Metalation and Alkylation of 3,6-Dihydrothiazine 1-Oxides Prepared via Diels-Alder Cycloadditions of *N*-Sulfinyl Dienophiles

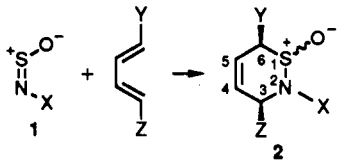
Scott I. Bell, M. Parvez, and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received May 11, 1990

The deprotonation of various 3,6-dihydrothiazine 1-oxides using LDA or methyllithium has been investigated. It was found that the stability and chemistry of these lithiated heterocycles are highly dependent upon the nature of the ring nitrogen substituent. Thus, *N*-alkyldihydrothiazine oxides can be metalated at C-6 to give species postulated as **9**, which undergo predominantly anti alkylation with alkyl halides. Alternatively, with MeOD, **9** is deuterated at C-6 primarily in a syn mode. N-Silylated heterocycles ring open rapidly and stereoselectively upon metalation to give dienic sulfinamides like **19**, which can be reclosed to the starting dihydrothiazine oxides. *N*-Phenyl-substituted 3,6-dihydrothiazine 1-oxides upon metalation give mixtures of pyrroles and N–S bond cleavage products. Attempts to generate the dianion from NH dihydrothiazine oxide **17** led only to low yields of C-4 alkylated products with alkyl halides.

A wide variety of readily available *N*-sulfinyl compounds **1** react with 1,3-dienes in [4 + 2]-cycloadditions to provide 3,6-dihydrothiazine 1-oxides **2** (eq 1).[1] *N*-Sulfinyl com-

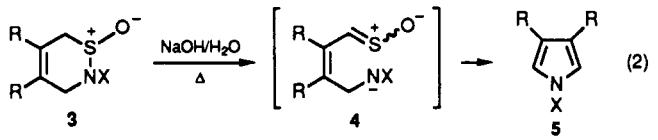


(1)

X = Ar, COR, CO_2R, SO_2R, $\overset{+}{S}Me_2$, CN, $(RO)_2PO$, $\overset{+}{N}Me_2$, alkyl

pounds bearing electron-withdrawing substituents X react rapidly in this process, and adducts are usually cleanly produced at or below room temperature. *N*-Alkyl-substituted sulfinyl compounds can also be effectively used as dienophiles, provided the reactions are conducted at high pressure or in the presence of a Lewis acid.[2] In general, these Diels–Alder reactions show excellent regio- and stereospecificity.[1] Also, these heterocycles **2** are configurationally stable at sulfur.

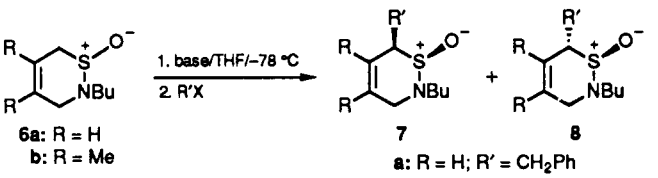
We have recently demonstrated that dihydrothiazine oxides are valuable synthons for the stereoselective synthesis of a variety of nitrogen-containing molecules.[1] With the aim of extending this methodology, we considered the possibility of metalating and alkylating these heterocycles at C-6 possibly to provide systems not readily prepared by a direct Diels–Alder process. It is known that dihydrothiazine oxides **3** bearing electron-withdrawing groups on nitrogen are converted to pyrroles **5** presumably via a vinyl sulfine **4** (eq 2) upon treatment with aqueous base.[3,4] Since this undesired transformation was of concern, we decided to first investigate the metalation of *N*-alkyldihydrothiazine oxides, which we anticipated would be less likely to ring open to a species like **4**.



(2)

X = Ar, CO_2Et, $PO(OEt)_2$

Scheme I



6a: R = H
b: R = Me

a: R = H; R′ = CH_2Ph
b: R = H; R′ = Me
c: R = Me; R′ = CH_2Ph
d: R = Me; R′ = Me

R	base	R′X	yield	isomer ratio (7:8)
H	LDA	$PhCH_2Br$	96%	34:66
H	MeLi	$PhCH_2Br$	82%	28:72
H	LDA	MeI	76%	45:55
H	MeLi	MeI	72%	45:55
Me	LDA	$PhCH_2Br$	99%	11:89
Me	MeLi	$PhCH_2Br$	77%	9:91
Me	LDA	MeI	90%	23:77
Me	MeLi	MeI	80%	22:78

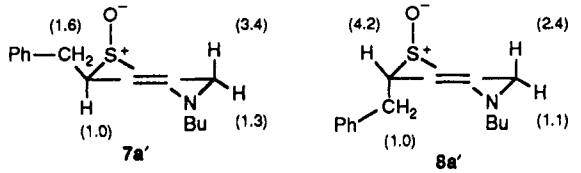
We therefore examined the deprotonation and alkylation of adducts **6a** and **6b**, prepared in good yield by the high pressure promoted[2] cycloaddition of *N*-sulfinylbutylamine[5] with butadiene and 2,3-dimethylbutadiene, respectively. Dihydrothiazine oxides **6a/b** could be lithiated about equally well with either LDA or methyllithium at −78 °C for 30–60 min. Alkylation of these anions with methyl iodide and benzyl bromide resulted in chromatographically separable isomeric products **7** and **8** (Scheme I). As can be seen, alkylation occurs preferentially anti to the dihydrothiazine oxide oxygen to give **8** as the major product in all cases (vide infra).

