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An efficient one-pot strategy for the synthesis of 4-methylene-2-thiazolidinethiones in water

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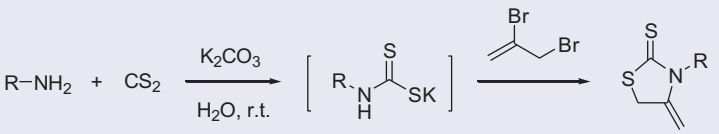
ABSTRACT

A simple and efficient, one-pot strategy for the preparation of 4-methylene-2-thiazolidinethiones has been developed. This protocol involved condensation of primary amines with carbon disulfide in water to generate the dithiocarbamate salts *in situ*, which coupled with 2,3-dibromopropene, followed by intramolecular cyclization to the corresponding heterocycles in moderate to good yields.

GRAPHICAL ABSTRACT



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Introduction

Thiazolidine-2-thiones are a class of important five-membered heteroaromatic compounds containing both S and N atoms attaching on the carbon of C=S bond, which are usually used as useful organic intermediates,[1–3] especially in pharmaceutical chemistry and asymmetric synthesis.[4–7] Due to these reasons, the synthesis of thiazolidine-2-thiones with different substituents has become one of hot spots in organic synthesis chemistry in recent decades. Thiazolidine-2-thione derivatives were usually prepared from *β*-amino alcohols and carbon disulfide.[8–10] In addition, they could be synthesized by the palladium catalyzed reactions of propargylamine derivatives with carbon disulfide,[11] and by the functionalized ion-exchange resins catalyzed cycloaddition of CS_2 with aziridines or propargyl amines.[12] Recently, some multi-component and one-pot approaches to the thiazolidine-2-thiones have been described.[13–16] Weng and coworkers discovered a switchable copper-catalyzed cascade synthesis of 5-methylene-thiazolidine-2-thiones from *N*-(2-bromoallyl)amines and carbon disulfide.[17] Anitha and Kumara Swamy constructed thiazolidine-2-thiones in good to excellent yields *via* the base promoting the cyclization of epoxy-sulfonamides and carbon disulfide.[18] Although some useful methods for the their preparation through the reaction of vicinal

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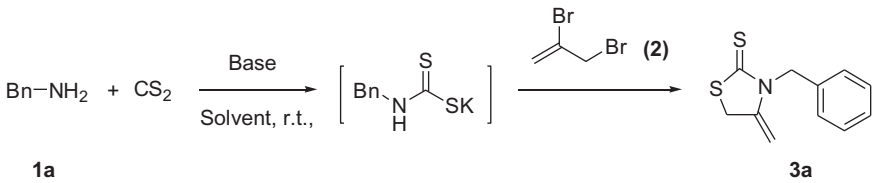


Scheme 1. Optimization of one-pot reaction conditions for **3a** formation.

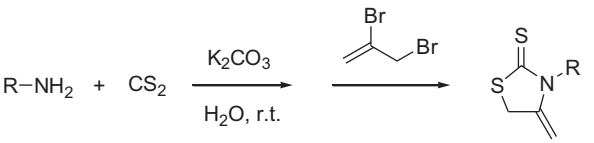
Table 1. Screening of reaction conditions in the synthesis of **3a**.[a]

Entry	Molar ratio (**1a**/CS_2/**2**)	Base (equiv.)	Solvent	Yield (%)[b]
1	1:1:1	None	THF	52
2	1:2:1	None	THF	58
3	1:3:1	None	THF	60
4	1:3:1	None	CH_3CN	50
5	1:3:1	None	DMF	61
6	1:3:1	None	EtOH	56
7	1:3:1.5	None	THF	64[c]
8	1.5:3:1	None	THF	75
9	1.5:3:2	None	THF	73
10	1.5:3:1	None	H_2O	72
11	1.5:3:1	Et_3N (2.5)	THF	83
12	1.5:3:1	Et_3N (2.5)	H_2O	85
13	1.5:3:1	NaOH (2.5)	H_2O	72
14	1.5:3:1	KOH (2.5)	H_2O	78
15	1.5:3:1	K_3PO_4 (2.5)	H_2O	71
16	1.5:3:1	K_2CO_3 (2.5)	H_2O	84
17	1.5:3:1	K_2CO_3 (3.0)	H_2O	83
18	1.5:3:1	K_2CO_3 (2.0)	H_2O	80
19	1.5:3:1	K_2CO_3 (1.5)	H_2O	75
20	1.5:3:1	K_2CO_3 (1.0)	H_2O	70

