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# Two Novel Domino Reactions Triggered by Thiyl-Radical Addition to Vinylcyclopropyl Oxime Ether

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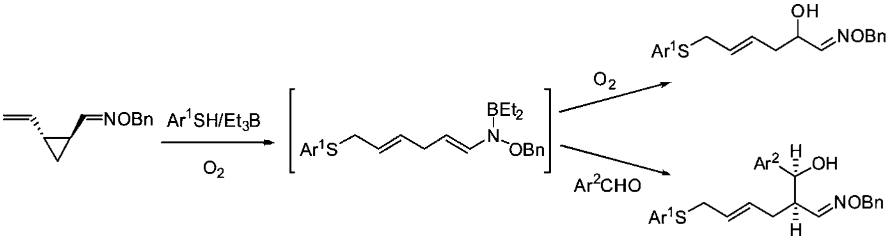
## ABSTRACT



**Two domino reactions of vinylcyclopropyl oxime ethers involving (i) thiyl radical addition, ring-opening, and hydroxylation reactions and (ii) thiyl radical addition, ring-opening, and aldol-type reactions were developed.**

The classical thiol−olefin co-oxygenation reaction, traditionally called hydroxysulfenylation, is an instrumental step in the multistep synthesis of functionalized cyclic peroxide. Hydroxysulfenylation is one of the interesting modes of reactions in organic synthesis that leads to the production of many functionalized products.[1] A diverse array of hydroxysulfenylations including the electron-rich or electron-deficient alkenes as radical acceptors has been documented.[2] The ring-opening hydroxysulfenylation reaction is poorly understood. Feldman and Parvez have widened the scope of the thiol−olefin co-oxygenation reaction on vinylcyclopropyl derivatives and opened avenues to the synthesis of sulfur-free five-membered cyclic peroxides.[3] On the other hand, the multicomponent reaction involving the domino process is an important field of research and attracts great interest and use in organic syntheses. A handful of examples on the thiophenol-catalyzed domino reaction leading to the production of the cyclopentane derivatives have been reported.[4] However, the domino reaction involving a multiprocess leading to the formation of the carbon−sulfur and carbon−carbon bond is restricted. Recently, we have published two

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(1) (a) Beckwith, A. L. J.; Wagner, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 7099. (b) Iriuchijima, S.; Maniwa, K.; Sakakibara, T.; Tsuchihashi, G. *J. Org. Chem.* **1974**, *39*, 1170. (c) LeBel, N. A.; Czaja, R. F.; DeBoer, A. *J. Org. Chem.* **1969**, *34*, 3112. (d) Ito, O. In *S-Centered Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999 193. (e) Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D. *Tetrahedron* **2002**, *58*, 2449. (f) Kim, J.; Li, H. B.; Rosenthal, A. S.; Sang, D.; Shapiro, T. A.; Bachi, M. D.; Posner, G. H. *Tetrahedron* **2006**, *62*, 4120. (g) Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273. (h) Bertrand, M. P.; Ferreri, C. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; p 485.

(2) (a) O'Neill, P. M.; Mukhtar, A.; Ward, S. A.; Bickley, J. F.; Davies, J.; Bachi, M. D.; Stocks, P. A. *Org. Lett.* **2004**, *6*, 3035. (b) O'Neill, P. M.; Verissimo, E.; Ward, S. A.; Davies, J.; Korshin, E. E.; Araujo, N.; Pugh, M. D.; Cristiano, M. L. S.; Stocks, P. A.; Bachi, M. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2991. (c) Baucherel, X.; Uziel, J.; Juge, S. *J. Org. Chem.* **2001**, *66*, 4504. (d) Ueda, M.; Miyabe, H.; Shimizu, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5600.

(3) (a) Feldman, K. S.; Simpson, R. E.; Parvez, M. *J. Am. Chem. Soc.* **1986**, *108*, 1328. (b) Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878. (c) Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985.

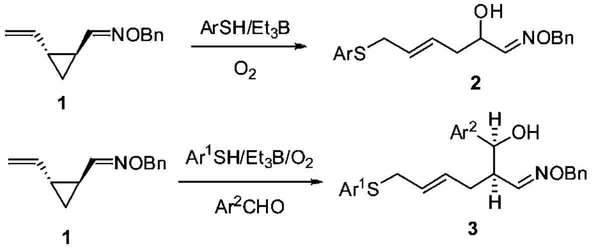
(4) (a) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (b) Feldman, K. S.; Berven, H. M.; Weinreb, P. H. *J. Am. Chem. Soc.* **1993**, *115*, 11364. (c) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1543–1988; *29*, 5135. (d) Kim, S.; Lee, S. *Tetrahedron Lett.* **1991**, *32*, 6575. (e) Huval, C. C.; Singleton, D. A. *J. Org. Chem.* **1994**, *59*, 2020. (f) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780.

