(m, 9, aromatic), 8.77 (s, 1, NH), 9.74 (s, 1, NH); mass spectrum (CI pos) [$M^+ + 1$] 268 (100). Anal. Calcd for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; N, 5.24. Found: C, 76.37; H, 6.39; N, 5.16.

1-Methyl-5*H*-benzo[*h*]-1*H*-pyrano[4,3-*h*]pyrid-2-one (27e). α-Bromoacetic acid (0.23 g, 1.66 mmol) was added to a solution of *N*-methyl-2-(propargyloxy)thiobenzamide (0.28 g, 1.38 mmol) and triethylamine (1.00 g, 9.93 mmol) in benzene (50 mL). The reaction mixture was stirred for 6 h before an additional amount of α-bromoacetic acid (0.23 g, 1.66 mmol) was added and stirring continued overnight. The separated materials were collected by filtration and washed well with benzene. DCC (0.28 g, 1.38 mmol) was added in small portions to the above mother liquor, and the resultant solution was stirred at ambient temperature overnight, filtered, and concentrated under reduced pressure to a brown oil. This material was purified by column chromatography (alumina, eluent 50% ethyl acetate–dichloromethane) and gave a yellow oil, which crystallized from methanol: 0.06 g (21%); mp 100–102 °C; IR (KBr) 1620 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3, NCH_3), 4.80 (s, 2, OCH_2), 6.54–7.68 (m, 6, aromatic); mass spectrum (CI pos) [$M^+ + 1$] 214 (100). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.22; H, 5.07; N, 6.32.

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Synthesis of Isoxazoles and Isothiazoles from α-Oxo Ketene Dithioacetals

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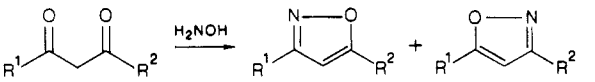
α-Oxo ketene dithioacetals derived from cyclohexanone, cyclopentanone, and 3-pentanone and 3,3-bis(methylthio)propenal afforded oximes **5–8**, respectively, upon treatment with hydroxylamine in ethanol at reflux. Oximes **5**, **7**, and **8** were converted into isoxazoles upon treatment with Amberlyst 15 ion exchange resin and gave isothiazoles by reaction with thionyl chloride and pyridine in methylene chloride. Oxime **6** gave isothiazole **13** with both procedures. Carbon NMR data are reported for the oximes, isoxazoles, and isothiazoles.

The α-oxo ketene dithioacetal functionality has proven to be a versatile three-carbon synthon[1] that is particularly useful in the synthesis of heterocyclic compounds. During the course of our studies on this functionality, we have endeavored to develop regiospecific transformations involving either initial reaction at the ketone carbonyl[2] or at the β-carbon[2b,3] of the enone system. Although a few isoxazoles have been prepared from α-oxo ketene dithioacetals,[4] it seemed curious that the ketene dithioacetals were derived only from aryl cyanomethyl ketones. The literature reports contained no indication of the generality of the synthetic method with α-oxo ketene dithioacetals derived from aliphatic ketones.

We now report that hydroxylamine reacts with α-oxo ketene dithioacetals derived from aliphatic ketones to afford the corresponding oximes, which can be converted into either isoxazoles or isothiazoles depending upon the reaction conditions employed for ring closure. The methodology provides the first synthesis of isoxazoles from α-oxo ketene dithioacetals in a process not involving initial conjugate addition of the hydroxylamine and this aspect greatly extends the synthetic route to a range of ketones other than β-keto nitriles. The method also provides the first reported synthesis of isothiazoles from α-oxo ketene dithioacetals. The reactions are clean and afford the heterocycles in good to excellent yields.

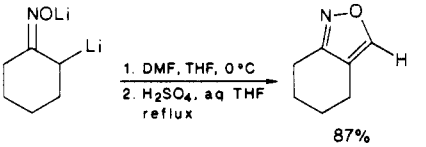
Background

Isoxazoles are most frequently prepared by reaction of 1,3-diketones with hydroxylamine (eq 1).[5] The procedure



(1)

works well for symmetrical 1,3-diketones and can be extended to unsymmetrical 1,3-diketones that have alkyl groups of moderately different steric bulk attached to the carbonyl carbons. If the two alkyl groups are of similar steric bulk, a mixture of regioisomers is obtained.[5,6] More recently, Olofson[7a] has addressed this limitation by formylation of oxime dianions with *N*,*N*-dimethylformamide (eq 2). Subsequent acid-catalyzed cyclization affords the



