



## Synthesis of Cyclic Sulfides by Nickel Complexes Catalyzed Electroreduction of Unsaturated Thioacetates and Thiosulfonates

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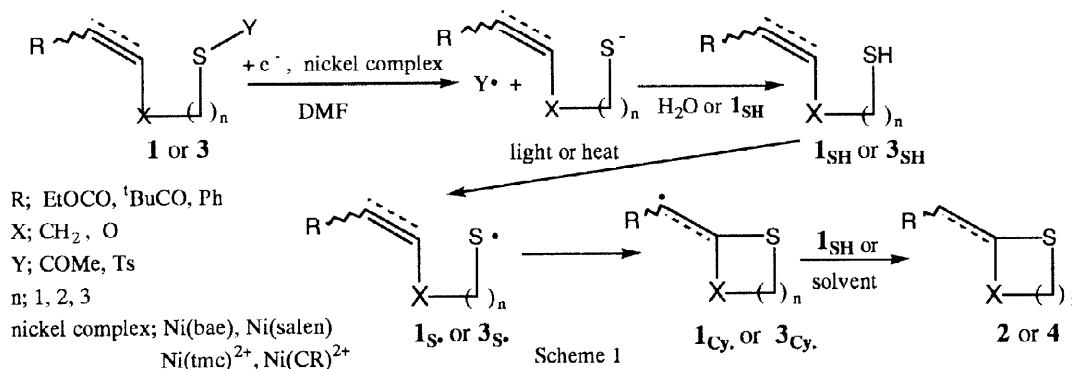
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**Abstract:** Functionalized cyclic sulfides with four to six membered rings were synthesized by ring closure of the labile thiols which were formed in situ by the nickel complex catalyzed electroreduction of the thioacetates and thiosulfonates having suitably placed electrophilic olefins or acetylenes. © 1998 Elsevier Science Ltd. All rights reserved.

The chemistry of saturated cyclic sulfides has been of great interest, since they are important models in the study of heteroatomic compounds in petroleum and also serve as the starting materials for synthesis of polymers and polyfunctional biologically active compounds.<sup>1)</sup> The most general method for constructing cyclic sulfides<sup>2)</sup> involves base-,<sup>1a, 1b, 3)</sup> acid-<sup>4)</sup> or reduction-<sup>5)</sup> induced ring closure of protected thiols having a suitably placed leaving group or other electrophilic functionality, and halocyclization reaction of unsaturated sulfides.<sup>6)</sup> Although these methods largely follow predictable regiochemical pathways and provide straightforward approach to three to six-membered cyclic sulfides, they often involve harsh reaction where the limited functionality or leaving group could be permitted. While other method such as photolysis of free ethylenic or acetylenic thiols tends to provide a mixture of isomeric thiacycloalkanes with different numbers in the ring and has an other problem that ethylenic or acetylenic thiols are labile and polymerize even at low temperature in several hours.<sup>7)</sup>

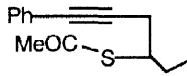
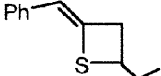
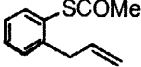
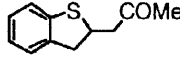
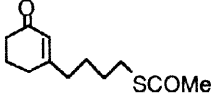
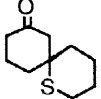
In the course of studies developing the methodology conducting radical reactions by the use of the nickel complex catalyzed electroreduction,<sup>8)</sup> we found that electroreduction of the thioacetate **1a** and thiosulfonate **1e** could be catalyzed by the nickel complexes, A: Ni(II)(bae)<sup>9)</sup> or B: Ni(II)(salen)<sup>9)</sup>, and C: Ni(II)(tmc)<sup>2+</sup><sup>9)</sup> or D: Ni(II)(CR)<sup>2+</sup><sup>9)</sup>, respectively. This observation encouraged us to examine the synthesis of the functionalized cyclic sulfides by ring closure of the thiols that would be formed in situ by catalytic electroreduction of the thioacetates and thiosulfonates using these complexes as catalysts, which is expected to proceed according to Scheme 1.



