



Reactions of cyclopropenethiones and acetylenedicarboxylates: synthesis of substituted thioethers and thiocyclobutanones

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ABSTRACT

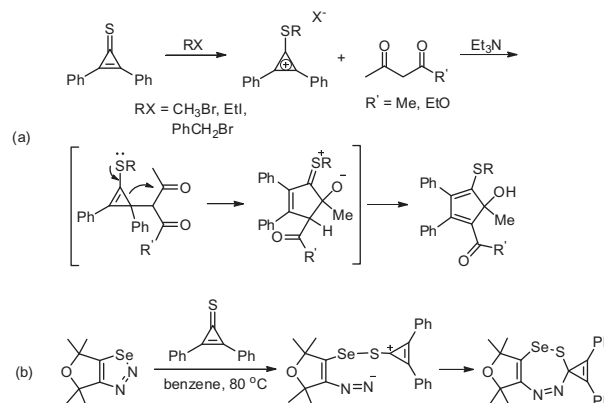
The reaction of cyclopropenethiones and electron-deficient alkynes has been described in this context. The corresponding thioethers and thiocyclobutanones were afforded depending on the reaction conditions and the employed substrates. Ambient water participated in the reaction on the basis of deuterium labeling experiment. In the plausible reaction mechanism, we propose that the reaction might proceed through an autocatalytic process.

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In recent years, cyclopropenones¹ have drawn great attention from organic chemists as a result of their unique structures and reactivities. Cyclopropenethione, as the thiosulfate product of cyclopropenone, has similar reactivity as that of cyclopropenone and is also very important in organic chemistry.² However, the application of cyclopropenethiones in organic synthesis remains undeveloped. Most of cyclopropenethione related reactions are involved with the ring-opening cycloadditions.³ For example, Ramamurthy and co-workers⁴ have demonstrated the regioselective α -cleavage reactions in arylalkylcyclopropenethiones. More recently, it has been reported that cyclopropenethiones also could readily react with alkyl halides (Scheme 1a), such as methyl bromide, ethyl iodide, and benzyl bromide, to give the corresponding cyclopropenium salts, which next underwent cascade to give cyclized products.⁵ Moreover, carbon–sulfur double bond can also take part in the reaction as well. Tokitoh⁶ reported that treatment of the selenadiazole with diphenylcyclopropenethione led to a characteristic and interesting cyclization product (Scheme 1b). Furthermore, 2,3-diphenyl cyclopropenethione,⁷ 2,3-diamino-⁸ and 2,3-bis(alkylthio)-substituted ones⁹ all could undergo intriguing cyclizations to construct novel structures in organic syntheses.

As for the underdevelopment of cyclopropenethiones, we wondered whether cyclopropenethiones would react with electron-deficient alkynes to give interesting cyclization products. Initially, we used the cyclopropenethione (**1a**) and methyl acetylenedicarboxylate (**2a**) as substrates and mixed them together in toluene

for 12 h. We found that thioether (**3a**) was formed in 42% yield. The examination of solvents such as dichloromethane, acetonitrile, 1,4-dioxane, diethyl ether, and chloroform revealed that **3a** was formed in the best yield when the reaction was carried out in acetonitrile (Table 1, entries 2, 4–7, and 9). In tetrahydrofuran and *N,N*-dimethylformamide, none of **3a** could be formed. Conducting the reaction in a sealed tube did not give better results (Table 1, entry 10). Raising the reaction temperature or increasing the loading of **2a** did not afford **3a** in higher yield (Table 1, entries 11–12).



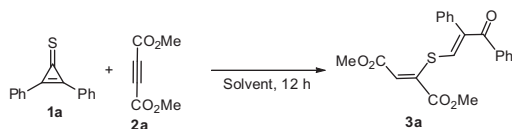
Scheme 1. (a) Cyclopropenethiones reacted with alkyl halides and next underwent cascade with ethylacetoacetate. (b) Reaction on carbon–sulfur double bond.

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Table 1

Preliminary screening of the reaction conditions



Entry ^a	Solvent	Conversion ^b (%)	Yield (%) ^c /3a ^c
1	Toluene	77	42
2	DCM	73	43
3	THF	32	n.d.
4	MeCN	66	54
5	DCE	73	39
6	1,4-Dioxane	66	9
7	Et ₂ O	70	42
8	DMF	32	Trace
9	CHCl ₃	68	20
10 ^d	MeCN	66	30
11 ^e	MeCN	82	12
12 ^f	MeCN	59	32

^a Conditions (unless otherwise specified): **1a** (0.2 mmol), **2a** (0.3 mmol), and solvent (2 mL) were added into schlenk tube under argon, and the reaction mixture was stirred for 12 h.

