

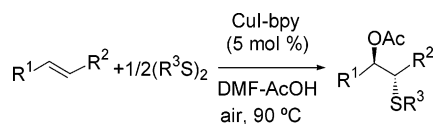
Copper-Catalyzed 1,2-Hydroxysulfenylation of Alkene Using Disulfide via Cleavage of the S–S Bond

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Copper-catalyzed 1,2-hydroxysulfenylation of alkenes can be carried out by the use of disulfides and acetic acid in air. This reaction regio- and anti-selectively gave the corresponding 1,2-acetoxysulfides. Furthermore, the present method enables the use of both organosulfide groups of disulfide.

Transition-metal-catalyzed introduction of a sulfide-group to an unsaturated carbon–carbon bond is an important procedure in organic synthesis.¹ In particular, hydrosulfenylation or disulfenylation of alkene or alkyne using thiol or disulfide has been developed by many researchers.^{2,3} Although hydroxysulfenylation of alkene is a convenient procedure for the purpose of direct introduction both organothio- and hydroxy-groups, a catalytic process is developed rarely. These compounds obtained herein can be synthesized by ring-opening of epoxides by thiol.^{4,5}

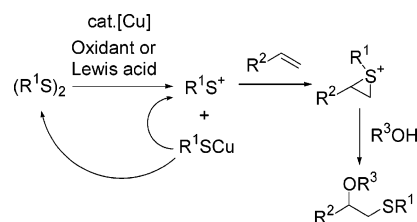
(1) (a) Baird, C. P.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973–2003. (b) Payner, C. M. *Contemp. Org. Synth.* **1996**, 3, 499–533. (c) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, 100, 3205–3220.

(2) Hydrosulfenylation of alkene: (a) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, 121, 8675–8676. (b) Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, 128, 1446–1447. Hydrosulfenylation of alkyne: (c) Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, 114, 5902–5903. (d) Bäckvall, J.-E.; Ericsson, A. *J. Org. Chem.* **1994**, 59, 5850–5851. (e) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, 121, 5108–5114.

(3) Disulfenylation of alkene: (a) Caserio, M. C.; Fisher, C. L.; Kim, J. K. *J. Org. Chem.* **1985**, 50, 4390–4393. (b) Kondo, T.; Uenoyama, S.; Fujita, K.; Mitsudo, T. *J. Am. Chem. Soc.* **1999**, 121, 482–483. (c) Usugi, S.-i.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, 6, 601–603. Disulfenylation of alkyne: (d) Kuniyasu, H.; Ogawa, A.; Miyaura, S.-i.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1991**, 113, 9796–9803. (e) Arisawa, M.; Yamaguchi, M. *Org. Lett.* **2001**, 3, 763–764. (f) Ananikov, V. P.; Beletskaya, I. P.; Aleksandrov, G. G.; Eremenko, I. L. *Organometallics* **2003**, 22, 1414–1421. (g) Ananikov, V. P.; Kabeshov, M. A.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y. *Organometallics* **2005**, 24, 1275–1283. (h) Mono, A. V.; Nogueira, C. W.; Barbosa, N. B. V.; Menezes, P. H.; Rocha, J. B. T.; Zeni, G. *J. Org. Chem.* **2005**, 70, 5257–5268.

(4) Usually, a reaction of epoxide with thiol gives two regio-isomers. (a) Takeuchi, H.; Kitajima, K.; Yamamoto, Y.; Mizuno, K. *J. Chem. Soc., Perkin Trans. 2* **1993**, 199–203. (b) Toshimitsu, A.; Hiroasawa, C.; Nakano, K.; Mukai, T.; Tamao, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, 120, 355–356.

SCHEME 1. Strategy of 1,2-Hydroxysulfenylation of Alkene with Disulfide



As a rule, to synthesize hydroxysulfide with disulfide from alkene, employment of RS^+ is necessary. To date, a reaction using a stoichiometric oxidant such as $Pb(OAc)_4$ ^{6,7} or an addition of RSX^8 has been explored. However, methods for a transition-metal-catalyzed preparation of 1,2-hydroxysulfide using alkene and disulfide are very limited. For instance, a procedure by copper(II) acetate catalyst requires long reaction time and cannot use both sulfide groups in disulfide.⁹ This is attributable to the lower reactivity of the generated $RSCu(I)$ ¹⁰ as an intermediate.

