combined, dried ($CaSO_4$), and concentrated under vacuum to 0.80 g of white solid, mp 150–155 °C dec, which was shown by IR and NMR analysis to be **11**. Recrystallization of the solid from benzene gave 0.50 g of white solid, mp 154–155 °C (lit.[9] mp 144–148 °C dec).

5-Chloro-3-methyl-4-isothiazolecarboxylic Acid (16). Solutions of 1.0 g (0.00486 mol) of 93% pure ethyl 5-chloro-3-methyl-4-isothiazolecarboxylate (containing 7% of ethyl 3-methyl-4-isothiazolecarboxylate) in 50 mL of THF and 1.1 g (0.0225 mol) of NaOH in 50 mL of water were stirred together for 24 h. The solution was acidified strongly with dilute HCl and extracted with three 75-mL portions of ether. The ether layers were combined, dried ($CaSO_4$), and concentrated under vacuum to 0.85 g of white solid, mp 199–205 °C, that consisted of 94% of **16** and 6% of 3-methyl-4-isothiazolecarboxylic acid (NMR analysis in basic D_2O). Crystallization of the solid from 1,2-dichloroethane gave 0.60 g of solid, mp 205–206.5 °C (lit.[4] mp 205–207 °C).

Ethyl 3-Methyl-4-isothiazolecarboxylate (10). Treatment of ethyl β-aminocrotonate with triethylamine and thiophosgene according to a literature procedure,[7a] followed by redistillation of the product thus obtained, gave pure **10**, bp 71–72 °C (1.5 Torr) [lit.[7c] bp 102–103 °C (8 Torr)].

Registry No.—**2**, 2757-23-5; **12**, 63089-25-8; **13**, 63089-26-9; **16**, 22131-56-2; phenyl chloroformate, 1885-14-9; potassium thiocyanate, 333-20-0; 3-methyl-4-isothiazolecarboxylic acid, 15903-66-9.

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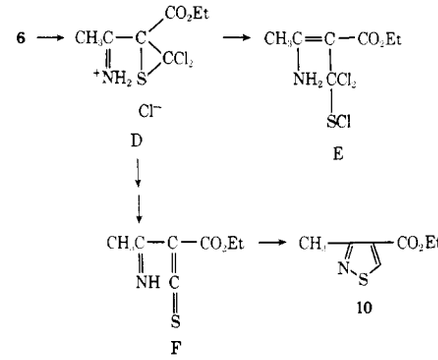
(10) Several mechanistic possibilities can be postulated starting, for example, with D and E, but the mechanisms are so highly speculative that we prefer not to dignify them with enumeration. Along these speculative lines, dechlorination and dehydrochlorination of D or an intermediate (other than E) formed from D could lead to F and thus **10**. Species F is probably an intermediate in the reaction[7] of thiophosgene with **1** to produce **10**.



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(14) Dr. Waite has acknowledged in a most cordial fashion that their structure assignment[1] for **3** rested strongly on analogies[1] and that, in light of the present work, the material that they isolated must have been **9**, the product that we obtained [J. A. Waite, private communication].

Reductive Sulfenylation. A General Method for the α-Sulfenylation of Cyclic Ketones

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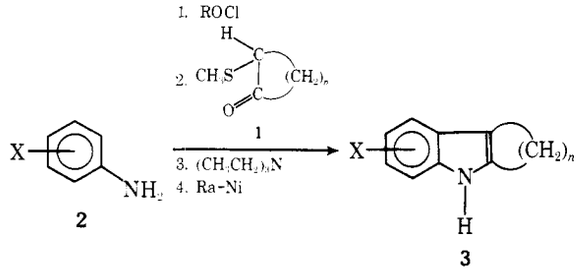
Received March 15, 1977

A general method has been developed for the reductive sulfenylation of cyclic α,β-unsaturated ketones. Sulfenylation with dimethyl disulfide has been shown to occur by preferential pseudoaxial attack on the intermediate enolate anions. The regiospecificity and preferential pseudoaxial attack were established by a combination of NMR and circular dichroism studies.