10.1021/ol900604a CCC: $40.75

separate reports on hydroxysulfenylation and the domino radical-addition-aldol-type reaction on the α,$\beta$-unsaturated oxime ethers.[2d,5]

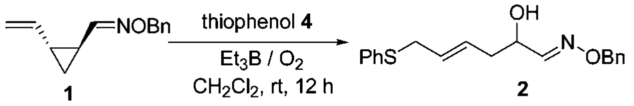
In this paper, we initially aimed to develop the thiyl radical addition and hydroxylation reaction on the vinylcyclopropyl oxime ether **1** to produce the α-hydroxy oxime ethers **2** which are crucial synthetic precursors to 1,2-amino alcohols abundantly found in many naturally occurring compounds.[6a] The oxime ethers **2** are also suitable intermediates for the synthesis of unnatural amino acids, $\beta$-blockers, and antibiotics.[6b−d] Our second goal was to develop a novel domino process for the synthesis of $\beta$-hydroxy oxime ethers **3**. These oxime ethers are 1,3-amino alcohol precursors found in many molecules of pharmaceutical and biological interest and constituents of several antibiotics[7] and other biologically active natural products (Scheme 1).[8]

**Scheme 1**



Initially, the possibility of thiyl radical addition to the olefin part, ring-opening of cyclopropane in the vinylcyclopropyl oxime ether **1**, and subsequent trapping of the intermediate radical by molecular oxygen was explored. The exposure of *E*-oxime ether **1** to thiophenol **4a** in the presence of triethylborane under an oxygen atmosphere did successfully provide the desired ring-opened hydroxysulfenylation product **2a** with a yield of 78% (Table 1, entry 5). Under a similar set of reaction conditions, the corresponding *Z*-isomer **1** with *p*-chlorothiophenol also provided the identical *E*-oxime ether **2b** with a yield of 87% (Table 1, entry 8).

**Table 1.** Hydroxysulfenylation of Vinylcyclopropyl Oxime Ether **1**

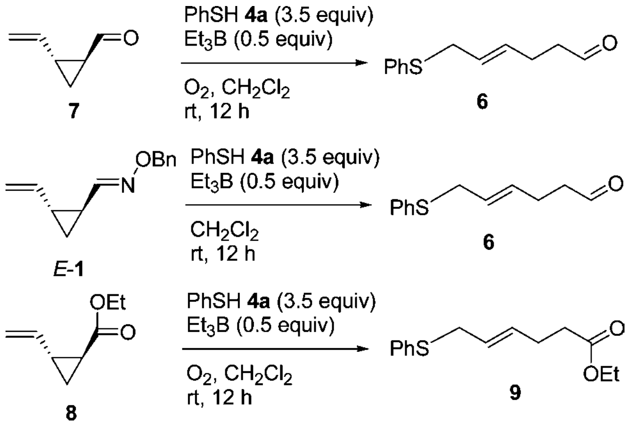


| entry | substrate | thiol (equiv) | $Et_3B$[a] (equiv) | 2a−c[b](%) |
|---|---|---|---|---|
| 1 | **1*E*** | PhSH **4a** (4) | 1.5 | **2a** (70) |
| 2 | **1*E*** | PhSH **4a** (4) | 1 | **2a** (72) |
| 3 | **1*E*** | PhSH **4a** (3) | 1 | **2a** (68)[c] |
| 4 | **1*E*** | PhSH **4a** (3.5) | 1 | **2a** (76) |
| 5 | **1*E*** | PhSH **4a** (3.5) | 0.5 | **2a** (78) |
| 6 | **1*E*** | *p*-Cl-$C_6H_4$SH **4b** (3.5) | 0.5 | **2b** (88) |
| 7 | **1*E*** | *p*-MeO-$C_6H_4$SH **4c** (3.5) | 0.5 | **2c** (84) |
| 8 | **1*Z*** | *p*-Cl-$C_6H_4$SH **4b** (3.5) | 0.5 | **2b** (87) |
| 9 | **1*Z*** | *p*-MeO-$C_6H_4$SH **4c** (3.5) | 0.5 | **2c** (82) |
| 10 | **1*E/Z*** | *p*-Cl-$C_6H_4$SH **4b** (3.5) | 0.5 | **2b** (86) |
| 11 | **1*E*** | PhSSPh **5** (3.5) | 0.5 | n.d. |

[a] A 1.04 M hexane solution was used. [b] Isolated yield. [c] Starting material (15%) was recovered.

