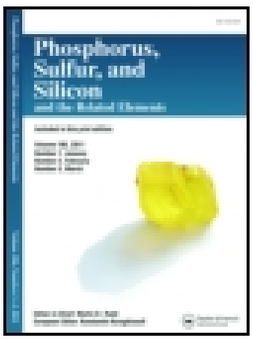

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SHORT COMMUNICATION

A new strategy for the synthesis of 2-mercaptobenzazole derivatives by green chemistry metrics

Esmail Vessally[a], Aazam Monfared[a], Zahra Eskandari[a], Morteza Abdoli[a], and Akram Hosseinian[b]*

[a]Department of Chemistry, Payame Noor University, Tehran, Iran; [b]School of Engineering Science, College of Engineering, University of Tehran, Tehran, Iran

ABSTRACT

A green and efficient method has been developed for the synthesis of 2-mercaptobenzazole derivatives *via* the reaction of commercially available aniline derivatives with low-cost and nontoxic potassium thiocyanate in water. The reactions proceeded smoothly under catalyst- and ligand-free conditions to give the corresponding products in good to excellent yields. The versatility, low cost, and environmental friendliness, in combination with high yields and easy work-up makes the procedure noteworthy.

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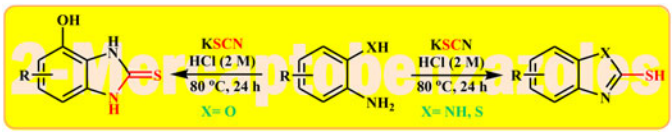
KEYWORDS
2-Mercaptobenzazoles; potassium thiocyanate; aqueous medium; catalyst-free; ligand-free

GRAPHICAL ABSTRACT



Introduction

The preparation of 2-thio-substituted benzazoles (benzimidazoles, benzothiazoles, benzoxazoles) has developed into an interesting topic for synthetic organic chemists, as these molecules show an impressive variety of biological properties such as anticancer, anti-convulsion, anti-inflammatory, antifungal, and antioxidant properties.[1–5] Several commercially available drugs are derived from 2-thio-substituted benzazo-core entities (Figure 1) and many researchers have been working to explore these motifs to their maximum potential against several diseases or disorders.[6–10] Traditionally, 2-mercaptobenzazoles are prepared through the reactions of the corresponding anilines (1,2-phenylenediamines, 2-aminophenols, 2-aminothiophenols) with carbon disulfide (Scheme 1, route a).[11] However, carbon disulfide is a toxic reagent and may cause serious environmental pollution, health, and safety problems. Alternatively, the cyclization of aniline derivatives with potassium *O*-ethyl dithiocarbonate/phenyl chlorothionocarbonate for the synthesis of titled compounds were developed by Deligeorgiev[12] and Sun,[13] respectively (Scheme 1, routes a, b). Nevertheless, the instability, toxicity and/or unpleasant odor of these reagents impede their application. Very recently, Dong reported an efficient synthesis of 2-mercaptobenzazoles by cyclization of anilines with tetramethylthiuram disulfide using water as solvent (Scheme 1, route c).[14] However, tetramethylthiuram disulfide is a highly allergenic compound.[15] Thus, the development of an efficient and economical protocol for the synthesis of 2-mercaptobenzazoles by "Green Chemistry" methods is still a significant issue.

Recently, the development of eco-friendly reaction systems using water as a reaction medium has been the subject of considerable degree of attention because water is safe, cheap, widely available, and environmentally-benign as compared with organic solvents.[16] In recent years, significant efforts have been devoted to the synthesis of valuable sulfur-containing compounds employing thiocyanate salts (e.g. KSCN, NaSCN, NH_4SCN) as inexpensive, nontoxic, and versatile synthetic intermediates.[17] In connection with our interest in green chemistry[18] and following our research on the synthesis of sulfur-containing compounds,[19] herein we propose a novel and environment friendly synthesis of 2-mercaptobenzazole derivatives through the reaction of the corresponding anilines with potassium thiocyanate under catalyst- and ligand-free conditions in aqueous medium.