87%

(2)

desired isoxazole. The procedure can afford 5-aryl-substituted isoxazoles but cannot be employed for the synthesis of 5-alkyl-substituted derivatives since *N*,*N*-dimethylacetamide or higher amide homologues tend to undergo deprotonation under the reaction conditions. The

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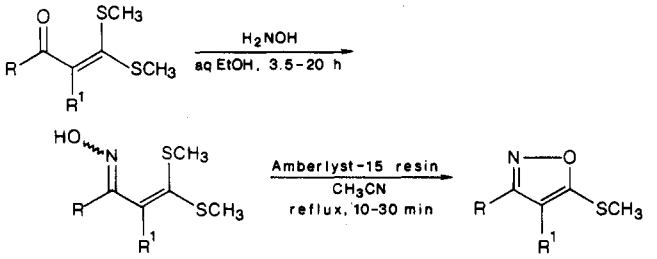
Table I. Synthesis of Isoxazoles from α-Oxo Ketene Dithioacetals

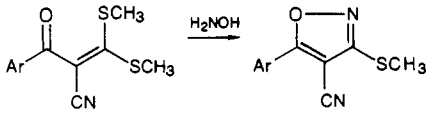


entry	compd	α oxo ketene dithioacetal R	R¹	oxime (% yield)[a]	g resin[b] / mmol oxime	isoxazole (% yield)[a]
1	1	$-(CH_2)_4-$		5 (98)	1.0	9 (40)
2					0.50	(50)
3					0.25	(80–83)
4	2	$-(CH_2)_3-$		6 (99)		c
5	3	Et	Me	7 (80)	1.0	10 (70)
6					0.25	(88–91)
7	4	H	H	8 (86)	0.25	11 (75)

[a] Yields are based upon crude products homogeneous by TLC. NMR spectra of the crude products show no identifiable impurities. [b] Amberlyst-15 ion exchange resin was used. [c] No isoxazole formed.

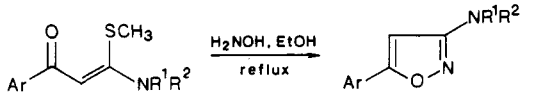
5-alkylisoxazoles can be prepared in low to moderate yields by a modification of the method that utilizes carbocations obtained by the O-alkylation of amides.[7b]

α-Oxo ketene dithioacetals derived from aryl cyanomethyl ketones have been converted into isoxazoles by reaction with hydroxylamine in a one-pot procedure (eq 3).[4] The regiochemistry suggests that the reaction pro-



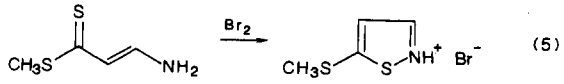
(3)

ceeds by initial conjugate addition of the hydroxylamine followed by subsequent cyclization. Consistent with this view, a recent report[8] describes the formation of an oxime from an α-oxo ketene dithioacetal derived from an aryl ketone upon reaction with hydroxylamine. The isoxazole was not observed and conversion of the oxime to an isoxazole was not examined. Similarly, α-oxo ketene *S,N*-acetals[9] are reported to give isoxazoles upon treatment with hydroxylamine and the regiochemistry is again suggestive of initial conjugate addition of the amine (eq 4). Presumably, the vinylogous amide functionality suppresses oxime formation.



(4)

The first synthesis of a mononuclear isothiazole was reported in 1956.[10] Perhaps the most general routes to this ring system involve oxidation of compounds that can exist as imino–enethiol tautomers[11] (eq 5[11b]) or the oxi-



(5)

dative cyclization of β-mercaptoacrylonitriles.[12] Synthetic routes from olefins and acetylenes are less versatile in terms of substitution patterns.

Results and Discussion

The α-oxo ketene dithioacetals were readily prepared by established procedures.[13] The formylketene dithioacetal was prepared from ethyl 3,3-bis(methylthio)-2-propenoate via a reduction–oxidation sequence as previously reported[2b] with one minor change. Activated MnO_2 oxidation of the allylic alcohol to the aldehyde **4** proved faster and gave superior yields in acetonitrile than in petroleum ether as originally described.

