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Reaction of α-Chloro Sulfoxides with Carbonyl and Thiocarbonyl Compounds

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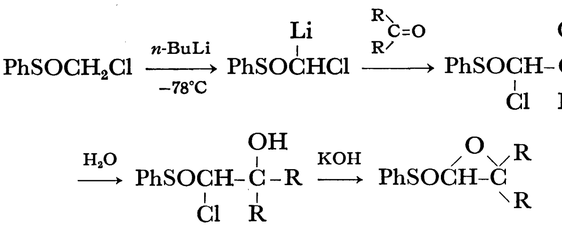
Chloromethyl methyl sulfoxide undergoes a Darzens-type reaction with carbonyl compounds in the presence of potassium *t*-butoxide in *t*-butanol to afford methylsulfinyloxirane derivatives. The stereochemistry of this reaction has been studied. The reaction with a symmetrical ketone appeared to proceed stereospecifically to give only one isomer. On the other hand, the reaction with unsymmetrical ketones such as pinacolone or acetophenone produced a mixture of two diastereoisomers, in which a thermodynamically unstable isomer was predominant. The reaction with thiobenzophenone gave 1,1-diphenyl-2-methylsulfinylethylene which seems to have been formed from the intermediacy of 2,2-diphenyl-3-methylsulfinylthiirane. Mechanisms of these reactions are also discussed.

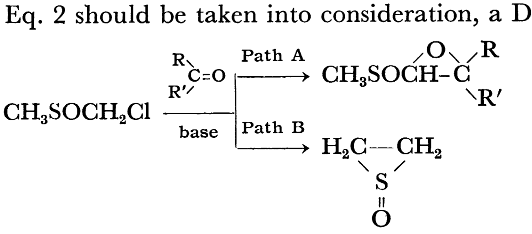
Preparation of α-chlorosulfoxides can be readily accomplished by the reaction of sulfoxides with ordinary chlorinating agents such as chlorine,[1] sulfuryl chloride,[2] *t*-butyl hypochlorite,[3] or *N*-chlorosuccinimide.[4] We have examined the synthetic utility of these α-chlorosulfoxides, particularly chloromethyl methyl sulfoxide, in order to find a way to obtain sulfoxide derivatives of a new type. Application of Darzens-type condensation to α-chlorosulfoxide, *i.e.*, the reaction with carbonyl compounds in the presence of a base, is of considerable interest.

In 1969, Durst reported that the metallation of chloromethyl phenyl sulfoxide followed by the addition to ketones, hydrolysis and successive dehydrochlorination with a base gave phenylsulfinyloxiranes as shown in the following.[5]



Eq. (1)

When alkyl chloromethyl sulfoxide is subjected to reaction with carbonyl compounds, two reactions as shown in Eq. 2 should be taken into consideration, a Darzens-type (Path A) and a Ramberg-Bäcklund-type (Path B).



Eq. (2)

We studied the reaction of chloromethyl methyl sulfoxide with carbonyl compounds in the presence of a base in order to see which reaction this sulfoxide favors. During the course of our investigation, Tavares and his co-workers reported that chloromethyl *p*-tolyl sulfoxide is directly converted into *p*-tolylsulfinyloxiranes by treatment with carbonyl compounds and potassium *t*-butoxide in *t*-butanol–ether.[6] However, Durst and Tin pointed out that Tavares' procedure might be restricted to the sulfoxides which cannot undergo the Ramberg-Bäcklund-type reaction and they prepared methylsulfinyloxiranes by a procedure similar to that shown in Eq. (1).[7]

We found that the reaction of chloromethyl methyl sulfoxide with carbonyl compounds in the presence of potassium *t*-butoxide resulted in the formation of methylsulfinyloxiranes. The application of this reaction to unsymmetrical ketones was investigated. Two diastereomeric isomers of methylsulfinyloxiranes were obtained, and the stereochemistry of these isomers was studied in order to elucidate the steric course of the reaction. In the present paper, we describe the results as well as a study on the reaction with thiobenzophenone.

