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Silica gel promoted synthesis of *N*-sulfonylcyclothioureas in water

Guo-Xiang Wan, Liang Xu, Xiao-Si Ma, Ning Ma *

Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, PR China

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ABSTRACT

N-Sulfonylcyclothioureas were synthesized from *N*-sulfonyldiamines and CS_2 with moderate to good yields in silica gel-water system. Moreover, the silica gel can be recycled for at least three times.

Because water is natural, nontoxic, cheap, and readily available, it is thought to be an ideal solvent for both laboratory and industrial chemical processes.[1] Although water is a clean solvent, aqueous organic reactions frequently suffer from poor solubility of the substrates.[2] In order to solve this problem, co-solvents or phase-transfer catalysts (PTC) were introduced to organic transformations in water.[3] An alternative approach is to use silica gel (SG)-water system, which was originally established by Minakata et al. in the research of formation and ring opening of aziridines.[4] Substrates contact each other more efficiently in this system than only in water because they can be adsorbed to the surface of SG by the hydrophobic interactions between the surface of SG and the organic molecule. In this context, SG promotes the aqueous organic reactions like PTC. Furthermore, SG was reported to promote various organic transformations in organic media. SG facilitated these reactions due to its adsorptive nature and moderate surface acidity.[5]

Thioureas represent a versatile and useful class of application in medicinal chemistry, asymmetric catalysis and building blocks in the synthesis of heterocycles.[6,7] As a kind of derivatives of thioureas, *N*-sulfonylcyclothioureas are synthetic intermediates for a variety of compounds and they are present as important substructures of bioactive compounds.[8] Direct sulfonamidation of cyclothioureas by sulfonyl chlorides in the presence of organic or inorganic bases is the general procedure for the synthesis of *N*-sulfonylcyclothioureas. Another synthetic route is the conversion of *N*-sulfonyldiamine to the target structures by thiophosgene. The alternative synthesis of *N*-sulfonylcyclothioureas is achieved via sulfonyl thioisocyanate, which is prepared from sulfonamide and CS_2 in the presence of $SOCl_2$ or $COCl_2$. Since the aforementioned methods are frequently limited by harsh reaction conditions, low yields, long reaction times, and use of toxic solvents or catalysts,[9–12] they are rarely described as "green" reactions. Although the synthesis of thiourea derivatives in water under sodium hydroxide and reflux condition has been investigated just recently,[13] the synthesis of *N*-sulfonylcyclothioureas from *N*-sulfonyldiamines and CS_2 in SG-water system has not been exploited. As a part of our continuing effort to develop green synthetic protocol for sulfonylthioureas,[14] we herein report an efficient and practical approach to *N*-sulfonylcyclothioureas via the reaction of *N*-sulfonyldiamines and CS_2 in water promoted by silica gel (Fig. 1).

Initially, *N*-(2-aminoethyl)-4-methylbenzenesulfonamide (**1c**) was used as a typical substrate to investigate the reaction conditions. When **1c** (1.5 mmol) was treated with CS_2 (2.0 mmol) in H_2O at room temperature for 12 h, 1-(4-methylphenylsulfonyl)imidazolidine-2-thione (**2c**) was obtained only in 8% yield (Table 1, entry 1). The use of equivalent NaOH improved the yield to 18% (Table 1, entry 2). When SG (0.50 g) was added instead of sodium hydroxide, the yield of **2c** achieved 60% (Table 1, entry 3). While ethanol was used as the reaction media the yield decreased to 36% (Table 1, entry 4). The addition of NaOH into the SG-H_2O system did not affect on the yields remarkably, either at room temperature or at 45 °C (Table 1, entries 5 and 6). However, the synthetic condition for 1-(4-methylphenylsulfonyl)-1,3-dihydro-2*H*-benzimidazole-2-thione (**2o**) was a little different. The reaction of **1o** with CS_2 in H_2O at room temperature did not proceed (Table 1, entries 1 and 2). In SG-H_2O system, the product **2o** was not observed no matter even if the ethanol existed (Table 1, entries 3 and 4). The addition of NaOH at room temperature led to the desired product **2o** in a poor yield of 27% (Table 1, entry

* Corresponding author.
E-mail address: mntju@tju.edu.cn (N. Ma).