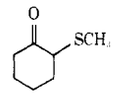
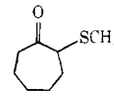
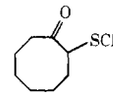
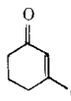
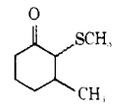
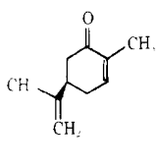
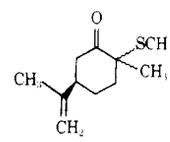
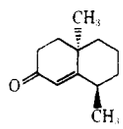
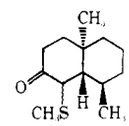
As part of our general program of exploring the scope and utility of our versatile indole synthesis,[2] and in anticipation of our utilization of this process in the preparation of polycyclic natural product intermediates, we found ourselves in need of highly specific methods for the addition of an α-methylthio function to a variety of cyclic ketones. The availability of cyclic ketones of general formula **1** would permit the conversion of anilines of general formula **2** into indoles of general formula **3** according to the procedure outlined. Thus,



we had a particular interest in regiospecifically methylsulfenylating cyclic ketones. While a variety of methods have appeared in the literature for the sulfenylation of ketones,[2–5] most of these methods can be traced back to the initial functionalization of a mixture of the thermodynamically most stable enolate anion[2,3] or enol form of the ketonic precursor[4,5] and the thermodynamically less stable enolate or enol form. This provides little control over regiospecificity. In view of the regiospecificity attained in the reductive alkylation of α,β-unsaturated ketones,[6] we investigated the sulfenylation of lithium enolates generated from the lithium in liquid ammonia reduction of α,β-unsaturated ketones. We now wish to report that the reductive sulfenylation of α,β-unsaturated ketones is a useful method for the regiospecific introduction of the thiomethoxyl moiety.

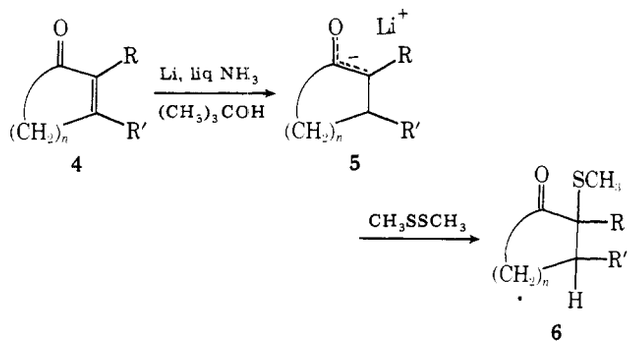
In a general procedure, a solution of 1 equiv of α,β-unsaturated ketone and 1 equiv of *tert*-butyl alcohol in ether was added to a solution of 2.2 equiv of lithium in liquid ammonia. After 1 h, 1 equiv of dimethyl disulfide was added and allowed to react, and the product was isolated. In this way, **4** could be

Table I. Yields Obtained in the Reductive Methylsulfenylation of Cyclic α,β-Unsaturated Ketones

Starting ketone	Registry no.	Product	Registry no.	% yield
	930-68-7		52190-35-9	43
	1121-66-0		52190-36-0	62
	1728-25-2		52190-37-1	38
	1193-18-6		Cis, 63017-47-0 Trans, 63017-48-1	48[a]
	6485-40-1		Cis, 63017-49-2 Trans, 63017-50-5	47[b]
	17990-00-0		Epimer I, 63017-51-6 Epimer II, 63087-56-9	65[c]

[a] A 55:45 mixture of epimers was obtained. [b] An 83:17 mixture of epimers was obtained. [c] A mixture of epimers at C-1 was obtained.

cleanly converted into **5**, which on sulfenylation gave **6**. As has been well established in the literature,[6,7] exchange reactions of **5** are relatively slow. Thus, excellent regiospecificity was obtained in the sulfenylation to give **6**. Table I lists the ketones studied and the yields obtained by this procedure. In general, the yields were sufficiently high to make this a synthetically useful procedure.