Results and Discussion

Potassium *t*-butoxide was added to a solution of *t*-butanol containing chloromethyl methyl sulfoxide and benzophenone, and the solution was kept at room temperature with stirring. After the usual work-up, colorless crystals, mp 109—110°C, were obtained in a 62% yield. The IR spectrum of the product showed an absorption at 1034 cm^{-1}, characteristic of a sulfinyl group, and no absorption around 4000—3000 cm^{-1} and 1800—1600 cm^{-1}, indicating that the product has neither hydroxyl nor carbonyl group. In its NMR spectrum, four singlets appeared at δ 7.37 (5H), 7.35 (5H), 4.58 (1H), and 2.57 (3H, CH_3SO).[8] These data as well as the following facts show the structure of this material to be 2,2-diphenyl-3-methylsulfinyloxirane (**1**). The reduction of **1** with lithium aluminum hydride gave 1,1-diphenyl-2-methylthioethanol, which was independently synthesized by the reduction of 1,1-diphenyl-2-

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[1] G. Tsuchihashi and S. Iriuchijima, This Bulletin, **43**, 2271 (1970).

[2] G. Tsuchihashi, K. Ogura, S. Iriuchijima, and S. Tomisawa, *Synthesis*, **1971**, 89.

[3] S. Iriuchijima and G. Tsuchihashi, *Tetrahedron Lett.*, **1969**, 5259.

[4] G. Tsuchihashi and K. Ogura, This Bulletin, **44**, 1726 (1971).

[5] T. Durst, *J. Amer. Chem. Soc.*, **91**, 1034 (1969).

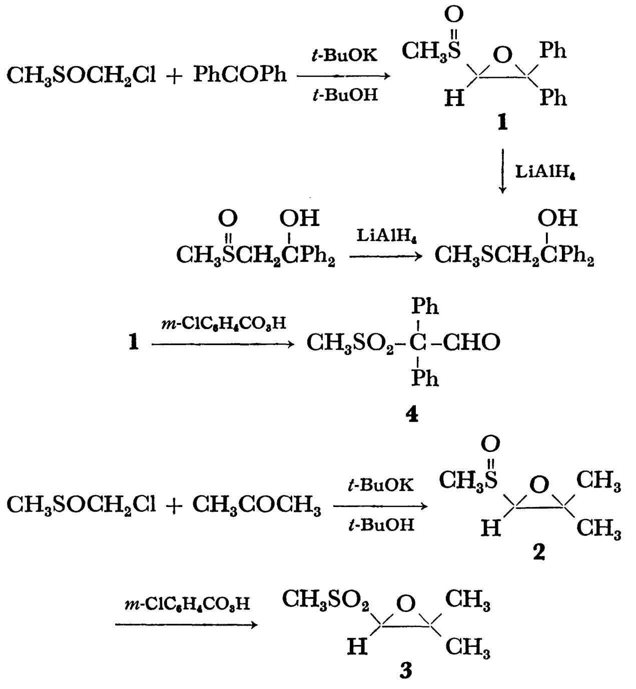
[6] D. F. Tavares, R. E. Estep, and M. Blezard, *Tetrahedron Lett.*, **1970**, 2373.

[7] T. Durst and K.-C. Tin, *ibid.*, **1970**, 2369.

[8] The protons of a normal methylsulfinyl group showed an NMR signal near δ 2.6. For example, dimethyl sulfoxide: δ 2.62; methyl methylthiomethyl sulfoxide: δ 2.59.

methylsulfinylethanol.[9]

Similarly, acetone reacted with chloromethyl methyl sulfoxide in the presence of potassium *t*-butoxide to afford a methylsulfinyloxirane in a 95% yield, its structure being assigned to 2,2-dimethyl-3-methylsulfinyloxirane (**2**) from its physical properties [IR (KBr): 1039 cm^{-1}, NMR (in CCl_4): δ 3.80 (s, 1H), 2.66 (s, 3H), 1.48 (s, 3H), and 1.45 (s, 3H)]. Oxidation of **2** gave the corresponding sulfone **3**.[10]