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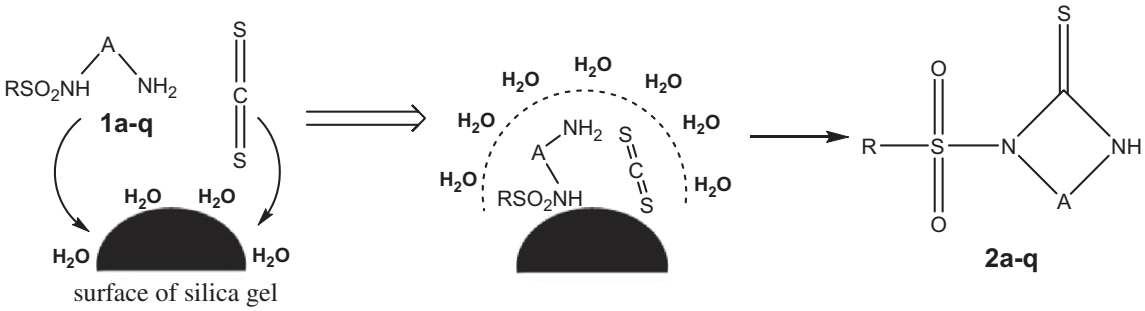
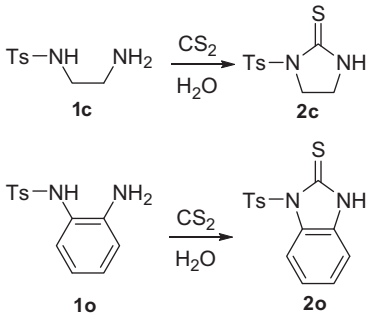


R = C_6H_5, 2-MeC_6H_4, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeCONHC_6H_4$, Me;

A = $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_6$, 1,2-C_6H_4, 1,2-C_6H_{10}

Figure 1. Cyclization of *N*-sulfonyldiamines and CS_2 in SG-H_2O.

Table 1
Optimization of the reaction conditions[a]



Entry	Base	Media	Temp	Yield[b] (%)	
				2c	**2o**
1	—	H_2O	rt	8	0
2	NaOH	H_2O	rt	18	0
3	—	SG-H_2O	rt	60	0
4	—	SG-EtOH	rt	36	0
5	NaOH	SG-H_2O	rt	58	27
6	NaOH	SG-H_2O	45 °C	61	75

[a] **1c** or **1o** (1.5 mmol), CS_2 (2.0 mmol), H_2O or EtOH (5 ml), silica gel (0 or 0.5 g), NaOH (0 or 1 equiv), 12 h.
[b] Isolated yield.

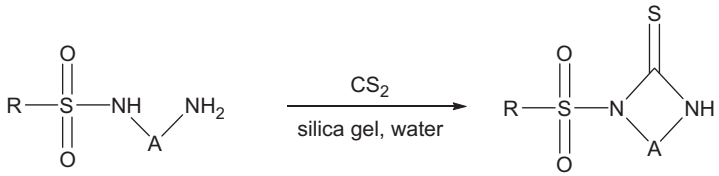
5). Satisfactorily, the reaction furnished **2o** in good yield (75%) at 45 °C (Table 1, entry 6). Therefore, the synthesis of *N*-sulfonylcyclothioureas from *N*-sulfonyldiamines and CS_2 is thought to be fulfilled under two different conditions: condition A, SG-H_2O system at room temperature for *N*-sulfonylethylenediamines as substrates; condition B, SG-NaOH-H_2O system at 45 °C for *N*-sulfonyl-1,2-benzenediamines as substrates. Additional experiments showed that 200–300 mesh of SG performed better than 100–200 and 60–100 mesh. Furthermore, the SG could be recycled at least three times without the loss of catalytic activity.