The electroreductive cyclizations of thioacetates<sup>10)</sup> and thiosulfonates<sup>10)</sup> were performed in DMF (10 or 20 ml) in a divided or an undivided cell containing a substrate (0.5 or 1.0 mmol), a nickel complex (0.2 - 0.3 equiv. based on the substrate) and supporting electrolyte (Et<sub>4</sub>NClO<sub>4</sub>: 0.1 M) using a graphite plate as a cathode

at a constant current of 2 - 3 mA under an inert gas at ambient temperature until 1 - 2 F/mol of electricity was consumed. The results are summarized in Table 1.

Table 1. Cyclic Sulfides Formed from Thioacetates or Thiosulfonates by Nickel Complex Catalyzed Electroreduction <sup>a)</sup>

Entry	Thioester or Thiosulfonate					Products, Yield % <sup>b)</sup> (Z : E ratio) <sup>c)</sup>		
	1	3	2	4				
	R	X	Y	n	Ni Complex <sup>d)</sup>			
1	<b>1a</b>	EtOCO	CH <sub>2</sub>	COMe	2	B	<b>2a</b>	56 (3 : 1)
2	<b>1a</b>					e)	<b>2a</b>	0 <sup>e)</sup>
3	<b>1b</b>	EtOCO	CH <sub>2</sub>	COMe	3	B	<b>2b</b>	45 (1 : 1)
4	<b>1c</b>	Ph	CH <sub>2</sub>	COMe	2	B	<b>2c</b>	58 (Z only)
5	<b>1d</b>	Ph	CH <sub>2</sub>	COMe	3	B	<b>2d</b>	61 (Z only)
6	<b>1e</b>	<sup>t</sup> BuCO	CH <sub>2</sub>	Ts	2	C	<b>2e</b>	81 (4 : 1)
7	<b>1f</b>	EtOCO	S	Ts	2	D	<b>2f</b>	71 <sup>f)</sup>
8	<b>1g</b>	Ph	CH <sub>2</sub>	Ts	2	D	<b>2g</b>	0 <sup>g)</sup>
9	<b>3h</b>	EtOCO	O	COMe	2	A	<b>4h</b>	54
10	<b>3i</b>	EtOCO	O	Ts	2	C	<b>4i</b>	0 <sup>h)</sup>
11	<b>1j</b>					B	<b>2j</b>	 82
12	<b>3k</b>					A	<b>4k</b>	 26
13	<b>3l</b>					B	<b>4l</b>	 47

a) Electrolyzed as described in the text. b) Isolated yield based on the thioacetate or thiosulfonate.

c) Determined by <sup>1</sup>H NMR integration of olefinic proton. Major isomer was assigned as Z based on NOE difference spectroscopy. d) As for structure, see note 9.

e) Electrolyzed without nickel complex. **1a** was recovered in 81 % yield. f) Accompanied with 14 % of the corresponding disulfide. g) The disulfide was yielded (94 %). h) The disulfide was yielded (88 %).

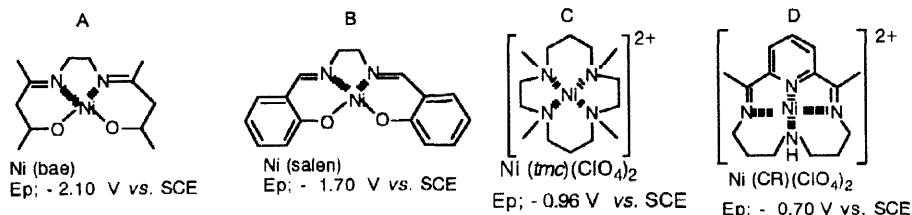
The results in Table 1 show that the ring closure of the thiols conducted by the present catalytic electroreductive method affords the cyclic sulfides with four to six membered rings in excellent to good yields except for that of the thiosulfonates **1g** and **3i** via *exo* mode cyclization as separable mixtures of stereoisomers of *E* and *Z* where *Z* isomer predominated. <sup>11)</sup> The modest to high selectivity for formation of

