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Studies on the Reaction of Thiiranes with Tributyltin Hydride

Mark H. Izraelewicz,[†] Mohamud Nur,[†]
Richard T. Spring,[†] and Edward Turos*

Department of Chemistry, State University of New York at Buffalo, Amherst, New York 14260

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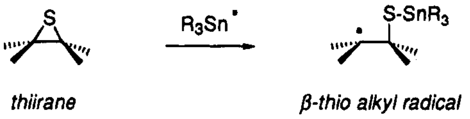
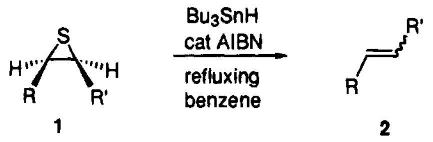
A number of methods have been introduced in recent years for the regiospecific generation of free radicals from the reaction of tributyltin hydride with various organosulfur functionality, including thioethers, isothiocyanates, thioamides, thiocarbonates, and xanthate esters.[1,2] During the course of recent studies in our laboratory, we had the opportunity to investigate the reaction of tributyltin hydride with thiiranes. The expectation was that thiiranes, easily prepared[3] in racemic or in optically active form, would undergo ring opening upon reaction with tributyltin radical to generate β-thioalkyl radicals (eq 1),[4] which we planned to utilize as intermediates[5] for the formation of carbon−carbon bonds and sulfur-containing rings (*vide infra*).



(1)

Table 1. Bu$_3$SnH-Induced Desulfurization Reactions of Thiiranes



	Isolated %yields, E:Z ratios of olefins **2**	
a	R=H; R'=$(CH_2)_6CH_3$	(95%)
b	R'=$CH_2O(CH_2)_7CH_3$	(99%)
c	R'=$(CH_2)_4CH{=}CH_2$	(85%)
d	R'=$CH_2OCH_2C{\equiv}CPh$	(65%)
e	R'=CH_2OPh	(93%)
f	R'=$CH_2O(4\text{-}NO_2Ph)$	(recovered thiirane)
g	R=R'= CH_2OCH_2Ph	(96%, 5:1 E:Z mixture)
h	CH_2OSiMe_2tBu	(98%, 5:1 E:Z mixture)
i	$CH_2OC(O)Ph$	(recovered thiirane)

To begin our studies, we first examined the reactions of a series of thiiranes with tributyltin hydride under conditions that would favor trapping of the ring-opened radical intermediate by hydrogen atom abstraction from tin hydride (Table 1). These reactions were carried out under nitrogen by slow addition of a solution of the thiirane (1 mmol) and a trace amount of the initiator, azobis(isobutyronitrile) (AIBN), in benzene to a solution of tributyltin hydride (1.5 mmol) in refluxing benzene.[6] As expected, the thiiranes were consumed immediately upon addition to the tin hydride solution. However, after evaporation and purification of the crude product mixture by flash chromatography, none of the tin hydride addition product was isolated. Instead, only the corresponding olefin products were obtained. The same outcome for the reaction was observed if larger amounts of tin hydride (5 equiv) were used or if the order of addition was reversed (addition of tin hydride *to* the refluxing thiirane solution). As shown in Table 1, alkyl and α-alkoxy thiiranes readily undergo desulfurization[7] under these conditions to give the olefins in high yield.[8] Curiously, the presence of certain types of electron-withdrawing functionality in the molecule protects the thiirane from desulfurization. Thus, thiiranes **1f** and **1i** are recovered from the reaction without change, even if large amounts (5 equiv) of tin hydride are used. At the moment, we can not give an adequate explanation for this unusual effect. As shown for bis-thiirane **3**, desulfurization of both rings takes place cleanly by using an appropriate amount of tin hydride (use of a limiting amount of Bu$_3$SnH in the reaction, not surprisingly, results in the formation of a mixture comprised of starting material plus mono- and dielimination products). The analogous *epoxides* and *episulfoxides* of the substrates shown in Table 1 are completely inert toward tributyltin hydride under the described conditions, indicating that the presence of ring strain alone is not sufficient for inducing the radical addition. This was demonstrated through com-

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[†] Undergraduate Research Student.

(1) For reviews on free radical reactions in synthesis, refer to: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon Press: New York, 1986; Vol. 5. (b) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

(2) For discussions on the chemistry of Bu$_3$SnH, see (a) Neumann, W. P. *Synthesis* **1987**, 665. (b) Kupchik, E. J. In *Organotin Compounds*; Sawyer, A. K., Ed.; Marcel Dekker: New York, 1971; Vol. 1, Ch. 2, pp 7–79.