Treatment of the α-oxo ketene dithioacetals with hydroxylamine in aqueous ethanol heated to reflux gave the oximes in good yields (Table I). The cyclic ketones **1** and **2** and aldehyde **4** gave oximes stereoselectivity while the acyclic ketone **3** gave a mixture of syn and anti stereoisomers. The syn or anti geometry of oximes is readily determined from ^{13}C NMR spectroscopy since the α-carbons syn to the oxime hydroxyl group are shifted upfield relative to the anti α′-carbons as a result of the γ-effect.[14] The syn α-carbons (δ 25.7, 27.1, 21.0) of the oximes of cyclohexanone, cyclopentanone, and 3-pentanone, respectively, are upfield from the corresponding anti α-carbons (δ 31.9, 30.6, 27.1). The allylic carbon C_γ or C_δ chemical shift remains fairly constant for a series of α-oxo ketene dithioacetals and vinylogous thiol esters[3] and serves as a reference point in assignment of chemical shifts. The syn/anti isomers of oxime **7** are readily identified from the mixture while the ^{13}C spectrum of oxime **5** (C_α δ 24.5) is consistent with the anti isomer and that of **6** (C_α δ 35.7) with the syn isomer (syn to the double bond). The geometry of **8** is assumed to be anti to the double bond. The geometrical assignments for **5**, **6**, and **8** in the absence of mixtures must be viewed as tentative.

The cyclization of oxime **7** to isoxazole **10** was initially effected with both $HgCl_2/CH_2Cl_2$ and Amberlyst 15 acidic

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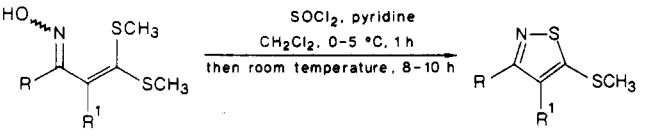
ionic exchange resin. The Amberlyst catalyst provided material displaying a cleaner TLC chromatogram and NMR spectrum and the use of $HgCl_2$ was not examined further. Cyclization with the Amberlyst resin was first tried in CH_2Cl_2 and oximes **7**, **5**, and **6** required 0.5, 1, and 1.5 h, respectively, for disappearance of starting material. The reactions proved faster in acetonitrile, requiring only 10, 20, and 30 min, respectively. The material balance recovered from the reaction mixture was sensitive to the amount of Amberlyst resin used. On a 1.0-mmol scale the yields of product increased monotonically in all cases as the Amberlyst 15 resin was decreased from 1.0 to 0.5 to 0.25 g (Table I, entries 1–3 and 5–6). These yields are based upon the weight of crude recovered product and hence reflect material loss with increasing weight of Amberlyst resin used. Whether this loss is due to decomposition or product absorption on the ion exchange resin is not known. Isoxazoles **9–11** displayed characteristic spectral properties consistent with the proposed structures. Each compound gave a parent molecular ion in the mass spectrum and a ^{13}C spectrum showing absorptions characteristic of an isoxazole.

The formation of isothiazoles from the corresponding oximes was unanticipated and was initially observed as an anomalous reaction. The product obtained from the cyclopentanone oxime (**6**) upon treatment with Amberlyst 15 resin exhibits ^1H and ^{13}C NMR spectra that appeared consistent with the expected isoxazole. The low resolution mass spectrum, however, displays a prominent peak at m/e 171 corresponding to 16 mass units higher than that expected for the isoxazole and suggested the possible incorporation of an oxygen atom in the product. Possible *N*-oxides or nitroso or peroxide compounds were dismissed upon consideration of the full spectra data. Closer examination of the ^{13}C spectrum revealed disparate absorptions in the sp^2 region from those observed for isoxazoles **9–11**. In particular, the C=N (δ 179.8) absorption and the highest upfield sp^2 carbon (δ 140.1) were shifted significantly further downfield than that expected for an isoxazole (δ 159.3–167.0 and 100.7–113.6, respectively) while the middle sp^2 absorption was in the range of values observed for isoxazoles **9–11**. Comparisons with model heterocyclic systems[15] suggested isothiazole **13** and crude additivity analysis provided calculated chemical shifts surprisingly close to those observed experimentally. The conclusion arrived at by analysis of the ^{13}C NMR data was confirmed by C, H, and S combustion analyses. The yield of isothiazole **13** also decreased with an increase in the amount of Amberlyst resin used (Table II).