The relative stereochemistry and conformation of alkylated products **7** and **8** were established by proton NMR europium induced shift experiments. We previously found, using a combination of ^1H NMR europium induced shift experiments and X-ray crystallography, that *N*-CO_2CH_2Ph-substituted 3,6-dihydrothiazine 1-oxides exist in conformations having the S–O bond quasiaxial, which we attributed to an anomeric effect.[6] Stockburn and Hanson found a similar situation with another *N*-carbamate-substituted system via crystallography.[7] The results with **7** and **8** were consistent with the earlier work.[2] For example, **7a** showed the relative downfield induced shifts indicated in structure **7a′**, which is in accord with the

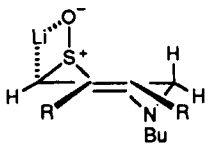
(1) For recent reviews, see: Weinreb, S. M. *Acc. Chem. Res.* **1988**, *21*, 313. Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987; Chapter 1.
(2) Bell, S. I.; Weinreb, S. M. *Tetrahedron Lett.* **1988**, *29*, 4233.
(3) Wichterle, O.; Rocek, J. *Collect. Czech. Chem. Commun.* **1954**, *19*, 282. Wucherpfennig, W. *Liebigs Ann. Chem.* **1971**, *746*, 16. Grill, H.; Kresze, G. *Liebigs Ann. Chem.* **1971**, *749*, 171. Ichimura, K.; Ichikawa, S.; Imamura, K. *Bull. Soc. Chem. Jpn.* **1976**, *49*, 1157.
(4) Cf.: Gaoni, Y. *Tetrahedron Lett.* **1982**, *23*, 2051.
(5) Klamann, D.; Sass, C.; Zelenka, M. *Chem. Ber.* **1959**, *92*, 1910.
(6) Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7861.
(7) Hanson, P.; Stockburn, W. A. *J. Chem. Soc., Perkin Trans. 2* **1985**, 589.

0022-3263/91/1956-0373$02.50/0

configuration and conformation shown, assuming Eu complexation occurs at the axial oxygen.[6,8] This supposition was, in fact, confirmed by X-ray crystallography of **7a**. An ORTEP plot of this compound, which nicely shows the conformation of the heterocyclic ring, is presented in Figure 1. Isomeric alkylation product **8a** showed the relative induced ^{1}H NMR shifts listed in **8a'**.

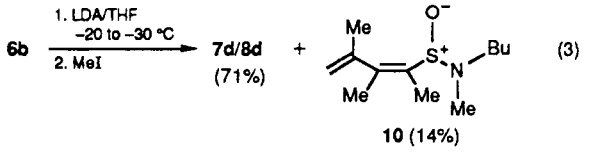


Although there is no close analogy to a metalated dihydrothiazine oxide,[9,10] our stereochemical results are reminiscent of those obtained with sulfoxide-stabilized carbanions.[11] Thus, the lithium atom may be bonded to both the α-carbon and the quasiaxial oxygen, sterically blocking the top face of **9** and causing alkylation to occur anti to the oxygen.[11] Alkylations of the carbanions derived from both **6a** and **6b** were more anti stereoselective with benzyl bromide than with methyl iodide (Scheme I), in accord with this steric argument. More puzzling, however, is the higher anti alkylation selectivity observed with 4,5-dimethyl-3,6-dihydrothiazine 1-oxide (**6b**) vs the unsubstituted system **6a**. Perhaps increased $A^{1,2}$ strain in the dimethylated system **9b** vs **9a** results in a conformational twisting or a change in hybridization at C-6, which is reflected in the slight difference in alkylation stereoselectivity.



9a: R = H
b: R = Me

One minor problem which arises in these reactions is a tendency for the monoalkylated product to ring open to a dienic sulfinamide **10** (eq 3) if the temperature is allowed to rise or if extended reaction times are used. Interestingly, the alternative ring opening process shown in eq 2 to form a pyrrole was not observed here (vide infra).



We further investigated the analogy between **9** and metalated sulfoxides. It is known that oxygenated electrophiles react with α-lithio sulfoxides in a syn manner, presumably via precoordination with the metal.[9,12] Treatment of lithiated 3,6-dihydrothiazine oxide **6a** with

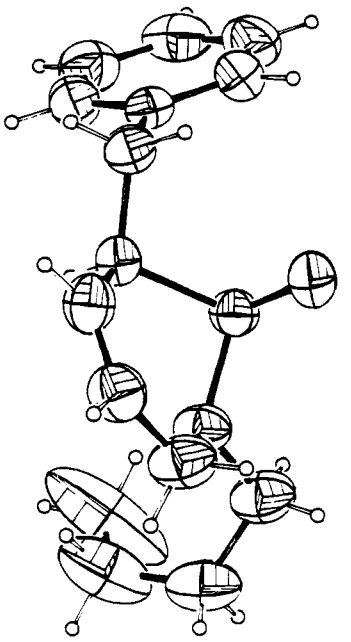
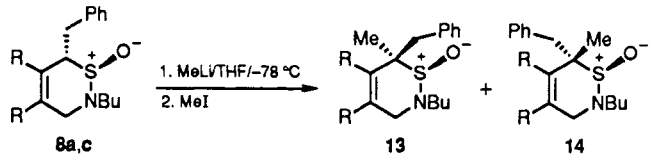


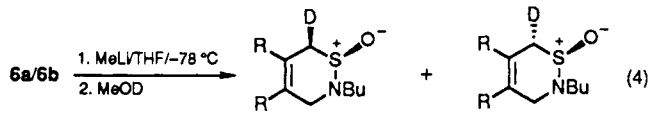
Figure 1. ORTEP drawing of 3,6-dihydrothiazine 1-oxide **7a**.