(3) (a) Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897. (b) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4114 and references cited.

(4) β-Thio-substituted alkyl radicals have been generated previously by free radical addition of thiols to double bonds, a process known to be rapidly reversible and to form the more stable alkyl radical. See (a) Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273. (b) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1994**, *59*, 2818. For studies on intramolecular free radical additions of thiols to double bonds, see (a) Surzur, J.-M.; Crozet, M.-P.; Dupuy, C. *C.R. Acad. Sc. Paris* **1967**, *264*, 610. (b) Surzur, J.-M.; Crozet, M.-P.; Dupuy, C. *Tetrahedron Lett.* **1971**, 2025. (c) Crozet, M.-P.; Kaafarafi, M.; Kassar, W.; Surzur, J.-M. *Tetrahedron Lett.* **1982**, 5039. For related examples involving sulfonyl radical additions to olefins, see (a) Phillips, E. D.; Whitham, G. H. *Tetrahedron Lett.* **1993**, *34*, 2537. (b) Phillips, E. D.; Whitham, G. H. *Tetrahedron Lett.* **1993**, *34*, 2541.

(5) For recent synthetic applications utilizing the reversible addition of phenylthiyl radical to vinyl epoxides or vinylcyclopropanes to give ring-opened radical intermediates, see (a) Rawal, V. H.; Krishnamurthy, V. *Tetrahedron Lett.* **1992**, *33*, 3439. (b) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100. (c) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr. *Tetrahedron Lett.* **1989**, *30*, 5845. (d) Feldman, K. S.; Fisher, T. E. *Tetrahedron* **1989**, *45*, 2969. (e) Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985. (f) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (g) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780. (h) Singleton, D. A.; Church, K. M.; Lucero, M. J. *Tetrahedron Lett.* **1990**, *31*, 5551. (i) Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *Tetrahedron Lett.* **1988**, *29*, 955. (j) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135.

(6) Purging the reaction mixture with argon or oxygen prior to or during the reaction, or degassing the solution using the freeze-pump-thaw method, does not affect the outcome of the reaction. Additionally, although thiiranes are known to lose sulfur under thermal conditions (see Chew, W.; Harpp, D. N. *Tetrahedron Lett.* **1992**, 45 and references cited therein), control experiments show that each of the thiiranes in Table 1 are stable in refluxing benzene in the *absence* of the hydride reagent.

(7) For lead references on methods for the desulfurization of thiiranes, see Kamata, M.; Murayama, K.; Miyashi, T. *Tetrahedron Lett.* **1989**, 4129 and those listed in ref 7.

(8) Yields shown in Table 1 are based on the amounts of material isolated after flash chromatography or vacuum distillation.

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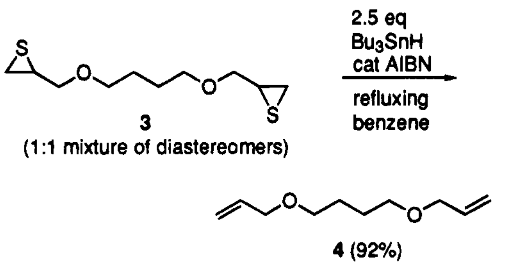
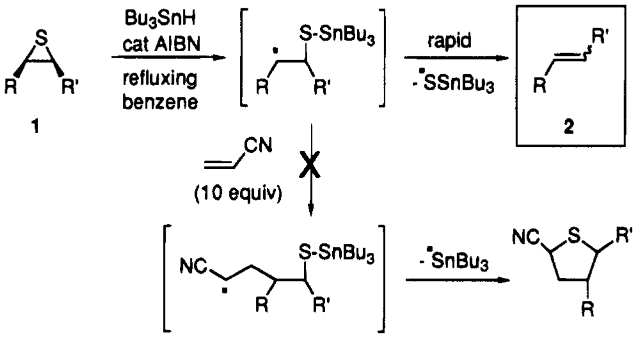


petition experiments in which equimolar mixtures of the epoxide−thiirane or episulfoxide−thiirane are treated with 1 equiv of Bu_3SnH. The ^1H NMR spectra of the crude products reveal that 1:1 mixtures of recovered epoxide−olefin products (or recovered episulfoxide−olefin products) are produced. Under identical conditions, an equimolar ratio of thiirane **1e** and benzyl 4-pentenyl sulfide[9] upon treatment with 1 equiv of tin hydride led to the formation of the expected olefin product **2e** and an equal amount of recovered benzyl 4-pentenyl sulfide. This illustrates the effect that ring strain has on promoting radical additions to thiiranes in comparison to dialkyl sulfides.[10]