The formation of the isothiazole from the five-membered oxime presumably occurred as a result of the strain in a [3.3.0] fused isoxazole system[7] and the longer N–S and S–C bonds favoring formation of the isothiazole. This mode of ring closure suggested that reaction conditions could be chosen to favor formation of the isothiazoles instead of isoxazoles. The methodology required conversion of the oxime hydroxyl group into a good leaving group that could be displaced by the sulfur substituent. To this end oxime **6** was treated with thionyl chloride in pyridine and isothiazole **13** was obtained in 85% yield (Table II). The procedure could be extended to the cyclohexanone system but afforded four major products when employed with the 3-pentanone derivative. Subsequent experimentation demonstrated that good yields could be obtained in the acyclic systems when the oximes in methylene chloride were slowly added dropwise to a solution of thionyl chloride in pyridine.

Table II. Synthesis of Isothiazoles from α-Oxo Ketene Dithioacetals



compd	oxime R	oxime R^1	isothiazole	% yield[a,b]
5	$-(CH_2)_4-$		**12**	84
6	$-(CH_2)_3-$		**13**	85
				73[c]
				50[d]
				25[e]
7	Et	Me	**14**	80
8	H	H	**15**	60

[a] Yields are based upon crude products homogeneous by TLC. NMR spectra of the crude products show no identifiable impurities. [b] Cyclization was effected with thionyl chloride/pyridine in methylene chloride unless otherwise noted. [c] Cyclization was effected with 0.25 g of Amberlyst resin/mmol oxime. [d] Cyclization was effected with 0.50 g of resin/mmol oxime. [e] Cyclization was effected with 1.0 g of resin/mmol oxime.

In summary, these procedures provide a convenient high yield route to 5-(alkylthio)isoxazoles or -isothiazoles. The latter compounds have previously been prepared by thiolate substitution reactions on the heterocyclic ring systems.[11,16] The 5-alkylthio substituent can be oxidized to the sulfoxide or sulfone[16,17] and could provide opportunities for a wider range of substitution reactions. The benzenesulfonyl group in 3-(phenylsulfonyl)isoxazolines undergoes substitution by lithium alkoxides, cyanide, and alkyl- and aryllithium reagents.[18] Utilization of nickel-promoted Grignard coupling reactions on the alkylthio derivatives or cuprate additions to the sulfone analogues could potentially afford a general strategy to 5-alkyl-substituted derivatives. Finally, the recently reported[8] preparation of an oxime from an α-oxo ketene dithioacetal derived from an aryl ketone suggests that the present method can be extended to the synthesis of 3-aryl-5-(methylthio)isoxazoles and -isothiazoles.

Experimental Section

NMR spectra were recorded as $CDCl_3$ solutions on either a JEOL-FX 90Q (unless specified) or IBM-NR-200 AF instrument. Proton NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. The carbon NMR chemical shifts are in parts per million downfield from TMS and referenced with respect to internal $CDCl_3$ (δ 77.0 for center line). The carbon NMR absorptions are listed in the following order: C=N, [C_α, C_β, C_γ, C_δ to the C=N for sp^3 carbons], αC=N (sp^2 carbon adjacent to the C=N), βC=N (sp^2 carbon adjacent to the C=N), and SCH_3. Carbon NMR assignments that may be reversed are indicated with an asterisk. Infrared spectra were recorded on a Nicolet 5DX FT IR spectrometer as $CHCl_3$ solutions unless otherwise noted. Mass spectral measurements were performed on a Hewlett-Packard 5840 gas chromatography/mass spectrometer at 70 eV and mass data are tabulated as m/e and intensity expressed as a percent of the base peak. Both electron impact (EI) and chemical ionization (CI) measurements were obtained. Melting points were determined on a Haake Buchler melting point ap-

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paratus. Elemental analyses were determined by Atlanta Microlab Inc., Atlanta, GA.

Tetrahydrofuran was distilled from sodium–benzophenone ketyl at atmospheric pressure immediately prior to use. Spectrograde acetonitrile and dichloromethane were distilled and stored over 4-Å molecular sieves. Amberlyst 15 ion exchange resin suitable for nonaqueous catalysis was purchased from Aldrich.

General Procedure A: Synthesis of Oximes. An aqueous ethanol hydroxylamine solution was generated from 25 mmol of hydroxylamine hydrochloride (1.73 g), 25 mmol of KOH (1.4 g) in 5 mL of water, and 25 mL of 95% ethanol. The clear solution was neutral to litmus paper. To this hydroxylamine solution was added 5.0 mmol of the appropriate α-oxo ketene dithioacetal. The solution was heated to reflux and stirred for 3.5 to 20 h depending upon the particular ketone. The reaction was monitored by TLC (R_f 0.1–0.2, petroleum ether/10% ether, v/v) until all starting material was consumed. The solution was cooled to room temperature, ethanol was removed in vacuo, and the concentrated reaction mixture was then poured into a separatory funnel containing 100 mL of ice-cold water and 100 mL of methylene chloride. The organic layer was separated and dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo gave 80–95% yields of oximes as either a single compound or as a mixture of anti/syn geometrical isomers. These isomers were not separated.