With these optimized conditions in hand, we explored the scope of the reaction. As seen in Table 2, *N*-(2-aminoethyl)benzenesulfonamide (**1a**) reacted with CS_2 under condition A to produce **2a** in moderate yield (63%, entry 1). Similarly, *N*-(2-aminoethyl)-2-methylbenzenesulfonamide (**1b**) underwent cyclization reaction to produce the corresponding *N*-sulfonylcyclothiourea **2b** in 60% yield (Table 2, entry 2). Encouraged by these results, we turned our attention to *N*-sulfonyldiamines with strong electron-withdrawing group. To our delight, *N*-(2-aminoethyl)-3-nitrobenzenesulfonamide (**1d**) and *N*-(2-aminoethyl)-2-nitrobenzenesulfonamide (**1e**) furnished the corresponding **2d** and **2e** in moderate to good yields (64% and 72%, Table 2, entries 4 and 5). The halogen substituted *N*-sulfonyldiamines **1f** and **1g** also gave the corresponding products in reasonable yields (69% and 68%, Table 2, entries 6 and 7). *N*-sulfonylcyclothioureas **2a**–**g** were synthesized in SG-H_2O system without inorganic base at room temperature for 12 h (condition A).

However, the other *N*-sulfonylcyclothioureas **2h–q** were synthesized in the presence of sodium hydroxide at 45 °C in SG-H_2O (condition B, Table 2, entries 8–17). For example, the chiral *N*-[(1*R*,2*R*)-2-aminocyclohexyl]-4-methylbenzenesulfonamide (**1h**) was converted to **2h** in good yield (75%, Table 2, entry 8). *N*-(3-Aminopropyl)benzenesulfonamide (**1i**) and *N*-(3-Aminopropyl)-4-methyl-benzenesulfonamide (**1j**) also led to good yields of **2i** and **2j**, respectively (both 75%, Table 2, entries 9 and 10). Moreover, *N*-sulfonyl butanediamine and *N*-sulfonyl hexanediamines reacted with CS_2 to produce the corresponding seven- and nine-membered *N*-sulfonylcyclothioureas in good yields (Table 2, entries 11–13). *N*-(2-Aminophenyl)benzenesulfonamide (**1n**) and its acetamido derivative **1p** afforded the corresponding products **2n** (87%) and **2p** (65%) in moderate to good yields, respectively (Table 2, entries 14, 16). *N*-Mesyl-1,2-benzenediamine (**1q**) underwent similar reaction to produce the corresponding product **2q** in good yield (85%, Table 2, entry 17). The above results indicated that the nucleophilic ability of the amino group decreased when it bonded directly to benzene or cyclohexane ring, because of the delocalization of the nitrogen lone-pair electrons into the aromatic system and/or steric hindrance. To enhance the nucleophilic ability, bases such as NaOH should be introduced into the SG-H_2O system. NaOH might not only diminish both the amine-SG and amine-H_2O interactions, but also abstract a proton from the sulfonamido group to form an anion and facilitate the nucleophilic cyclization. Furthermore, *N*-Cbz diamines (**1r–1s**) were not converted to the corresponding cyclothiourea derivatives under both condition A and condition B (Table 2, entries 18–20).

It is commonly thought that the reaction of primary amine with CS_2 produces the corresponding isocyanate via thiocarbamic acid. Recently Prabhu and co-workers proposed a new pathway through amino dithiol derivative as an intermediate for the reaction of a primary amine, a secondary amine, and CS_2.[13] Since both sulfonyl dithiocarbamic acid **4** and symmetric disulfonyl thiourea **6** were not isolated in the synthesis of **2**, the cyclization of *N*-sulfonyldiamine with CS_2 in SG-H_2O system was also likely to have been achieved via the sulfonamido dithiol derivative **3** or its sodium salt as the intermediate. *N*-Sulfonyldiamines and CS_2 was adsorbed on the surface of SG simultaneously, which facilitated the synergic nucleophilic addition of amino and sulfonamido group to the two C=S bonds of CS_2. To determine if SG promotes the reaction by acid catalysis, additional experiments were conducted. The SG was pre-

