Water-Mediated Multicomponent Reaction: A Facile and Efficient Synthesis of Multisubstituted Thiazolidine-2-thiones

Shi-Feng Gan, Jie-Ping Wan, Yuan-Jiang Pan, Cui-Rong Sun*

Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. of China
Fax +86(571)87951629; E-mail: suncuirong@zju.edu.cn

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Abstract: A facile, efficient, and green method for the synthesis of multisubstituted thiazolidine-2-thione derivatives via a three-component reaction of amine, carbon disulfide, and α-bromoketone is described. By using water as the reaction medium, the reaction proceeds smoothly to give corresponding products in good to excellent yields.

Key words: green method, synthesis, thiazolidine-2-thione, MCR, heterocyclic compounds

With the advantages of atom-efficient transformation, easily available starting materials, high product structural diversity, multicomponent reactions (MCR)[1] have attracted great interest from chemical and medicinal communities. During the past decades, MCR have witnessed great progress as a widely applicable synthetic strategy. However, developing novel MCR of broad tolerance and simple operation for small molecule synthesis is still one of the main goals in this field.

Thiazolidine-2-thione is a five-membered heterocyclic scaffold containing both S and N atoms attaching on the carbon of C=S bond, which has been extensively studied in the past decades.[2] And the thiazolidine-2-thione moiety have been reported to possess versatile functions. For example, polyHPMA terminated with a thiazolidine-2-thione functional group can be conjugated to a protein surface via covalent amide bonding and form protein–polyHPMA conjugates,[3] copolymers adopting the thiazolidine-2-thione as reactive groups in the side chains are suitable for the synthesis of polymeric drugs and polymer-modified biologically active compounds.[4] What is more, thiazolidine-2-thione and its derivatives have been discovered as excellent ligands in coordination chemistry.[5]

There are currently a number of synthetic methodologies available for the synthesis of thiazolidine-2-thione unit.[6] Humphlett[7] developed a protocol for the synthesis of 4-hydoxythiazolidine-2-thione by employing the reaction of ammonium dithiocarbamate and α-halo aldehydes or ketones. Recently, Endo[8] and co-workers described a highly efficient chemical fixation of carbon disulfide to aziridine to form 1,3-thioxazolidine-2-thiones based on Foglia's[9] protocol. Later, a simple three-component synthesis of 4,5-disubstituted 3-amino-4-hydroxy-thiazolidine-2-thiones involving aryl hydrazines, carbon disulfide, and organic halides has been reported by Li.[10] In spite of their sound utilities, these reported methods suffer from several disadvantages such as harsh reaction conditions, difficult-to-obtain starting materials, unsatisfactory yields, prolonged reaction times, or poor substrate tolerance. Therefore, searching for more facile and practical synthetic routes to multisubstituted thiazolidine-2-thiones is still highly desirable work.

Developing organic reactions in water has become highly popular in recent years due to its specific properties in mediating organic reactions and its friendliness to the environment.[11] Previously, we successfully used water as a reaction medium to accomplish the synthesis of 1,2-disubstituted benzimidazoles and quinoxalines in excellent efficiency and selectivity.[12] As our ongoing efforts in exploring environmentally benign synthesis, herein we report a novel, efficient, and green synthesis of multisubstituted thiazolidine-2-thiones in water by the three-component reaction of amines, carbon disulfide, and α-bromoketones.

Initially, the reaction of benzylamine (0.5 mmol), carbon disulfide (0.5 mmol), and benzoyl bromomethane (0.5 mmol) was performed in THF at room temperature for one hour without any catalyst, affording the desired thiazolidine-2-thione **3a** in 36% yield (Table 1, entry 1). In order to improve the reaction efficiency, we varied the molar ratios of the reactants, when a ratio of 1.5:1:3 (**1a**/**2a**/CS_2) was used, the product was isolated in the highest yield among the entries (Table 1, entry 1–3). To our delight, when water was used as the alternative medium of THF, a similarly good result was obtained (Table 1, entry 4).

To further improve the efficiency of this green synthetic approach, various catalysts such as $MgCl_2$, Et_3N, K_3PO_4, and K_2CO_3 have been applied to promote this transformation (Table 1, entries 5–10). The results revealed that the presence of base catalyst was necessary to drive the process to completion rapidly, and 0.5 mol equivalents K_2CO_3 turned out to be the most suitable promoter for the reaction. The reaction conditions were then finally established as shown in entry 8 (Table 1).