Scheme II



R	yield	isomer ratio (13:14)
H	56%	56:44
Me	81%	76:24

MeOD in fact produced mainly the syn monodeuterio compound **11a** and minor amounts of anti isomer **12a** (eq 4). In the case of **6b** only the syn isomer **11b** was formed.



The stereochemistry of **11** and **12** was proven by ^{1}H europium shift experiments and was best quantitated by integration of the ^{2}H NMR spectrum of the mixtures.[13] Thus, this result nicely parallels the sulfoxide chemistry and lends further support for a chelated structure like **9** for the lithio dihydrothiazine oxides.

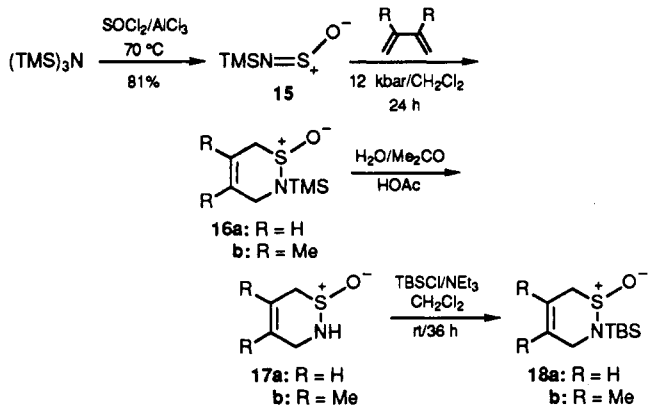
Dihydrothiazine oxides that are monosubstituted at C-6 have also been investigated in the deprotonation/alkylation process. Thus, heterocycles **8a** and **8c** could be lithiated under the usual conditions, followed by treatment with methyl iodide, to afford dialkyl products **13** and **14** (Scheme II). In both cases, anti alkylation predominated, although selectivities were rather low. Once again, ^{1}H europium shift experiments were used to establish the stereochemistry of these products.

Several attempts were also made to metalate the isomeric dihydrothiazine oxides **7a** and **7c**. Interestingly, under conditions that allow for deprotonation of heterocycles **8a,c**, compounds **7a,c** were unchanged, nor did increasing

(8) See also: Mock, W. L.; Nugent, R. M. *J. Am. Chem. Soc.* **1975**, *97*, 6521.
(9) For an excellent review of sulfur-stabilized carbanions, see: Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.
(10) Acyclic analogues of dihydrothiazine oxides (e.g. allylic sulfinamides) have been lithiated and alkylated, but stereochemistry was not investigated: Baudin, J.-B.; Julia, S. A. *Tetrahedron Lett.* **1988**, *29*, 3255.
(11) See, for example: Biellmann, J. F.; Vicens, J. J. *Tetrahedron Lett.* **1978**, 467. Durst, T.; Molin, M. *Ibid.* **1975**, 63. Chassaing, G.; Lett, R.; Marquet, A. *Ibid.* **1978**, 471.
(12) Hutchinson, B. J.; Anderson, K. K.; Katritzky, A. R. *J. Am. Chem. Soc.* **1969**, *91*, 3839. Biellmann, J. F.; Vicens, J. J. *Tetrahedron Lett.* **1978**, 467. Bory, S.; Marquet, A. *Ibid.* **1973**, 4155.

(13) We are grateful to Dr. Alan Freyer for obtaining this data for us.

Scheme III

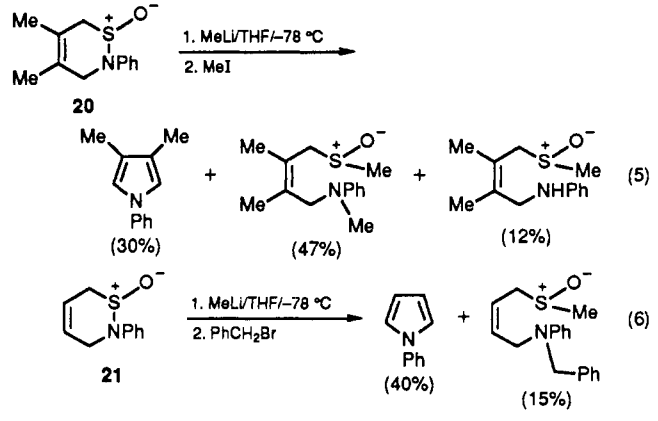


the reaction time have any effect. Therefore, it appears that a syn oxygen significantly promotes the rate of deprotonation in these systems (cf. conformational structures **7a'** and **8a'**), presumably via precoordination with the lithium base.

We next examined the metalation of *N*-silyl-substituted dihydrothiazine oxides. High-pressure cycloaddition of *N*-silylsulfinyl compound **15**[14] (Scheme III) with 1,3-butadiene or 2,3-dimethylbutadiene gave adducts **16a** and **16b**, respectively, in excellent yields. However, the TMS group in **16a,b** was hydrolytically labile, and thus was purposely removed on workup to afford NH compounds **17a,b**. N-Silylation of **17a,b** with TBSCl gave stable dihydrothiazine oxides **18a,b** in high yields.

Unlike the *N*-alkyl series of heterocycles, *N*-TBS compounds **18a** and **18b** upon treatment with methyllithium rapidly and cleanly ring opened in a stereoselective manner to afford dienic sulfinamides **19a** and **19b**, respectively (Scheme IV). To our surprise, the ring opening can be reversed by treatment of the sulfinamides with sodium hydride, providing the initial dihydrothiazine oxides in about 70% yields.

