Carbonyl Addition and Alkylation Reactions of Isothiazolidine 1-Oxide, the Sulfur Analog of 2-Pyrrolidone

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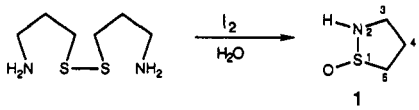
Isothiazolidine 1-oxide is the sulfur analog of 2-pyrrolidone. A series of reactions at both the nitrogen and the α-sulfinyl carbon have been carried out. N-Deprotonation under phase-transfer conditions in the presence of *p*-nitrobenzyl bromide gives 2-(*p*-nitrobenzyl)isothiazolidine 1-oxide, the first cyclic sulfinamide to be characterized by X-ray analysis. Other N-substituted derivatives are also described. The dianion formed using 2 equiv of alkyllithium undergoes stereoselective monosubstitution with ketones and benzyl chloride at the carbon α to the sulfinyl group. With benzophenone, the syn product predominates as shown by X-ray analysis. Acetone also gives the syn product; however, with benzyl chloride, the anti product predominates. Unlike open-chain sulfinamides, the presence of a hydroxyl substituent on the carbon β to the sulfinyl group in cyclic sulfinamides does not facilitate thermal elimination of SO_2 at 153 °C, even after 5 h.

Introduction

Isothiazolidine 1-oxide, **1**, a cyclic sulfinamide, is the sulfur analog of 2-pyrrolidone. Recently we described the synthesis of a series of N-substituted monosaturated and bicyclic saturated sulfinamides via the oxidative cyclization of secondary amine disulfides.[1,2]



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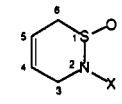
In order to determine whether this saturated cyclic sulfinamide could be derivatized selectively at the nitrogen and at the α-sulfinyl carbon, C-5, without ring cleavage, we have utilized several different deprotonation reagents followed by nucleophilic reactions with a variety of electrophiles. The only other work on the reactions of cyclic sulfinamides was reported by Weinreb et al.[3] They studied alkylation reactions of the unsaturated six-membered ring, 3,6-dihydrothiazine 1-oxide, with substituents on the nitrogen atom. Because of the unsatur-

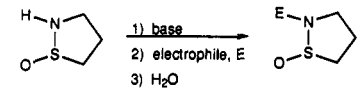


X = Bu, TMS, TBDMS, H.

ation, the α-sulfinyl position, C-6, is also an allylic position so the chemistry of this heterocycle is much different from that of the isothiazolidine 1-oxide reported here.

Results and Discussion

N-Substitution. N-Alkylations of isothiazolidine 1-oxide, **1**, with methyl bromoacetate and *p*-nitrobenzyl bromide were accomplished by phase-transfer catalysis by treatment of the sulfinamide with pulverized potassium hydroxide and tetrabutylammonium bromide (TBAB) in THF followed by the alkyl bromide at 0 °C.[4] 2-(*p*-Nitrobenzyl)isothiazolidine 1-oxide, **2**, is the first cyclic sulfinamide to be characterized by the X-ray crystal structure which is shown in Figure 1.



2-Benzylisothiazolidine 1-oxide was isolated when the monoanion of **1** was generated using LDA at 0 °C and treated with benzyl bromide. An N-silylated derivative, 2-(*tert*-butyldimethylsilyl)isothiazolidine 1-oxide, was obtained when **1** was deprotonated with 1 equiv of *n*-butyllithium and treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) at −78 °C.[5] The only N-substitution reaction carried out on 3,6-dihydrothiazine 1-oxide was silyl substitution by TBDMSCl using triethylamine as the base.[3]

α-Sulfinyl Substitution. Initially, deprotonation at C-5 as well as the nitrogen was carried out to assign the methylene protons of **1**. Compound **1** was treated with 2.5 equiv of *sec*-butyllithium for 15 min at −45 °C and quenched with D_2O.[3] Analysis of the ^1H NMR of the product indicated that two protons on each molecule had been exchanged. The NH signal was not present, and the ^1H signals at 2.8 and 3.0 ppm integrated to only 0.79 and 0.21, respectively.