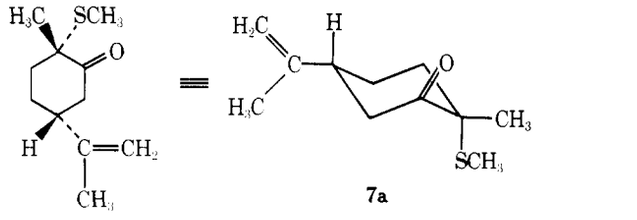


4 5 6

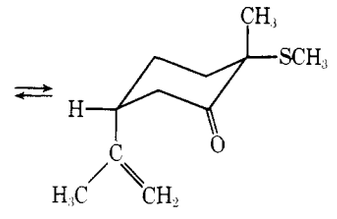
Some aspects of the general procedure merit comment. While good results were obtained with most cyclic ketones, cyclopentenone failed to yield monosulfenylated material under our conditions. Instead, a very low yield of disulfenylated material (4%) was obtained in addition to oligomeric material. In terms of the stereochemistry of the methylsulfenylation reaction, a mixture of epimers was obtained in all cases where mixed stereochemistry was possible.[8]

An intriguing aspect of these sulfenylations was associated with the direction from which the dimethyl disulfide approaches the enolate anion. In principle, the choices are either pseudoaxial or pseudoequitorial attack. Comparison with alkylation of enolate anions indicates that the balance between these two modes of reaction may be delicate, with some slight preference for the axial approach.[9] On the basis of NMR analysis, it has been suggested that sulfenylation also gives preferential pseudoaxial attack.[3d] Our findings would tend to substantiate this claim. In the case of the reductive sulfenylation of 3-methyl-2-cyclohexenone, NMR evidence suggested that the cis/trans ratio was 55:45.[10] More convincing evidence was available from the reductive sulfenylation of *l*-carvone (*p*-mentha-6,8-dien-2-one). Separation of the 83:17 mixture gave pure samples of **7** and **8**, respectively. Since the α-methylthio group interacts strongly with the carbonyl, a very enhanced carbonyl absorption occurred in the UV between 300 and 315 nm (ε 250–300).[12] More importantly, the fact that **7** and **8** were optically active permitted the analysis of their circular dichroism spectra.[13] The major isomer, which was tentatively assigned structure **7**, was expected to have a strong positive Cotton effect on the basis of the octant rule.[14] It was observed that the major isomer showed a $[\theta]$ of +30 100 at 312 nm. This is consistent with the presence of an axial α-methylthio group in a positive quadrant. These results imply that the major conformer present in solution is **7a** and that there is relatively little contribution from conformer **7b**.

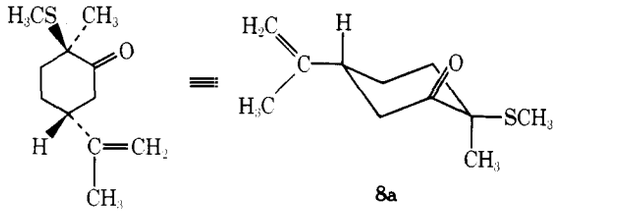
In the case of the minor isomer, which was tentatively assigned structure **8a**, a small positive Cotton effect would be expected if **8a** were the major conformer. Instead, we found that the minor isomer exhibited a negative Cotton effect with a $[\theta]$ of −11 000 at 313 nm. The negative curve implies a major contribution from conformer **8b**. As Trost has shown,[3d] an α-methylthio group interacts with a carbonyl in such a way that the axial stereochemistry is preferred by 0.4 kcal/mol. This is in contrast to the methylthio group as a normal cyclohexane substituent, which prefers to be equitorial by 1.0 kcal/mol (at −90 °C).[15] If we estimate the $\Delta G°$ for an isopropenyl group to be ca. 1.65 kcal/mol,[16] we can make a rough estimate of the equilibrium between **7a** and **7b** and, more importantly, of the equilibrium between **8a** and **8b**. For **7**, estimates based on $\Delta G°$ values predict that the **7a–7b** ratio would be greater than 99:1 at room temperature. For **8**, the same approach predicts an **8a–8b** ratio of ca. 3:7. Surprisingly **8b**, which has an axial isopropenyl group, should be the preferred conformer. This is entirely consistent with the observed