As an approach to solve the problem, we researched a condition whereby $(R^1S)_2$ or R^1S^+ was formed by the oxidation of $R^1SCu(I)$ (Scheme 1) and found that a copper-catalyzed reaction can be carried out in the presence of acetic acid. In this paper, we wish to describe the methodology of a copper-catalyzed 1,2-hydroxysulfenylation of alkene using disulfide in DMF–AcOH.

Initially, the addition of various ROH was investigated in order to optimize the reaction condition. In a combination of DMF with alcohol or H_2O using CuI –bpy (10 mol %), no product was detected (Table 1, entries 1–3). Surprisingly, the use of ethylene glycol afforded the corresponding hydroxysulfide **3** in 74% yield without the other regio-isomer (Table 1, entry 4). It is noteworthy that in the case with CuI –bpy (5 mol %) in acetic acid and DMF, 1,2-acetoxysulfide **3** could be obtained in 92% yield (Table 1, entry 5). Two phenylsulfide groups in

(5) (a) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Katritzky, A. R., Meth-Cohn O., Rees, C. W., Eds.; Academic Press: San Diego, 1994. (b) Swiss, K. A.; Liotta, D. C. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press Ltd.: New York, 1991; Vol. 7, pp 515–526.

(6) (a) Trost, B. M.; Ochiai, M.; McDougal, P. G. *J. Am. Chem. Soc.* **1978**, 100, 7103–7106. (b) Toshimitsu, A.; Aoi, T.; Owada, H.; Uemura, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1980**, 412–413. (c) Bewick A.; Mellor, J. M.; Owton, W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1039–1044. (d) Samii, Z. K. M. A. E.; Ashmawy, M. I. A.; Mello, J. M. *Tetrahedron Lett.* **1986**, 27, 5289–5292.

(7) (a) Wirth, T., Ed. *Organoselenium Chemistry*; Topics in Current Chemistry, Vol. 208; Springer-Verlag: Heidelberg, Germany, 2000. (b) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1986**, 51, 1724–1729. (c) Back, T. G.; Moussa, Z. *Org. Lett.* **2000**, 2, 3007–3009. (d) Bosman, C.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* **1994**, 35, 6525–6528. (e) Uneyama, K.; Kanai, M. *Tetrahedron Lett.* **1990**, 31, 3583–3586.

(8) (a) Benati, L.; Mantevecci, P. C.; Spagnolo, P. *Tetrahedron Lett.* **1984**, 25, 2039–2042. (b) Brownbridge, P. *Tetrahedron Lett.* **1984**, 25, 3759–3762. (c) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, 43, 1208–1217. (d) Tuladhar, S. M.; Fallis, A. G. *Tetrahedron Lett.* **1987**, 28, 523–526. (e) Reich, H. J. *J. Org. Chem.* **1973**, 38, 428–429. (f) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, 39, 429–430.

(9) Bewick A.; Mellor, J. M.; Milano, D.; Owton, W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1045–1048.

(10) (a) Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, 69, 915–920. (b) Taniguchi, N. *J. Org. Chem.* **2004**, 69, 6904–6906. (c) Taniguchi, N. *Synlett* **2005**, 1687–1690. (d) Taniguchi, N.; Onami, T. *Synlett* **2003**, 829–832.

TABLE 1. Copper-Catalyzed 1,2-Hydroxysulfenylation of Styrene with Disulfide

entry	ROH	[Cu] (mol %)	3 (%) ^d
1 ^a	MeOH	CuI (10)	0
2 ^a	<i>n</i> -PrOH	CuI (10)	trace
3 ^a	H ₂ O	CuI (10)	0
4 ^{a,b,c}	(HOCH ₂) ₂	CuI (10)	74
5	AcOH	CuI (5)	92
6 ^e	AcOH	CuI (5)	55
7	AcOH	CuBr (5)	52
8	AcOH	CuCl (5)	trace
9	AcOH	CuCl ₂ (5)	trace
10	AcOH	CuOAc (5)	trace
11	AcOH	Cu(OAc) ₂ (5)	trace
12	AcOH	none	0