Based upon the effects of $Eu(fod)_3$ on the chemical shifts, it was possible to assign the signal centered at 3.0 ppm as the proton syn to the sulfinyl oxygen and the signal at 2.8 ppm as the anti proton. The deuterium NMR also showed two signals with a ratio of 79:21 due to the syn to anti product, respectively.[6]

The ^{13}C NMR spectrum revealed a splitting of the farthest downfield signal into three lines which indicates that the resonance at 55.47 ppm is due to C-5. This

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(1) Wagner, B. J.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1990**, *55*, 4156.

(2) Wagner, B. J.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1990**, *55*, 5940.

(3) Bell, S. I.; Parvez, M.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 373.

(4) (a) Nilsson, B. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1990**, *33*, 580. (b) Reuschling, D.; Pietsch, H.; Linkies, A. *Tetrahedron Lett.* **1978**, 615. (c) Takahata, H.; Hashizume, T.; Yamazaki, T. *Heterocycles* **1979**, *12*, 1449.

(5) Pratt, J. R., Massey, W. D., Pinkerton, F. H.; Thames, S. F. *J. Org. Chem.* **1975**, *40*, 1090.

(6) (a) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277. (b) Biellmann, J. F.; Vicens, J. J. *Tetrahedron Lett.* **1978**, 467. (c) Chassaing, G.; Lett, R.; Marquet, A. *Tetrahedron Lett.* **1978**, 471.

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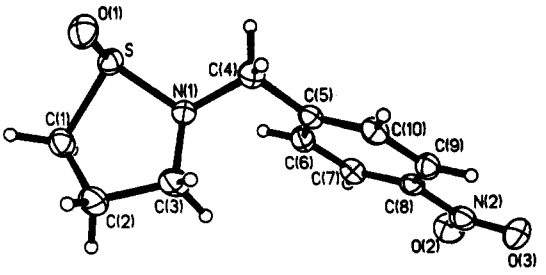
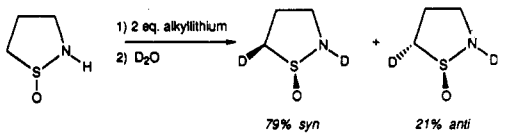


Figure 1.

experiment also confirmed that the protons on C-3 of 1 resonate farther downfield (δ 3.5–2.9) than the protons on C-5 (δ 3.0–2.5). The protons on C-4 resonate the farthest upfield (δ 2.7–2.1).

The explanation for the preference of the syn isomer was based upon the parallel reaction of the α-sulfinyl carbanion of tetrahydrothiophene 1-oxide with oxygen-containing electrophiles.[6]



For alkylation and carbonyl addition reactions, 1 was always treated with 2 equiv of *sec*- or *tert*-butyllithium. Surprisingly, *n*-butyllithium would not deprotonate C-5 of 1 even though both LDA and methyllithium deprotonate C-6 of 3,6-dihydrothiazine 1-oxide. This is probably because the hydrogen on C-6 of 3,6-dihydrothiazine 1-oxide is also allylic. 5-Benzylisothiazolidine 1-oxide was formed as the only product in the reaction of the dianion of 1 with 2 equiv of benzyl chloride. The anti/syn ratio of 82:18 is predicted because benzyl chloride contains no oxygen. No nitrogen alkylation or dibenzylation was observed by GC/MS of the crude reaction mixture. In contrast to these results, Weinreb et al. reported that attempts to generate the dianion from 3,6-dihydrothiazine 1-oxide followed by treatment with benzyl bromide led only to low yields of products alkylated at C-4, the other allylic position.[3] With 3,6-dihydrothiazine 1-oxide, alkyl substitution at C-6 was obtained only when the nitrogen atom was substituted with a butyl group.