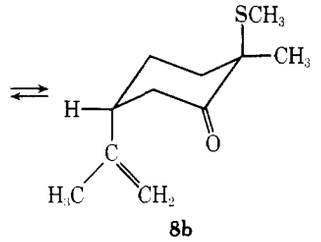
7 7a



7b



8 8a



8b

circular dichroism spectrum of **8** and with the NMR spectrum of the minor product, which shows a splitting of the vinylic protons. In conformer **8b**, the magnetic environment of the two vinylic protons would be quite different.

In summary, we have shown that reductive sulfenylation is a viable method for the regiospecific introduction of a methylthio group α to a carbonyl group. Furthermore, sulfenylation appears to parallel alkylation of enolate anions in terms of preferred pseudoaxial attack. This is in line with the generally stated premise[18] "if a cyclohexanone derivative already has one alkyl substituent at the α position, the proportion of the second alkyl group introduced at this α position from an axial direction is enhanced."

Experimental Section[19]

General Procedure for the Reductive Sulfenylation of Cyclic α,β-Unsaturated Ketones. To a solution of 2 equiv of lithium wire dissolved in liquid ammonia (3 mL of ammonia/mmol of lithium) at −78 °C under nitrogen was added dropwise a solution of 1 equiv each of α,β-unsaturated ketone and *tert*-butyl alcohol in anhydrous ether (1 mL of ether/mmol of ketone). After stirring for 30 min at −78 °C, the cooling bath was removed and the reaction mixture was allowed to reflux (dry ice condenser) for an additional 30 min. Ether (1 mL/mmol of ketone) was added, the reaction mixture was cooled to −78 °C, and 1 equiv of dimethyl disulfide in ether (1 mL/mmol of disulfide) was added quickly, followed by an additional equal volume of ether. After stirring for 1 h at −78 °C, the cooling bath was removed, the dry ice condenser was replaced by a water-cooled condenser, and the ammonia was allowed to evaporate (12 h). The reaction mixture was carefully acidified with 3 N hydrochloric acid and the layers were separated. The aqueous layer was extracted with ether and the combined ether extracts were washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated in vacuo. Unless otherwise noted, the residue was purified by fractional distillation.

2-(Methylthio)cyclohexanone. According to the general procedure outlined above, 2-cyclohexenone (4.36 g, 45 mmol) was sulfenylated with dimethyl disulfide (4.30 mL, 45 mmol) to yield 2.85 g (43%) of 2-(methylthio)cyclohexanone: bp 56–57 °C (0.28 mm); n^{25}_D 1.5086; IR (neat) 2930, 2860, 1705, 1450, 1425, 1230, 1120, 915, 825 cm^{-1}; UV (hexane) λ_{max} (ε) 215 (1089), 250 (330), 307 (242), 314 nm (242); NMR (CCl_4) δ 3.32–2.58 (2 H, br m), 2.47–1.65 (7 H, br m), 1.98 (3 H, s, SCH_3) [lit.[2] bp 45.5–48.0 °C (0.2 mm); n^{24}_D 1.5088].

2-(Methylthio)cycloheptanone. According to the general procedure outlined above 5.00 g (45 mmol) of 2-cycloheptenone was sulfenylated with 4.3 mL (45 mmol) of dimethyl disulfide to give 4.4 g (28 mmol, 62%) of 2-(methylthio)cycloheptanone: bp 53–54 °C (0.5 mm); n^{26}_D 1.5094; IR (neat) 2920, 2850, 1695, 1455, 1320, 1245, 1165, 935 cm^{-1}; UV (hexane) λ_{max} (ε) 216 (1780), 248 (538), 305 nm (270); NMR (CCl_4) δ 3.18–2.50 (2 H, br m), 2.50–1.05 (11 H, br m), 2.00 (3 H, s, SCH_3) [lit.[20] bp 66–67 °C (0.5 mm); n^{21}_D 1.511]. A 2,4-dinitrophenylhydrazone derivative was prepared, mp 129–130 °C [lit.[20] mp 128 °C].