Table 2
The scope of the cyclization of *N*-monosulfonyldiamine and CS_2



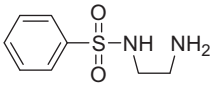
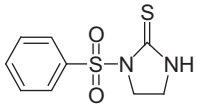
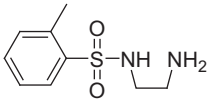
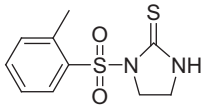
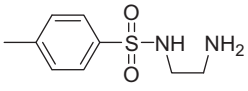
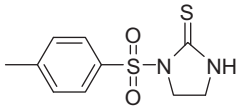
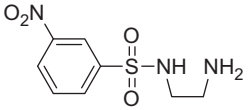
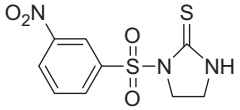
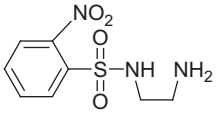
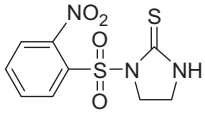
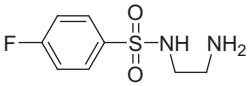
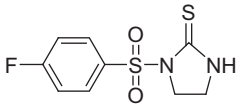
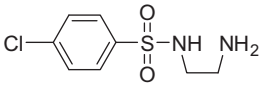
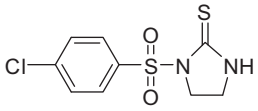
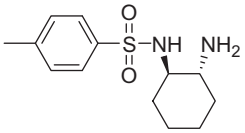
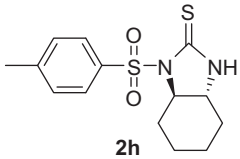
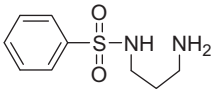
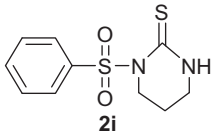
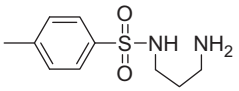
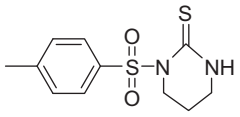
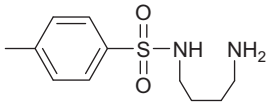
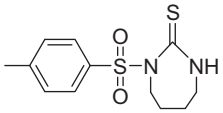
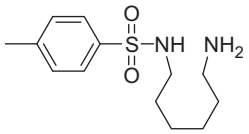
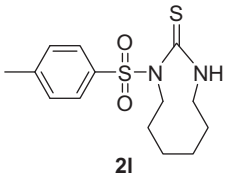
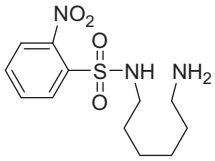
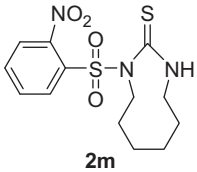
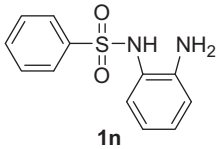
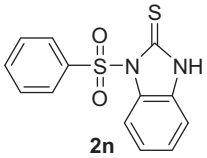
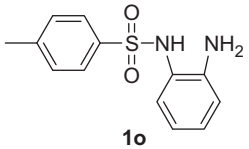
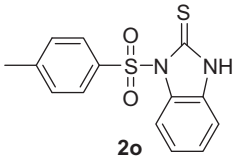
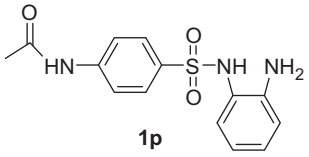
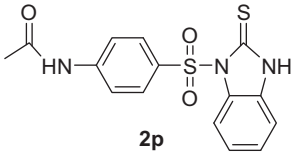
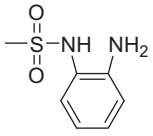
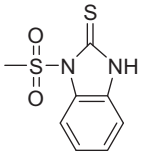
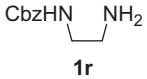
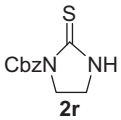
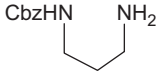
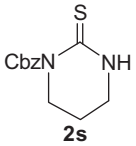
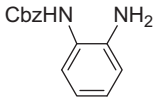
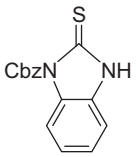
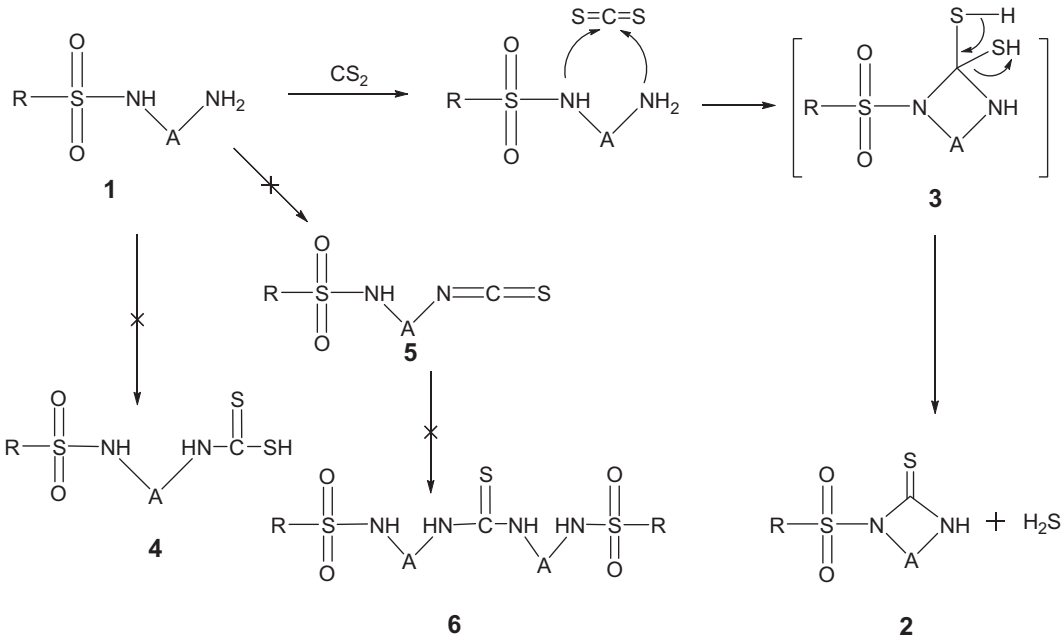
Entry	Substrate	Product	Condition[a]	Yield[b] (%)
1	 **1a**	 **2a**	A	63
2	 **1b**	 **2b**	A	60
3	 **1c**	 **2c**	A	60
4	 **1d**	 **2d**	A	64
5	 **1e**	 **2e**	A	72
6	 **1f**	 **2f**	A	69
7	 **1g**	 **2g**	A	68
8	 **1h**	 **2h**	B	75
9	 **1i**	 **2i**	B	75
10	 **1j**	 **2j**	B	75