The syn diastereomers were stereoselectively formed in the reaction of the dianion of 1 with benzophenone and acetone. The X-ray crystal structure of *syn*-5-(1,1-diphenyl-1-hydroxymethyl)isothiazolidine 1-oxide, 3, is shown in Figure 2 and discussed below. Corey reported that open-chain β-hydroxysulfinamides undergo 99% decomposition to the alkene, amine, and SO_2 within 5 h in refluxing dry benzene.[7] In contrast, the *syn*-benzophenone adduct of isothiazolidine 1-oxide was stable in refluxing DMF (bp = 153 °C) for at least 5 h. Models show that the syn-relationship of the sulfinyl oxygen and the carbinol groups in this β-hydroxysulfinamide may inhibit the formation of the sulfurane transition state proposed for the elimination reaction to occur.[7]

N-Sulfonation. Isothiazolidine 1-oxides and β-lactams hydrolyze at about the same rate.[1] Since a monobactam is a β-lactam antibiotic containing an SO_3 group, we decided to prepare the sulfonated sulfinamide and to test

(7) Corey, E. J.; Durst, T. *J. Am. Chem. Soc.* **1968**, *90*, 5548.

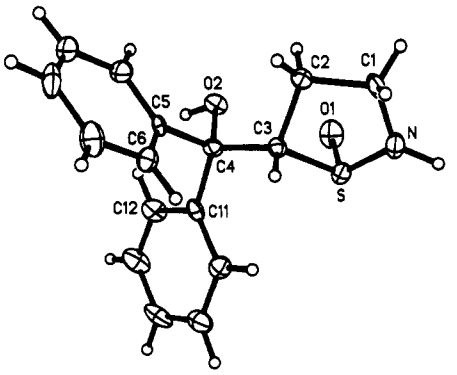
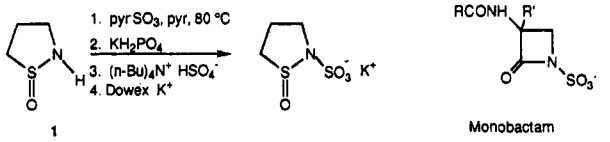


Figure 2.

it for antibiotic activity.[8] The nitrogen was sulfonated with the pyridine–sulfur trioxide complex to give a yellow oil which gave the correct high-resolution mass spectrum and NMR spectrum of an N-sulfonated sulfinamide.



We tested the sulfonated sulfinamide for antibiotic activity against *Escherichia coli* BL21 (DE3), *Bacillus subtilis* DB2, and *B. subtilis* SO113. No activity was noted at any concentration including 2 mg/mL. The sulfonate was also tested for β-lactamase inhibitory activity in conjugation with ampicillin against *E. coli* BL21 (DE3)/PET 8C, and again no activity was noted.

X-ray Crystal Structures of Cyclic Sulfinamides. Computer projections of the 2-(*p*-nitrobenzyl)isothiazolidine 1-oxide, 2, and *syn*-5-(1,1-diphenyl-1-hydroxymethyl)isothiazolidine 1-oxide, 3, are reproduced in Figures 1 and 2.[9] The rings are nonplanar as expected for a molecule containing a trivalent sulfur with a lone pair of electrons. The sum of the bond angles around sulfur is 307.5° and 305.9°, respectively. This pyramidal geometry is in the normal range for trigonal sulfur regardless of the atoms attached.[2] The sum of the bond angles around nitrogen in 2 is 346.0° which indicates a hybridization for nitrogen intermediate between sp^3 (328.5°) and sp^2 (360°). Thus, it is apparent that there is little p–d π bonding between nitrogen and sulfur.

Conclusion. Isothiazolidine 1-oxide, 1, has a chemistry which is different from acyclic sulfinamides,[7] 3,6-dihydrothiazine 1-oxides,[3] and cyclic sulfonamides. N-Alkylation can be achieved by the same phase-transfer methods used with carboxamides whereas α-sulfinyl substitution requires the use of *sec*- or *tert*-butyllithium. N-Sulfonation proceeds directly by use of the pyridine·SO_3 complex. α-Sulfinyl substitution occurs even without N-protection regio- and stereoselectively depending on whether the

(8) Floyd, D. M.; Fritz, A. W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 5160.

