Sulfur Disproportionation

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Elemental Sulfur Disproportionation in the Redox Condensation Reaction between *o*-Halonitrobenzenes and Benzylamines

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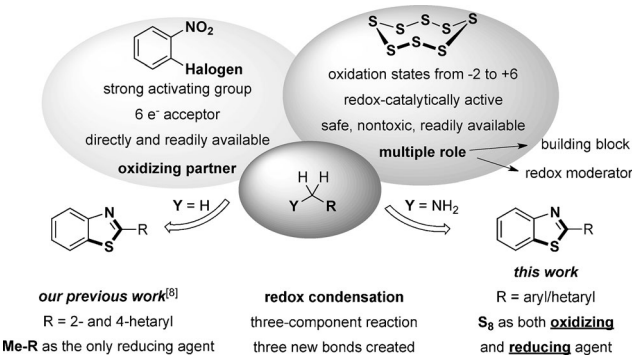
Abstract: *The disproportionation of elemental sulfur at moderate temperatures is investigated in the redox condensation involving o-halonitrobenzenes* ***1*** *and benzylamines* ***2****. As a redox moderator, elemental sulfur plays the dual role of both electron donor and acceptor, generating its lowest and highest oxidation states:* S^{-2} *(sulfide equivalent) in benzothiazole* ***3*** *and* S^{+6} *(sulfate equivalent) in sulfamate* ***4****, and filling the electron gap of the global redox condensation process. Along with this process, a cascade of reactions of reduction of the nitro group of* ***1****, oxidation of the aminomethyl group of* ***2****, metal-free aromatic halogen substitution, and condensation finally led to 2-arylbenzothiazoles* ***3****.*

One of the most challenging requirements in organic synthesis is the development of shortcut approaches to interesting complex molecules from simple, inexpensive, and readily available starting materials. This can be achieved efficiently through cascade and multicomponent processes.[1] Redox condensations have become a powerful synthetic tool thanks to their step- and redox-economical nature when they occur independent of any metal or cofactor. In these transformations, the oxidation degree is adjusted by reorganization of oxidation states between the reaction centers of the oxidizing and reducing partners to yield the final condensed product. Most of the redox condensation reactions reported are based on a balanced two-electron transfer process.[2]

In this context, readily available[3,4] nitroarenes are a very attractive target for reactivity investigation. As a six-electron acceptor, their nitro groups can be transformed to a wide range of useful nitrogen-containing compounds, including amides and aza heterocycles (Scheme 1) without prior reduction into anilines as in most traditional approaches. Moreover, as a powerful electron-withdrawing group, the nitro groups are among the most efficient activating substituents for nucleophilic displacement of an *o*-halo group by other nucleophiles, even without a metal catalyst. Nevertheless, to date only a handful of methodologies have been reported that are able to perform a redox condensation of aromatic nitro groups.[5] This can be explained by the fact that the six-electron transfer to the nitro group is a highly complex cascade process and apparently requires a more efficient electron transfer agent.



Scheme 1. Cascade redox condensation involving *o*-nitrohalobenzenes, elemental sulfur, and a reducing partner leading to benzothiazoles.

Elemental sulfur, which is involved in different types of metabolic processes, could be a promising candidate for such an electron transfer agent. The power of sulfur in mediating/catalyzing/participating in redox reactions relies on its capability to exist in numerous oxidation states, ranging from -2 to $+6$, and to form products with a homologous sulfur chain. Elemental sulfur was reported to play a key role in the anaerobic respiration cycle of several bacteria,[6] both as starting oxidant and reduced product, even before the advent of oxygenic photosynthesis.[7]

Based on these properties, we recently reported a straightforward step- and redox-economical approach to 2-hetaryl benzothiazoles by a reaction involving 2- or 4-aza methylhetarene, *o*-halonitrobenzenes, and elemental sulfur.[8] The electron deficiency in this reaction is compensated by the oxidation of the methylhetarene components. In continuation of reactivity studies of elemental sulfur under metal-free conditions, we wish to generalize this reaction to other substrates for the synthesis of 2-arylbenzothiazoles. We hypothesized that benzothiazoles bearing other 2-aryl groups may be accessible if the methyl groups of the reducing partner methylhetarene are replaced by a more readily oxidizable aminomethyl. Because benzylamines are in general more basic than methylhetarenes, this functional group replacement can maintain and even increase the activation of elemental sulfur.

