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Synthesis of 2-Mercaptobenzothiazoles via DBU-Promoted Tandem Reaction of *o*-Haloanilines and Carbon Disulfide

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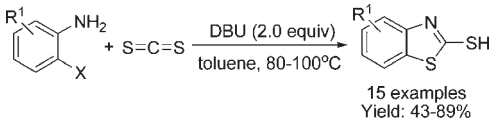
ABSTRACT



An efficient strategy for the synthesis of a variety of 2-mercaptobenzothiazole derivatives has been developed. The reaction proceeded from *o*-haloaniline derivatives and carbon disulfide via a tandem reaction in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the corresponding 2-mercaptobenzothiazole derivatives in good to excellent yields.

2-Mercaptobenzothiazoles (MBTs), categorized as significant derivatives of benzothiazoles, have frequently been used as core structures for development of pharmaceutical agents.[1] Recently, successful examples (Figure 1) include heat shock protein-90 (HSP) inhibitors,[2] cathepsin-D inhibitors[3] and protoporphyrinogen IX oxidase (PPO) inhibitors.[4] Very recently 6-methyl-2-mercaptobenzothiazole was demonstrated as a radioprotective chemical, which has been applied in the treatment of cancer patients during radiotherapy in order to protect the normal tissues adjacent to the treated tumor.[5] 6-Trifluoromethyl-2-mercaptobenzothiazole was evaluated as a potent antibacterial against *Staphylococcus aureus*, *Escherichia coli*, and other clinical isolates with different antimicrobial resistance profiles.[6] Furthermore, profited by special electronizc properties, MBTs spontaneously acted as a significant ligand to metallic complexes, which were regarded as the promising luminescent materials.[7] Conventionally, protocols for preparation of 2-mercaptobenzothiazoles included the reaction of thiocarbanilide with sulfur or interaction of *o*-aminothiophenol with carbon disulfide under high pressure.[8] Another way to prepare 2-mercaptobenzothiazoles was by nucleophilic aromatic substitution (S_NAr)

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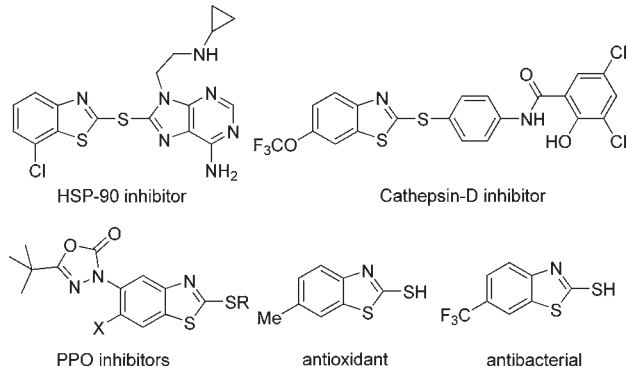

Figure 1. Examples of some biologically active compounds.

reaction of a potassium/sodium *o*-ethyl dithiocarbonate with *o*-haloaniline followed by a subsequent cyclization.[6,9] Although some approaches to the 2-mercaptobenzothiazole derivatives have been developed, the methods often suffer from harsh reaction conditions, limited substrates, poor substituent tolerance, and low yields. Accordingly, development of a facile and scalable route to construct the MBT scaffold is still desirable.

Recently, a transition-metal-mediated cascade reaction provided a straightforward method for the synthesis of various useful heterocyclic compounds via C−X (X = N, O, and S) bond formation.[10−12] For example, benzothiazole could be efficiently formed via *S*-arylation/condensative cyclization processes.[12a−d] More recently, our group performed copper-catalyzed reactions for the synthesis of heterocycles by using heterocumulenes such as isothiocyanates and carbodiimides, which provided a straightforward method to heterocyclic compounds.[13] Encouraged by these results, we first screened copper-catalyzed reaction conditions by using *o*-iodoaniline and carbon disulfide as a model reaction (Table 1). Surprisingly, a more highly efficient tandem reaction for the synthesis of 2-mercaptobenzothiazole derivatives was observed in the absence of a copper salt (entry 12, Table 1). Herein, we report the unexpected transition-metal-free intramolecular tandem condensation/*S*-arylation reaction of *o*-haloanilines and carbon disulfide leading to 2-mercaptobenzothiazole derivatives.