General Procedure B: Synthesis of Isoxazoles. Strongly acidic Amberlyst 15 ion exchange resin (1.0 g) was added to 4.0 mmol of the appopriate oxime in 20 mL of dry spectral grade acetonitrile and the mixture was heated to reflux and stirred for 15–20 min. The progress of the reaction was monitored by TLC (R_f 0.26–0.40, petroleum ether/15% ether, v/v)) and worked up when starting material had completely disappeared. The Amberlyst resin was filtered off and washed with anhydrous ether. Removal of the solvent in vacuo afforded crude isoxazoles as yellow oils in 75–90% yields. The crude products were relatively clean by both TLC and NMR (>90–95%) and analytically pure samples were obtained by column chromatography.

General Procedure C: Synthesis of Isothiazoles. Dry methylene chloride (25 mL) was cooled to 0–5 °C with an ice/water bath under nitrogen. Thionyl chloride (5 mmol) was added dropwise and the solution was stirred for 10 min. Pyridine (5 mmol) was added to the thionyl chloride solution, which was stirred for an additional 15 min at 0 °C. The appropriate oxime (4 mmol) in dry methylene chloride was added dropwise to the solution over a period of 1 min (cyclic oximes) to 25 min (acyclic oximes). The solution was stirred for 1 h at 0 °C, warmed to room temperature slowly, and then stirred for another 8–10 h. When TLC analysis showed complete disappearance of oxime, the reaction mixture was diluted with 60 mL of diethyl ether and washed with 10% HCl (3 × 20 mL), saturated sodium bicarbonate (2 × 20 mL), distilled water, and brine. The organic phase was dried over anhydrous $MgSO_4$. Filtration and removal of solvent in vacuo afforded crude isothiazoles in high yields (75–90%). The crude products were relatively clean by TLC and NMR (>90–95%) and analytically pure samples were obtained by column chromatography.

2-[Bis(methylthio)methylidene]cyclohexanone Oxime (5). Procedure A was followed and the reaction mixture was heated at reflux for 4 h. Workup and concentration in vacuo afforded a nearly quantitative yield (93–98%, ≥95% by NMR) of crude oxime: IR (neat) 3599 (m), 3304 (s, br), 2927 (s), 2860 (m), 1442 (s), 1417 (s), 1286 (m), 1147 (m), 966 (s), 906 (m), 884 (m), 843 (m) cm^{-1}; ^1H NMR δ 1.43–1.88 (m, 4 H), 2.28 (s, 3 H), 2.31 (s, 3 H), 2.45–2.95 (m, 4 H), 8.86 (br s, 1 H); ^{13}C NMR δ 158.4, 24.4, 25.8, 25.8, 34.0, 132.7, 139.3, 17.6, 17.7; mass spectrum, *m/e* (intensity) CI 218.1 (72, $M^+ + 1$), 200.1 (100, $M^+ - HOH$), 170.1 (48, $M^+ - HSCH_3$).

2-[Bis(methylthio)methylidene]cyclopentanone Oxime (6). Ketone **2** (742 mg, 3.9 mmol) was reacted with 16 mmol of hydroxylamine as described in procedure A. The solution was heated to reflux for 4 h to afford a nearly quantitative yield (98%, ≥95% by NMR) of crude oxime. A sample was recrystallized from methanol: mp 139–140.7 °C; IR 3577 (s), 3287 (vs, br), 3004 (s), 2918 (s), 1540 (s), 1425 (s), 1237 (s), 966 (m), 933 (vs), 884 (s) cm^{-1}; ^1H NMR δ 1.77 (p, J = 7.5 Hz, 2 H), 2.35 (s, 3 H), 2.41 (s, 3 H), 2.50–2.95 (m, 4 H), 10.14 (br s, 1 H); ^{13}C NMR (50.3 MHz) δ 161.4, 35.7, 21.2, 29.6, 132.0, 139.7, 17.5 (2 C); mass spectrum, *m/e* (intensity) CI 204.1 (100, $M^+ + 1$), 186.1 (78, $M^+ - HOH$, 156.1 (60, $M^+ - HSCH_3$); EI 203.1 (70, M^+), 186.1 (100, $M^+ - OH$), 171.1 (45, $M^+ - OH - CH_3$).