After the optimization, different amines and α-bromoketones were probed for the scope of the reaction (Table 2). By using water as the reaction medium at room temperature, the corresponding products were afforded in good to excellent yields. Among the different aliphatic primary

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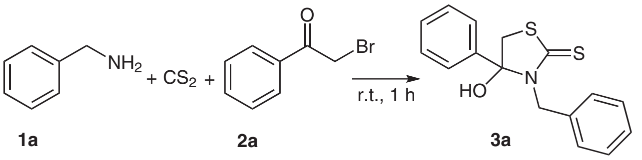
Table 1 Synthesis of 3-Benzyl-4-hydroxy-4-phenylthiazolidine-2-thione (**3a**) under Different Conditions[a]



Entry	Molar ratio **1a**/**2a**/CS_2	Catalyst (equiv)	Solvent	Yield (%)[b]
1	1:1:1	none	THF	36
2	1:1:2	none	THF	39
3	1.5:1:3	none	THF	77
4	1.5:1:3	none	H_2O	75
5	1.5:1:3	$MgCl_2$ (0.5)	H_2O	72
6	1.5:1:3	Et_3N (0.5)	H_2O	92
7	1.5:1:3	K_3PO_4 (0.5)	H_2O	93
8	1.5:1:3	K_2CO_3 (0.5)	H_2O	94
9	1.5:1:3	K_2CO_3 (0.3)	H_2O	91
10	1.5:1:3	K_2CO_3 (0.1)	H_2O	76

[a] All reactions were carried out at open atmosphere.
[b] Isolated yield based on **2a**.

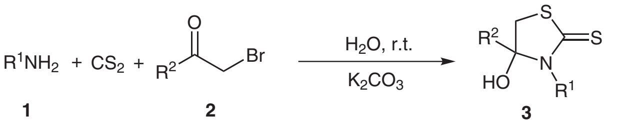
amines including benzylamine, *n*-propylamine, *n*-butylamine, allylamine, no significant impact on the yield was observed. However, a low yield (30%) was observed when aromatic amine (Table 2, entry 25) was utilized in the same reaction, this phenomenon probably resulted from the decrease of nucleophilicity of the nitrogen atom.[10] In addition, as shown in Table 2, this water-mediated MCR was also tolerant to different substituents on the arene unit, both electron-donating and electron-withdrawing ones, of the α-bromoketones.

Besides, a similar reaction using aliphatic α-bromoketone was also investigated, and corresponding product **3z** from the reaction using 1-bromo-2-butanone was obtained in modest yield (Table 2, entry 26).

The structures of all products were characterized by IR, ^{1}H NMR, ^{13}C NMR, ESI-MS, and HRMS analysis, and the structure of **3a** was additionally confirmed by the X-ray single-crystal diffraction (Figure 1).[13]

On the basis of the experimental results and the literature,[10] a possible mechanism for the formation of multisubstituted thiazolidine-2-thione derivatives is presented in Scheme 1. The initial step in this reaction is the nucleophilic attack of amine **1**[14] to carbon disulfide to afford the key intermediate **4**, which subsequently reacts with **2** to form another intermediate **5**, and intermediate **5** undergoes an intramolecular cyclization to give the final product **3**.

Table 2 One-Pot Synthesis of Multisubstituted Thiazolidine-2-thione Derivatives in Water[a]