Initially, we used the *o*-iodoaniline **1a** and carbon disulfide as the starting materials and CuI as catalyst, Cs_2CO_3 as base in toluene at 80 °C. However, the product **2a** was not observed, and only the starting material **1a** was remained (Table 1, entry 1). Then different bases such as K_2CO_3, K_3PO_4, ^{t}BuONa, Et_3N, 1,4-diazobicyclo[2.2.2]octane (DABCO), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were screened (entries 2−7). The results demonstrated that the organic bases were efficient than inorganic bases. DBU showed an excellent performance as base in the reaction condition (entry 7). No reaction was observed in the absence of a base (entry 8). Next, the ligands were examined in the reaction. *N*,*N*′-dimethylethane-1,2-diamine (DMEDA), *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA), and 1,10-phenanthroline gave the similar yield compared with ligand free condition (entries 9−11). Surprisingly, the reaction also worked well in the absence of a copper catalyst at 80 °C (entry 12). The solvents were also evaluated in the reaction. Toluene was superior to 1,4-dioxane, CH_3CN, DMF, and DMSO (entries 13−16). The reaction showed a dependence on the temperature. When the reaction was treated at 70 °C, the yield was moderate and a considerable amount of stating material **1a** remained (entry 17).

On the basis of these results, the optimal condition involved the following parameters: DBU as a base, toluene as a solvent, and reaction temperature at 80 °C. Under these optimized conditions, a study on the substrate scope was carried out, and the results are summarized in Table 2. First, we used *o*-iodoaniline derivatives **1** to react with carbon disulfide. Both methyl group and fluorine atom on phenyl showed good performance (entries 2 and 3). Then *o*-bromoaniline and its derivatives were applied under the reaction conditions at 100 °C. In general, electron-donating and electron-withdrawing substituents on the *o*-bromoaniline ring have generated 2-mercaptobenzothiazoles in

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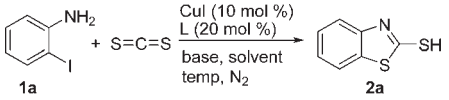
Table 1. Optimization between *o*-Iodoaniline and Carbon Disulfide[a]



entry	base	ligand	solvent	temp (°C)	yield of **2a** (%)[b]
1	Cs_2CO_3		toluene	80	NR
2	K_2CO_3		toluene	80	NR
3	K_3PO_4		toluene	80	NR
4	^tBuONa		toluene	80	33
5	Et_3N		toluene	80	57
6	DABCO		toluene	80	65
7	DBU		toluene	80	86
8			toluene	80	NR
9	DBU	DMEDA	toluene	80	83
10	DBU	TMEDA	toluene	80	80
11	DBU	1,10-phenanthroline	toluene	80	82
12[c]	DBU		toluene	80	84
13	DBU		1,4-dioxane	80	79
14	DBU		CH_3CN	80	54
15	DBU		DMF	80	44
16	DBU		DMSO	80	41
17	DBU		toluene	70	68

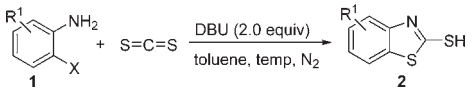
[a] Unless otherwise noted the reactions were performed in a sealed tube with **1a** (0.5 mmol), carbon disulfide (1.0 mmol), CuI (10 mol %), and ligand (20 mol %) in solvent (1 mL) for 24 h. [b] The yields were evaluated by NMR with $Cl_2C{=}CHCl$ as internal standard. [c] CuI was not added in the reaction.