the **Z-2** suggests that the transfer of a hydrogen atom or proton occurs preferentially from the anti-side with respect to the sulfur atom in the cyclized vinyl radical  $1_{cy}\bullet$ . The thioacetate **1a** was recovered in 81 % yield after consumption of electricity of 2F/mol from the electrolysis of **1a** performed without addition of the nickel complex. The 4-membered cyclic sulfide **2j** was provided in 82 % yield, which has been reported not to be formed by photolysis induced cyclization of the closely related pent-4-yne-1-thiol derivatives.<sup>7)</sup> The mildness of the reaction condition of the present method is likely to keep the extremely strained thiacyclobutane not to cause the ring opening. The cyclization of the thioacetate having the nonactivated olefin **3k** formed a product of which double bond terminal is substituted by an acetyl group, **4k**. The results of entries 4, 5, and 11, and entry 12 indicate that not only a Michael acceptor also both a phenyl acetylenic group and a non-activated olefin work as a thiol acceptor. These features of the products along with Baldwin's rule<sup>12)</sup> and the kinetic data for ring-closure of 4-pentenyl radical<sup>13)</sup> seem to suggest that the active species which react with the acceptor group of the thioacetates or thiosulfonates are the corresponding thiyl radicals  $1_{s}\bullet$  formed from the thiol  $1_{SH}$  by the reaction with light or heat. In the electrolysis of the thiosulfonates, **1g** and **3i**, the initially formed thiols  $1_{SH}$  seem to displace the sulfonate group from another molecule of the thiosulfonates to form the undesired disulfides. The formations of the corresponding disulfides were not observed in the case of thioacetates, which might be related to the difference in the nature as a leaving group between tosyl and acetyl group.

In conclusion, the present catalytic electroreductive method that is conducted at ambient temperature in neutral solution which does not need to be desiccated, and so permits various functionalities could be a convenient general method to provide functionalized cyclic sulfides in the predictable regiochemical and stereochemical pathways.

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6. a) Ren, X.-F. ; Turos, E. ; Lake, C. H. ; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468-6483; b) Ren, X.-F. ; Konaklieva, M. I. ; Turos, E. ; Krajkowski, L. M. ; Lake, C. H. ; Janik, T. S. ; Churchill, M. R. *ibid.* 6484-6495.
7. a) Dupuy, C. ; Crozet, M.-P. ; Surzur, J.-M. *Bull. Soc. Chim. Fr. II* **1980**, 361-373; b) Bastien, G. ; Surzur, J.-M. *Bull. Soc. Chim. Fr. II* **1982**, 84-88.
8. Ten articles including the first one, Ozaki, S. ; Matsushita, H. ; Ohmori, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1120-1122; the latest one, Ozaki, S. ; Matsui, E. ; Waku, J. ; Ohmori, H. *Tetrahedron Lett.* **1997**, *38*, 2705-2708.
9. The nickel complexes used as catalysts are shown below.

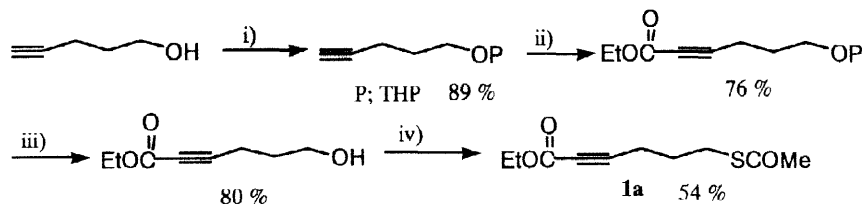


All complexes are stable and can be stored at ambient temperature for several years.

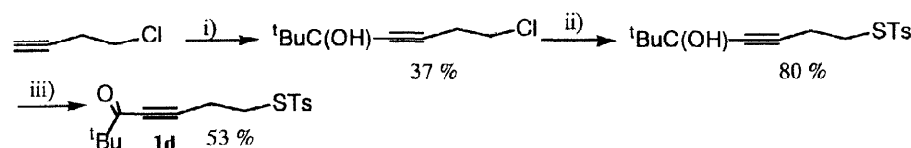
The cyclic voltammetric behaviors of Ni(II)(bae) and Ni(II)(salen) in the presence of thioacetate **1a** suggested that these complexes would transfer an electron to **1a** but not to ethyl 6-hydroxy-2-hexynoate, though both **1a** and the hexynoate exhibit each reductive peak at the similar potential, around -2.30 V vs. SCE. The detailed procedures of cyclic voltammetry are available in the literatures shown below.