(9) The experimental parameters for the X-ray structure determinations of 2-(*p*-nitrobenzyl)isothiazolidine 1-oxide, 1, and of *syn*-5-(1,1-diphenyl-1-hydroxymethyl)isothiazolidine 1-oxide, 3, along with atomic coordinates, isotropic thermal parameters, a listing of the bond distances and bond angles as well as hydrogen-atom coordinates are included as supplementary material. The atomic coordinates have been deposited with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

electrophile contains oxygen as previously shown for reactions of tetrahydrothiophene 1-oxide.

Experimental Section

^1H, ^2H, and ^{13}C spectra were recorded on a General Electric QE-300 FT spectrometer and are reported in parts per million referenced from tetramethylsilane or deuteriochloroform. Infrared spectra were obtained on an IBM IR-32 spectrometer. High-resolution mass spectra were obtained at the Facility for Advanced Instrumentation, UC Davis.

Bis(3-aminopropyl) disulfide and isothiazolidine 1-oxide, 1, were prepared by the method of Doi and Musker[1] with the following modifications: After Soxhlet extraction, the salts were removed by flash chromatography of the crude oil through silica gel with 5% EtOH/$CHCl_3$. The $CHCl_3$ was scrupulously removed from the purified oil by stirring under vacuum (1.5 Torr) to prevent the formation of dichlorocarbene and the brown color which developed when the alkyllithium reagent was added later.

2-Benzylisothiazolidine 1-Oxide. To a stirred solution of 1 (712 mg, 6.78 mmol) at 0 °C under a stream of N_2 was added 25 mL of dry THF. A 1.5 M solution of lithium diisopropylamide mono(tetrahydrofuran) (4.52 mL, 6.78 mmol) was added dropwise over a 3-min period. The resulting solution was stirred for 45 min, and benzyl bromide (808 μL, 6.78 mmol) in 7 mL of dry THF was added dropwise via a syringe. The mixture was allowed to warm to room temperature during which time the solution clarified and became golden in color. After the addition of 20 mL of water, the solution was extracted with methylene chloride (5 × 25 mL), dried ($MgSO_4$), and concentrated and the resulting oil flash chromatographed (9:1 acetonitrile/methylene chloride) to yield 416 mg (31%) of a yellow oil: ^1H NMR ($CDCl_3$) δ 7.33–7.26 (m, 5 H, aromatic), 4.50 (d, J = 15.0 Hz, 1 H, NCHAr), 4.19 (d, J = 15.3 Hz, 1 H, NCHAr), 3.38 (m, 1 H, NCH), 3.18 (m, 1 H, NCH), 3.06–2.92 (m, 2 H, SCH_2), 2.63 (m, 1 H, CCHC), 2.20 (m, 1 H, CCHC); ^{13}C NMR δ ($CDCl_3$) 136.91, 128.52, 128.26, 127.66, 56.12, 52.13, 50.83, 22.83; HRMS (PI-FAB) 196.079 $(M + 1)^+$, $C_{10}H_{13}NOS$ requires 195.072.