1,1-Bis(methylthio)-2-methyl-3-pentanone Oxime (7). α-Oxo ketene dithioacetal **3** (760 mg, 4 mmol) was reacted with 16 mmol of hydroxylamine according to procedure A by heating at reflux for 18 h. Purification by medium pressure liquid chromatography (R_f 0.15, petroleum ether/30% ether) gave a 73:27 mixture of anti (to double bond)/syn isomers in 75% yield: IR 3580 (s), 3305 (vs, br), 2978 (s), 2925 (s), 1694 (m), 1462 (s), 1435 (s), 1369 (m), 972 (s), 926 (s), 899 (s) cm^{-1}; ^1H NMR (200 MHz) anti isomer δ 1.05 (t, J = 8.0 Hz, 3 H), 2.11 (s, 3 H), 2.22 (s, 3 H), 2.30 (s, 3 H), 2.58 (q, J = 8.0 Hz, 2 H), 9.30 (br s, 1 H); ^{13}C NMR (50.3 MHz) anti isomer δ 163.0, 21.6*, 9.7, 21.0* (CH_3C=C), 133.6, 139.3, 16.5, 17.3; ^1H NMR (200 MHz) syn isomer δ 1.12 (t, J = 8.0 Hz, 3 H), 2.01 (s, 3 H), 2.22 (s, 3 H), 2.31 (s, 3 H), 2.41 (q, J = 8.0 Hz, 2 H), 9.30 (br s, 1 H); ^{13}C NMR (50.3 MHz) syn isomer δ 161.5, 26.6, 10.6, 19.4 (CH_3C=C), 130.3, 139.5, 16.3, 17.1; mass spectrum, *m/e* (intensity) EI 205.1 (33, M^+), 188.1 (100, $M^+ - OH$).

3,3-Bis(methylthio)propenal Oxime (8). 3,3-Bis(methylthio)propenal (408 mg, 2.5 mmol) was reacted with 10 mmol of hydroxylamine according to procedure A and the solution was heated at reflux for 9 h to afford (86% yield) oxime **8** (R_f 0.10, petroleum ether/15% ether). These reaction conditions may be more vigorous than is necessary. A significant amount of unidentified byproduct was formed: IR (neat) 3259 (vs, br), 2921 (s), 2860 (m), 1547 (m), 1418 (m), 1154 (m), 1073 (w, br), 897 (s, br); ^1H NMR (200 MHz) δ 2.39 (s, 3 H), 2.43 (s, 3 H), 6.24 (d, J = 4.5 Hz, 1 H), 6.69 (v br s, 1 H), 9.06 (v br s, 1 H); mass spectrum, *m/e* (intensity) CI 164.2 (100, $M^+ + 1$), 146.2 (28, $M^+ - HOH$).

3-(Methylthio)-4,5,6,7-tetrahydro-2,1-benzisoxazole (9). General procedure B was followed and the reaction mixture was heated to reflux and stirred for 30 min under nitrogen. The isoxazole was obtained in 81% (≥95% by NMR) yield. Purification by silica gel column chromatography (R_f 0.28, petroleum ether/15% ether) gave an analytically pure sample of **9**: IR 3001 (s), 2941 (s), 2862 (s), 1684 (m), 1625 (m), 1599 (s), 1447 (vs), 1414 (s), 1321 (m), 1165 (m), 1010 (m), 977 (m), 951 (m), 845 (m) cm^{-1}; ^1H NMR δ 1.75 (p, J = 3 Hz, 4 H), 2.16–2.93 (m, 4 H), 2.52 (s, 3 H); ^{13}C NMR (50.3 MHz) δ 159.3, 22.1*, 21.5*, 18.9, 21.9*, 113.2, 161.2, 14.9; mass spectrum, *m/e* (intensity) CI 170.1 (100, $M^+ + 1$); EI 169.1 (76, M^+), 122.1 (26, $M^+ - SCH_3$), 80.1 (100).

Anal. Calcd for $C_8H_{11}ONS$: C, 56.77; H, 6.55. Found: C, 56.81; H, 6.56.