a) Stolzenberg, A. M.; Stershic, M. T. *J. Am. Chem. Soc.* **1988**, *110*, 5397-5403; b) Ozaki, S.; Matsushita, H.; Ohmori, H.; *J. Chem. Soc., Perkin Trans. 1* **1993**, 649-651

10. The thioester **1a** and thiosulfonate **1d** were prepared as shown below.



i) THP (1.4 eq.), Et<sub>2</sub>O, 0 °C; ii) EtMgBr, THF, reflux 1h, then ClCO<sub>2</sub>Et, -20 °C to 3 °C; iii) Pyridinium *p*-TsO (0.1 eq.), MeOH, 55 °C 1.5h; iv) DEAD (2 eq.), PPh<sub>3</sub> (2 eq.), THF, 0 °C, the alcohol, HSCOMe, 1h.

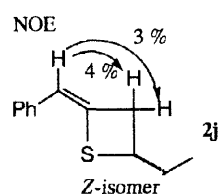
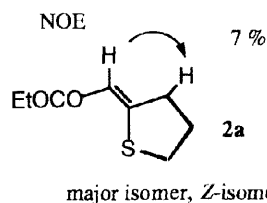


i) <sup>n</sup>BuLi, <sup>t</sup>BuCHO (1.1 eq.), THF, -78 °C; ii) TsSK (1.5 eq.), CH<sub>3</sub>CN-HMPA, reflux; iii) MnO<sub>2</sub> (20 eq.), CCl<sub>4</sub>, r. t.

11. All products **2** and **4** exhibited <sup>13</sup>C NMR and <sup>1</sup>H NMR spectra which were consistent with assigned structures.

<sup>1</sup>H NMR spectra for *E*- and *Z*-**2a** and **2j**: *E*-**2a** (300 MHz, CDCl<sub>3</sub>) δ 5.88(**1H**, t, J 1.9, C=CH), 4.13(2H, q, J 7.1, CH<sub>2</sub>CH<sub>3</sub>), 3.19(2H, td, J 7.1, 2.0, CCH<sub>2</sub>), 3.04(2H, t, J 6.3, SCH<sub>2</sub>), 2.17(2H, q, J 6.6, SCH<sub>2</sub>CH<sub>2</sub>), 1.26(3H, t, J 7.1, Me); *Z*-**2a** (300 MHz, CDCl<sub>3</sub>), 5.93(1H, t, J 1.4, C=CH), 4.19(2H, q, J 7.09, CH<sub>2</sub>CH<sub>3</sub>), 3.08(2H, t, J 6.4, SCH<sub>2</sub>), 2.80(2H, td, J 6.9, 1.3, CCH<sub>2</sub>), 2.06(2H, q, J 6.7, SCH<sub>2</sub>CH<sub>2</sub>), 1.28(3H, t, J 7.1, Me); **2j** (300 MHz, CDCl<sub>3</sub>) δ 7.46(2H, d, J 7.0, ArH), 7.33-7.22(3H, m, ArH), 5.91(1H, dd, J 3.1, 2.9, C=CH), 3.84-3.75(1H, m, CH<sub>2</sub>CH), 3.09(1H, ddd, J 16.9, 8.6, 2.9, CHC(H)H), 2.68(1H, ddd, J 16.9, 6.2, 3.1, CHC(H)H), 1.81-1.71(2H, m, MeCH<sub>2</sub>), 1.02(3H, t, J 7.2, MeCH<sub>2</sub>)

The stereochemical assignments of **2a** and **2j** were done based on NOE difference spectroscopy. The minor isomer of **2a** did not show the enhancement.



12. Baldwin's rule, which is best applied to systems containing only first row elements, indicates that 4-*exo-dig* cyclizations in nucleophilic ring closure are disfavored processes.

Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

13. The ring closure of the 4-pentenyl radical proceeds slowly at ordinary temperature, but there can be little doubt that it will exclusively follow the *exo*-mode.

a) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1083-1092; b) Beckwith, A. L. J. *Tetrahedron* **1981**, *32*, 3073-3100.