 8–9). Changing the amount of $Na_2S·9H_2O$ and $NaHCO_3$ from 10 to 100 mol% resulted in little change in the yields of **3a** when the amount of $Na_2S·9H_2O$ and $NaHCO_3$ was between 20 and 100 mol% (Entries 2, 10–12). Furthermore, the weak acid AcOH also could promote the reactions of **1a** and **2a** smoothly in the presence of $Na_2S·9H_2O$ (Entries 13–14). However, only AcOH produced a very low yield of benzothiazole (Entry 15), indicating AcOH was not an efficient catalyst to cleave S–S bond. Therefore, the optimized reaction conditions for the synthesis of benzothiazole were $Na_2S·9H_2O$ (0.2–0.5 equiv), $NaHCO_3$ (or AcOH, 0.2–0.5 equiv), DMF and the reaction mixture were stirred at 100 °C under the inert gas atmosphere for 6 h and subsequently in air for 2 h.

Table 1
Optimization of the reaction conditions for the preparation of 3a[a]



1a 2a 3a

Entry	$Na_2S·9H_2O$	$NaHCO_3$ (equiv.)	Solvent	T (°C)	Yield[b] (%)
1	0.2	—	DMF	100	21
2	0.2	0.2	DMF	100	89
3	—	—	DMF	100	NR
4	—	0.2	DMF	100	20
5	0.2	0.2	Dioxane	100	7
6	0.2	0.2	DMSO	100	21
7	0.2	0.2	NMP	100	62
8	0.2	0.2	DMF	90	33
9	0.2	0.2	DMF	110	60
10	0.1	0.1	DMF	100	10
11	0.5	0.5	DMF	100	88
12	1.0	1.0	DMF	100	86
13[c]	0.2	0.2	DMF	100	82
14[c]	0.5	0.5	DMF	100	89
15[c]	—	1.0	DMF	100	25

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), $Na_2S·9H_2O$ (0.1–1.0 equiv), $NaHCO_3$ (0.1–1.0 equiv), and solvent (3 mL), stirred under N_2 atmosphere for 6 h then under air for 2 h.
[b] Determined by LC analysis.
[c] AcOH was used to replace $NaHCO_3$.

Under the optimized reaction conditions, the scope of this synthetic method was investigated by preparing various 2-substituted benzothiazole derivatives (Table 2), we observed that the reaction could tolerate many functional groups such as chloro, bromo, fluoro, cyano, hydroxyl, 3,4-dimethoxy, 4-methoxy, and methyl groups (Entries 2–9). It was found that the desired product **3** could be obtained with high yields from the reaction of **1a** with electron-withdrawing groups or electron-donating groups on the benzaldehyde. Furthermore, heterocyclic aldehydes such as thiophene-3-carbaldehyde and furan-2-carbaldehyde could also react with **1a** to form the product with high yields (Entries 10–11). A 4-substituted disulfide could also produce the target product with high yield (Entry 12). Sometimes, AcOH should be used to improve the yield of the corresponding target product because the stronger acidity of AcOH compared to that of $NaHCO_3$ could smoothly promote the reaction of **1** with **2**.

To understand the mechanism of formation of benzothiazoles from disulfides and benzaldehyde in the presence of $Na_2S·9H_2O$ and $NaHCO_3$, the reaction of disulfide **1a** with $Na_2S·9H_2O$ and $NaHCO_3$ in DMF was monitored by LC–MS which has been illustrated in Fig. 1. Most of disulfide **1a** was converted to 2-aminobenzenethiol after disulfide **1a** reacted with $Na_2S·9H_2O$ in DMF for 25 min, which suggested that $Na_2S·9H_2O$ could break the S–S bond of the disulfide