Herein, we report the first noncatalyzed and general access to benzothiazoles by a redox condensation reaction of *o*-halonitrobenzenes, benzylamines, and elemental sulfur. In particular, we describe a disproportionation behavior of elemental sulfur without a catalyst, thereby filling the electron gap for the unbalanced electron transfer process.

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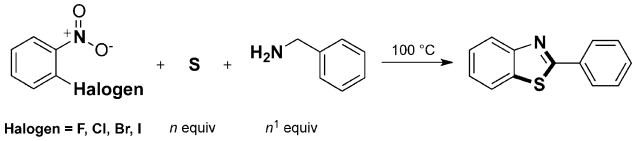
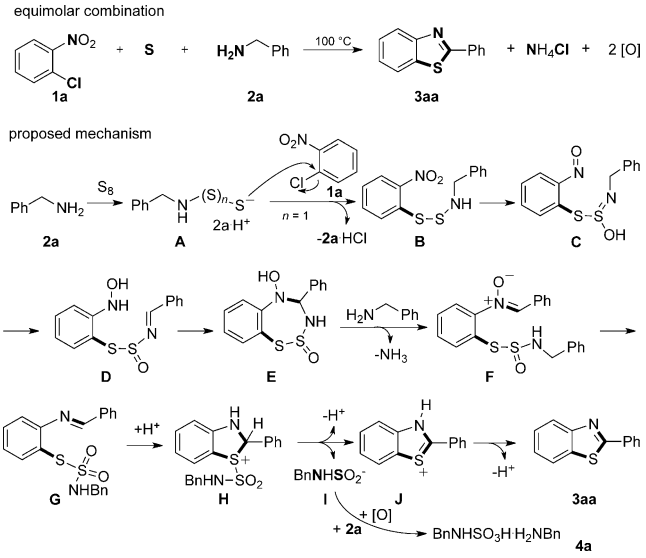
Table 1: Reaction between 2-halonitrobenzenes **1**, benzylamine (**2a**), and elemental sulfur.



Halogen = F, Cl, Br, I (**1**) | *n* equiv | n^1 equiv (**2a**) | (**3aa**)

Entry[a]	X	*n*	n^1	Yield [%]
1	Cl	1.5	2	72
2	Br	1.5	2	76
3	I	1.5	2	72
4	F	1.5	2	25
5[c]	Cl	1.5	2	75
6[d]	Cl	1.5	2.5	52
7[c]	**Cl**	**1.5**	**2.5**	**78**
8	Cl	1.5	3	76
9	Cl	2	2.5	68

[a] Reaction conditions: *o*-halonitrobenzene **1** (5 mmol, 1 equiv), S (*n* equiv, 32 g mol^{-1}), benzylamine (**2a**) (n^1 equiv), 100 °C, 16 h. [b] Yield of the isolated product. [c] Pyridine (1 mL) was used. [d] Reaction was performed at 90 °C.



Scheme 2. Proposed reaction pathway.

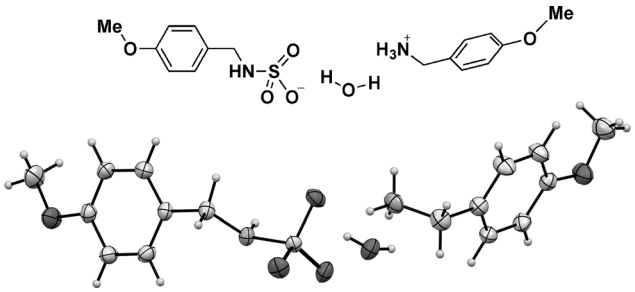


Figure 1. X-ray crystal structure of *p*-$MeOC_6H_4CH_2NHSO_3H{\cdot}H_2NCH_2C_6H_4$-*p*-OMe monohydrate (see the Supporting Information for details).