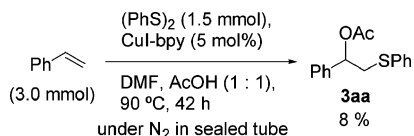
^a The reaction was carried out at 100 °C. ^b DMF was not used. ^c The reaction was performed for 48 h. ^d Isolated yields after silica gel chromatography. ^e The reaction was carried out in AcOH (0.3 mL).

disulfide were consumed completely. However, the use of CuBr decreased the yield to 52% (Table 1, entry 7). Although other copper salts (CuCl, CuCl₂, CuOAc, and Cu(OAc)₂) were investigated, these showed no effects (Table 1, entries 8–11). In the absence of a copper-catalyst, the reaction was not promoted at all (Table 1, entry 12).

On the basis of the described result, we next carried out a copper-catalyzed 1,2-acetoxysulfenylation of various alkenes **1** using disulfides **2** in DMF–AcOH. As shown in Table 2, the reaction between the terminal alkenes **1** with disulfides **2** could regio-selectively afford the corresponding 1,2-acetoxysulfides in good yields (Table 2, entries 1–9). Furthermore, the use of *trans*- β -methylstyrene or intramolecular alkene gave derivatives having anti-stereochemistry between the phenylthio and acetoxy groups (Table 2, entries 10–16).¹¹ The use of diphenyl diselenide (**2g**) could also afford the same results (Table 2, entries 7, 14, and 17). Thus we were able to perform a copper-catalyzed 1,2-acetoxysulfenylation of alkene with disulfide in good yield.

For the purpose of investigation of this reaction mechanism, we carried out a reaction of styrene with (PhS)₂ in the absence of oxygen. When the reaction was carried out under nitrogen atmosphere, **3aa** was obtained in only 8% yield (Scheme 2).

SCHEME 2. Reaction of Styrene with (PhS)₂ in the Absence of Oxygen



Then, the reactivity of PhSCu(I) considered as an intermediate was examined.¹² Although this complex could not perform sulfenylation of styrene under nitrogen, (PhS)₂ was obtained in

(11) These stereochemistry were decided by a comparison between 1,2-acetoxysulfide of entry 13 or 16 and authentic samples. These authentic compounds were prepared by acetylation of the hydroxyl group after solvolysis of cis-epoxides: Ruano, J. L. G.; Martínez, M. C.; Rodríguez, J. H.; Olefirowicz, E. M.; Eliel, E. L. *J. Org. Chem.* **1992**, *57*, 4215–4224.

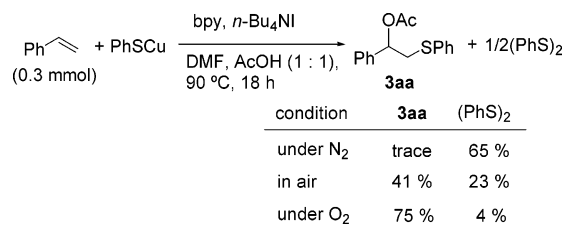
(12) *Organic Syntheses*; John Wiley & Sons: New York, 1973; Collect. Vol. V, pp 107–110.

TABLE 2. Copper-Catalyzed 1,2-Acetoxysulfenylations of Alkenes with Disulfides

Entry	3	Time (h)	3 (%) ^b	Entry	3	Time (h)	3 (%) ^b
1		18	92	10		18	93
2		18	84	11		18	70
3		18	83	12		24	61
4		18	71	13		36	63
5		36	80	14		20	67
6		36	66	15		18	82
7		18	95	16		36	75
8		18	94	17		18	72
9		22	88				

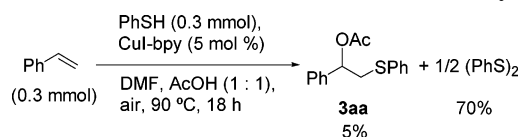
^a Reaction conditions: alkene (0.3 mmol), (R³Y)₂ (0.15 mmol), and CuI–bpy (1:1, 5 mol %) in DMF (0.2 mL) and AcOH (0.2 mL) were treated at 90 °C. ^b Isolated yields after silica gel chromatography.

