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Catalyst-free and Additive-free Method for the Synthesis of Benzothiazolethiones from *o*-Iodoanilines, DMSO and Potassium Sulfide

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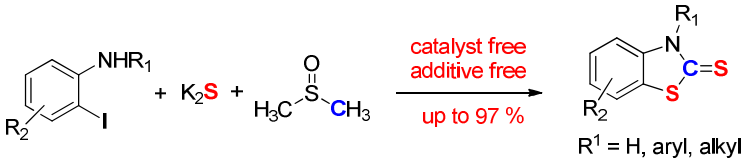

Under catalyst-free and additive-free conditions, a novel, convenient, environment-friendly method for synthesis of benzothiazolethiones has been developed from *o*-iodoanilines, K_2S and DMSO.

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Under catalyst-free and additive-free conditions, a novel, convenient, eco-friendly method for synthesis of benzothiazolethiones has been developed. The three-component reaction of *o*-iodoanilines and K_2S with DMSO proceeded smoothly and obtained the corresponding benzothiazolethiones with good isolated yields. Meanwhile, this method could be used for the synthesis of thioureas from primary diamines. Furthermore, mechanism research showed that DMSO not only functioned as a carbon source, but also as a mild oxidant in this reaction.

2-Mercaptobenzothiazole derivatives have frequently been used as core structures for development of pharmaceutical agents.[1] They exist in numerous bioactive molecules (Figure 1), such as protoporphyrinogen IX oxidase (PPO) inhibitors **1**,[1b] radiation protectant **2**[1c] for protective normal tissue radiation protective agents, antibacterial agents **3**[1d] against staphylococcus aureus, heat shock protein-90 (HSP) inhibitors **4**[1e] and CCR3 antagonists **5**.[1f] Consequently, the research and development of synthetic methods for benzothiazolethiones continues to be one of the most active areas in synthetic chemistry.[2-5] The conventional methods involve the condensation of carbon disulfide with *o*-aminothiopheols,[3] *o*-haloanilines,[4] or *o*-halonitrobenzenes.[5] Nevertheless, the toxic and unpleasant odor of carbon disulfide impedes its application. Alternatively, the nucleophilic aromatic substitution reactions of *o*-haloanilines with potassium/sodium *o*-ethyl dithiocarbonate for synthesis of benzothiazolethiones were developed by Yang[6] and Zhu[7] respectively. Recently, Dong[8] reported a green and efficient synthesis of benzothiazolethiones by cyclization of 2-aminothiophenols with tetramethylthiuram disulfide using H_2O as solvent. However, the complex sulphur source needed several steps to prepare. And on this basis, our group[9] found that benzothiazolethiones could be synthesized via copper-catalyzed tandem multiple C-S bonds formation from 2-iodoaniline, K_2S and isocyanides. Although these methods avoid the use of CS_2 and complex sulphur source, and also has good substrate suitability, it requires the addition of metal catalyst and ligand, which leads to not only high reaction cost but also stoichiometric amounts of waste in the reaction. Accordingly, it is highly desirable to develop a greener and more environment-friendly approach to benzothiazolethiones from cheap and easy to handle sulphur source under transition-metal-free or additive-free reaction conditions.[10]