We started our investigation by the reaction of *o*-chloronitrobenzene (**1a**) with benzylamine (**2a**) and elemental sulfur. Simple heating of the mixture to 100 °C led, to our delight, to the condensed product 2-phenylbenzothiazole (**3aa**) in good yield (Table 1, entry 1).[9] Both *o*-bromonitrobenzene and *o*-iodonitrobenzene were also competent substrates (entries 2 and 3) but the reaction with *o*-fluoronitrobenzene resulted in a low yield of **3aa** along with a significant quantity of *N*-benzyl-*o*-nitroaniline (≈50%; entry 4). We assumed that the driving force for this side reaction is due to the propensity of the fluoride to act as a better leaving group than its heavier halogen congeners in aromatic nucleophilic substitution. The addition of a small quantity of pyridine to the reaction with *o*-chloronitrobenzene (**1a**) facilitated the stirring and resulted in a slightly higher yield (entry 5). A reduction of the temperature (90 °C, entry 6) resulted in a drop of the yield (52% versus 75%). In this case, a significant amount of *N*-benzylbenzaldimine was formed (almost equimolar to **3aa**). A slightly higher amount of **2a** (2.5 equiv) improved the yield, however, a lower yield is obtained when 3 equiv of **2a** was used (entry 8). Finally, an increase of the elemental sulfur molar ratio did not lead to any beneficial improvement (entry 9), possibly because more side products, including *N*-benzylbenzaldimine and *N*-benzylthiobenzamide (see below), were produced, rendering the purification difficult.

It should be noted that performing the reactions with inorganic sulfides such as Na_2S, K_2S, and $(NH_4)_2S$ instead of elemental sulfur led to several complications.[10] Moreover, because of the strong reducing power of these sulfide salts, the reaction is accompanied by the reduction of nitro to azoxy or amino groups without fixation of the phenyl group derived from benzylamine (**2a**).

Although the precise reaction stoichiometry and order of redox processes cannot be specified at this time, several pertinent observations for the mechanism have been obtained. An equimolar combination of the three starting materials would theoretically result in the desired 2-phenylbenzothiazole **3** along with NH_4Cl and 2[O] equivalents (Scheme 2). These two oxygen equivalents must be fixed by a reducing agent. To shed light on the possible pathway of the reaction, we analyzed the reaction mixture closely (entry 7, Table 1) by ^{1}H NMR spectroscopy, column chromatography, HPLC, and X-ray diffraction (Figure 1). We noticed that along with the desired product **3aa**, the main by-products were $PhCH_2NHSO_3H{\cdot}H_2NCH_2Ph$[11] and NH_4Cl.[12] Only traces of *N*-benzylthiobenzamide (dimerizing sulfuration of benzylamine)[13] and of *o*-chloroaniline (reduction of the nitro group of *o*-chloronitrobenzene) were observed. This result clearly demonstrated that elemental sulfur is the main component responsible for electronic compensation, only one benzylamine molecule was oxidized and only one nitro group was reduced to yield the 2-phenylbenzothiazole. The principle mechanistic pathway involves elemental sulfur which can undergo a disproportionation, and is split into two different oxidation states, S^{-2} in benzothiazole **3aa** and S^{+6} in $PhCH_2NHSO_3H{\cdot}H_2NCH_2Ph$ along with the nitro group reduction. This chemical behavior of elemental sulfur plays an important role in the sulfur cycle involving different oxidation