The *N*-phenyl-substituted dihydrothiazine oxides **20** and **21**[15] were next investigated using the conditions shown in eqs 5 and 6. In these cases, mixtures of products were

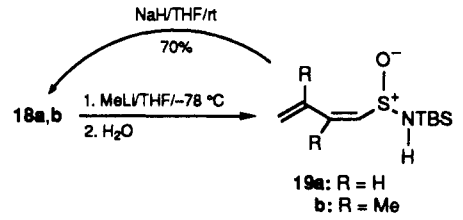


produced with pyrroles being seen for the first time (cf. eq 2). In addition, products of attack by methyllithium on sulfur and subsequent ring opening were observed. We have previously used this type of ring cleavage in transformations of dihydrothiazine oxides having electron-withdrawing groups on nitrogen.[1]

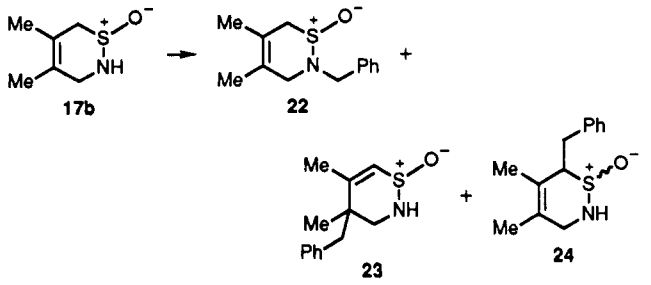
(14) Scherer, O. J.; Hornig, P. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 729.

(15) Wichterle, O.; Rocek, J. *Chem. Listy* **1953**, *47*, 1768. Kresze, G.; Maschke, A.; Albrecht, R.; Bederke, K.; Patzchke, H. P.; Smalla, H.; Trede, A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 89.

Scheme IV



Scheme V



conditions	yield	products
1. 2.5 equiv of LDA/–40 °C/THF; 2. $PhCH_2Br$	37%	**22**
1. 2 equiv of BuLi/–78 °C/THF; 2. $PhCH_2Br$	41%	**22**:**23** (70:30)
1. 2 equiv of BuLi/–78 °C/THF; 2. $PhCH_2Br$	38%	**22**:**23** (84:16)
1. 2.5 equiv of LDA/–40 °C/HMPA/THF; 2. $PhCH_2Br$	98%	**22**
1. NaH/–40 °C/DMF; 2. $PhCH_2Br$	81%	**22**

Finally, we attempted to convert heterocycle **17b** to the corresponding dianion. As can be seen in Scheme V, formation of this dianion was difficult and in the few experiments where it was apparently generated, alkylation occurred *only* at C-4. In no instance did we observe any of the C-6 alkylation product **24**.

In summary, we have found that the metalation chemistry of 3,6-dihydrothiazine 1-oxides is critically dependent upon the nature of the substituent on nitrogen. Metalation/alkylation of *N*-alkyldihydrothiazine oxides occur at C-6 with anti stereoselectivity relative to the sulfur oxygen when using alkyl halides. N-Silylated heterocycles, on the other hand, stereoselectively ring open to dienic sulfinamides, which themselves may have some interesting chemistry. Metalations of the *N*-aryl and N-H heterocycles do not appear to be synthetically useful. We are continuing to explore the chemistry and synthetic utility of these readily available cycloadducts of *N*-sulfinyl dienophiles.

Experimental Section

General Procedure for the High-Pressure Diels–Alder Reaction of *N*-Sulfinylbutylamine. A solution of 0.190 g (1.60 mmol) of *N*-sulfinylbutylamine and 1.60 mmol of the 1,3-diene in 3.5 mL of dry CH_2Cl_2 was placed in a 5-mL Luerlok plastic syringe, capped, and subjected to 12 kbar of pressure for 24 h.[16] The solvent was removed in vacuo, and the residue was flash chromatographed on silica gel, eluting with ethyl acetate/hexanes (1:1) to give a slightly yellow liquid product, which was further purified by Kugelrohr distillation (0.10 mmHg, 50–80 °C) to give the product as a clear colorless liquid.

6a: oil; 89% yield; ^1H NMR (360 MHz, $CDCl_3$) δ 5.92 (1 H, m), 5.67 (1 H, m), 3.63 (1 H, m), 3.49–3.28 (2 H, m), 3.15 (2 H, m), 2.86 (1 H, m), 1.55 (2 H, m), 1.29 (2 H, m), 0.88 (3 H, t, J = 7.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 125.6, 114.3, 54.4, 48.9, 42.2, 29.4, 19.7, 13.4; IR (film) 3040, 2970, 2880, 1470, 1400, 1385, 1200, 1165, 1130, 1110, 1085, 885, 825, 690, 645 cm^{-1}.

6b: oil; 96% yield; ^1H NMR (360 MHz, $CDCl_3$) δ 3.50 (1 H, m), 3.41 (1 H, m), 3.09 (2 H, m), 2.94 (1 H, d, J = 16.3 Hz), 1.68

(16) High pressure reactions were carried out in a LECO Model PG-200-HPC pressure system. We thank Professor Raymond L. Funk for use of this instrument.

(3 H, s), 1.63 (3 H, s), 1.52 (2 H, m), 1.26 (2 H, m), 0.84 (3 H, t, J = 7.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 124.3, 114.4, 54.1, 53.9, 47.2, 29.5, 19.8, 19.2, 16.9, 13.6; IR (film) 2960, 2930, 2860, 1450, 1380, 1340, 1235, 1170, 1145, 1080, 1030, 980, 940, 855, 725, 660 cm^{-1}.