The amount of thiophenol and triethylborane used has an impact on the chemical efficiency and yield of the reaction products. To achieve good conversion and yield, more than 3 equiv of thiophenol was necessary for this reaction (Table 1, entries 1−5). After several sets of reactions were screened, the use of 0.5 equiv of triethylborane was found to deliver good yields from the reaction (Table 1, entry 5). Substituted thiophenols carrying either electron-donating or -withdrawing groups on a benzene ring also worked well under our reaction conditions (Table 1, entries 6 and 7). High yields and the best results were observed when 3.5 equiv of *p*-chlorothiophenol **4b** was used (Table 1, entry 6). *E*-Selectivity was found throughout the screening of the reaction irrespective of the configuration of the oxime ether **1** (Table 1, entries 8 and 9). A mixture of *E*/*Z* isomers **1** led to the formation of *E*-oxime ether **2** in good yields (Table 1, entry 10). The hydroxysulfenylation product **2** was not found when diphenyl disulfide **5** was used as a thiyl radical source (Table 1, entry 11).

**Scheme 2.** Thiol Radical-Addition Reaction of Vinylcyclopropyl Derivatives



In order to reveal the reaction route of our domino hydroxysulfenylation reaction, additional reactions were

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[5] (a) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190. (b) For our reviews on radical reactions of imines, see: (c) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140. (d) Naito, T. *Heterocycles* **1999**, *50*, 505.

[6] (a) Bergemier, S. C. *Tetrahedron* **2000**, *56*, 2561. (b) Yadav, J. S.; Reddy, A. R.; Narsaiah, A. V.; Reddy, B. V. S. *J. Mol. Catal. A* **2007**, *261*, 207. (c) Corey, E. J.; Zhang, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931. (d) Bose, D. S.; Narsaiah, A. V. *Bioorg. Med. Chem.* **2005**, *3*, 627.

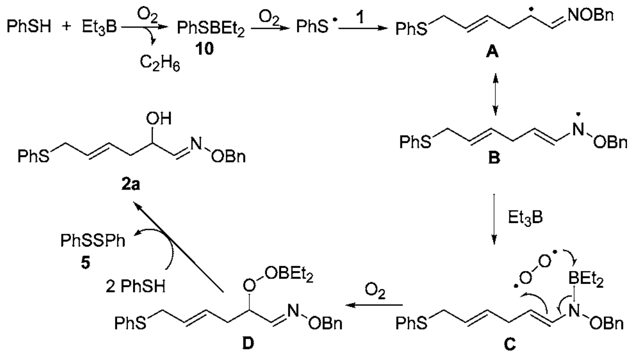
[7] (a) Weinreb, S. M.; Melnick, M. *J. Org. Chem.* **1988**, *53*, 850. (b) Ohno, M.; Wang, Y.; Izawa, T.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 6465.

[8] (a) Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956. (b) Jager, V.; Muller, I. *Tetrahedron Lett.* **1982**, *23*, 4777. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1996**, *51*, 2590. (d) Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett.* **1986**, *27*, 1265. (e) Vaultier, M.; Tirel, P. J.; Carrie, R. *Tetrahedron Lett.* **1989**, *30*, 1947.

carried out (Scheme 2). In the absence of sufficient amounts of oxygen, the reaction of the oxime ether **1** did not give hydroxy sulfide **2a** but hydrolyzed aldehyde **6**. However, in the presence of sufficient amounts of oxygen, vinylcyclopropylaldehyde **7** and ester **8** gave the corresponding thiol addition and ring-opened products **6** and **9**, respectively (Scheme 2). The formation of the Michael-type of adducts **6** and **9** demonstrated that the oxime ether group is very important for our domino type of hydroxylation reaction.

The $^1$H NMR spectra of the reaction mixture of **1** with thiophenol and triethylborane in $CD_2Cl_2$ under nitrogen atmosphere exhibited a doublet signal ($J$ = 13.5 Hz) at $\delta$ 6.66 ppm due to the $\alpha$-proton of the enamine. According to our previous report,[5a] this observation suggests the formation of *E*-boryl enamine **C** (Scheme 3). Considering the results, (i) involving the significance of the oxime ether group, (ii) characterization of the *E*-boryl enamine intermediate **C**, and (iii) feasible formation of aldehyde **6** in the absence of sufficient amounts of oxygen, the proposed reaction route for the domino hydroxysulfenylation reaction is presented in Scheme 3.