Results and discussion

To test our hypothesis, we chose benzene-1,2-diamine **1a** as the model substrate to optimize the reaction conditions, and a variety of solvents were screened, as show in Table 1. Firstly, the reaction was carried out in methanol at ambient temperature under air conditions. However, the reaction did not initiate at all after 24 h (Table 1, entry 1). Performing

CONTACT Akram Hosseinian hoseinian@ut.ac.ir
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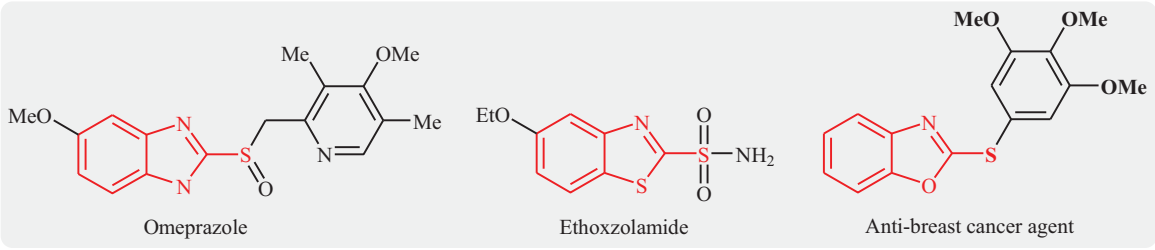
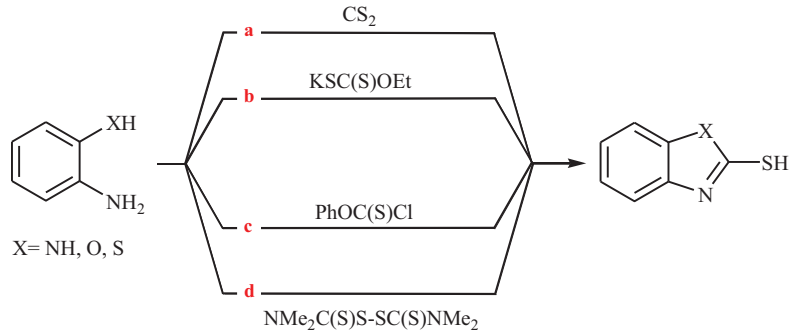
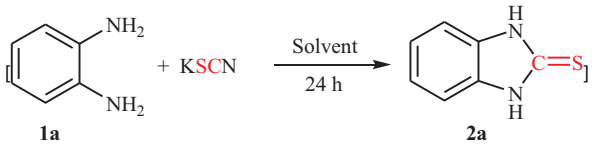


Figure 1. Selected examples of drugs containing 2-mercaptobenzazole scaffold.



Scheme 1. Main synthetic routes to 2-mercaptobenzazoles.

Table 1. Screening of the reaction conditions for the cyclization of benzene-1,2-diamine **1a** with KSCN.[a]



1a **2a**

Entry	Solvent	Temperature (°C)	Yield (%)[b]
1	MeOH	25	NR[c]
2	MeOH	reflux	NR
3	EtOH	25	NR
4	EtOH	reflux	NR
5	EtOH/H_2O	25	trace
6[d]	EtOH/H_2O	25	26
7	HCl (1 M)	25	53
8	HCl (1 M)	80	82
9	HCl (2 M)	80	87
10	HCl (3 M)	80	79

[a]Reaction conditions: aniline (0.2 g, 1.0 equiv.), KSCN (1.0 equiv.), solvent (4 mL).
[b]Isolated yields.
[c]No reaction.
[d]One drop of HCl were added to the reaction mixture.