Procedure for Alkylation of Dihydrothiazine Oxides with Lithium Diisopropylamide. A solution of 0.250 mmol of the dihydrothiazine oxide in 1 mL of dry THF was added dropwise to a cold (−78 °C, under Ar) solution of 0.375 mmol of lithium diisopropylamide in 2 mL of dry THF. After the mixture was stirred for 1 h at −78 °C, 0.375 mmol of the alkyl halide was added. The mixture was stirred for 1.5 h at −78 °C and was slowly warmed to room temperature over 2 h. The solvent was then removed in vacuo, and the product 3,6-dihydrothiazine oxide isomers were separated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1).

Procedure for Alkylation with Methyllithium. To a solution of 0.250 mmol of the dihydrothiazine oxide in 3 mL of dry THF at −78 °C under an argon atmosphere was added dropwise 0.300 mmol of methyllithium (1.5 M solution in ether). After the solution was stirred at −78 °C for 30 min, 0.300 mmol of the alkyl halide was added. The mixture was kept at −78 °C for 1.5 h before being slowly warmed to room temperature over 2.5 h. The solvent was then removed in vacuo, and the product 3,6-dihydrothiazine oxide isomers were separated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1). For yields and isomer ratios of alkylated products see Scheme I.

7a: mp 57–59 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34–7.22 (5 H, m), 5.90 (1 H, m), 5.44 (1 H, dd, J = 10.8 Hz, 1.8 Hz), 3.68–3.50 (2 H, m), 3.32 (1 H, m), 3.15 (2 H, m), 2.92 (1 H, m), 2.82 (1 H, m), 1.55 (2 H, m), 0.88 (3 H, t, J = 7.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.0, 129.3, 128.5, 126.7, 125.4, 119.7, 58.8, 54.7, 43.0, 36.4, 29.7, 19.9, 13.6; IR (film) 3040, 2980, 2940, 2880, 1500, 1450, 1380, 1130, 1090, 800, 755, 710, 675 cm^{-1}.

8a: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.35–7.15 (5 H, m), 5.65 (1 H, m), 3.62 (1 H, m), 3.38 (2 H, m), 3.20 (1 H, m), 2.90 (2 H, m), 2.73 (1 H, dd, J = 13.8, 8.3 Hz), 1.61 (2 H, m), 1.37 (2 H, m), 0.92 (3 H, t, J = 7.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.1, 128.7, 128.4, 126.5, 125.0, 120.1, 60.8, 54.3, 42.7, 38.7, 29.7, 19.7, 13.5; IR (film) 3040, 2960, 2885, 1500, 1460, 1385, 1200, 1130, 1080, 810, 760, 710 cm^{-1}.

7b: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.90 (1 H, m), 5.41 (1 H, m), 3.85 (1 H, m), 3.45–3.29 (2 H, m), 3.22 (1 H, m), 2.83 (1 H, m), 1.60 (2 H, m), 1.35 (3 H, d, J = 2.7 Hz), 1.40 (2 H, m), 0.91 (3 H, t, J = 4.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 124.7, 121.4, 54.3, 51.6, 42.3, 29.4, 19.7, 15.5, 13.4; IR (film) 3015, 2965, 2935, 2880, 1460, 1380, 1130, 1110, 1080, 795, 620 cm^{-1}; MS m/z (relative intensity) 187 (12), 139 (3.9), 124 (1.6), 96 (1.9), 82 (5.7), 69 (6.6), 68 (100), 67 (29.0), 66 (1.7), 57 (4.9), 55 (2.6), 53 (4.8), 42 (3.1), 41 (9.3), 39 (3.8), 29 (5.4), 28 (6.0), 27 (3.3); HRMS calcd for $C_9H_{17}NOS$ 187.1031, found 187.1026.

8b: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.90 (1 H, m), 5.78 (1 H, m), 3.63 (1 H, m), 3.31 (1 H, m), 3.20 (2 H, m), 2.95 (1 H, m), 1.60 (2 H, m), 1.38 (2 H, m), 1.27 (3 H, d, J = 7.1 Hz), 0.93 (3 H, t, J = 7.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 124.2, 121.5, 54.3, 54.1, 42.3, 29.6, 19.6, 16.9, 13.4; IR (film) 3040, 2980, 2940, 2880, 1455, 1385, 1200, 1125, 1115, 1090, 800, 710, 650 cm^{-1}; MS m/z (relative intensity) 187 (10), 139 (3.6), 124 (1.6), 96 (2.1), 82 (2.1), 69 (6.1), 68 (100), 67 (24), 57 (4.3), 55 (2.3), 53 (4.3), 42 (2.9), 41 (8.1), 39 (3.4), 29 (4.3), 28 (3.8); HRMS calcd for $C_9H_{17}NOS$ 187.1031, found 187.1043.

7c: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.27 (5 H, m), 3.52 (2 H, m), 3.24 (1 H, dd, J = 14.1, 4.3 Hz), 3.10–2.90 (2 H, m), 2.71 (2 H, m), 1.75 (3 H, s), 1.66 (3 H, s), 1.43 (2 H, m), 1.18 (2 H, m), 0.78 (3 H, t, J = 7.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.2, 129.6, 128.5, 125.8, 122.0, 118.9, 66.6, 54.6, 47.7, 33.8, 29.7, 20.0, 17.7, 16.4, 13.7; IR (film) 3060, 3020, 2940, 2860, 1600, 1490, 1455, 1380, 1260, 1135, 1070, 1030, 980, 940, 910, 750, 700 cm^{-1}; MS m/z (relative intensity) 291 (0.5), 172 (30), 158 (13), 157 (100), 152 (44), 143 (18), 142 (12), 129 (17), 94 (19), 91 (29), 79 (7.6), 77 (10), 57 (6.3), 41 (17), 29 (12); HRMS calcd for $C_{17}H_{25}NOS$ 291.1657, found 291.1657.