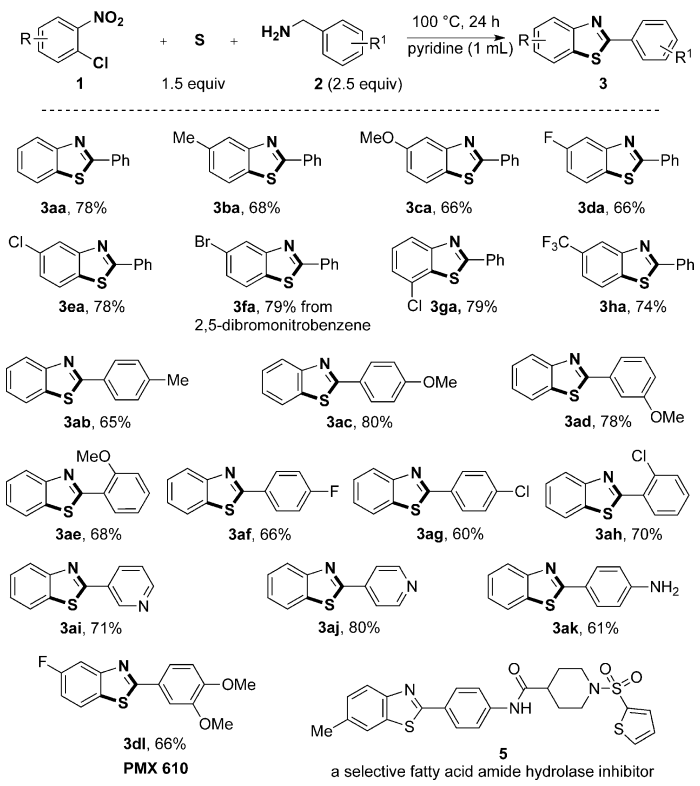
states and is frequently observed in microbiological systems.[14]

Consequently, based on the present observations and the previously reported mechanisms,[8,15] we speculated that the first step would be the activation of elemental sulfur by a nucleophilic attack of benzylamine (**2a**) on the S_8 ring, generating benzylammonium polysulfide **A** with variable chain length by means of degenerate exchange. The strongly nucleophilic S terminus of **A** can attack **1a** easily, even without a catalyst thanks to the activating effect of the *o*-nitro group of **1a**. For the sake of simplicity, only intermediates containing two sulfur atoms were presented. The next steps **B**→**F** describe a very general intramolecular redox process including N–O reductive cleavage and sulfur atom insertion. Reduction of the nitro group could be effected in a stepwise fashion in which both benzyl group (**C**→**D**) and sulfur atom (**B**→**C**, **F**→**G**) could play the role of reducing agents. The nitroso intermediate **C** could be easily reduced to the hydroxylamine **D** through the benzylic hydrogen transfer assisted by the vicinal sulfoxide group. Although the reduction order is not clear at the moment, we cannot exclude the possible reducing role of the by-product **I** (generated in the step **H**→**J**[16] Vigorous evolution of ammonia observed at the beginning of the reaction could be explained by the transamination step **E**→**F**. This step is thermodynamically favorable because the more volatile and less nucleophilic NH_3 is displaced by $BnNH_2$ (**2a**). When the reaction was carried out in a closed tube, reabsorption of ammonia was possible by H^+ generated in the steps **H**→**J** and **J**→**3aa**, thus reducing the required quantities of **2a**. *N*-benzylbenzaldimine could be formed by the attack of **2a** on any intermediate bearing a benzylidene group, i.e., **D**–**H** (entry 6, Table 1). On the other hand, *N*-benzylthiobenzamide is yielded by either an independent reaction between **2a** and S_8 or between *N*-benzylbenzaldimine and S_8 as we have previously described.[13]

Compared to our previous work in which methylhetarenes were used as the building block and the only reducing agent,[8] here, sulfur plays the role of a redox moderator, i.e., acting as both oxidizing (transformed into benzothiazole **3**) and reducing (oxidized into sulfamate **4aa**) agent, thus providing the deficient electrons of the global transformation. Benzylamine **2a**, in turn, only acts as the building block for the construction of benzothiazole **3aa** and sulfamate **4**.