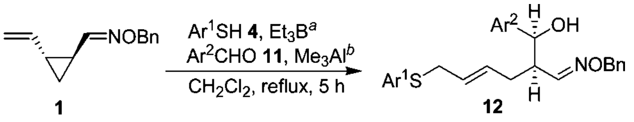
**Scheme 3.** Reaction Mechanism

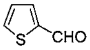
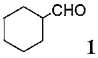


Triethylborane is known to immediately react with thiophenol to give diethyl phenylthioborane **10** and ethane gas.[2d,9] Homolytic cleavage of the B−S bond by molecular oxygen at the boron atom generates the thiyl radical,[10] which reacts with vinylcyclopropyl oxime ether **1** to produce the homoallylic carbon-centered radical **A**. Radical **A** is not very stable, but more stable aminyl radical **B** is captured by triethylborane to afford the *E*-boryl enamine intermediate **C**, which can undergo an ene-type reaction with oxygen to form intermediate **D**. The peroxide **D** will be readily reduced by thiophenol to give the final alcohol **2a** accompanying the formation of the diphenyl disulfide **5**. However, hydroxysulfenylation of **1** with diphenyl disulfide **5** did not proceed (Table 1, entry 11), which excluded the regeneration of the thiyl radical from **5** in the reaction mechanism.

Next, we explored the possibility of the thiyl radical addition to **1** and subsequent ionic trapping of the *N*-boryl enamine intermediate **C** by a suitable eletrophile for the development of a new domino reaction triggered by thiyl radical addition (Table 2). The domino thiyl radical addition and aldol-type reaction of *E*-vinyl oxime ether **1** was first tested with *p*-methoxythiophenol **4c** as a thiyl radical precursor and *p*-chlorobenzaldehyde **11a** as an electrophile, respectively, in the presence of triethylborane. To achieve good conversion and yield of the domino product, the systematic study on the reaction conditions involving the ratio of the substrate, electrophile, and other reagents was investigated. The $\beta$-hydroxy oxime ether **12a** was isolated with a yield of 82% and good diastereoselectivity when 3.5 equiv of *p*-methoxythiophenol **4c**, 1 equiv of *p*-chlorobenzaldehyde **11a**, 1 equiv of triethylborane, and 1 equiv of trimethylaluminum were employed under an inert atmosphere (Table 2, entry 1). Encouraged by our expected domino reaction of **1**, we surveyed the scope of using different thiophenols and aldehydes. Substituents on the thiophenol ring with both electron-withdrawing and electron-donating groups proved to be tolerated (Table 2, entries 1−5 and 7), and simple thiophenol **4a** was also effective (Table 2, entry 6). As an electrophile, *p*-methoxy- and *o*-methoxybenzaldehydes **11b**,**c** and 2-furfural **11d** worked effectively and were found to be good trapping agents (Table 2, entries 4, 5, and 7, respectively). In related reactions, formaldehyde did not work well but cyclohexylaldehyde **11e** gave the same type of $\beta$-hydroxy oxime ether **12g** in good yields.

**Table 2.** Thiol Radical-Addition and Aldol-Type Reaction of Oxime Ether **1**



| entry | **1** | thiol[c] | aldehyde[d] | **12**[e,f] (%) |
|---|---|---|---|---|
| 1 | *E* | *p*-MeO-$C_6H_4SH$ **4c** | *p*-Cl-$C_6H_4CHO$ **11a** | **12a** (82) |
| 2 | *Z* | *p*-MeO-$C_6H_4SH$ **4c** | *p*-Cl-$C_6H_4CHO$ **11a** | **12a** (81) |
| 3 | *E* / *Z*[g] | *p*-Cl-$C_6H_4SH$ **4b** | *p*-Cl-$C_6H_4CHO$ **11a** | **12b** (85)[c] |
| 4 | *E* / *Z*[g] | *p*-Cl-$C_6H_4SH$ **4b** | *p*-OMe-$C_6H_4CHO$ **11b** | **12c** (83) |
| 5 | *E* | *p*-Cl-$C_6H_4SH$ **4b** | *o*-OMe-$C_6H_4CHO$ **11c** | **12d** (84) |
| 6 | *E* | PhSH **4a** | *p*-Cl-$C_6H_4CHO$ **11a** | **12e** (80) |
| 7 | *E* | *p*-Cl-$C_6H_4SH$ **4b** |  **11d** | **12f** (83) |
| 8 | *Z* | *p*-Cl-$C_6H_4SH$ **4b** |  **11e** | **12g** (78) |

[a] A 1.04 M hexane solution (1 equiv) was used. [b] A 1.07 M hexane solution (1 equiv) was used. [c] Thiophenol (3.5 equiv) was used. [d] Aldehyde (1 equiv) was used. [e] **12a**−**g** were obtained as the *E*-isomer only; diastereomeric ratios were 9:1−7:3. [f] Isolated yield. [g] A mixture of *E*/*Z* isomers was used.