3-Ethyl-4-methyl-5-(methylthio)isoxazole (10). General procedure B was employed and the solution was heated to reflux for 10 min to afford **10** in 91% yield (≥95% by NMR). Purification by silica gel column chromatography (R_f 0.40, petroleum ether/15% ether, v/v) gave an analytically pure sample: IR (neat) 2976 (s), 2927 (s), 2877 (w), 1721 (m), 1680 (w), 1598 (m), 1450 (s), 1409 (s), 1310 (m), 1048 (m), 974 (m, br), 900 (w, br), 794 (m, br); ^1H NMR δ 1.27 (t, J = 7.2 Hz, 3 H), 1.93 (s, 3 H), 2.51 (s, 3 H), 2.61 (q, J = 7.2 Hz, 2 H); ^{13}C NMR δ 165.1, 18.9, 7.2, 11.7 (CH_3C=C), 112.4, 161.3, 15.7; mass spectrum, *m/e* (intensity) CI 158.1 (100, $M^+ + 1$), 110 (14).

Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05. Found: C, 53.57; H, 7.07.

5-(Methylthio)isoxazole (11).[19] General procedure B was used and the solution was heated to reflux for 20 min. Purification by filtering through a silica gel column (R_f 0.26, petroleum ether/15% ether, v/v) afforded isoxazole **11** in 75% yield (removal of solvent in vacuo should be carried out at ice-bath temperatures because of product volatility): IR 2964 (s), 2930 (m), 1439 (vs), 1257 (s), 1089 (s), 1022 (s), 801 (vs) cm^{-1}; ^1H NMR δ 2.50 (s, 3 H), 6.09 (d, J = 1.80 Hz, 1 H), 8.22 (d, J = 1.80 Hz, 1 H); ^{13}C NMR δ 167.0, 100.7, 150.4, 15.0.

3-(Methylthio)-4,5,6,7-tetrahydro-2,1-benzisothiazole (12). General procedure C was employed and the reaction mixture was heated at reflux for 7 h. Workup (R_f 0.27, petroleum ether/10% ether, v/v) gave crude **12** in 84% yield: IR 2997 (m), 2950 (s), 2864 (w), 1440 (s), 1375 (s), 1315 (m), 1262 (s), 1103 (s), 1010 (s), 871 (w), 805 (vs); ^1H NMR δ 1.65–2.01 (m, 4 H), 2.48 (s, 3 H),

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2.30–2.60 (m, 2 H), 2.64–2.94 (m, 2 H); ^{13}C NMR δ 167.9, 29.8, 23.0*, 22.7*, 24.1, 131.2, 156.5, 18.0; mass spectrum, *m/e* (intensity) EI 185.1 (100, M^+), 170.1 (50, $M^+ - CH_3$), 138.1 (60, $M^+ - SCH_3$).

Anal. Calcd for $C_8H_{11}NS_2$: C, 51.85; H, 5.98. Found: C, 51.76; H, 6.02.

5,6-Dihydro-3-(methylthio)-4*H*-cyclopent[*c*]isothiazole (13). Either general procedure B (heated to reflux for 0.75 h) or C (heated to reflux for 8 h) was used to obtained this isothiazole. Workup gave crude **13** in 75% (procedure D) and 85% (procedure E) yield. Purification by silica gel column chromatography (R_f 0.23, petroleum ether/10% ether, v/v) gave an analytically pure sample of **13**: IR 2999 (s), 2996 (s), 2926 (m), 2853 (w), 1427 (s), 1381 (s), 954 (m), 757 (s) cm^{-1}; ^1H NMR δ 2.48 (s, 3 H), 2.40–2.63 (m, 6 H); ^{13}C NMR δ 179.8, 29.3, 24.2, 28.7, 140.1, 151.7, 18.3; mass spectrum, *m/e* (intensity) CI 172.2 (100, $M^+ + 1$); EI 171.1 (100, M^+), 124.1 (60, $M^+ - SCH_3$).

Anal. Calcd for $C_7H_9NS_2$: C, 49.09; H, 5.30; S, 37.45. Found: C, 49.09; H, 5.32; S, 37.53.

3-Ethyl-4-methyl-5-(methylthio)isothiazole (14). Oxime **7** (688 mg, 3.34 mmol) dissolved in dry methylene chloride (3.5 mL) was added dropwise over a period of 25 min to a solution of $SOCl_2$ (0.3 mL) and pyridine (0.6 mL) at 0 °C under nitrogen and then the solution was stirred at room temperature for 9 h. Workup (R_f 0.16, petroleum ether/10% ether, v/v) gave crude **14** in 80% (≥95% by NMR) yield: IR (neat) 2976 (s), 2927 (m), 2877 (w), 1680 (m), 1516 (m), 1261 (vs), 1097 (s), 1015 (s), 966 (s), 810 (vs) cm^{-1}, ^1H NMR (200 MHz) δ 2.35 (s, 3 H), 2.44 (s, 3 H), 1.35 (t, J = 7.5 Hz, 3 H), 2.91 (q, J = 7.5 Hz, 2 H); ^{13}C NMR (50.3 MHz) δ 173.6, 27.2, 13.9, 15.3 (CH_3C=C), 123.9, 155.0, 21.6; mass spectrum, *m/e* (intensity) CI 174.2 (100, $M^+ + 1$); EI 173.1 (100, M^+), 158.1 (67, $M^+ - CH_3$).