2-(*p*-Nitrobenzyl)isothiazolidine 1-Oxide, 2. To a mechanically stirred solution of pulverized potassium hydroxide pellets (379 mg, 6.75 mmol) and tetrabutylammonium bromide (389 mg, 1.21 mmol) in 35 mL of THF under N_2 at 0 °C was added a solution of 1 (643 mg, 6.12 mmol) and *p*-nitrobenzyl bromide (1.32 g, 6.12 mmol) in 15 mL of THF over a 6-min period. The ice bath was removed after 20 min, and the mixture was stirred for 5 h. The solution was then filtered through Celite and the solvent removed giving a brown gum which was taken up in 40 mL of methylene chloride and extracted with water (3 × 30 mL), washed with brine, dried ($MgSO_4$), and concentrated yielding a reddish gum. Flash chromatography (9:1 acetonitrile/methylene chloride) yielded 90 mg (6%) of a pale yellow solid: mp 86–87.5 °C; ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 8.41 Hz, 2 H, Ar), 7.52 (d, J = 8.11 Hz, 2 H, Ar), 4.58 (d, J = 15.0 Hz, 1 H, NCHAr), 4.37 (d, J = 15.0 Hz, 1 H, NCHAr), 3.45 (m, 1 H, NCH), 3.22 (m 1 H, NCH), 3.16–2.95 (m, 2 H, SCH_2), 2.69 (m, 1 H, CCHC), 2.29 (m, 1 H, CCHC); ^{13}C NMR ($CDCl_3$) δ 147.69, 144.58, 129.07, 124.03, 123.98, 56.43, 51.80, 51.42, 23.19; IR (film) 1653, 1518, 1475, 1348, 1080 cm^{-1}. X-ray crystal analysis[8] was performed to confirm the structure. Compound 2 was also prepared in 2% yield by N-deprotonation with *sec*-butyllithium.

2-(*tert*-Butyldimethylsilyl)isothiazolidine 1-Oxide. Compound 1 (210 mg, 2.00 mmol) was dissolved in 25 mL of dry THF and cooled under N_2 to −45 °C. *n*-BuLi (1.25 mL, 2.00 mmol) was added dropwise and the solution allowed to stir at −45 °C for 15 min. TBDMSCl (301 mg, 2.00 mmol) was dissolved in 20 mL of dry THF and cooled under N_2 to −78 °C. The cold TBDMSCl solution was added dropwise to the deprotonated sulfinamide with a cannula. Halfway through the addition, the sulfinamide solution was removed from the cooling bath and allowed to warm to room temperature. The THF was removed under vacuum using a rotary evaporator, and the remaining oil was redissolved in ether. Filtration of the LiCl salts and evaporation of the ether gave a pale yellow oil. This was purified by flash chromatography on silica gel using 3% EtOH/$CHCl_3$ to give 304 mg (69%) of a very pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.262 (s, 3 H), 0.293 (s, 3 H), 0.918 (s, 9 H), 2.15 (m, 1 H), 2.58 (m, 1 H), 2.80 (m, 1 H), 3.01 (m, 1 H), 3.41 (m, 1 H), 3.81 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.41, 19.51, 24.05, 26.76, 51.96, 58.00; HRMS (HRFAB) m/z 220.1194 $(M + 1)^+$, $C_9H_{21}NOSSi$, requires m/z 219.1113.

The high-resolution mass spectral analysis revealed the presence of an M − 16 peak due to the loss of oxygen from the sulfur and indicated that the nitrogen was the silylated heteroatom.

Methyl (1-Oxo-2-isothiazolidinyl)acetate. To a mechanically stirred mixture of pulverized potassium hydroxide pellets (990 mg, 17.6 mmol) and tetrabutylammonium bromide (948 mg, 2.93 mmol) in 35 mL of THF at 0 °C under a stream of N_2 was added 1 (1.54 g, 14.7 mmol) and methyl bromoacetate (1.39 mL, 14.7 mmol) in 20 mL of THF. The ice bath was removed after 30 min, and the mixture was stirred for 8 h. The solution was filtered through a pad of Celite, the solvent was removed under reduced pressure, and the resulting brown oil was flash chromatographed (95:5 chloroform/ethanol) yielding 960 mg (37%) of a yellow oil: ^1H NMR ($CDCl_3$) δ 4.26 (d, J = 18.0 Hz, 1 H, NCHCO), 3.87 (d, J = 18.3 Hz, 1 H, NCHCO), 3.75 (s, 3 H, OCH_3), 3.57 (m, 1 H, NCH), 3.37 (m, 1 H, NCH), 3.15–2.95 (m, 2 H, SCH_2), 2.74 (m, 1 H, CCHC), 2.38 (m, 1 H CCHC); ^{13}C NMR ($CDCl_3$) δ 170.26, 56.20, 52.87, 52.20, 49.36, 23.76; IR (film) 3459, 2953, 2876, 1744, 1211, 1076, 1026 cm^{-1}; HRMS 177.0454 $(M)^+$, $C_6H_{11}NO_3S$ requires 177.0459.

