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Sulfur-Catalyzed Oxidative Coupling of Dibenzyl Disulfides with Amines: Access to Thioamides and Aza Heterocycles

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Abstract. In the presence of catalytic amounts of elemental sulfur, dibenzyl disulfide/DMSO was found to be an excellent thiobenzoylating agent of amines to provide a wide range of thioamides. The reaction becomes autocatalytic when anilines substituted by an *o*-cyclizable group were used as nucleophile, leading to the corresponding 2-aryl aza heterocycles.

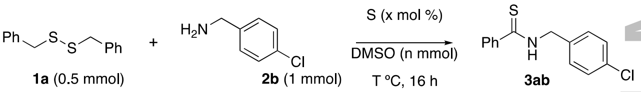
Keywords: sulfur; DMSO; autocatalytic; redox condensation; thioamide

Despite extensive use of sulfur in organic synthesis as a stoichiometric reagent (sulfurating, oxidizing or reducing agent),[1] its role as catalyst was underexplored. Apart from some examples on the oxidative amination of carbon monoxide,[2] sulfur was used as a catalyst in the presence of iron powder[3] or salts for redox condensation of aromatic nitro compounds.[4] The catalytic activities of sulfur were based on some intrinsic properties of this element, of which its wide range of oxidation states, the ease of S-S bond scission, and the high nucleophilicity of the polysulfide chain resulted in the reaction medium are among the most influencing factors. In this paper, we disclosed a new catalytic activity of sulfur in the oxidative coupling reaction between dibenzyl disulfides and amines.

For this purpose, we initiated our research by studying a model reaction between dibenzyl disulfide **1a** with *p*-chlorobenzylamine **2b** using DMSO as an oxidant (Table 1).

In the absence of elemental sulfur, heating this mixture at 80 ºC did not lead to any perceptible change, both starting materials remained unchanged (entry 1). In the present of 25 mol % (8 mg) of elemental sulfur, a stoichiometric mixture of starting substrates led to the expected thioamide **3ab**[5] in nearly quantitative yield (entry 2). Using DMSO in stoichiometric amount lowered slightly the yield (entry 3). The sulfur catalytic activity decreased with lower catalytic loading (entry 4) or at a lower temperature (entry 5). Although sulfur was known to promote sulfurative self-condensation of benzylamine to *N*-benzylthiobenzamide,[5b] such product was formed only in trace amounts in the present reaction mixture. This could be explained by the fact that sulfur was used only in catalytic amount and involved in the catalytic cycle for the formation of the expected thioamide.

Table 1. Screening of the reaction conditions



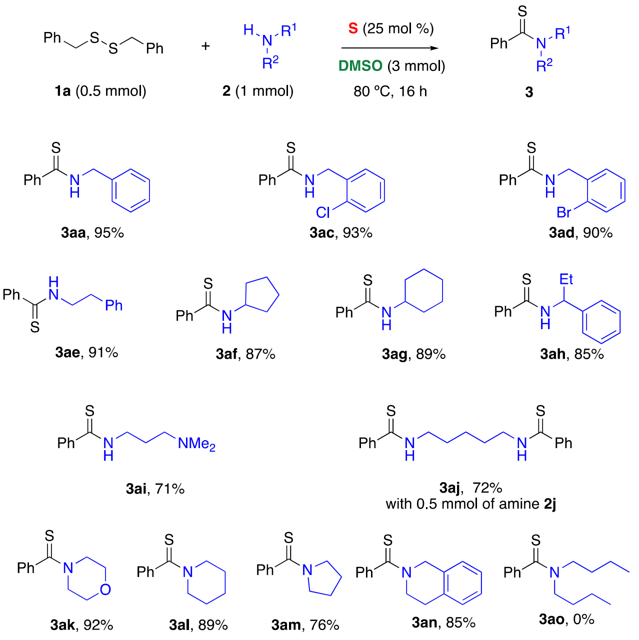
Entry[a]	x	n[b]	Temp. (°C)	Yield (%)
1	0	3	80	0
2	25	3	80	95
3	25	1.5	80	92
4	5	3	80	60
5	25	3	60	85
6	25	0[c]	80	0

[a] Reaction conditions: dibenzyl disulfide **1a** (0.5 mmol), sulfur (x mol %, 32 mg/mmol), amine **2b** (1 mmol), DMSO (n mmol), T °C, 16 h. [b] 3 equiv of DMSO corresponds to 3 mmol of DMSO or 0.2 mL. [c] DMF (0.2 mL) was used in place of DMSO.