SCHEME 3. A Reactivity of PhSCu



65% yield.¹³ This fact shows that disulfide is produced by the decomposition of PhSCu under acidic conditions. In the presence of oxygen, it could afford **3aa** in good yields by the addition of *n*-Bu₄NI (Scheme 3).¹⁴ In addition, the use of PhSH afforded **3aa** in only 5% yield (Scheme 4).¹⁵ Therefore, oxygen is necessary for the present reaction; disulfide can be reproduced from PhSCu under acidic conditions rather than the generation of thiol.

SCHEME 4. Reaction between Benzenethiol with Styrene



From these results, a reaction mechanism is considered as follows (Figure 1). After the CuI-catalyst acted on the disulfide

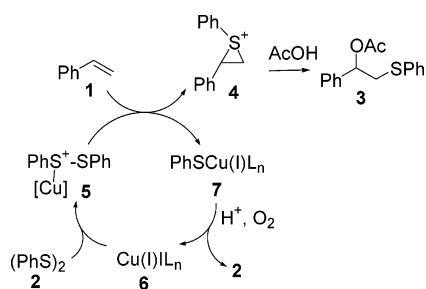


FIGURE 1. A plausible reaction mechanism.

as a Lewis acid or co-oxidant in air, reaction of intermediates **5** with styrene **1** gives sulfonium ion **4** and PhSCu(I) **7**.¹⁶ Sequentially, 1,2-acetoxysulfide **3** was obtained in DMF–AcOH. PhSCu **7** gives disulfide **2** and Cu(I)L_n again under acidic conditions in air because **7** cannot carry out sulfenylation of alkene.

In conclusion, we achieved copper-catalyzed 1,2-hydroxysulfenylation of alkene using disulfide and acetic acid in air. This reaction regio- and anti-selectively gives the corresponding

(13) The treatment of PhSCu (0.3 mmol), bpy (0.3 mmol) in DMF (1.0 mL), and H₂O (1.0 mL) at 100 °C for 18 h afforded (PhS)₂ in only 5% yield. But the use of AcOH instead of H₂O gave disulfide in 66% yield. Consequently, it is difficult to produce (PhS)₂ from PhSCu under neutral conditions.

(14) *n*-Bu₄NI was added as a source of I[−] because Cu(OAc) cannot promote the 1,2-acetoxysulfenylation of alkene with disulfide.

(15) Additive products of PhSH were not detected under this condition.

(16) Takeuchi, H.; Hiyama, T.; Kamai, N.; Oya, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2301–2305.

1,2-acetoxysulfides and enables the use of both organosulfide-groups in disulfide. Furthermore, the present procedure is also available for diselenide.

Experimental Section

Typical Procedure. Reaction of Styrene with Diphenyl Disulfide in DMF–AcOH. To a mixture of CuI (2.9 mg, 0.015 mmol), bpy (2.3 mg, 0.015 mmol), DMF (0.2 mL), and AcOH (0.2 mL) were added diphenyl disulfide (32.8 mg, 0.15 mmol) and styrene (31.2 mg, 0.3 mmol), and the mixture was stirred at 90 °C for 18 h in air. After evaporation of the solvent, the residue was dissolved in Et₂O. The solution was washed with H₂O and saturated sodium chloride and dried over anhydrous magnesium sulfate. Chromatography on silica gel (20% Et₂O in hexane) gave 1-acetoxy-1-phenyl-2-phenylthioethane (Table 2, entry 1) (75.1 mg, 92%). ¹H NMR (270 MHz, CDCl₃): δ 2.01 (s, 3H), 3.23 (dd, *J* = 13.8 and 5.3 Hz, 1H), 3.40 (dd, *J* = 13.8 and 7.9 Hz, 1H), 5.88 (dd, *J* = 7.9 and 5.3 Hz, 1H), 7.15–7.39 (m, 10H). ¹³C NMR (67.5 MHz, CDCl₃): δ 20.9, 40.0, 74.5, 126.5, 126.6, 128.4, 128.5, 128.9, 130.1, 135.6, 138.9, 170.0. IR (neat): 3061, 3033, 1743, 1583 cm^{−1}. Anal. Calcd for C₁₆H₁₆O₂S: C, 70.56; H, 5.92. Found: C, 70.35; H, 5.83.

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Supporting Information Available: Experimental procedures and analytical data (¹H and ¹³C NMR spectra). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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