2-(Methylthio)cyclooctanone. The general procedure was employed using 4.0 g (32 mmol) of 2-cyclooctenone with 3.1 mL (32 mmol) of dimethyl disulfide to yield 2.1 g (12 mmol, 38%) of 2-(methylthio)cyclooctanone: bp 58–62 °C (0.55 mm); n^{25}_D 1.5138; IR (neat) 2905, 2850, 1690, 1470, 1450, 1330, 1225, 1160, 1125, 1060, 848 cm^{-1}; UV (hexane) λ_{max} (ε) 215 (1928), 248 (710), 306 nm (291); NMR (CCl_4) δ 3.20–2.46 (2 H, br m), 2.45–0.71 (11 H, br m), 1.91 (3 H, s, SCH_3) [lit.[21] bp 59–61 °C (0.5 mm); n^{20}_D 1.5130].

3-Methyl-2-(methylthio)cyclohexanone. Reductive sulfenylation of 10.0 g (91 mmol) of 3-methyl-2-cyclohexenone with 24.5 mL (273 mmol) of dimethyl disulfide according to the general procedure described above gave 6.92 g (44 mmol, 48%) of 3-methyl-2-(methylthio)cyclohexanone as a 55:45 mixture of epimers, bp 94–95 °C (7.0 mm). The mixture of epimers could not be separated in our laboratory by vapor-phase chromatography. Thus, the ratio of epimers was determined by NMR analysis. All physical properties were those of this mixture: n^{25}_D 1.5020; IR (neat) 2940, 2870, 1670, 1430, 1381, 1350, 1328, 1253, 1197, 1050, 1040, 962, 885, 755 cm^{-1}; NMR (CCl_4) δ 3.17–2.62 (2 H, m), 2.54–1.00 (6 H, m), 2.00 and 1.97 (3 H, 2s, 2 SCH_3), 1.14 and 1.12 (3 H, 2d, J = 6.5 Hz, 2 $CHCH_3$).

Anal. Calcd for $C_8H_{14}OS$: C, 60.72; H, 8.92; S, 20.25. Found: C, 60.72; H, 8.89; S, 20.54.

$\Delta^{8(9)}$-1-(Methylthio)-2-*p*-menthenone. The general procedure was employed using 6.81 g (45 mmol) of *l*-carvone and 4.3 mL (45 mmol) of dimethyl disulfide to yield 4.2 g (21 mmol, 47%) of a 17:83 mixture of epimers of $\Delta^{8(9)}$-1-(methylthio)-2-*p*-menthenone: bp 61–63 °C (0.15 mm); n^{25}_D 1.5091.

Anal. Calcd for $C_{11}H_{18}OS$: C, 66.62; H, 9.14; S, 16.17. Found: C, 66.91; H, 9.16; S, 15.90.

The epimers were preparatively separated by VPC on a 10 ft × 1/4 in. 10% SE-30 on 60/80 Chromosorb W column at 160 °C. The major isomer eluted first and had the following physical properties: IR (neat) 3380, 3075, 2920, 2850, 1695, 1655, 1440, 1375, 1270, 1190, 1075, 890 cm^{-1}; UV (hexane) λ_{max} (ε) 249 (430), 304 nm (264); NMR (CCl_4) δ 4.75 (2 H, s, $=CH_2$), 3.22–1.43 (7 H, br m), 1.85 (3 H, s, SCH_3), 1.76 (3 H, s, allylic CH_3), 1.30 (3 H, s, α-CH_3); *m/e* calcd for $C_{11}H_{18}OS$ 198.108, found 198.107.

Minor isomer: IR (neat) 3375, 3075, 2915, 2845, 1695, 1440, 1380, 1270, 1190, 1075, 890 cm^{-1}; UV (hexane) λ_{max} (ε) 248 (358), 307 nm (242); NMR (CCl_4) δ 4.89 and 4.65 (2 H, 2s, $=CH_2$), 3.45–1.46 (7 H, br m), 1.82 (3 H, s, SCH_3), 1.70 (3 H, s, allylic CH_3), 1.23 (3 H, s, α-CH_3); *m/e* calcd for $C_{11}H_{18}OS$ 198.108, found 198.109.