Anal. Calcd for $C_7H_{11}NS_2$: C, 48.51; H, 6.40. Found: C, 48.60; H, 6.47.

5-(Methylthio)isothiazole (15). General procedure C was employed and afforded isothiazole **15** in 60% yield (≥95% pure by NMR, R_f 0.28, petroleum ether/10% ether, v/v): IR 2997 (s), 2926 (s), 1490 (m), 1443 (m), 1396 (vs), 1336 (m), 1286 (m), 970 (m), 907 (m), 828 (s), 804 (s), 725 (m) cm^{-1}; ^1H NMR δ 2.62 (s, 3 H), 7.02 (s, 1 H), 8.34 (s, 1 H); ^{13}C NMR (50.3 MHz) δ 164.0, 121.2, 157.6, 18.8; mass spectrum *m/e* (intensity) EI 131.1 (100, M^+).

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Registry No. **1**, 17649-90-0; **2**, 17649-89-7; **3**, 51507-08-5; **4**, 78263-38-4; **5**, 118631-08-6; **6**, 118631-09-7; **7**, 118631-10-0; **8**, 118631-11-1; **9**, 118631-12-2; **10**, 118631-13-3; **11**, 68289-72-5; **12**, 118631-14-4; **13**, 118631-15-5; **14**, 118631-16-6; **15**, 45438-78-6.

Formation of Thiocarbonyl Compounds in the Reaction of Ebselen Oxide with Thiols

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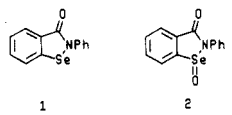
Reaction of α-toluenethiol with Ebselen oxide, **2**, affords dibenzyl disulfide and seleno sulfide **5**, R = $PhCH_2$. In the course of this reaction, thiobenzaldehyde is formed and can be trapped with cyclopentadiene in 90% yield. Reaction of 2-propene-1-thiol with **2** afforded thioacrolein dimer in 69% yield and seleno sulfide **5**, R = CH_2-CH=CH_2. Trapping, stereochemical, and isotopic exchange studies were used to determine if in the reaction of **2** with 1-heptanethiol, cyclohexanethiol, and *N*-acetyl-D,L-cysteine thiocarbonyl compounds heptanethial, cyclohexanethione, and 2-acetamino-3-thioxopropanoic acid (α-thioformyl-*N*-acetylglycine), respectively, are also formed. These studies showed that free thiocarbonyl compounds are not formed in these reactions.

The selenium heterocycle 2-phenyl-1,2-benziso-selenazol-3(2*H*)-one, **1** (Ebselen, PZ 51),[1] is a remarkably good catalyst for the oxidation of glutathione (GSH) to GSSG by hydroperoxides.[2] Interest in this catalytic activity has been stimulated because of its possible relevance to the mechanism of action of the selenium-containing enzyme glutathione peroxidase.[3] Ebselen is readily oxidized to the corresponding oxide **2** by hydrogen peroxide.[4] The rapid reactions of Ebselen oxide, **2**, with thiols have been reported[4,5] to give Ebselen and the corresponding disulfides by the suggested pathway shown in eq 1. Ebselen, **1**, further reacts with thiols to give the corresponding seleno sulfides **5**. In a related reaction of α-toluenethiol



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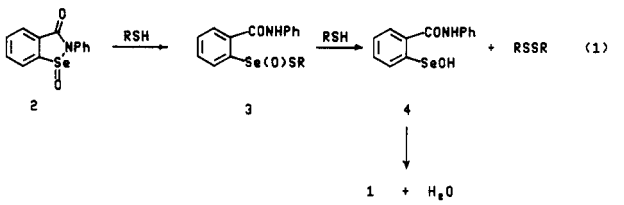

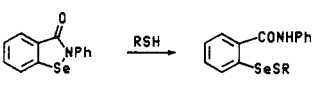

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