The mechanism of this desulfurization reaction most likely entails an initial ring opening of the thiirane by attack of tin radical on the sulfur center of **1**. Cleavage of the carbon−sulfur thiirane bond leads to the generation of a transient β-thioalkyl radical intermediate, which spontaneously eliminates thiyl radical[11] to give olefin **2**. Indeed, reactions involving *Z*-disubstituted thiiranes **1h** and **1i** provide 5:1 mixtures of *E*- and *Z*-olefin products, as would be expected for the involvement of a β-thioalkyl radical intermediate. However, attempts to trap this transient species by carrying out the reaction in the presence of a large quantity of acrylonitrile or tetracyanoethylene failed to afford products of radical trapping and instead gave only the olefin by loss of thiyl radical.[12] Efforts to capture the radical intramolecularly proved equally unsuccessful, as illustrated for the reactions of unsaturated thiiranes **1c** and **1d** and aryl thiirane **1e**. For example, in the case of the acetylenic episulfide **1d**, we anticipated that the β-thio radical initially formed could conceivably undergo a rapid 5-exo ring closure,[13] with the resulting vinyl radical species then either abstracting a hydrogen atom from tin hydride or attacking the sulfur center to dispel the tin radical to form the bicyclic ring (Scheme 1). However, only olefin product **2d** is obtained in 65% yield, plus a small amount of stannylated material probably arising from the addition of tin hydride across the triple bond. From these experiments we conclude that the rate at which thiyl radical is expelled[14] from the β-thioalkyl radical intermediate must occur considerably faster than the intramolecular or intermolecular addition of the alkyl radical to the double or triple bond.



Thus, the reaction of thiiranes with tributyltin hydride offers an efficient method for desulfurization under mild, nonionizing conditions. From these experiments it would appear that efforts to utilize the initial β-thioalkyl radical intermediate formed in this manner for subsequent bond-forming processes would be thwarted by the rapid rate in which this species loses thiyl radical.

Experimental Section

Reactions were performed under N_2 or Ar. Glassware and syringes were predried overnight in an oven at 120 °C and assembled while still hot. Tributyltin hydride and AIBN were purchased from Aldrich Chemical Co. and used without further purification. The thiiranes were prepared by treatment of the corresponding epoxide with thiourea in ethanol. Epoxides used to prepare thiiranes **1a,c,e,f** were purchased from Aldrich Chemical Co. and used without further purification. Epoxides used to prepare thiiranes **1b**, **1d**, and **3** were synthesized from epibromohydrin and the appropriate alcohol.[15] Epoxides needed to prepare thiiranes **1g−i** were obtained from (*Z*)-2-butene-1,4-diol by derivatization of the alcohol groups (2.2 equiv of NaH, CH_2Cl_2, and then benzyl bromide, $tBuMe_2SiCl$, or benzoyl chloride overnight) and epoxidation (mCPBA, CH_2Cl_2). The structures of the olefin products were assigned by comparison of their ^1H NMR spectra to those of known compounds. Benzene was freshly distilled from CaH_2. TLC was carried out using EM Reagents plates with fluorescence indicator (SiO_2-60, F-254), and flash chromatography was performed using J. T. Baker flash chromatography silica gel (40 μm). ^1H NMR spectra were recorded at 400 MHz in $CDCl_3$ with $CHCl_3$ as internal standard.

Representative Procedure. To a refluxing solution of 1,2-epithio-3-phenoxypropane (**1e**, 166 mg, 1.0 mmol) in benzene

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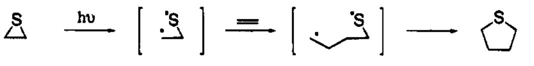
[9] We thank Mr. Xiao-Feng Ren for preparing this compound.

[10] Dialkyl sulfides are generally poor substrates for tin hydride reactions. (See ref 2a, p 676.) We thank one of the reviewers for pointing this out and for suggesting this experiment.