8c: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.29–7.06 (5 H, m), 3.13 (2 H, m), 2.94–2.70 (2 H, m), 1.66 (3 H, s), 1.65 (3 H, s), 1.58 (2 H, m), 1.34 (2 H, m), 0.89 (3 H, t, J = 7.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.1, 128.7, 128.3, 126.4, 124.4, 119.6, 66.4, 53.9, 48.0, 38.0, 29.7, 19.8, 19.1, 16.9, 13.6; IR (film) 3030, 2960, 1600, 1495, 1450, 1380, 1030, 755, 710, 670 cm^{-1}; MS m/z (relative intensity) 291 (1.6), 172 (32), 158 (13), 157 (100), 152 (54), 143 (17), 129 (12), 94 (22), 91 (36), 82 (23), 67 (14), 41 (22), 29 (16); HRMS calcd for $C_{17}H_{25}NOS$ 291.1657, found 291.1655.

7d: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.60 (1 H, m), 3.34 (1 H, m), 3.10 (2 H, m) 2.83 (1 H, m), 1.67 (6 H, s), 1.60 (2 H, m), 1.35 (3 H, d, J = 7.4 Hz), 1.32 (2 H, m), 0.89 (3 H, t, J = 7.3 Hz); IR (film) 2970, 2940, 2880, 1455, 1385, 1150, 1090, 1045, 715 cm^{-1}.

8d: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.45 (1 H, m), 3.12 (2 H, m), 2.99–2.80 (2 H, m), 1.71 (3 H, m), 1.65 (3 H, m), 1.53 (2 H, m), 1.31 (2 H, m), 1.19 (3 H, d, J = 7.0 Hz), 0.87 (3 H, t, J = 7.3 Hz); IR (film) 2980, 2940, 2880, 1455, 1385, 1160, 1090, 1035, 985, 725, 670 cm^{-1}.

Crystal Structure Determination of Dihydrothiazine Oxide 7a. Crystal data: monoclinic, $P2_1/n$, a = 5.870 (2) Å, b = 18.424 (2) Å, c = 13.643 (4) Å, β = 90.81 (3)°, v = 1475.2 Å^3, Z = 4, D_c = 1.186 g cm^{-3}, $F(000)$ = 568 Cu Kα radiation, λ = 1.5418 Å, μ = 18.06 cm^{-1}.

Accurate cell dimensions and a crystal orientation matrix were determined on an Enraf-Nonius CAD4 diffractometer by a least-squares refinement of the setting angles of 25 reflections with θ in the range 15–30°. Intensity data were collected by the $\omega/2\theta$ scan method using monochromatized radiation in the range $5 < \theta < 65°$. The intensities of three reflections, chosen as standards, were monitored at regular intervals and decreased by 6.2% over the course of the data collection; this decay was corrected for by appropriate scaling. Intensities of 2498 unique reflections were measured, of which 2139 had $I > 3\sigma(I)$, and were used in the structure solution and refinement. Data were corrected for Lorentz and polarization factors; absorption was ignored.

The structure was solved by direct methods. Refinement of the structure was by full-matrix least-squares calculations, initially with isotropic and finally with anisotropic temperature factors for the non-hydrogen atoms. At an intermediate stage in the refinement, a difference map revealed all hydrogen atoms which were included in subsequent cycles at geometrically idealized positions with isotropic thermal parameters. Refinement converged with R = 0.063 and $R_w = (\Sigma w^2/\Sigma F_o^2)^{1/2}$ = 0.108. In the refinement cycles, weights were derived from the counting statistics. Scattering factors were those of Cromer and Mann[17] and Stewart, Davidson, and Simpson,[18] and allowance was made for anomalous dispersion.[19] A difference map calculated at the conclusion of the refinement had no chemically significant features.[20]

Procedure for Alkylation of C-6 Substituted Dihydrothiazine Oxides. To a solution of 0.150 mmol of the C-6 monoalkylated dihydrothiazine oxide in 2 mL of dry THF at −78 °C under an argon atmosphere was added 0.180 mmol of methyllithium (1.5 M solution in ether). After stirring the mixture for 10 min, 25.5 mg (0.180 mmol) of methyl iodide was added. The mixture was stirred at −78 °C for 2 h and slowly warmed to room temperature over 2.5 h. The solvent was removed in vacuo, and the isomeric products were separated by flash chromatography on silica gel, eluting with ethyl acetate–hexanes (3:7).

13a: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40 (5 H, m), 5.84 (1 H, m), 5.58 (1 H, m), 3.59 (1 H, m), 3.30 (2 H, m), 2.80 (1 H, d, J = 13.5 Hz), 1.56 (2 H, m), 1.27 (2 H, m), 1.18 (3 H, s), 0.87 (3 H, t, J = 9.8 Hz); IR (film) 3040, 2960, 2880, 1735, 1460, 1385, 1280, 1130, 1080, 780, 750, 715 cm^{-1}; MS m/z (relative intensity) 278 (0.5), 229 (7.4), 214 (8.5), 159 (59), 157 (9.9), 144 (13), 143 (100), 142 (7.2), 129 (33), 128 (19), 115 (11), 105 (7.9), 91 (35), 80 (7.5), 65 (7.5), 42 (8.5), 41 (15), 29 (11), 28 (11); HRMS calcd for $C_{16}H_{23}NOS$ 277.1500, found 277.1508.