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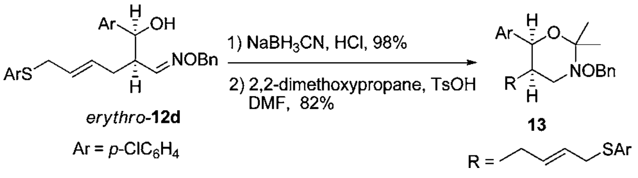
(9) Triethylborane immediately reacts with RSH to give $RSBEt_2$; see: Gilman, H.; Nelson, J. F. *J. Am. Chem. Soc.* **1937**, *59*, 935.

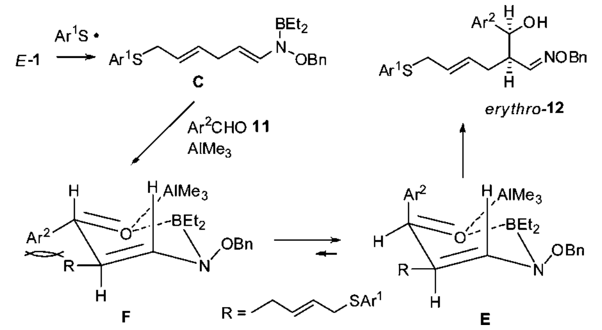
(10) (a) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J. L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 1647. (b) Masuda, Y.; Hoshi, M.; Nunokawa, Y.; Arase, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1444.

The *erythro*-configuration of the major isomer **12b** was determined by the formation of its cyclic *cis*-acetonide derivative **13** of the corresponding reduced 1,3-amino alcohol (Scheme 4).[11] According to our previous report on the domino hydroxysulfenylation reaction, the reaction is believed to proceed via the formation of an *E*-boryl enamine intermediate **C**[5a] and subsequent trapping by the aldehyde **11** to afford the desired compound **12**. The preferential *erythro*-selectivity of the aldol-type reaction can be explained by invoking a six-membered-ring transition state **E** as shown in Scheme 5. The *E*-boryl enamine **C** reacts with the $Me_3Al$-activated aldehyde in such a fashion that steric repulsion between the sulfide chain substituent and aryl group of the aldehyde **11** is minimized.

**Scheme 4.** Preparation of Cyclic Acetonide Derivative



**Scheme 5.** Possible Transition State of the Domino Aldol-Type Reaction



As reported in Houk's study on the aldol reaction of an enamine with acetaldehyde, an axial or equatorial methyl group on acetaldehyde is predicted to be almost equal in energy, and thus, it is not unusual to find an axial Ar$^2$ group in the transition state.[12]

In conclusion, we have succeeded in two domino reactions of vinylcyclopropyl oxime ethers involving thiyl radical addition−ring-opening reaction−hydroxylation and thiyl radical addition−ring-opening−aldol-type reactions. Both domino reactions construct highly functionalized acyclic $\varepsilon$-thio-$\delta,\gamma$-unsaturated-$\alpha$-hydroxy oxime ethers and $\varepsilon$-thio-$\delta,\gamma$-unsaturated-$\beta$-hydroxymethyl oxime ethers, which are versatile intermediates in organic synthesis and play an important role in biological and chemical processes.[13] Additionally, the success of our multicomponent reaction with vinylcyclopropyl oxime ether provided the impetus to develop the allyl sulfide containing 1,3-amino alcohol compounds in a single operation.

**Acknowledgment.** We acknowledge the support of the research grants-in-aid for Scientific Research (B) (to T.N.) and C (to O.M.) from the Japan Society for the Promotion of Science (JSPS) and Scientific Research on Priority Areas (A) (to T.N.) from the Ministry of Education, Culture, Sports and Technology. H.R. thanks the JSPS for a research grant and financial assistance.

**Supporting Information Available:** Experimental procedures, characterization data, and copies of $^1H$ NMR and $^{13}C$ NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] See the Supporting Information for the reduction and acetonide formation. The *cis*-configuration of the cyclic acetonide **13** was deduced by NMR coupling constant and the NOESY.

[12] Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

[13] (a) Cremlyn, R. J. *An Introduction to Organo-Sulfur Chemistry*; Wiley & Sons: New York, 1996. (b) Recently, one invention relates that allyl sulfide with another composition was used in an effective amount of formulation, including emulsion, to repel blood-feeding ectoparasitic arthropods. See Int. Patent No. PCT/CA2008/000591.