[11] We believe the initial byproduct of the reaction to be tributyltinthiol, which likely undergoes disproportionation to bis(tributyltin) sulfide. For a discussion on organotin−sulfur chemistry, see Schumann, H.; Schumann-Ruidisch, I. In *Organotin Compounds*; Sawyer, A. K., Ed.; Marcel Dekker: New York, 1971; Vol. 2, Ch. 6, pp 297−508.

[12] These attempts to trap the initial ring-opened β-thioalkyl radical intermediate with an olefin or acetylene are reminiscent of earlier reports of a photochemical ring expansion of thiirane done in the presence of ethylene. This reaction involves the formation of a relatively long-lived triplet diradical species, which upon trapping by ethylene affords a low yield of tetrahydrothiophene. (a) Sidhu, R. S.; Lown, E. M.; Strausz, O. P.; Gunning, H. E. *J. Am. Chem. Soc.* **1966**, *88*, 254. (b) Kumar, R.; Sidhu, K. S. *Indian J. Chem.* **1973**, *11*, 899.

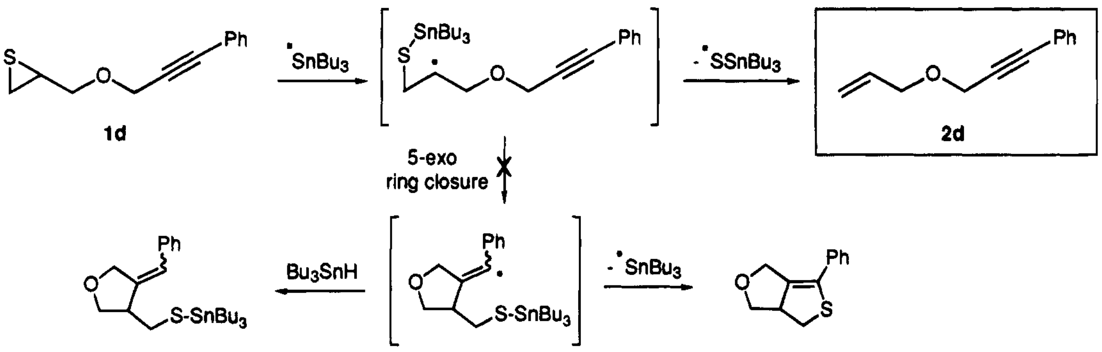


[13] For comparison, the rate of the analogous 5-hexenyl radical cyclization to cyclopentylmethyl radical has been measured to be 2 × 10^5 s^{-1} at 25 °C (Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739).

[14] We are hesitant to draw firm conclusions about the rate of this thiyl radical elimination, since the nature of the thiyl group is known to affect the rate of elimination of β-thio-substituted alkyl radicals. We can, however, speculate that the rate of β-cleavage of $Bu_3SnS^\bullet$ would be roughly as fast as the loss of $BuS^\bullet$, which has been estimated to be 2.7 × 10^5 s^{-1}. Wagner and co-workers have determined that the rates of β-cleavage follow the trend: I > SOPh > SCN > SPh > Br > SO_2Ph > Cl > SO_2Bu > SBu > SAc (Wagner, P. J.; Sedon, J. H.; Lindstrom, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 2579). Studies also reveal that phenylthiyl radical additions to olefins are more highly reversible than those involving alkylthiyl radicals. Griller has reported that *tert*-butylthiyl radical adds irreversibly to 1,1-dicyclopropylethylene due to the combination of the rapid ring opening of the initial dicyclopropylmethyl radical and the slow rate of *tert*-butylthiyl elimination (McPhee, D. J.; Campredon, M.; Lesage, M.; Griller, D. *J. Am. Chem. Soc.* **1989**, *111*, 7563).

[15] The glycidol ethers were prepared by phase-transfer etherification. See Mouzin, G.; Cousse, H.; Rieu, J.-P.; Duflos, A. *Synthesis* **1983**, 117.

Scheme 1



(25 mL) containing AIBN (1 mg) was added dropwise over 30 min a solution of Bu_3SnH (435 mg, 1.5 mmol) in benzene (25 mL). After the addition was complete, the mixture was evaporated *in vacuo* and purified by flash chromatography to afford 125 mg (93%) of 3-phenoxypropene (**2e**).

Acknowledgment. We thank Ms. Monika Konaklieva for preparing some of the epoxides required for the synthesis of thiiranes used in these experiments.

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