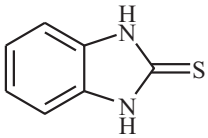
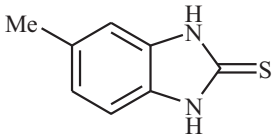
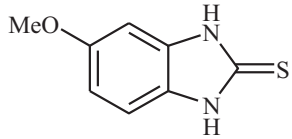
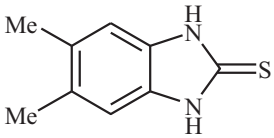
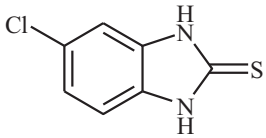
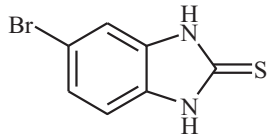
the reaction under reflux conditions gave identical results (Table 1, entry 2). Likewise, no product was detected when the reaction was performed in ethanol (Table 1, entries 3, 4) but in the presence of an ethanol–water solvent, a very low yield was noticed (Table 1, entry 5). It was pleasing to observe that adding a single drop of concentrated hydrochloric acid to the reaction mixture afforded a 26% yield of the desired product **2a** (Table 1, entry 6). The results encouraged us to further explore and optimize the conditions. Interestingly, the yield of benzo[*d*]imidazole-2(3*H*)-thione **2a** increased from 26% to 53% when the reaction was carried out in 1.0 M HCl solution as the solvent at ambient temperature (Table 1, entry 7). At 80 °C, the formation of **2a** increased and the expected product was isolated in 82% yield (Table 1, entry 8). When the reaction was carried out in HCl (2 M), the yield slightly increased to 87% (Table 1, entry 9). It is noteworthy that increasing of the concentration of the solution to 3 M did not improve the outcome of the reaction and **2a** was isolated in 79% yield (Table 1, entry 10). Thus, the optimal reaction conditions were determined to be aqueous hydrochloric acid (2.0 M) as the solvent at 80 °C for 24 hours.

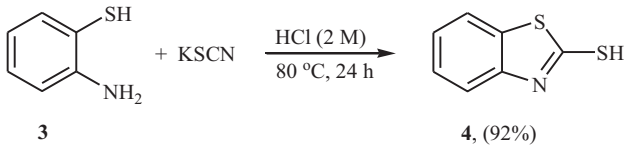
With the optimized reaction conditions in hand, we proceeded to explore the scope of the reaction with various 1,2-diaminobenzenes, as summarized in Table 2. Interestingly, both electron-rich and electron-deficient 1,2-diaminobenzenes **1** reacted efficiently under the optimized conditions and provided the expected benzimidazole-2-thiones **2** in good to excellent yields. Pleasingly, the reaction was successfully performed on a gram scale to give isolated yields comparable to those obtained from small-scale reactions.

Inspired by these results, we applied this procedure for the synthesis of 2-mercaptobenzothiazole **4** from the corresponding 2-aminothiophenol **3**. As shown in Scheme 2, the protocol worked well for this reaction and afforded the expected product in excellent yield (92%).

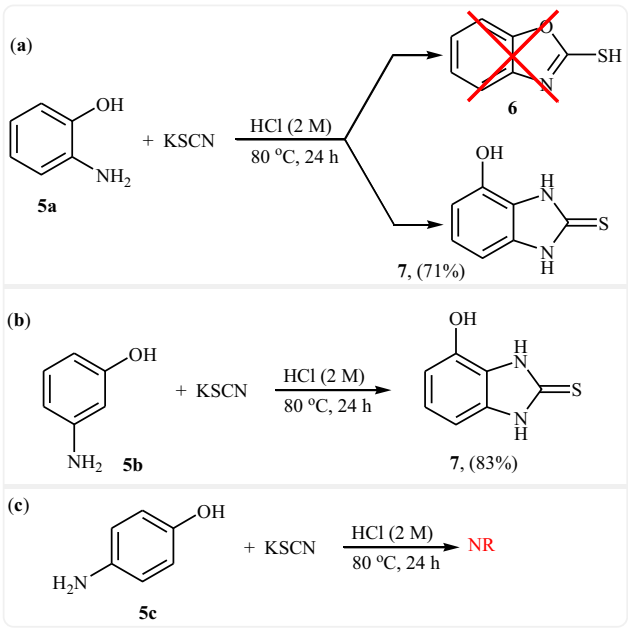
Next, we turned our attention to extend this protocol to the synthesis of 2-mercaptobenzoxazole derivatives. Thus the reaction of 2-aminophenol **5a** with KSCN was carried out under standard conditions. Surprisingly, the synthesis of 2-mercaptobenzoxazole **6** under these conditions was hampered due to the unexpected formation of 4-hydroxy-1*H*-benzo[*d*]imidazole-2(3*H*)-thione **7** in 71% yield as the sole product (Scheme 3a). Interestingly, the reaction of 3-aminophenol **5 b** with KSCN under the same conditions resulted in the formation of the same product **7** in slightly higher yield (Scheme 3b). However, 4-aminophenol failed to participate in the reaction (Scheme 3c).