Finally, the crucial role of DMSO to the success of the reaction was confirmed as its replacement by DMF did not lead to any trace of **3ab**.

With the optimized conditions in hand, we evaluated first the scope for amines (Scheme 1). Benzylamine **2a** as well as its derivatives bearing a halogen group in the *ortho* position **2c,d** gave the expected product **3aa**, **3ac** and **3ad** without any difficulty. Other primary amines **2e-h** with increasing steric hindrance at their alpha position were also competent substrates. Diamine **2i** reacted exclusively at the primary function. When cadaverine **2j** (0.5 equiv) was used as nucleophile, dibenzoylated product

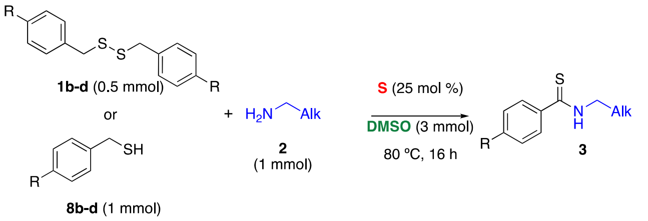
3aj was obtained in excellent yield. Cyclic secondary amines **2k-n** with different ring sizes reacted without any incident. Similar to benzylamines, although tetrahydroisoquinoline **2n** was expected to be sulfurized at the alpha position,[6] its reaction with Bn_2S_2 led cleanly to the desired thioamide **3an** as a 2:3 mixture of two rotamers. The reaction with an open chained aliphatic secondary amine such as dibutylamine **2o** was found to be complex and accompanied by various sulfuration reactions of the butyl chains.



Scheme 1. Thiobenzamides 3 from aliphatic amines 2

Next, we examined the reactivity of other dibenzyl disulfides with some representative alkylamines. As presented in Table 2, disulfides **1b-d** were all highly reactive and gave the expected products in excellent yields (entries 1, 3 and 5).

Table 2. Reaction of disulfides or thiols 8 with amines 2

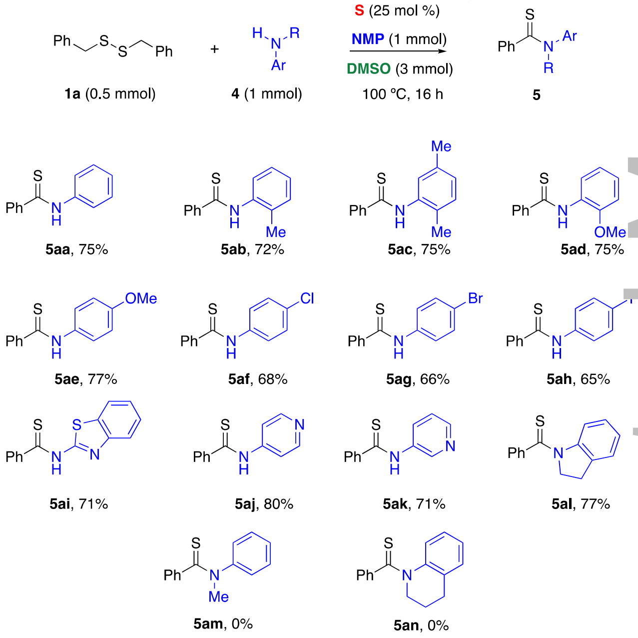


Entry[a)]	R	1/8	$AlkCH_2NH_2$, **2**	**3**, yield (%)
1	*t*-Bu	**1b**	$BnNH_2$, **2a**	**3ba**, 92
2	*t*-Bu	**8b**	$BnNH_2$, **2a**	**3ba**, 87
3	OMe	**1c**	$3\text{-}MeOC_6H_4CH_2NH_2$, **2p**	**3cp**, 89
4	OMe	**8c**	$3\text{-}MeOC_6H_4CH_2NH_2$, **2p**	**3cp**, 85
5	Cl	**1d**	$BnCH_2NH_2$, **2e**	**3de**, 87
6	Cl	**8d**	$BnCH_2NH_2$, **2e**	**3de**, 85

[a)] Reaction conditions: diarylmethyl disulfide **1** (0.5 mmol) or arylmethanethiols **8** (1 mmol), sulfur (25 mol %, 32 mg/mmol), amine **2b** (1 mmol), DMSO (3 mmol, 0.2 mL), 80 °C, 16 h.