Scheme 1

When pinacolone was subjected to this Darzens-type reaction of chloromethyl methyl sulfoxide, a mixture shown by NMR analysis to consist of two isomeric methylsulfinyloxiranes **5** and **6** (3: 1) was formed in a 66% yield. One isomer (the major component) could be isolated, showing four singlets at δ 3.78 (1H), 2.58 (3H), 1.48 (3H), and 1.00 (9H) in its NMR spectrum and an absorption at 1034 cm^{-1} in its IR spectrum. In the NMR spectrum of the other isomer, four singlets also appeared at δ 3.44 (1H), 2.88 (3H), 1.40 (3H), and 1.08 (9H). These data are consistent with the structures given in formulas **5** and **6**. The stereochemical structure of the major component was unambiguously determined on the basis of the result of an intramolecular nuclear Overhauser effect. It was found that irradiation of the methyl signal in the NMR spectrum of the major component caused a significant increase (15%) in the intensity of the methine proton which was not effected by irradiation of the *t*-butyl signal, as shown in Fig. 1. This indicates that the methyl group and the methine proton of the major component are close together in space. Thus its stereochemical structure was assigned to be **5** in which hydrogen atom and methyl group are in *cis* position.

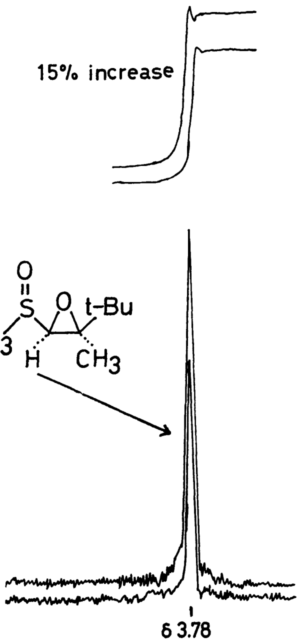
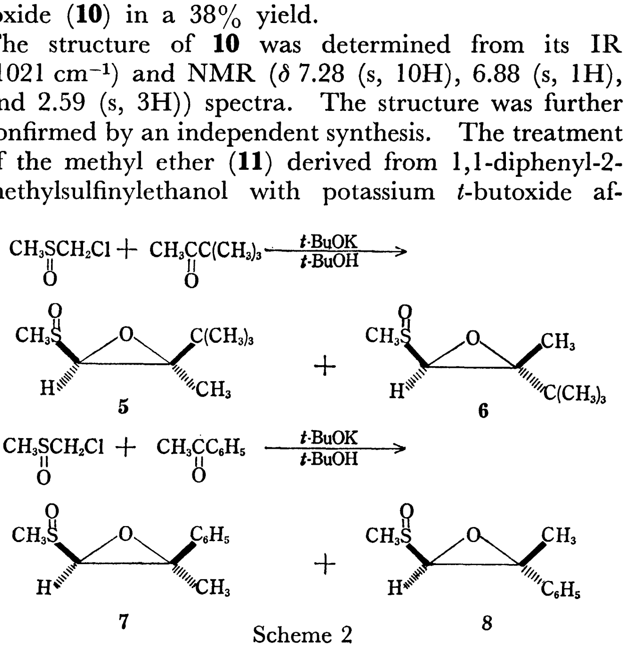


Fig. 1. Intramolecular Overhauser Effect of **5**. irradiation of the methyl signal (δ 1.41)

Acetophenone reacted with chloromethyl methyl sulfoxide by an action of potassium *t*-butoxide to afford a mixture of two diastereoisomers, **7** and **8** (3: 2) in a 60% yield. We tentatively assigned the stereochemical formulas **7** and **8** to the structures of the major and the minor products, respectively, by considering a similar stereochemical course to that of the reaction of pinacolone with chloromethyl methyl sulfoxide.

The reaction of thiobenzophenone with chloromethyl methyl sulfoxide in the presence of potassium *t*-butoxide did not give the expected product, 2,2-diphenyl-3-methylsulfinylthiirane **9**, but an α,β-unsaturated sulfoxide (**10**) in a 38% yield.