Having established the optimized conditions and understood the disproportionation behavior of elemental sulfur in this reaction, we next examined the possibility to apply this process to the synthesis of a series of 2-arylbenzothiazoles (Scheme 3). A straightforward access to functionalize such molecules from readily available starting materials is particularly appealing because these heterocycles are widely represented in pharmaceuticals and functional materials.

Under the optimized conditions, a wide range of substrates with different substituents at various positions ranging from simple methyl (**3ba**, **3ab**), methoxy (**3ca**, **3ac**, **3ad**, **3ae**, **3dl**) to halogens such as F (**3da**, **3dl**), Cl (**3ea**, **3ga**, **3ag**, **3ah**), Br (**3fa**), and CF_3 (**3ha**), as well as an aromatic amino group



Scheme 3. Scope of benzothiazoles **3**.

(**3ak**) were tested and led to benzothiazoles in moderate to good yields. *o*-Chloronitrobenzenes were used in all cases (except **3fa** wherein 2,5-dibromonitrobenzene, a cheaper substrate than 2-chloro-5-bromonitrobenzene, was used as the oxidizing partner).

As heteroaromatic substrates, 3- and 4-picolylamines gave the corresponding benzothiazoles **3ai** and **3aj**. It is noteworthy that **3ai** could not be obtained by our previously described approach starting from 3-picoline.[8] The reaction with aliphatic amines such as octylamine failed to provide the corresponding benzothiazole, suggesting that under the present conditions, a benzylic amine is required for the reaction to succeed.

Finally, our method can be conveniently applied to the synthesis of benzothiazoles **3ak** and **3dl** with interesting biological activities: 1) fluorinated benzothiazole **3dl** or **PMX 610** exhibiting potent and selective inhibitory activity against lung, colon, and breast cancer cell lines,[17] and 2) aminobenzothiazole **3ak**, a demethylated derivative of the direct precursor of benzothiazole **5**, which was identified as a selective fatty acid amide hydrolase inhibitor at nanomolar concentrations.[18] Both **3dl** and **3ak** could be obtained in a single step from commercially available starting materials.

Traditional approaches to 2-arylbenzothiazoles could be roughly classified by the number of new sigma bonds created.[19] To date, the most common methods are based on reactions with the formation of only one[20] or two[21] new sigma bonds. In this context, our three-component approach with three newly generated bonds[22] is obviously of high

value, highlighted by the total absence of metal catalysts and the direct use of *o*-chloronitrobenzenes, elemental sulfur, and benzylamines, readily obtainable from common chemical suppliers.

In summary, we described an interesting disproportionation phenomenon of elemental sulfur in a redox condensation between *o*-halonitrobenzenes **1** and benzylamines **2**. When the exchange electron numbers between oxidizing and reducing partners are not the same, this chemical behavior is an efficient means of adaptation to equilibrate the electron deficiency. Exploiting this unique property of elemental sulfur, we have developed a simple, three-component, metal-free, and general approach to 2-arylbenzothiazoles, which are omnipresent structural motifs in a number of biologically active compounds. A wide range of substrates should be investigated in order to broaden the generality of these reactions and to understand the mechanism.

Experimental Section

A mixture of *o*-chloronitrobenzene **1** (5 mmol) (2,5-dibromonitrobenzene was used to synthesize **3fa**), sulfur (240 mg, 7.5 mmol), and amine **2** (12.5 mmol) in pyridine (1 mL) was stirred under an argon atmosphere in a 25 mL test tube with pressure equalization at 100 °C for 16 h. After being cooled to room temperature, the volatiles were removed in vacuo. The crude reaction mixture was triturated with CH_2Cl_2 (5×2 mL). The combined CH_2Cl_2 layers were concentrated and purified by silica gel column chromatography (heptane/EtOAc) to afford the desired benzothiazole **3** (see the Supporting Information).

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