It should be noted that the reductive precursor of these disulfides **1b-d**, i.e. arylmethanethiols **8b-d**,[7] which are more readily commercially available, could be used directly under the same conditions. In these cases, the first step is an oxidative dimerization of thiols to disulfides catalyzed by elemental sulfur activated by the aliphatic amine.

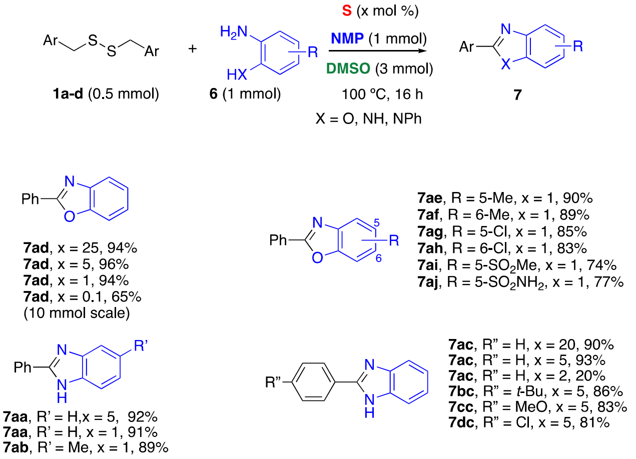
Compared to the previous report using molecular iodine as a catalyst for similar reactions between an aliphatic amine with dibenzyl disulfide,[8] the sulfur catalyst displayed higher reactivity with lower reaction temperature (60-80 °C *vs* 100 °C), leading to higher yields even with stoichiometric amounts of both amine and dibenzyl disulfide substrates and required only a slight excess of DMSO oxidant (3 equiv *vs* 15 equiv). Moreover, it should be mentioned that due to high reactivity of molecular iodine with aniline, especially in the presence of electron donating groups in their aromatic ring, the molecular iodine catalytic system is not applicable to such substrates. Consequently, we were interested in investigating the catalytic activity of sulfur with aromatic anilines (Scheme 2).



Scheme 2. Thiobenzamides 3 from aromatic amines 2

Our first attempt on aniline **4a** resulted in recovery of both starting materials without any trace of the expected thiobenzanilide **5aa**. We reasoned that if sulfur was not catalytically active for aniline, it was because aniline was not enough basic to render elemental sulfur from the inactive form S_8 to activated species as in cases of aliphatic amines. To overcome this drawback due to low basicity of aniline and based on our previous observations on elemental sulfur chemical behavior,[9] an aliphatic tertiary amine was added to the reaction mixture to activate S_8. To our delight, *N*-methylpiperidine was found to be particularly suitable for this role. The expected thioanilide **5aa** was formed and isolated in excellent yield. Interestingly, our reaction conditions could be applied to a range of *o*-substituted anilines **4b-d** reacted without any difficulty. Other aromatic amines substituted in the *para* position by a methoxy **4e** or different halogen atoms **4f-h** reacted in a similar manner. The presence of halogen substituents is particularly useful for further functionalization, especially in case of bromo and iodo derivatives **4g**,**h**. Heteroaromatic amines such as 2-aminobenzothiazole **4i**, 3- and 4-amino- pyridines **4j**,**k** exhibited high reactivity and provided the expected products **5ai-5ak** in moderate to good yields. Interestingly, while *N*-methylaniline **4m** and tetrahydroquinolione **4n** were shown to be completely unreactive, indoline **4l** displayed excellent performance to provide the expected thioamide **5al** in 77% yield. Such a quite different performance in this reaction could be explained on the basis of steric hindrance and stereoelectronic effect of the nitrogen atom of indoline.