Tetra-*n*-butylammonium Salt of 1-Oxoisothiazolidine-2-sulfonate. To a stirred solution of 1 (280 mg, 2.7 mmol) in 15 mL of freshly distilled pyridine in an oil bath at 80 °C under a stream of N_2 was added pyridine–sulfur trioxide complex (1.27 g, 7.98 mmol). After 30 min, the mixture was poured into 50 mL of 1.0 M KH_2PO_4 and extracted with methylene chloride (6 × 25 mL). The organic layer was extracted with 1.0 M KH_2PO_4 (2 × 15 mL). The resulting two aqueous extracts were combined, and tetrabutylammonium hydrogen sulfate (907 mg, 2.67 mmol) was added followed by extraction with methylene chloride (9 × 30 mL), drying ($MgSO_4$), and concentration to give 430 mg (38%) of a golden oil: ($C_3H_6NO_4S_2^-$ anion) ^1H NMR ($CDCl_3$) δ 3.91 (m, 1 H, NCH), 3.67 (m, 1 H, NCH), 2.90–2.75 (m, 2 H, SCH_2), 2.66 (m, 1 H, CCHC), 2.36 (m, 1 H, CCHC); ^{13}C NMR ($CDCl_3$) δ 55.80, 50.34, 23.99; IR (film) 3475, 2959, 2875, 1472, 1233, 1085, 1038 cm^{-1}; HRMS (NI-FAB) 183.976 $(M)^+$, $C_3H_6NO_4S_2^-$ anion requires 183.978. The potassium salt was obtained by passing a solution of the ammonium salt through Dowex 50W.

2,5-Dideuterioisothiazolidine 1-Oxide. To a stirred solution of 10 mL of THF at −45 °C under a stream of N_2 was added 1 (194 mg, 1.85 mmol) in 3 mL of THF. *sec*-Butyllithium (4.1 mL, 4.6 mmol) was then added to the pale yellow solution with the mixture first becoming cloudy and then turning to a golden yellow color. After 15 min the dianion was quenched with 5 mL of deuterium oxide, extracted with chloroform (3 × 10 mL), dried (Na_2SO_4), and concentrated yielding a golden yellow oil: ^1H NMR ($CDCl_3$) δ 4.78 (br, residual NH), 3.75 (m, 1 H, NCH), 3.34 (m, 1 H, NCH), 2.95, 2.79 (m, 1 H, SCH), 2.48 (m, 1 H, CCHC), 2.16 (m, 1 H, CCHC); ^{13}C NMR ($CDCl_3$) δ 55.47 (t), 47.38, 21.71.

Upon addition of 1.8 mg of $Eu(fod)_3$ to 14.8 mg of protonated 1 the signal at 2.8 ppm was virtually unaffected while the signal centered at 3.0 ppm was shifted downfield to 3.1 ppm. Thus, the downfield signal is the proton syn to the sulfinyl oxygen. The deuterium NMR also showed two signals which integrated to a ratio of syn to anti product equal to 79 to 21.

2-Benzylisothiazolidine 1-Oxide. Compound 1 (118 mg, 1.12 mmol) was dissolved in 15 mL of dry THF and cooled under N_2 to −45 °C. *s*-BuLi (2.02 mL, 2.02 mmol) was added dropwise to the cold solution, and the resulting lemon-yellow solution was allowed to stir at −45 °C for 15 min. (Use of 2 or more equiv of base resulted in formation of large amounts of an impurity).