Table 2 (*continued*)

Entry	Substrate	Product	Condition[a]	Yield[b] (%)
11	 **1k**	 **2k**	B	72
12	 **1l**	 **2l**	B	81
13	 **1m**	 **2m**	B	81
14	 **1n**	 **2n**	B	87
15	 **1o**	 **2o**	B	75
16	 **1p**	 **2p**	B	65
17	 **1q**	 **2q**	B	85
18	 **1r**	 **2r**	A, B	–
19	 **1s**	 **2s**	A, B	–
20	 **1t**	 **2t**	A, B	–

[a] Condition A: **1** (1.5 mmol), CS_2 (2.0 mmol), silica gel (0.5 g), H_2O (5 ml), rt, 12 h; Condition B: **1** (1.5 mmol), CS_2 (2.0 mmol), NaOH (1.5 mmol), silica gel (0.5 g), H_2O (5 ml), 45 °C, 12 h.

[b] Isolated yield.



Scheme 1. Possible route for the cyclization reaction (SG was omitted for clarity).

treated in an oven to transform silanol (≡SiOH) groups partially to siloxane bridges (≡SiOSi≡).[5d] It might result in poorer acidity of SG because the silanol group is commonly thought to be responsible for the Lewis or Brønsted acidity of SG. As the result, pre-heated SG did not show lower promoting activity than normal SG. Therefore, SG probably mainly plays a role via the adsorptive nature of its surface, which is similar to that described by Minakata et al.[4] The surface area of silica gel available for a reaction in SG-H_2O system would be quite large compared with that of the interface in a conventional liquid-liquid biphasic system. Thus, based on the aforementioned literatures and our observation, the plausible mechanism is proposed as depicted in Scheme 1.

In conclusion, we have developed a mild and efficient method for the synthesis of *N*-sulfonylcyclothioureas via the reaction of *N*-sulfonyldiamines with CS_2 in silica gel-water system. This protocol is appropriate for the cyclization of a variety of *N*-sulfonyl diamines on a cheap, neutral, environmentally benign, and recyclable surface of silica gel.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.075.

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