At this stage, we wanted to extend the reaction to aniline substrates bearing another potentially reactive functions at the *ortho* position (Scheme 3).



[a] Reaction conditions: dibenzyl disulfide **1a** (1 mmol), sulfur (x mol %, 32 mg/mmol), amine **2b** (1 mmol), DMSO (n mmol), T °C, 16 h.

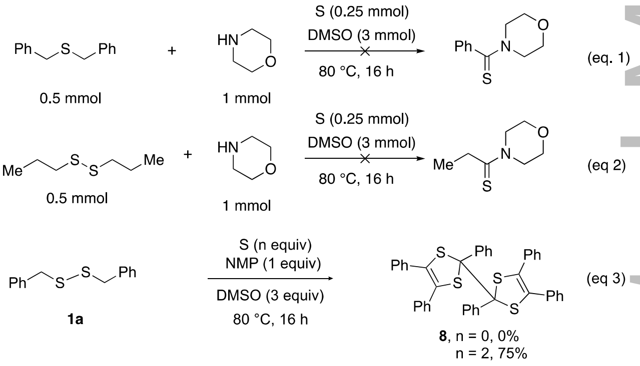
Scheme 3. Formation of aza heterocycles[a]

The reaction of *o*-aminophenol **6d** (X = OH) with dibenzyl disulfide **1a** in the presence of NMP led to benzoxazole **7ad** in excellent yield under the same conditions used for anilines **4** with 25 mol % of sulfur catalyst. The primary by-product of the formation of the heterocycles is obviously hydrogen sulfur, which was next oxidized by DMSO to elemental sulfur. Overall, the reaction became autocatalytic as the amount of sulfur gradually increased as the reaction proceeded. To verify this hypothesis, we focused our attention on variation of sulfur content and set up some control experiments. In the absence of sulfur, both starting materials remained unchanged and no trace of benzoxazole **7ad** was detected. On the other hand, the reaction conditions remained efficient with the catalyst loading of 5 mol % and even with only 1 mol %. Lower the catalyst loading below this threshold became impractical for weighing such a small amount of sulfur. Consequently, we were obliged to scale up the reaction tenfold to evaluate the catalyst loading as low as 0.1 mol % (0.32 mg S for 20 gr of the expected product!). Unfortunately, the yield for this experiment remained moderate (65%), possibly due to unwanted destruction of sulfur by the oxidation into its catalytically unreactive forms by trace of oxygen.

The optimized conditions using only 1 mol % of sulfur were next evaluated with an array of *o*-aminophenols **6e-6j** bearing functional groups with different electronic natures. Pleasingly, all of them led to the expected 2-phenylbenzoxazoles **7ae-7aj** in excellent yields. Lower yields of benzoxazoles **7ai** and **7aj** could be attributed to their low solubilites.

Excellent yields were also observed with *o*-phenylenediamines **6a-b** (X = NH_2) to provide the benzimidazole products **7aa** and **7ab** in excellent yields.

When the nucleophilicity of one of the amino group of *o*-phenylenediamine core is attenuated by a phenyl group as for *o*-aminodiphenylamine **6c** (X = NHPh), only trace of the expected product **7ac** was formed with 1 mol % of sulfur but excellent reactivity could be achieved with 5 mol %. Comparable results were obtained with other dibenzyl disulfides substrates **1b-d** with **6c**.



