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Thione Reductions for Preparation of Five-Membered Heterocycles

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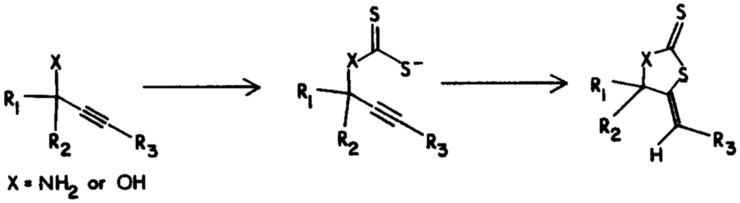
Summary: Facile reductions with tri-*n*-butyltin hydride convert a variety of five-membered 1,3-disubstituted heterocyclic thiones to the corresponding saturated derivatives.

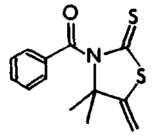
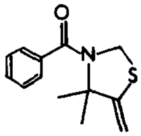
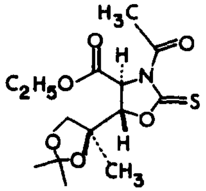
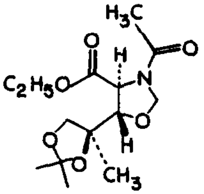
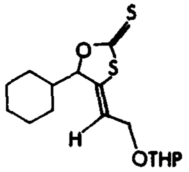
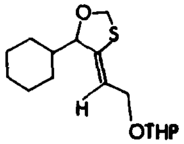
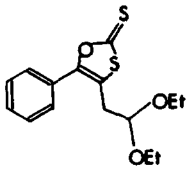
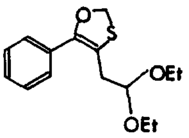
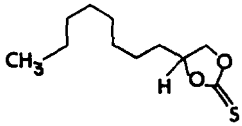
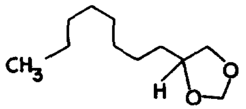
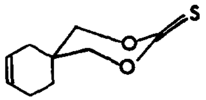
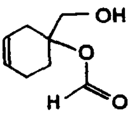
The importance of tin hydride reagents for selective transformations in highly functionalized molecules has been widely recognized.[1] Our interests in natural product synthesis, and more specifically, in the utility of heterocyclic systems for introduction and manipulations of stereochemical control, have led to a general preparation of saturated, five-membered heterocycles by reductive removal of a thione (C=S) moiety as generalized below.

Results are illustrated in Table I.[2] A wide variety of heterocyclic thiones are readily prepared. A procedure of particular interest for our efforts involves the condensation of carbon disulfide with α-acetylenic alcohols and amines (Entries 1, 3, 4).[3,4] The facile intramolecular addition of nucleophilic sulfur to the acetylene precludes successful formation of xanthates or dithiocarbamates in such systems. Instead, heterocyclic 1,3-oxathiolane-2-thiones and 1,3-thiazolidine-2-thiones are formed in excellent yields with *trans* addition to the triple bond and stereoselective formation of the *Z*-trisubstituted alkenes.[5]



In cases where extended conjugation is possible, the exocyclic olefin apparently prefers isomerization affording the endocyclic 1,3-oxathiole-2-thiones as seen in entry 4.[6] It is noteworthy to report that reaction of β-hydroxyacetylenes with carbon disulfide fails to provide the analogous six-membered heterocycles. As demonstrated by the example below, xanthate **1** is formed under standard conditions, and tri-*n*-butyltin hydride reduction proceeds normally yielding predominantly **2**.

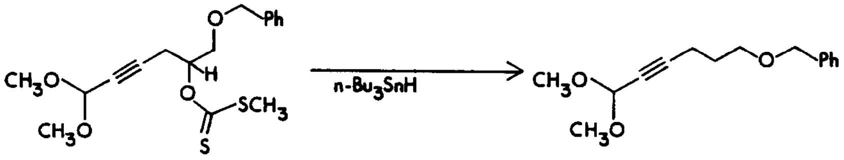
TABLE I.

	STARTING THIONE[a,b]	CONDITIONS[c]	PRODUCT	YIELD %
1.		30min		94
2.		2hr		75
3.		30min		75
4.		2hr		50
5.		45min; 65°C		82
6.		1hr; 65°C		81

(a) Entry 2 was prepared by condensation of ethyl isothiocyanatoacetate with 2,3-*O*-isopropylidene glyceraldehyde followed by acetylation (acetyl chloride).