^b Isolated yield.

^c Isolated yield.

^d **1a** (0.2 mmol), **2a** (0.3 mmol), and solvent (2 mL) were added into a sealed tube under argon, and the reaction mixture was stirred for 12 h.

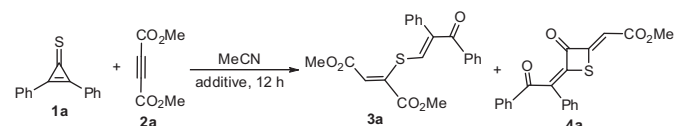
^e The reaction mixture was stirred at 60 °C.

^f The loading of **2a** was 0.4 mmol.

By slow addition of **2a** into the solution of **1a** in acetonitrile with a syringe pump, we found that **3a** was obtained in 38% yield along with another product, **4a**, in 21% yield (Table 2, entry 1). **4a** could not be formed when **1a** was slowly added by a syringe pump (Table 2, entry 2). Lengthening and shortening the reaction time did not give better results (Table 2, entries 3 and 4). Adding some

Table 2

Further screening of the reaction conditions



Entry ^a	Additive/(mol %)	Conversion ^b (%)	Yield (%) ^c /3a ^c	Yield (%) ^d /4a ^d
1	—	95	38	21
2 ^e	—	70	29	Trace
3 ^f	—	80	18	Trace
4 ^g	—	75	46	Trace
5	H ₂ O/0.5	39	33	Trace
6	H ₂ O/1.0	55	22	Trace
7 ^h	4 Å MS	75	24	Trace
8 ⁱ	Silica gel	66	39	Trace
9	S/1.5	95	24	29 ^j
10	S/3.0	100	30	16
11	PPh ₃ /0.2	100	38	Trace
12	DABCO/0.2	100	21	Trace

^a Conditions (unless otherwise specified): **1a** (0.2 mmol) and solvent (2 mL) were added into schlenk tube under argon. Then, **2a** (0.3 mmol) was added by a syringe in 2 h, and the reaction mixture was stirred for 12 h.

^b Isolated yield.

^c Isolated yield.

^d Isolated yield.

^e **1a** was added by a syringe.

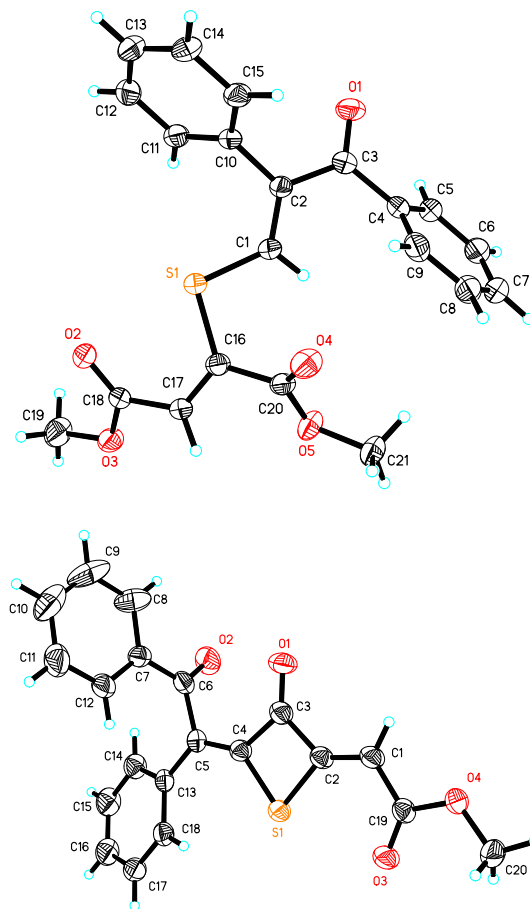
^f Reaction time was 18 h.

^g Reaction time was 6 h.

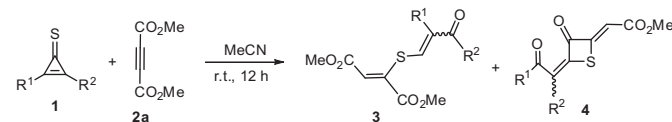
^h 200 mg 4 Å MS was added.

ⁱ 20 mg silica gel was added.

^j 5% of **1a** was included.