Benzyl chloride (0.258 mL, 2.25 mmol in 10 mL dry THF) was added dropwise via an addition funnel. The solution was removed from the cooling bath and allowed to warm to room temperature and then quenched with 5 mL of water. The aqueous layer was extracted with 4 × 20 mL of ether and dried over sodium sulfate. The solvent was then decanted and removed under vacuum using a rotary evaporator to yield 127 mg (58%) of a yellow oil. This was purified by gravity chromatography on silica gel with 2% EtOH/$CHCl_3$ eluent. After the first fraction eluted (R_f =

0.90), the solvent system was changed to 10% EtOH/$CHCl_3$ and the product was flash chromatographed (R_f = 0.30 in 2% EtOH/$CHCl_3$). The solvent was removed from both fractions under vacuum. Fraction 1 yielded a yellow oil (impurity): ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (m, 2 H), 5.20 (t, 1 H); GCMS m/z = 216, corresponds to $PhCH_2CH(Cl)Ph$. Fraction 2 yielded 55 mg (25%) of a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (m, 1 H), 2.55 (m, 2 H), 2.97 (m, 1 H), 3.48 (m, 1 H), 3.55 (m, 1 H), 3.83 (m, 1 H), 4.41 (broad, 1 H), 7.20–7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 27.21, 35.97, 47.50, 72.41, 127.4, 129.2; HRMS (HRFAB) gave a molecular ion peak of 195.0718 $(M)^+$, $C_{10}H_{13}NOS$, requires 195.2788. The water layer was evaporated to dryness, and the NMR spectrum revealed that some of the sulfinamide had hydrolyzed to γ-aminopropylsulfinic acid.

Upon addition of the shift reagent, tris[3-(heptafluoropropyl hydroxymethylene)-(−)-camphorato]europium(III), all peaks exhibited upfield shifts. However, one of the peaks centered at δ 2.55 ppm did not shift as far upfield as the other peaks in the spectrum and was assigned as α- to and syn to the S–O. Thus, the isolated product is the anti isomer.

Analysis of the crude oil by GCMS revealed two peaks of m/z 195. The peak areas correspond to 82% anti and 18% syn alkylation. There was no peak corresponding to the dialkylated product.

***syn*-5-(1,1-Diphenyl-1-hydroxymethyl)isothiazolidine 1-Oxide, 3.** Compound 1 (370 mg, 3.53 mmol) was dissolved in 10 mL of dry THF. The solution was placed under N_2 and cooled with stirring to −45 °C. *s*-BuLi (7.06 mL, 7.06 mmol) was added dropwise to the solution. Upon addition of the second equivalent of base, the solution turned lemon-yellow. The solution was allowed to stir for 15 min at −45 °C. At the end of this time, benzophenone (643 mg, 3.53 mmol in 10 mL dry THF) was added dropwise to the solution via an addition funnel. The solution immediately turned blue-green. The cooling bath was removed and the solution warmed slowly to room temperature, upon which it turned yellow. The reaction was quenched with 5 mL of water and transferred to a separatory funnel. An additional 20 mL water was added and the solution was extracted with 3 × 20 mL with ether. The combined ether extractions were washed once with water and once with brine and then dried over sodium sulfate. The dried ether solution was decanted from the sodium sulfate and concentrated under vacuum using a rotary evaporator. The resulting yellow oil was triturated 3× with hexane to remove *s*-BuLi residue (crude yield: 0.30 g; 30%) and then purified by gravity chromatography on silica gel using 2% EtOH/$CHCl_3$ eluent.