[a]All reactions were carried out at open atmosphere in the appropriate solvent (10 mL) using benzylamine (**1a**), CS_2, and 2,3-dibromopropene (**2**) at room temperature. For entries of 11–20, reaction of **1a** (1.5 mmol), CS_2 (3.0 mmol), and K_2CO_3 (2.5 mmol) at room temperature for 30 min; then **2** (1.0 mmol) was added and stirred for 60 min.
[b]Isolated yield after silica gel chromatography based on **2**.
[c]Isolated yield after silica gel chromatography based on **1a**.

amino alcohols, aziridines, allylamines, and propargylamines with carbon disulfide have been reported, it is still worth studying to develop facile and practical synthetic strategy to the functional thiazolidine-2-thione derivatives. Herein, we wish to report a simple, efficient and one-pot procedure for the synthesis of 4-methylene-thiazolidine-2-thiones by reaction of primary amines, carbon disulfide, and 2,3-dibromopropene in the presence of potassium carbonate, using water as the reaction medium, under mild and transition-metal-free conditions.

In order to find the most suitable reaction conditions for our purpose, benzylamine (**1a**), carbon disulfide and 2,3-dibromopropene (**2**) were chosen as model substrates for the preparation of 3-benzyl-4-methylene-thiazolidine-2-thione (**3a**), as shown in Scheme 1. Initially, the reaction of **1a** (1.0 mmol), carbon disulfide (1.0 mmol), and **2** (1.0 mmol) was performed in THF at room temperature for 2 h without any catalyst, affording the desired product **3a** in 52% yield (Table 1, entry 1). The effect of the solvents was then examined, and several polar solvents were screened. As shown in Table 1, the reaction proceeded well in the solvents, such as CH_3CN, EtOH, and DMF (entries 4–6), but the yields were not as good as that in THF. Besides, the molar ratios of the reactants were varied, when a molar ratio was 1.5:3:1 (**1a**/CS_2/**2**), the product was isolated in the



Scheme 2. Preparation of 3-substituted-4-methylene-thiazolidine-2-thiones.

Table 2. One-pot synthesis of 4-methylene-thiazolidine-2-thiones **3**.[a]

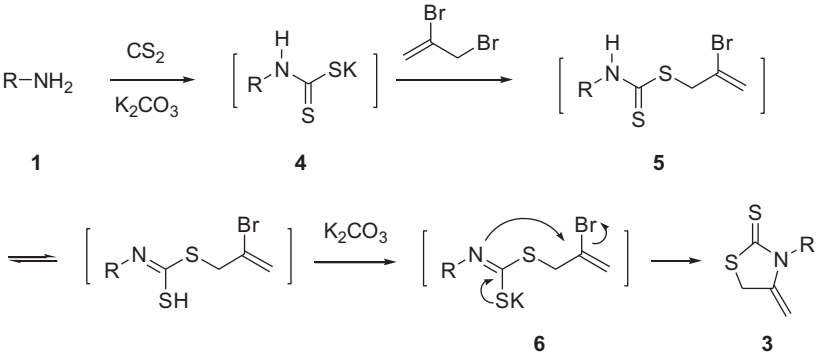
Entry	R	Products (**3**)	Yield (%)[b]
1	$C_6H_4CH_2$	**3a**	82
2	*n*-C_4H_9	**3b**	75
3	C_6H_5	**3c**	72
4	4-$CH_3OC_6H_4$	**3d**	92
5	2-$CH_3OC_6H_4$	**3e**	89
6	2-$CH_3C_6H_4$	**3f**	81
7	4-BrC_6H_4	**3g**	70
8	4-ClC_6H_4	**3h**	62
9	3-ClC_6H_4	**3i**	66
10	3-$NO_2C_6H_4$	**3j**	73
11	4-$NO_2C_6H_4$	–	–
12	4-CNC_6H_4	–	–
13	4-$CF_3C_6H_4$	–	–
14	2-ClC_6H_4	–	–
15	2-BrC_6H_4	–	–

[a]Reaction conditions: primary amines (1.5 mmol), CS_2 (3.0 mmol), K_2CO_3 (2.5 mmol), H_2O (10 mL), rt, 30–45 min; then 2,3-dibromopropene (**2**) (1.0 mmol), rt, 60–90 min.
[b]Isolated yield based on **2**.

highest yield among the entries (Table 1, entry 8). To our delight, when water was used as the alternative medium of THF, a similar good result was obtained (Table 1, entry 10). To further improve the efficiency of this synthetic approach, various bases, such as triethylamine, sodium hydroxide, potassium hydroxide, tripotassium phosphate, and potassium carbonate have been used to promote this transformation (Table 1, entries 11–16). The results indicated that the presence of base was conducive to the rapid completion of the process. Then, the reaction conditions were further optimized with potassium carbonate as a base, and it was found that 2.5 equivalent potassium carbonate was the most suitable reaction promoter, as shown in entry 16 (Table 1).