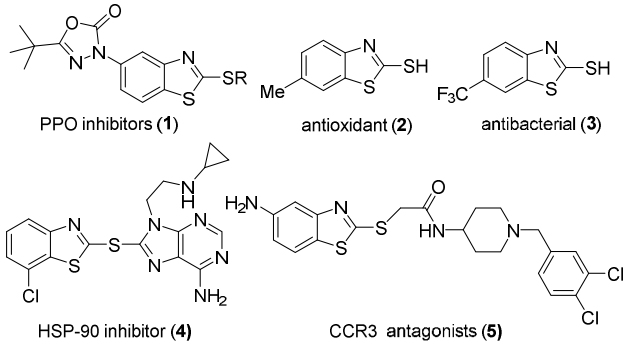

Figure 1. Examples of Some Biologically Active Compounds

In synthetic chemistry, dimethyl sulfoxide (DMSO) is not only utilized as a cheap, low-toxic and aprotic polar solvent but also as an important and various synthon.[11] Among them, DMSO as a one-carbon synthon was widely used in organic synthesis. In our previous work (Scheme 1, eq 1), the isocyanides as a C1 building block could be used to synthesize benzothiazolethiones.[9] Therefore, we attempted to use DMSO as C1 building block instead of isocyanides. Fortunately, benzothiazolethiones were obtained in good yields (Scheme 1, eq 2). To the best of our knowledge, this was the first successful example for construction of two C–S bonds and a C=S double bond from *o*-iodoaniline, K_2S and DMSO. Herein, we wished to detail our results.

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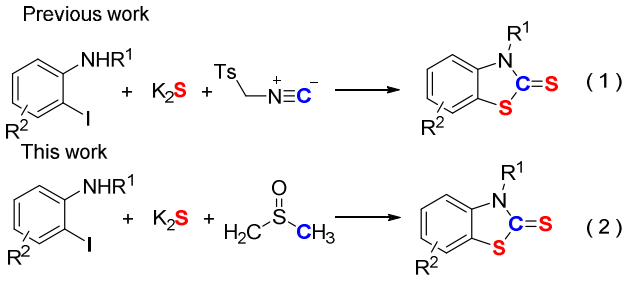
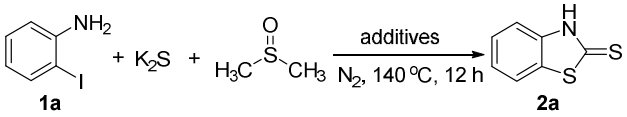
Scheme 1. Synthesis of Benzothiazolethiones



As shown in Table 1, the three-component reaction of *o*-iodoaniline with K_2S and DMSO were chosen as substrates to optimize the reaction conditions. Treatment of **1a** with 6 equivalents of K_2S, and 2 mL DMSO at 140 °C for 12 hours afforded the desired product **2a** in 70% yield (entry 1). Inspired by this result, the amount of K_2S was subsequently examined (entries 1-3), 6 equivalents of K_2S was found to give the best result. Notably, the reaction could not occur without K_2S (entries 4), or K_2CO_3 instead of K_2S (entries 5). These results indicated that the K_2S played an important role for the reaction. In the following studies, various additives such as $(CH_3CO)_2O$, KOH, I_2 and KI were tested, and they did not lead to a significant difference in the yield of **2a** (entries 6-9). Furthermore, lower temperature resulted in lower yields, and only 15% yield was obtained at 120 °C (entry 10). Finally, appling the conditions we developed previous in the related studies[9] (CuCl as catalyst, TMED as ligand), the desired product was isolated in 72% yield. Compare with catalyst-free conditions, no obvious change was observed. Therefore, we still selected the catalyst-free conditions as the optimized reaction conditions.

Table 1. Optimization of Reaction Conditions[a]