The fractions with an R_f value of 0.17 were combined and the solvent removed under vacuum to give 62 mg (6%) of a white solid. This solid, 3, was dissolved in ethyl acetate, and the solvent allowed to slowly evaporate over 1 week to give white needles: mp = 196–197 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (m, 1 H), 2.90 (m, 1 H), 3.53 (m, 1 H), 3.92 (m, 1 H), 4.08 (m, 1 H), 4.40 (s, 1 H), 5.94 (s, 1 H), 7.21–7.73 (m, 10 H); ^{13}C ($CDCl_3$) δ 22.64, 48.30, 71.36, 125.32, 126.28, 127.38, 127.84, 128.82, 129.01.

A GC/MS analysis of the crude oil containing both diastereomers showed two peaks corresponding to m/z 269. Analysis of the peak areas gave a ratio of syn/anti products of 95:5.

Use of *t*-BuLi as the base at −50 to −60 °C gave 13% syn product.

Thermal Stability of *syn*-5-(1,1-Diphenyl-1-hydroxymethyl)isothiazolidine 1-Oxide, 3. Compound 3 (14.4 mg, 0.054 mmol) was added to 10 mL of DMF and refluxed for 5 h. The solution was then cooled, and 5 mL water was added. The aqueous solution was extracted with 3 × 10 mL of ether. The ether was washed with water (2 × 10 mL) to remove any residual DMF and dried over sodium sulfate. The ether was decanted and removed under vacuum using a rotary evaporator. The residual white solid was analyzed by ^1H NMR ($CDCl_3$) and found to be the original starting material. In a separate experiment 3 was refluxed in C_6D_6 (bp = 79.1 °C) for 31.5 h with no change in the spectrum of the compound.

***syn*-5-(1,1-Dimethyl-1-hydroxymethyl)isothiazolidine 1-Oxide.** Compound 1 (187 mg, 1.78 mmol) was dissolved in 10 mL of dry THF and cooled under N_2 to −45 °C. *t*-BuLi (2.36 mL, 2.56 mmol) was added dropwise to the cold sulfinamide solution, and the resulting lemon-yellow solution was stirred for 15 min at −45 °C. Acetone (0.132 mL, 1.78 mmol) dissolved in dry THF was added through an addition funnel to the deprotonated sulfinamide. The white solution was removed from the cooling bath and allowed to warm to room temperature. It was then poured into 3 mL of water and the solvent removed under vacuum. The dry salts were triturated with acetonitrile and the solvent filtered through a scintered glass funnel. The acetonitrile was removed under vacuum to give 201 mg of a yellow oil. This oil was purified by flash chromatography using 7% EtOH/EtOAc as the eluent. Two fractions were obtained: the first (R_f = 0.29) was concentrated to give 50 mg (17%) of a white solid (the syn isomer): mp 64.5–66 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (s, 3 H), 1.62 (s, 3 H), 2.20 (m, 1 H), 2.65–2.85 (m, 2 H), 3.45 (m, 1 H), 3.85 (m, 1 H), 4.55 (broad, 1 H), 4.77 (broad, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.16, 30.01, 31.46, 48.38, 70.73, 72.50; HRMS (HRFAB) gave m/z 163.0667, $C_6H_{13}NO_2S$ requires m/z 163.234.

The second fraction from the column was further purified by flash chromatography using 10% EtOH/$CHCl_3$ as the eluent and showed a mixture of the anti diastereomer (20 mg (7%)) and the starting sulfinamide (97 mg): $R_{f(\text{anti-isomer})}$ = 0.15 (10% EtOH/$CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 3 H), 1.43 (s, 3 H), 1.90 (m, 1 H), 2.37 (m, 1 H), 2.49 (broad, 1 H), 3.21 (t, 1 H), 3.64 (m, 1 H), 3.88 (m, 1 H), 4.40 (broad, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.77, 27.81, 29.85, 48.00, 71.17, 87.24. If the yield is based on the amount of sulfinamide consumed, the syn isomer is formed in 36% yield and the anti isomer in 14% yield.

Thus, the overall conversion to the two diastereomers was 50%. A GC/MS of the crude oil showed two peaks with m/z 163. The ratio of syn/anti product was 72:28.

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Supplementary Material Available: Spectra of obtained compounds (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.