Next, under the optimal conditions, the scope and limitation of this one-pot reaction were explored using a wide range of aliphatic and aromatic amines (Scheme 2), and the results are listed in Table 2.

In general, as observed in Table 2, aliphatic primary amines such as benzylamine and *n*-butylamine worked well to give the desired products **3a** and **3b** in 82 and 75% yields, respectively (Table 2, entries 1 and 2). Furthermore, electron-rich aromatic amines are more readily to form the corresponding heterocyclic compounds. For example, aromatic amines with various electron-donating groups (Table 2, entries 4–6) in the *para* or *ortho* position could generate the products in good to excellent yields of 81–92%. In addition, when halogen groups were placed in the *para* or *meta* position of benzene ring, a long reaction time was needed, but the corresponding products (**3f**, **3g,** and **3h**) could still be obtained in a reasonable yield range of 62–70% (Table 2, entries 7–9).



Scheme 3. Proposed reaction mechanism.

When strong electron-withdrawing groups such as NO_2, CN, and CF_3 in the *para* position of benzene ring, the corresponding products could not be obtained under these conditions even after the reaction time is extended or at a higher temperature (Table 2, entries 11–13). However, 3-nitroaniline could be converted into corresponding product **3j** in 73% yield (Table 2, entry 10). On the other hand, it was worth noting here that aromatic amines bearing halide substituents in the *ortho* position, have no reaction observed (Table 2, entries 14 and 15), which may be due to the electron induction effect and steric hindrance effect of the halogens, preventing conversion of the amines to their corresponding dithiocarbamate salts.

On the basis of the experimental results and the literature,[19] a plausible mechanism for the formation of 4-methylene-thiazolidine-2-thiones is described in Scheme 3. The initial step of the reaction is the nucleophilic attack of amine **1** on carbon disulfide, which is activated by potassium carbonate, to afford the key intermediate dithiocarbamate salt **4**, and then reacts with 2,3-dibromopropene to form *S*-allyl dithiocarbamate **5**. The final product **3** was obtained by intramolecular cyclization of intermediate **6**.

In summary, we have described a novel, efficient, one-pot process for the synthesis of 4-methylene-thiazolidine-2-thiones in moderate to good yields from primary amines, carbon disulfide, and 2,3-dibromopropene, through the condensation, *S*-allylation and heterocyclization reaction in water successively.

Experimental

The reaction progress was detected by thin layer chromatography (TLC) on GF254 silica gel analytical aluminum plates, and the products were visualized by UV spectrophotometer. Column chromatography was performed on silica gel 60 (250–400 mesh). Melting points were measured with a Beijing-Taike X-4 apparatus without corrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated $CDCl_3$ or DMSO-d_6 on an Avance-Bruker 400 MHz NMR spectrometer (Bruker Optics Inc, Billerica, MA), operating at 400 and 100 MHz, respectively. FTIR analyses were performed with a Perkin-Elmer SP One FTIR spectrophotometer (PerkinElmer, Inc., Waltham, MA). Microanalyses were

performed with a Carlo Erba 1106 Elemental Analyzer. The other reagents and solvents were purchased from commercial suppliers and were used as received without further purification.

General procedure for the preparation of 4-methylene-2-thiazolidinethione

A mixture of K_2CO_3 (2.5 mmol), amine (1.5 mmol), and CS_2 (3.0 mmol) in H_2O (10.0 mL) was stirred at room temperature until the reaction was completed (determined by TLC). After 30–45 min, 2,3-dibromopropene (1.0 mmol) was added and the reaction continued for another 60–90 min under vigorous smagnetic stirring at room temperature. After completion, the organic matter was extracted with diethyl ether (2×10 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography (silica gel, petroleum ether–EtOAc) to afford the target compound.

Characterization data of all target compounds, copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material can be found *via* the "Supplementary Content".

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