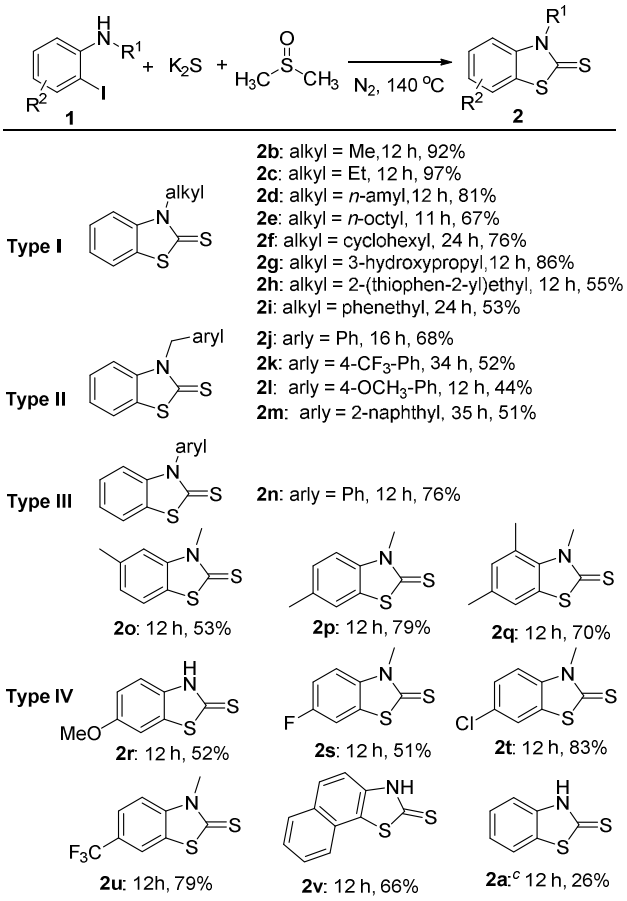


Entry	Variation from the standard conditions	Yield (%)[b]
1	none	70
2	K_2S (3 equiv.)	57%
3	K_2S (5 equiv.)	61%
4	without K_2S	N.D.
5	K_2CO_3 instead of K_2S	N.D.
6	$(CH_3CO)_2O$(1 equiv.)	30%
7	KOH (1 equiv.)	43%
8	I_2(0.5 equiv.)	61%
9	KI (1 equiv.)	50%
10[c]	none	15%
11	CuI (10 mol%), TMED (20 mol%)	72%

[a] Reaction conditions: **1a** (0.2 mmol), K_2S (1.2 mmol), DMSO (2 mL), under N_2 atmosphere in sealed Schlenk tube, at 140 °C for 12 h. [b] Isolated yields. [c] 120 °C.

Having the optimized reaction conditions in hand, we next surveyed the substrate (**1**) scope of the three-component reaction and the results were shown in Scheme 2. Firstly, the substitutents of the amino moiety (R^1) were investigated, which could be alkyl (type I), benzyl (type II) and aryl (type III), and various N-substituted benzothiazolethiones (**2b**-**2n**) were obtained in moderate to perfect yields. For type I, the amino moiety with short-chain alkyls such as methyl and ethyl were converted into the corresponding product **2b** and **2c** in 92% and 97% yield. In contrast, long-chain alkyl (**1d** and **1e**) and cycloalkyl (**1f**) substituted *o*-iodoanilines only give the desired product in good yields. Remarkably, 3-(3-hydroxypropyl)benzo[d]thiazole-2(3H)-thione could be afforded in 86% yield. Moreover, N-(thiophen-2-yl)ethyl and phenethyl substituted benzothiazolethiones were obtained in moderate yields only.

Scheme 2. Synthesis of Benzothiazolethiones[a,b]



[a] Reaction conditions: **1** (0.2 mmol), K_2S (1.2 mmol), DMSO (2 mL), under N_2 atmosphere in sealed Schlenk tube, at 140 °C. [b] Isolated yields. [c] *o*-bromoaniline instead of *o*-iodoaniline.

Similarly, N-benzyl substituted benzothiazolethiones (type II, **2j**-**2m**) could be achieved in moderate yields. These results showed the substituents did not remarkably affect the reaction. For type III, aryl substituted 3-phenylbenzo-[*d*]thiazole-2(3H)-thione was obtained in 76% yield (**2n**). Finally, the substituted groups on the benzene ring of *o*-iodoaniline were evaluated (type IV). Under the standard reaction conditions, the benzene rings bearing electron-