(b) Thiocarbonates were formed from diols and 1,1'-thiocarbonyldiimidazole (THF, 22°C).

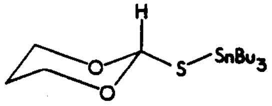
(c) Unless otherwise indicated, reactions were initiated at 60°C with heating to reflux.



1

2

For our study, reductions of a variety of heterocyclic thiones to the corresponding methylene compounds were conducted using excess tri-*n*-butyltin hydride (3-5 equivs, freshly distilled) in toluene with heating in the presence of a small amount of azobisisobutyronitrile (AIBN) initiator. Reactions were usually complete within two hours, and products were isolated by silica gel chromatography to remove more polar stannylsulfur by-products and remaining tin hydride. We have noted that monosubstituted thioamides (H-N-C=S) require acylation of nitrogen prior to reduction to avoid formation of stable iminosulfides by S-stannylation. Additionally, 1,3-dioxalanes (see entry 5) are formed without provoking the well known Corey-Winter reaction.[7,8] In contrast, the attempted formation of 1,3-dioxanes by reduction of their corresponding thiocarbonates results in ring opening and preparation of hydroxyformates (entry 6). We attribute this to stereoelectronic factors in the initial adduct 3 in which the equatorial stannylsulfide fails to undergo C-S bond cleavage as a result of poor interaction with oxygen lone electron pairs. Better orbital overlap in the five-membered cases stabilizes formation of the intermediate radical 4 (or cation) which is further reduced. Adduct 3 is immediately hydrolyzed on workup to the hydroxy-formates.



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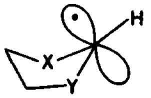

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Further utilization of this methodology is in progress.

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References

1. In addition to the well known procedures of dehalogenation of organic halides and hydrostannation of terminal acetylenes, tri-*n*-butyltin hydride has recently been used for: (a) acid chlorides to aldehydes; P. Four and F. Guibe, *J. Organic Chem.*, *46*, 4439 (1981); (b) deoxygenation of primary and secondary alcohols; D.H.R. Barton, N.B. Motherwell, and A. Stange, Synthesis 743 (1981); D.H.R. Barton and W.B. Motherwell, *Pure Appl. Chem.*, *53*, 15 (1981), and references therein; (c) desulfurization stannylations of allyl sulfides and sulfones; Y. Ueno, S. Aoki and M. Okawara, *J. Am. Chem. Soc.*, *101*, 1893 and 5414 (1979); (d) allyl sulfones to dienes; Y. Ueno, H. Sano, S. Aoki, M. Okawara, *Tetrahedron Lett.*, *22*, 2675 (1981); (e) denitration; N. Ono, H. Miyake, R. Tamura, G.E. Diaz, *Tetrahedron Lett.*, *22*, 1705 (1981); (f) stannylation of acetylenic alcohols; H.E. Ensley, R.B. Buescher, and K. Lee, *J. Organic Chem.*, *47*, 404 (1982).
2. In each case, yields are reported for purified products which were characterized by infrared, nuclear magnetic resonance (H'-NMR at 220 MHz), and mass spectral analysis, the results of which were fully in accord with assigned structures.
3. R. Fuks and H.G. Viehe, *Chemistry of Acetylenes*, Ed. H.G. Viehe, Marcel Dekker, New York (1969), pages 541-543.
4. Reactions of carbon disulfide with α-acetylenic alcohols have received little attention: K. Tomita, M. Nagano, and H. Oka, *Chem. Pharm. Bull.*, *16*, 914 and 1324 (1968).
5. Secondary α-acetylenic alcohols (from aldehydes and lithium acetylides) provide the 1,3-oxathiolane-2-thiones (excess CS_2, 8-10 equivs; THF; NaH (2-3 equivs); imidazole, 1 equiv; $22^{\circ}C$) in yields generally ranging from 84 to 96%. Products are purified by flash chromatography and crystallization. Tertiary α-acetylenic alcohols react very sluggishly (yields 10 to 50%).
6. Complete isomerization of the exocyclic olefin to an endocyclic isomer (entry 4) was accomplished with DBU in THF-isopropanol (7:1 by volume) at $22^{\circ}C$.
7. E.J. Corey and P.B. Hopkins, *Tetrahedron Lett.*, *23*, 1979 (1982).
8. Barton has reported the tin hydride reductive cleavage of secondary C-O bonding in conversions of thiocarbonates to deoxysugars under more vigorous conditions. D.H.R. Barton and R. Subramanian, *J. Chem. Soc. I*, 1718 (1977).

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