Scheme 4. Experiments with other thioacylating agents

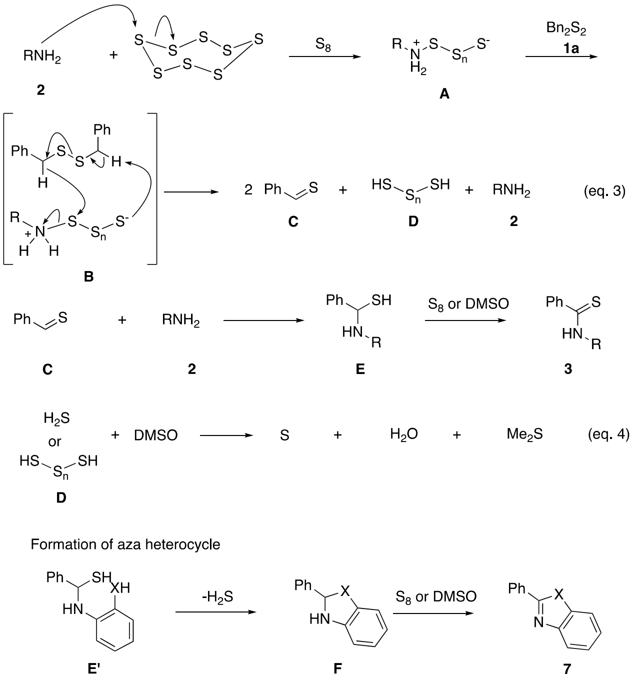
To shed light on the reaction mechanism, we performed some pertinent control experiments. When DMF was used in place of DMSO, the expected thioamide product was not formed (Table 1, entry 6). Most of the starting materials were recovered unchanged along with the formation of small amounts of mixture of dibenzyl oligosulfides. Other higher analogues of DMSO such as dipropyl sulfoxide, dibutyl sulfoxide proved to be less efficiency than DMSO in promoting this oxidative condensation.

When dibenzyl sulfide was used as thiobenzoyl source, the reaction with morpholine resulted in the recovery of all starting material (eq. 1, Scheme 4). On the other hand, dipropyl disulfide prove also to be totally inactive under the present conditions (eq. 2, Scheme 4). Additionally, when dibenzyl disulfide **1a** was heated with NMP in DMSO, depending on the presence of elemental sulfur, we obtained different results. In the absence of sulfur, 1a was recovered unchanged. On the other hand, the presence of sulfur was found to be of vital importance in breaking S-S bond of **1a**, leading to hexabenzylidyne tetrasulfide **8** as described in our previous work.[10]

These results showed clearly that a competent thioacylation agent should have an S-S bond at the benzylic position.

Based on this information on the reaction involving elemental sulfur and previous literature report, we proposed a mechanism starting with activation of elemental sulfur with aliphatic amines to provide zwitterion **A** (Scheme 5).

Reaction of this sulfur species, which is at the same time nucleophilic and oxidizing, with dibenzyl disulfide **1a**, would result in an oxidative fragmentation of **1a** to yield two molecules of thiobenzaldehyde **C** (eq. 3). Addition of amine **2** to thiobenzaldehyde **C** would lead to α-aminated benzenethiol **E**, which was next oxidized to thioamide **3** by either DMSO or elemental sulfur. The recycling of elemental sulfur could be achieved by the oxidation of dihydrogen sulfide or polysulfide **D** according to eq. 4.



Scheme 5. Proposed mechanism

In conclusion, we have reported in this manuscript an interesting catalytic activity of elemental sulfur in promoting oxidative condensation of dibenzyl disulfides **1** with a wide range of nitrogen nucleophiles, including aliphatic amines **2** and anilines **4** to provide the corresponding thiobenzamides **3** and **5**. Reductive precursor of dibenzyl disulfides **1**, i.e. phenylmethanethiols **8** could also be used for this kind of tramsformation. In case of anilines **6** *o*-substituted by a cyclizable group such as OH, NH_2 or NHPh, the corresponding benzoxazoles or benzimidazoles **7** were obtained in excellent yields and only a very small amount of elemental sulfur (1-5 mol %) was required as a result of the autocatalytic nature of the reaction. We hope that this preliminary result will pave the way for the development of other sulfur-catalyzed processes leading to useful products that are difficult or impossible to obtain otherwise.

Experimental Section

General procedure

A mixture of dibenzyl disulfide **1** (0.5 mmol), aliphatic amine 2 (1 mmol), elemental sulfur (0.25 mmol, 8 mg) and DMSO (3 mmol, 0.2 mL) was heated under an argon atmosphere in a 7-mL test tube at 80 °C for 16 h. In case of thioamides **5** or aza-heterocycle **7**, the reaction required *N*-methylpiperidine (1 mmol) and heating at 100 °C for 16 h. The reaction mixture was purified by column chromatography on silica gel (heptane:EtOAc or CH_2Cl_2:EtOAc).

For characterization, and copies of NMR spectra of all compounds, see Supporting Information.

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