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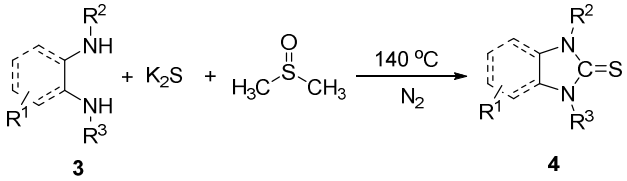
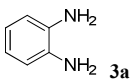
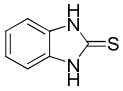
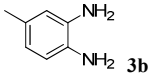
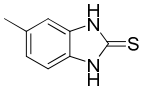
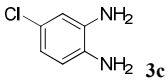
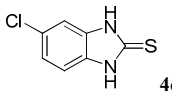
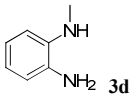
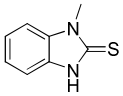
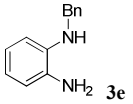
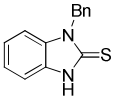
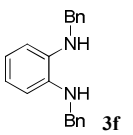
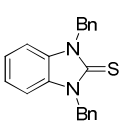
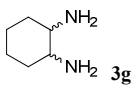
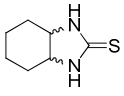
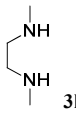
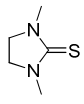
donating groups such as methyl and methoxyl or electron-withdrawing groups such as fluoro, chloro and trifluoromethyl were well tolerated and given the corresponding products in moderate to good yields. Generally, the activity of *o*-iodoanilines bearing electron-donating groups is higher than the activity of *o*-iodoanilines bearing electron-withdrawing groups. In addition, polycyclic 2-amino-1-iodonaphthalene could give the desired products **2v** in 66% yield. Unfortunately, the *o*-bromoaniline was not a proper substrate, and only obtained the benzothiazolethione (**2a**) in 26% yield.

Considering thioureas with widespread application in biological chemistry, natural products synthesis and material science,[12] we were curious about the possibility to apply this method to synthesis thiocarbamides. As expected, when the 1,2-diamines (0.4 mmol) was treated with three equivalent of K_2S under the similar reaction conditions, the corresponding products **4** were obtained in 24% to 88% yields (Tabe 2). To benzene-1,2-diamines, whether the substituent on the benzene ring or on the amino, the benzo[*d*]imidazole-2-thionesall were given in moderate yields. Importantly, cyclic cyclohexane-1,2-diamine **3g** was employed as a substrate, and the corresponding thiocarbamides were obtained in 88% isolated yield. Unfortunately, the linear N,N'-dimethylethane-1,2-diamine **3h** only transformed to the desired products1,3-dimethylimidazolidine-2-thione **4h** in 24% yield.

Table 2. Synthesis of Thiocarbamides[a]

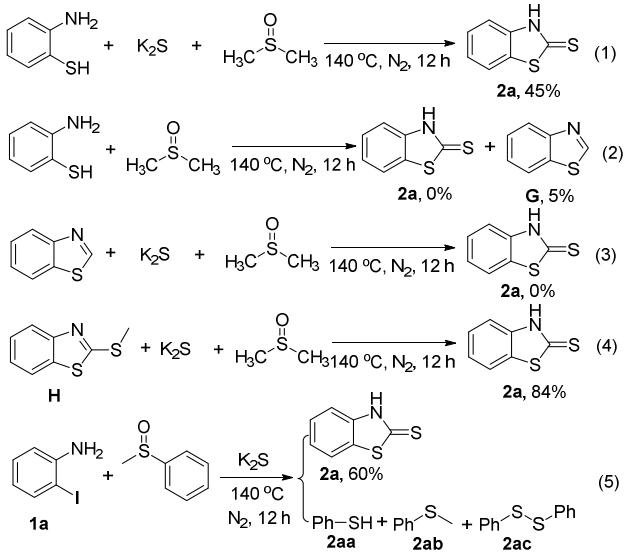


Entry	Substrate **3**	Product **4**	Yield (%)[b]
1	 **3a**	 **4a**	65 (24 h)
2	 **3b**	 **4b**	55 (30 h)
3	 **3c**	 **4c**	75 (24 h)
4	 **3d**	 **4d**	50 (12 h)
5	 **3e**	 **4e**	50 (12 h)
6	 **3f**	 **4f**	46 (12 h)
7	 **3g**	 **4g**	88 (12 h)
8	 **3h**	 **4h**	24 (12 h)

[a] Reaction conditions: **3** (0.4 mmol), K_2S (1.2 mmol), DMSO (2 mL), under N_2 atmosphere in sealed Schlenk tube, at 140 °C. [b] Isolated yields.