14a: oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.31 (5 H, m), 5.90 (1 H, m), 5.26 (1 H, m), 3.60 (1 H, m), 3.44–3.21 (2 H, m), 3.17 (1 H, m), 3.02 (2 H, m), 2.78 (1 H, d, J = 12.9 Hz), 1.69 (2 H, m), 1.41 (2 H, m), 1.22 (3 H, s), 0.95 (3 H, t, J = 7.4 Hz); IR (film)

(17) Cromer, D. T.; Mann, J. B. *Acta Crystallogr.* **1968**, *A24*, 321.
(18) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.
(19) Cromer, D. T.; Liberman, D. *J. Chem. Phys.* **1970**, *53*, 1891.
(20) All computer programs used were part of the Enraf-Nonius Structure Determination Package (SDP Plus, Version 1.0), Enraf-Nonius, Delft, Holland, 1982, and implemented on a PDP 11/34 computer.

3030, 2950, 2860, 1730, 1600, 1500, 1455, 1375, 1280, 1125, 1080, 770, 745, 715 cm^{-1}; MS m/z (relative intensity) 278 (0.6), 159 (62), 157 (9.7), 144 (13), 143 (100), 142 (6.3), 129 (33), 128 (19), 115 (9.7), 105 (6.2), 91 (30), 80 (7.0), 77 (65), 41 (13), 29 (9.5), 28 (13); HRMS calcd for $C_{16}H_{23}NOS$ 277.1500, found 277.1502.

13b: oil; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43 (2 H, m), 7.25 (3 H, m), 3.55 (2 H, m), 3.19 (1 H, d, J = 13.6 Hz), 3.07 (2 H, m), 2.96 (1 H, d, J = 13.6 Hz), 2.84 (1 H, m), 1.80 (3 H, s), 1.72 (3 H, s), 1.47 (2 H, m), 1.24 (2 H, m), 1.21 (3 H, s), 0.84 (3 H, t, J = 7.4 Hz); IR (film) 3040, 2940, 2880, 1665, 1500, 1460, 1365, 1175, 1080, 1040, 940, 770, 750, 710 cm^{-1}; MS m/z (relative intensity) 305 (1.0), 172 (10), 171 (72), 167 (13), 166 (100), 156 (8.2), 143 (9.9), 129 (6.8), 95 (6.0), 91 (33), 57 (6.7), 43 (6.8), 41 (16), 29 (13); HRMS calcd for $C_{18}H_{27}NOS$ 305.1813, found 305.1805.

14b: oil; ^1H NMR (360 MHz, $CDCl_3$) δ 7.27 (3 H, m), 7.11 (2 H, m), 3.53 (1 H, dd, J = 17.0, 1.0 Hz), 3.25 (2 H, m), 3.00 (1 H, m), 2.95 (1 H, d, J = 13.3 Hz), 2.83 (1 H, d, J = 13.3 Hz), 1.70 (3 H, s), 1.65 (2 H, m), 1.41 (2 H, m), 1.37 (3 H, s), 1.29 (3 H, s), 0.95 (3 H, t, J = 7.4 Hz); IR (film) 3050, 2955, 2880, 1735, 1505, 1460, 1385, 1280, 1135, 1090, 755, 715 cm^{-1}; MS m/z (relative intensity) 305 (0.7), 242 (6.0), 185 (9.3), 172 (8.8), 171 (58), 167 (13), 166 (100), 156 (7.3), 143 (7.9), 129 (6.1), 91 (32), 57 (6.5), 55 (6.3), 41 (15), 29 (12); HRMS calcd for $C_{18}H_{27}NOS$ 305.1813, found 305.1806.

Preparation of 3,6-Dihydrothiazine Oxides 17a and 17b. A solution of 0.320 g (2.50 mmol) of *N*-sulfinyl(trimethylsilyl)-amine[14] (**15**) and 2.75 mmol of the 1,3-diene in 3 mL of dry CH_2Cl_2 was placed in a 5-mL plastic Luerlok syringe, capped, and subjected to 12 kbar of pressure for 24 h.[16] The solvent was removed in vacuo, and the residue was dissolved in 15 mL of an acetone/water (3:1) mixture to which 2 drops of glacial acetic acid was added. The solution was stirred at room temperature for 2 h, at which time the solution was neutralized by addition of solid $NaHCO_3$ until bubbling ceased. The solvent was then removed in vacuo, and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate to give the product as a white solid.

17a: 75% yield; ^1H NMR (360 MHz, $CDCl_3$) δ 5.96 (1 H, m), 5.70 (1 H, m), 4.32 (2 H, s), 3.98 (1 H, m), 3.43 (2 H, m), 3.07 (1 H, m); IR (KBr) 3100 (br), 2870, 2820, 2760, 1445, 1410, 1370, 1325, 1180, 1145, 1075, 1020, 955, 920, 850, 800, 650 cm^{-1}.

17b: 81% yield; ^1H NMR (360 MHz, $CDCl_3$) δ 4.23 (1 H, s), 3.90 (1 H, d, J = 16.2 Hz), 3.43 (1 H, d, J = 15.9 Hz), 3.24 (1 H, d, J = 16.3 Hz), 2.88 (1 H, d, J = 16.4 Hz), 1.74 (3 H, s), 1.68 (3 H, s); IR (KBr) 3150 (br), 2980, 2910, 2850, 1435, 1400, 1375, 1335, 1275, 1230, 1175, 1110, 1020, 950, 920, 865, 835, 740, 695, 660 cm^{-1}.