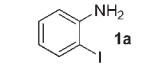
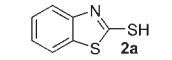
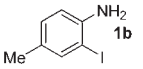
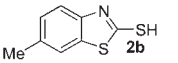
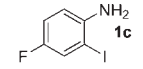
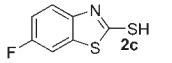
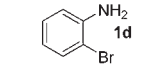
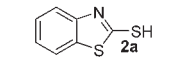
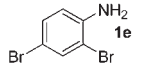
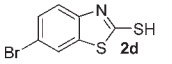
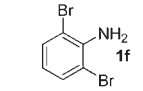
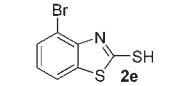
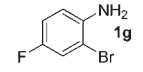
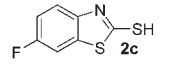
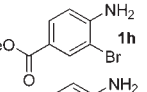
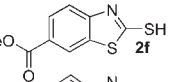
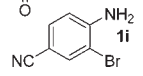
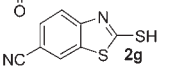
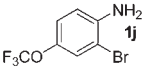
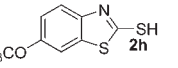
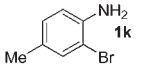
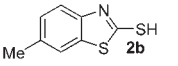
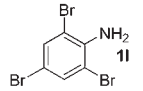
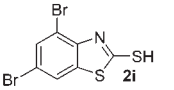
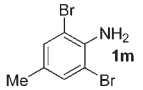
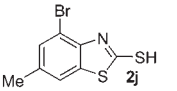
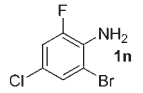
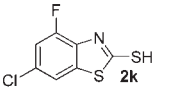
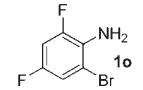
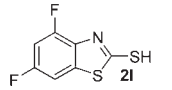
good to excellent yields. *para*-Substituents ranging from a weak electron-withdrawing group, such as Br, to a strong electron-withdrawing group, such as CO_2Me, CF_3O, and CN, along with an electron-donating Me group, all generated the corresponding substituted 2-mercaptobenzothiazole derivatives in satisfying yields (entries 5–11). A substrate with two substituents situated *para* and *ortho* to amino group also afforded a high yield of the corresponding 2-mercaptobenzothiazole derivatives (entries 12–15). It is noteworthy that when *o*-chloroaniline was used, the reaction did not proceed even when the reaction was treated at 120 °C for 36 h.

On the basis of the above results, the mechanism of this reaction is proposed as shown in Scheme 1. In the presence of organic base, such as DBU,[14] the nucleophilic nitrogen of *o*-haloaniline **1** would attack the carbon atom of carbon disulfide, which might be activated by $DBUH^+$ to form intermediate **3** (step a). The intermediate **3** could convert into the product **2** via an intramolecular S_NAr reaction (step b).

In summary, we have developed a simple, practical, and highly efficient base-promoted method for the synthesis of 2-mercaptobenzothiazole derivatives. The protocol uses readily available anilines and carbon disulfide as the

Table 2. Synthesis of 2-Mercaptobenzothiazole Derivatives[a]

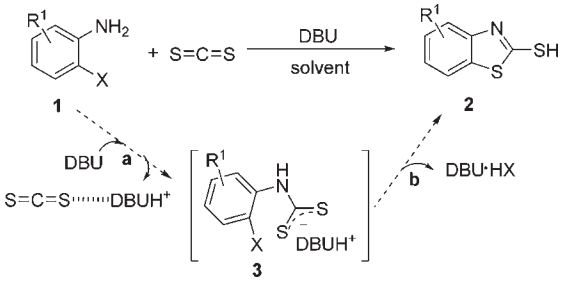


entry	substrate **1**	temp (°C)	time (h)	product	yield (%)[b]
1	 **1a**	80	24	 **2a**	82
2	 **1b**	80	24	 **2b**	76
3	 **1c**	80	24	 **2c**	89
4	 **1d**	100	24	 **2a**	80
5	 **1e**	100	24	 **2d**	57
6	 **1f**	100	24	 **2e**	62
7	 **1g**	100	16	 **2c**	83
8	 **1h**	100	16	 **2f**	78
9	 **1i**	100	24	 **2g**	65
10	 **1j**	100	16	 **2h**	79
11	 **1k**	100	24	 **2b**	74
12	 **1l**	100	24	 **2i**	54
13	 **1m**	100	24	 **2j**	60
14	 **1n**	100	16	 **2k**	82
15	 **1o**	100	16	 **2l**	86

[a] Unless otherwise noted the reactions were performed in a sealed tube with **1** (0.5 mmol), carbon disulfide (1.0 mmol), and DBU (1.0 mmol) in toluene (1 mL). [b] Isolated yields.

(14) (a) Wang, F.; Wang, Y.; Cai, L.; Miao, Z.; Chen, R. *Adv. Synth. Catal.* **2008**, *350*, 2733. (b) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517.

Scheme 1. Proposed Reaction Pathway



starting materials under the mild condition to afford the corresponding 2-mercaptobenzothiazoles in good to excellent yields. Furthermore, the reaction avoids utilization of any metals, and therefore compounds are of potential interest in both academic and pharmaceutical research. Further application of the system to pharmaceutical and biochemical areas is in progress.

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Supporting Information Available. Experimental procedures and full characterization including ^{1}H NMR and ^{13}C NMR data for compounds **2a**–**2l**. This material is available free of charge via the Internet at http://pubs.acs.org.