**Figure 1.** ORTEP drawings of **3a** and **4a**.

additives such as H₂O, 4 Å MS, PPh₃, DABCO, and silica gel into the reaction system (Table 2, entries 5–8, and 11–12), **4a** could not be formed as well. When 1.5 equiv of sulfur (S) was added, **4a** was formed in 29% yield along with **3a** in 24% yield and 5% of starting materials **1a** was recovered (Table 2, entry 6). Increasing S to 3 equiv, the yield of **4a** decreased to 16% (Table 2, entry 7). Thus, finally, we established the optimal reaction conditions: slow addition of **2** by a syringe pump in 2 h and carrying out the reaction in MeCN for 12 h at room temperature.

Table 3Scope of the reaction using **2a** as the model substrate

Entry ^a	Substrate	R ¹	R ²	Yield ^b (%) 3 (E/Z)	Yield ^b (%) 4 (E/Z)
1	1a	Ph	Ph	3a , 38 (>20:1)	4a , 21 (>20:1)
2	1b	2-MeC ₆ H ₄	2-MeC ₅ H ₄	n.d.	4b , 53 (1:1)
3	1c	3-MeC ₆ H ₄	3-MeC ₆ H ₄	n.d.	4c , 52 (6:1)
4	1d	4-MeC ₆ H ₄	4-MeC ₆ H ₄	3d , 43 (4:1)	n.d.
5	1e	3-ClC ₆ H ₄	3-ClC ₆ H ₄	3e , 37 (10:1)	n.d.
6	1f	4-ClC ₆ H ₄	4-ClC ₆ H ₄	3f , 43 (10:1)	n.d.
7	1g	Me	Ph	n.d.	4g , 43 (3:1)
8	1h	Bu	Bu	n.d.	n.d.

^a Conditions (unless otherwise specified): **1** (0.2 mmol) MeCN (2 mL) was added into schlenk tube, **2a** (0.3 mmol) was added by a syringe in 2 h, and the reaction mixture was stirred for 12 h.

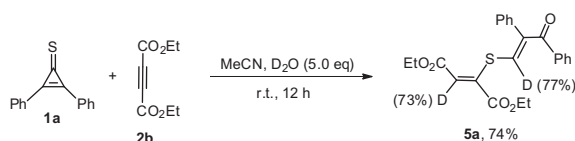
^b Isolated yield.

Table 4
Scope of the reaction using **2b** as the model substrate

Entry ^a	Substrate	R ¹	R ²	Yield ^b (%) 5 (E/Z)	Yield ^b (%) 6 (E/Z)
1	1a	Ph	Ph	5a , 76 (>20:1)	n.d.
2	1b	2-MeC ₆ H ₄	2-MeC ₆ H ₄	5b , 50 (>20:1)	n.d.
3	1d	4-MeC ₆ H ₄	4-MeC ₆ H ₄	5d , 56 (>20:1)	n.d.
4	1e	3-ClC ₆ H ₄	3-ClC ₆ H ₄	5e , 35 (>20:1)	n.d.
5	1f	4-ClC ₆ H ₄	4-ClC ₆ H ₄	5f , 59 (>20:1)	n.d.
6	1g	Me	Ph	5g , 50 (1:1)	n.d.
7	1h	Bu	Bu	n.d.	n.d.
8	1i	2-FC ₆ H ₄	2-FC ₆ H ₄	5i , 40 (>20:1)	n.d.

^a Conditions (unless otherwise specified): **1** (0.2 mmol) and MeCN (2 mL) were added into schlenk tube, **2b** (0.3 mmol) was added by a syringe in 2 h, and the reaction mixture was stirred for 12 h.

^b Isolated yield.



Scheme 2. Deuterium labeling experiment.

The structures of **3a** and **4a** were unambiguously determined by X-ray diffraction. Their ORTEP drawings are shown in Figure 1 and the CIF data are presented in the Supporting information.¹⁰

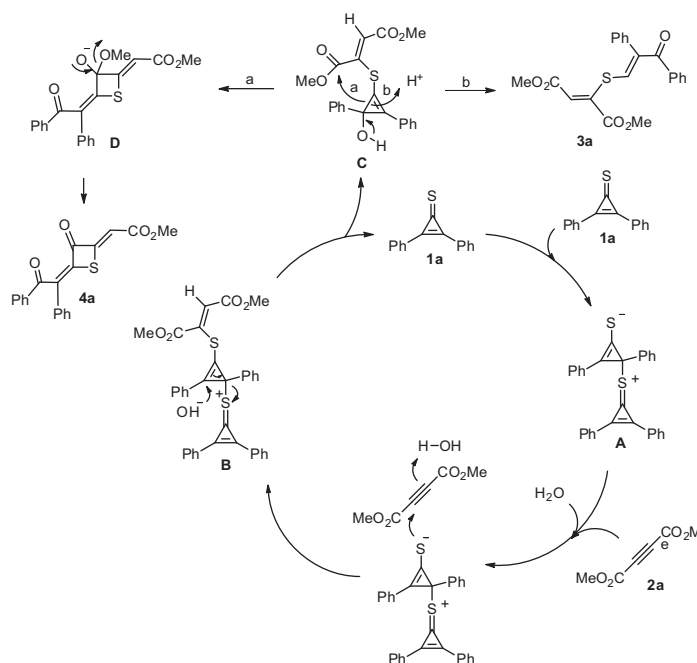
Next, with the optimized conditions in hand, we investigated the substrate scope of the reaction and the results are summarized in Table 3. By using **2a** as the model substrate, substrates **1** with different R¹ and R² substituents were tested. As can be seen from Table 3, as for R¹ = R² = Ph, the reaction proceeded smoothly to give the products **3a** and **4a** in 38% and 21% yields (E/Z >20:1),