Preparation of *N*-Silyl Compounds 18a and 18b. To a solution of 0.85 mmol of the dihydrothiazine oxide and 0.154 g (1.02 mmol) of *tert*-butyldimethylsilyl chloride under argon in 5 mL of dry CH_2Cl_2 was added 0.14 mL (1.02 mmol) of triethylamine. The solution was then stirred for 36 h at room temperature. The solvent was removed in vacuo, and the residue was flash chromatographed on silica gel, eluting with ethyl acetate/hexanes (6:4) to give the product as a clear, colorless liquid.

18a: 99% yield; ^1H NMR (360 MHz, $CDCl_3$) δ 5.94 (1 H, m), 5.75 (1 H, m), 3.93 (1 H, m), 3.43 (1 H, m), 3.30 (1 H, M), 3.10 (1 H, m), 0.88 (9 H, m), 0.25 (3 H, m), 0.18 (3 H, m); IR (film) 3415 (br), 3025, 2960, 2880, 2850, 1460, 1380, 1360, 1255, 1190, 1150, 1080, 1020, 970, 900, 870, 825, 815, 775, 680, 630 cm^{-1}.

18b: 97% yield; ^1H NMR (360 MHz, $CDCl_3$) δ 3.83 (1 H, d, J = 15.9 Hz), 3.38 (1 H, d, J = 15.9 Hz), 3.17 (1 H, d, J = 16.9 Hz), 2.88 (1 H, d, J = 16.5 Hz), 1.71 (3 H, s), 1.66 (3 H, s), 0.85 (9 H, s), 0.25 (3 H, d, J = 3.0 Hz), 0.19 (3 H, d, J = 3.9 Hz); IR (film) 3450 (br), 2950, 2880, 2850, 1460, 1390, 1360, 1250, 1165, 1125, 1080, 965, 890, 835, 805, 780, 735, 710, 680, 655 cm^{-1}.

General Procedure for Ring Opening of *N*-Silyldihydrothiazine Oxides. To a solution of 0.150 mmol of dihydrothiazine oxide in 2.5 mL of dry THF at −78 °C under an argon atmosphere was added 0.180 mmol of methyllithium (1.5 M solution in ether). The solution was stirred at −78 °C for 40 min before addition of 1 drop of water. The solution was warmed to room temperature, and the solvent was removed in vacuo. The residue was flash chromatographed on silica gel, eluting with ethyl acetate–hexanes (1:1) to give the dienic sulfinamide.

19a: 88% yield; mp 58–59 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.90 (1 H, dddd, J = 16.8, 10.7, 10.0, 1.0 Hz), 6.31 (1 H, dd, J = 10.7, 10.1 Hz), 6.18 (1 H, dd, J = 10.1, 1.0 Hz), 5.41 (1 H, dd, J = 16.8, 2.2 Hz), 5.37 (1 H, dd, J = 10.0, 2.2 Hz), 3.94 (1 H, s), 0.88 (9 H, s), 0.21 (6 H, s); IR (film) 3400 (br), 3120, 2950, 2920, 2880, 2850, 1565, 1460, 1405, 1360, 1330, 1255, 1055, 895, 840, 800, 770, 665 cm^{-1}; MS m/z (relative intensity) 231 (2.8), 183 (7.5), 174 (45), 129 (6.7), 126 (8.8), 111 (17), 106 (6.5), 100 (6.0), 86 (14), 85 (6.0), 84 (23), 76 (9.3), 75 (100), 74 (17), 73 (35), 68 (7.3), 59 (12), 57 (6.7), 49 (28), 47 (8.2), 45 (11), 44 (7.1), 41 (8.0), 28 (9.2); HRMS calcd for $C_{10}H_{20}NOSSi$ 231.1113, found 231.1101.

19b: 86% yield; mp 70–73 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.06 (1 H, d, J = 1.3 Hz), 5.08 (1 H, t, J = 1.6 Hz), 5.00 (1 H, d, J = 1.6 Hz), 3.84 (1 H, s), 1.90 (3 H, s), 1.86 (3 H, s), 0.89 (9 H, s), 0.19 (6 H, s); IR (film) 3020 (br), 2870, 2780, 1570, 1430, 1395, 1330, 1180, 1125, 1095, 1025, 970, 870, 820, 760, 650 cm^{-1}; MS m/z (relative intensity) 259 (23), 202 (44), 184 (14), 154 (15), 128 (16), 113 (21), 111 (17), 97 (17), 96 (27), 82 (16), 81 (81), 75 (100), 74 (69), 73 (45), 59 (19), 41 (17); HRMS calcd for $C_{12}H_{25}NOSSi$ 259.1426, found 259.1409.

Procedure for Reclosure of Dienes 19a,b to Dihydrothiazine Oxides 18a,b. To a stirred suspension of 2.5 mg (0.086 mmol) of sodium hydride (80% dispersion in mineral oil) in 0.5 mL of dry THF under argon at room temperature was added a solution of 0.043 mmol of the conjugated sulfinamide in 0.5 mL of dry THF. The solution was stirred for 3 h before addition of 1 drop of distilled water. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1) to give the N-silylated dihydrothiazine oxides in 70% yields.

Acknowledgment. We are grateful to the National Science Foundation (CHE-8902931) for generous financial support.

Supplementary Material Available: NMR spectra of new compounds and X-ray data for **7a** (35 pages). Ordering information is given on any current masthead page.