In order to reveal the reaction mechanism, a series of controlled experiments were performed (scheme3). Firstly, 45% of **2a** were afforded when the reaction of 2-aminobenzenethiol, K_2S and DMSO was performed under standard conditions (eq 1). No desired product **2a** was observed and 5% of benzothiazole (**G**) were isolated in the absence of K_2S under same reaction conditions (eq 2). These results indicated the sulfur source impossibly derived from DMSO. However, benzothiazole could not react with K_2S to benzothiazolethione (eq 3), but benzothiazolethione could be synthesized from 2-(methylthio)benzo[*d*]thiazole (**H**) (eq 4). These results indicate that this reaction probably involved the 2-(methylthio)benzo[*d*]thiazole as the intermediate. Moreover, by replacing DMSO with methyl phenyl sulfoxide under the standard reaction conditions, benzothiazolethione **2a** was obtained in 60% isolated yields, along with compounds of benzenethiol (**2aa**), methyl(phenyl)sulfide (**2ab)** and diphenyl disulfide (**2ac)** (eq 5) was detected from the reaction mixture via GC-MS analysis (see the ESI for details). This result proved the DMSO not only was the C1 source of benzothiazolethione and but also performed as an oxidant in this reaction. Finally, dimethyl sulfide was obviously observed *via* GC analysis of the model reaction of **1a**, K_2S and DMSO (see the ESI for details). This result proved DMSO acted as an oxidant to promote this reaction again.

Scheme3. Controlled Experiments



According to the experimental results and previous reports,[9,11,13] a proposed reaction mechanism for the

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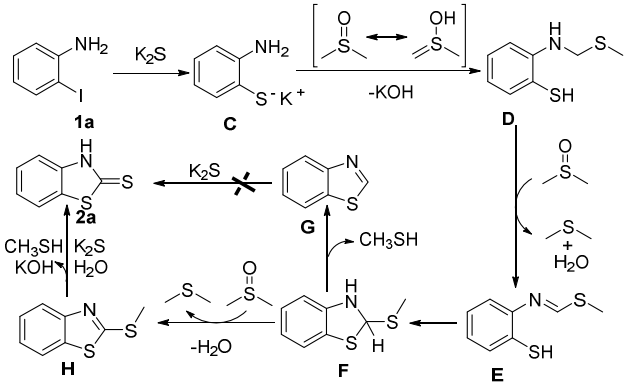
formation of **2a** from *o*-iodoaniline, DMSO and potassium sulfide is given in Scheme 4. Firstly, the intermediate **D** is obtained via nucleophilic addition reaction of the DMSO with intermediate **C**, which is formed by the S_NAr-type reaction of *o*-iodoaniline with K_2S. Subsequently, the intermediate **F** is afforded via the oxidation of intermediate **D** and sequentially undergoes the process of intramolecular nucleophilic addition. Intermediate **F** can transform into benzothiazole or 2-(methylthio)benzo[*d*]thiazolevia aromatization. However, the desired product **2a** was only obtained via the nucleophilic addition/elimination from 2-(methylthio)benzo[d]thiazole with K_2S.

Scheme 4. Possible Mechanism for the Formation of **2a**



In summary, we have disclosed a novel, convenient, eco-friendly method for synthesis of benzothiazolethiones from *o*-iodoanilines and K_2S with DMSO under catalyst-free and additive-free conditions. In this reaction, DMSO served as a C source and an oxidant. Notably, this method could also provide a general approach to construction of a thiocarbonyl group from simple, low-toxic, low-odor and readily available starting material. Further studies of this method will focus on the detailed mechanism and applications in organic synthesis.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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