Entry	1	R^1	R^2	Product	Yield (%)[b]
1	**1a**	Bn	Ph	**3a**	94
2	**1a**	Bn	4-ClC_6H_4	**3b**	90
3	**1a**	Bn	4-BrC_6H_4	**3c**	92
4	**1a**	Bn	4-$O_2NC_6H_4$	**3d**	86
5	**1a**	Bn	4-MeC_6H_4	**3e**	88
6	**1a**	Bn	4-$MeOC_6H_4$	**3f**	86
7	**1b**	Bu	Ph	**3g**	85
8	**1b**	Bu	4-ClC_6H_4	**3h**	80
9	**1b**	Bu	4-BrC_6H_4	**3i**	80
10	**1b**	Bu	4-$O_2NC_6H_4$	**3j**	70
11	**1b**	Bu	4-MeC_6H_4	**3k**	65
12	**1c**	allyl	Ph	**3l**	64
13	**1c**	allyl	4-ClC_6H_4	**3m**	60
14	**1c**	allyl	4-BrC_6H_4	**3n**	63
15	**1c**	allyl	4-$O_2NC_6H_4$	**3o**	70
16	**1c**	allyl	4-MeC_6H_4	**3p**	76
17	**1c**	allyl	4-$MeOC_6H_4$	**3q**	60
18	**1d**	Pr	Ph	**3r**	76
19	**1d**	Pr	4-ClC_6H_4	**3s**	80
20	**1d**	Pr	4-BrC_6H_4	**3t**	82
21	**1d**	Pr	4-$O_2NC_6H_4$	**3u**	81
22	**1d**	Pr	4-MeC_6H_4	**3v**	80
23	**1d**	Pr	4-$MeOC_6H_4$	**3w**	76
24	**1d**	Pr	3-$MeOC_6H_4$	**3x**	75
25	**1e**	Ph	4-ClC_6H_4	**3y**	30
26	**1b**	Bu	Et	**3z**	59

[a] Reaction conditions: amine (0.75 mmol), CS_2 (1.5 mmol), α-bromoketone (0.5 mmol), K_2CO_3 (0.25 mmol), r.t., 1 h.
[b] Isolated yield based on **2**.

In conclusion, we have reported a highly efficient and green protocol for one-pot synthesis of multisubstituted thiazolidine-2-thione derivatives starting from amines, carbon disulfide, and α-bromoketones. This newly developed procedure offers several advantages such as broad application scope, excellent yields, mild reaction conditions, simple operation, and environmental friendliness. The present study provided a useful supplement for the synthesis of thiazolidine-2-thione heterocycles.

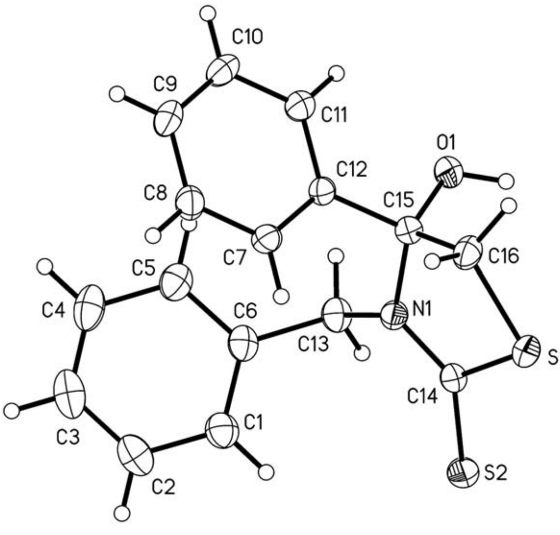
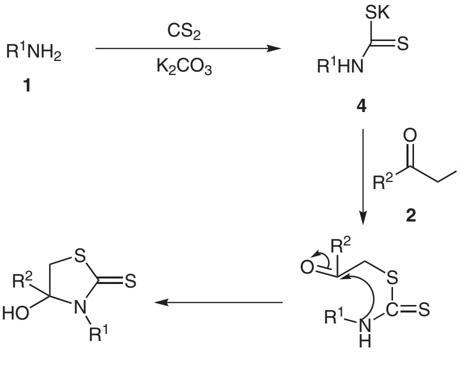


Figure 1 Crystal structure of **3a**



Scheme 1 Proposed mechanism for the formation of multisubstituted thiazolidine-2-thione derivatives

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 747685.

(14) **General Procedure**
To a solution of amines **1** (0.75 mmol) in H_2O (3 mL), CS_2 (1.5 mmol) and α-bromoketone **2** (0.5 mmol) were added. Subsequently, K_2CO_3 (0.25 mmol) was located to the mixture. After stirring the mixture at r.t. for 1 h, the mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried overnight with anhyd Na_2SO_4. After the organic solvent was removed, the residue was subjected to silical gel chromatography PE–EtOAc (5:1) as eluent to give pure products.