Table 2. Formation of benzimidazole-2-thiones **2** by reaction of benzene-1,2-diamine **1** with KSCN in water.

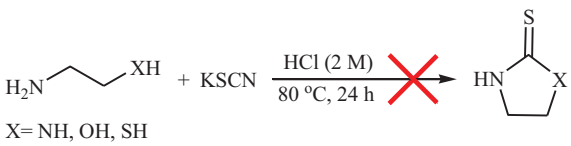
		
2a, (87%)	**2b**, (83%)	**2c**, (80%)
		
2d, (81%)	**2e**, (79%)	**2f**, (75%)



Scheme 2. Cyclization of 2-aminothiophenol with KSCN in water.

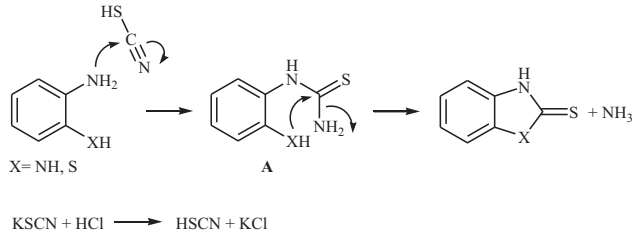


Scheme 3. Reaction of aminophenols with KSCN in aqueous medium.



Scheme 4. Reaction of aliphatic amine derivatives with KSCN.

Finally, we used analogous conditions for the cyclization of aliphatic amine derivatives (ethylenediamine, ethanolamine, and cysteamine) with KSCN. Unfortunately, these substrates did not give the desired azolidin-2-thions under the optimized reaction conditions (Scheme 4).



Scheme 5. Postulated reaction pathway.

A mechanism for the cyclization of 1,2-diaminobenzenes and 2-aminophenols with KSCN is proposed in Scheme 5. The reaction proceeds via generation of a thiourea intermediate **A** by nucleophilic addition of the amino group of the starting aniline to the carbon atom of *in situ* generated mercaptoformonitrile (from potassium thiocyanate and hydrochloric acid). Next, the intermediate **A** undergoes intramolecular nucleophilic addition to give the expected product and one molecule of ammonia. The mechanistic studies for the cyclization of aminophenoles and KSCN are currently under investigation in our laboratory.

Conclusions

In conclusion, we developed a novel, environmentally friendly and efficient protocol for the synthesis of 2-mercaptobenzazole derivatives through the reaction of low-cost commercially available potassium thiocyanate with anilines in aqueous medium. Without metal catalyst and ligand, the reaction tolerates a range of functional groups, obtaining the desired products in good to excellent yields. Furthermore, the products could be easily isolated from the reaction mixture by a simple filtration. Further investigations of the reaction mechanism and the extension of the substrate scope are currently underway in our laboratory.

Experimental

Experimental details and spectroscopic data of the products are compiled in the supplemental materials file.

Disclosure statement

No potential conflict of interest was reported by the authors.

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