respectively (Table 3, entry 1). When R¹ = R² = 2-MeC₆H₄ or 3-MeC₆H₄, the corresponding products **4b** and **4c** were obtained in 53% and 52% yields (E/Z = 1:1 and 6:1), respectively, but without the formation of thioether products, presumably due to the steric effect (Table 3, entries 2 and 3). As for substrates **1d**, **1e**, and **1f**, in which R¹ = R² = 4-MeC₆H₄ or 3-ClC₆H₄ or 4-ClC₆H₄, only thioether products **3d–3f** were produced without the formation of thiocyclobutanone products **4**, presumably due to the electronic effect (Table 3, entries 4–6). In the case of substrate **1g**, in which R¹ = Me, R² = Ph, **4g** was formed exclusively in 43% yield (E/Z = 3:1) (Table 3, entry 7). As for substrate **1h** (R¹ = R² = Bu), no reaction occurred (Table 3, entry 8).

To gain more insights into the substrate scope of the reaction, **2b** was used as the substrate to react with a variety of substrates **1** under the standard conditions and the results are summarized in Table 4. We found that no matter R¹ = R² are electron-poor or electron-rich aromatic rings, the reaction proceeded smoothly to exclusively give the corresponding product **5a–5f** and **5i** in 35–76 yields (E/Z >20:1), perhaps due to that the ethyl group in **2b** is sterically more bulky than that of methyl group in **2a** (Table 4, entries 1–5 and 8). As for **1g**, the desired product **5g** was obtained in 50% yield (E/Z = 1:1) (Table 4, entry 6). In the case of **1h**, no reaction occurred (Table 4, entry 7).

To figure out whether water participated in the reaction, we examined the deuterium labeling experiment with the addition of D₂O (5.0 equiv). As shown in Scheme 2, under the standard conditions, 5.0 equiv of D₂O was added and mixed into the reaction system and the corresponding product **5a** was afforded in 74% yield along with the deuterium incorporation at the two olefinic protons in 77% and 73% D contents, respectively, suggesting that ambient water was indeed involved in the reaction.

Based on the above investigations, we proposed a plausible reaction mechanism in Scheme 3. The nucleophilic addition of **1a** to another molecule of **1a** affords zwitterionic intermediate **A**. Then intermediate **B** is formed by nucleophilic addition of **A** to **2a** and subsequent capture of the proton from ambient water. The newly generated hydroxide anion (OH[−]) attacks intermediate **B** to give intermediate **C** and release one molecule of **1a**. Herein, the reaction can be divided into two possible pathways: path a,



Scheme 3. A plausible reaction mechanism.

ring-opening of the cyclopropene, and the subsequent attacks of the ester carbonyl group delivers intermediate **D**, which then kicks out OMe[−] to give product **4a**; path b, ring-opening of cyclopropene and the subsequent protonation to afford product **3a**.

On the basis of this reaction mechanism, it is quite clear that the production of **3** and **4** is favored if the concentration of intermediate **A** can be maintained at higher levels. This is why the reaction procedure is that substrate **2** was added slowly by a syringe into **1** in MeCN.

In conclusion, we have developed a novel reaction of cyclopropenethiones and electron-deficient alkynes to give the corresponding thioethers or thiocyclobutanones in moderate yields depending on the reaction conditions and the employed substrates. Ambient water participated in the reaction on the basis of deuterium labeling experiment. In the plausible reaction mechanism, we propose that this reaction might undergo an autocatalytic process due to that the sulfur atom in cyclopropenethione is quite nucleophilic and therefore, cyclopropenethione itself can serve as a catalyst for the reaction proceeding. This finding may enrich the chemistry of cyclopropenones and cyclopropenethiones and further investigation on the mechanistic insights is ongoing in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.07.041>.

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