8,10-Dimethyl-1-(methylthio)-2-decalone. In a slight modification of the general procedure, 0.52 g (75 mmol) of lithium in 200 mL of liquid ammonia was allowed to react with 6.10 g (34 mmol) of *trans*-8,10-dimethyl-1(9)-octal-2-one,[22] 2.70 g (34 mmol) of *tert*-butyl alcohol, and 9.2 mL (102 mmol) of dimethyl disulfide to yield 7.59 g of crude product, which was chromatographed on silica gel with benzene–petroleum ether as eluent to give 4.97 g (22 mmol, 65%) of 8,10-dimethyl-1-(methylthio)-2-decalone as a yellow oil: n^{25}_D 1.5262; IR (neat) 2882, 1695, 1458, 1385, 1232 cm^{-1}; NMR ($CDCl_3$) major peaks δ 3.03 (1 H, d, J = 5.9 Hz, SCH), 2.03 (3 H, s, SCH_3), 1.15 (3 H, s, 10-CH_3), 0.88 (3 H, d, J = 6.3 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{22}OS$: C, 68.97; H, 9.80; S, 14.16. Found: C, 68.95; H, 9.97; S, 14.17.

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spectra. We also wish to thank Professor A. Moscowitz for helpful discussions.

Registry No.—Dimethyl disulfide, 624-92-0.

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Sulfenylation of Amides

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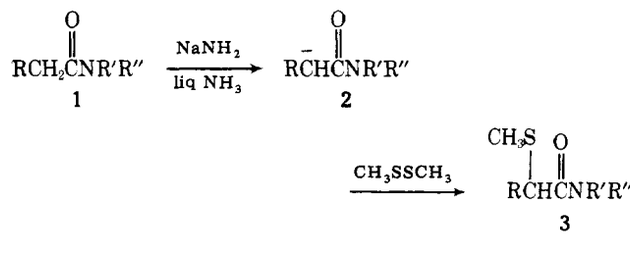
A variety of amides and lactams have been sulfenylated. It was found that, in general, lithium diisopropylamide in tetrahydrofuran was a useful base–solvent system for the α-monosulfenylation of N,N-disubstituted amides. In contrast, sodium amide in liquid ammonia was a superior base–solvent system for polysulfenylation of such amides.

Recently, we have described in detail the [2,3] sigmatropic rearrangement of ylides derived from azasulfonium salts as part of our general synthesis of indoles[1] and oxindoles.[2] Crucial to the preparation of the requisite azasulfonium salt precursors was the availability of a variety of sulfides. In connection with the synthesis of oxindoles, we were particularly concerned with the preparation of α-methylthioamides.[2] Of the various methods available for the introduction of an α-methylthio moiety, we were attracted to the possibility of directly sulfenylating anions of the appropriate amide or lactam with dimethyl disulfide. The recent comprehensive report on the sulfenylation of ketones and esters,[3,4] and of more direct relationship, the phenyl sulfenylation of 1-methyl-2-pyrrolidone and 1-methyl-2-piperidone recently described by Zoretic and Soja,[5] prompted us to report herein our results on the methyl sulfenylation of amides. Of particular interest in this regard are the major differences between the findings of Zoretic and Soja and those from our laboratory, especially those associated with the effect of different solvents on the nature of the reaction.

Previously, we[6] and others[7] had demonstrated the suitability of sodium amide as a base for the α-alkylation of amides. Thus, it seemed reasonable that treatment of **1** with sodium amide in liquid ammonia would produce **2,** which on reaction with dimethyl disulfide would yield **3.** In practice, this



1 2 3

reaction was not suitable for monosulfenylation of amides. When 1 equiv of *N*-methylpyrrolidone (**4**) was treated with 1 equiv of sodium amide in liquid ammonia, followed by the addition of 1 equiv of dimethyl disulfide, only the disubstituted lactam **5** and unreacted **4** were obtained. When 2 equiv