The structure of **10** was determined from its IR (1021 cm^{-1}) and NMR (δ 7.28 (s, 10H), 6.88 (s, 1H), and 2.59 (s, 3H)) spectra. The structure was further confirmed by an independent synthesis. The treatment of the methyl ether (**11**) derived from 1,1-diphenyl-2-methylsulfinylethanol with potassium *t*-butoxide af-



Scheme 2

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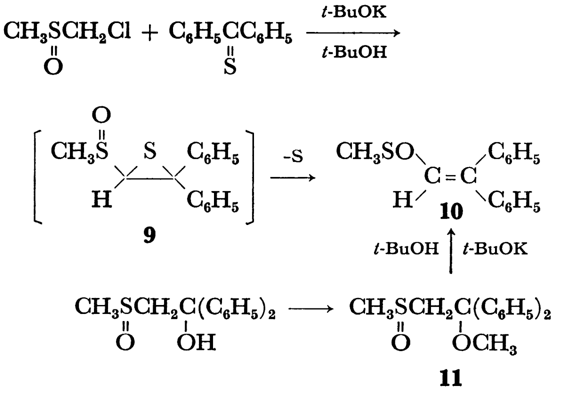
[9] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

[10] The oxidation of **1** with *m*-chloroperbenzoic acid, accompanied by a rearrangement, yielded diphenyl(methylsulfonyl)-acetaldehyde(**4**), of which the structure was assigned by its physical properties (see Experimental Section). The analogous rearrangements of α-epoxy sulfoxides and α-epoxy sulfones to the corresponding aldehydes were already reported.[6,7]

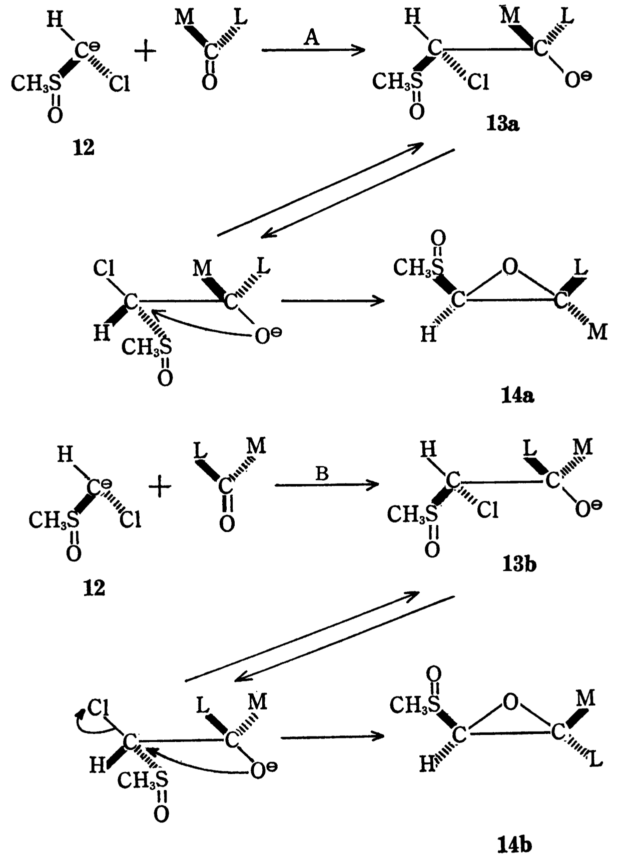


Scheme 3

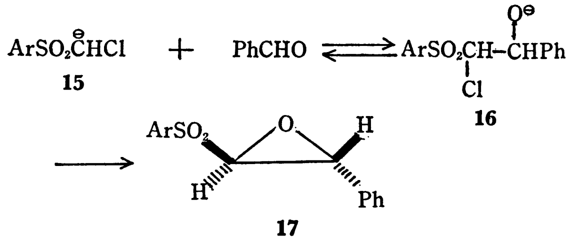
forded **10**. It is reasonable to assume that **10** was formed by the desulfurization of the expected product **9**.

It should be noted that only one isomer was given in the reaction of chloromethyl methyl sulfoxide with symmetrical ketones such as benzophenone or acetone. This is in line with the result reported by Durst who found a high stereoselectivity in the Darzens-type reaction of chloromethyl phenyl sulfoxide with cyclohexanone, acetone or benzophenone.[5] On the other hand, when an unsymmetrical ketone such as pinacolone or acetophenone was used as a carbonyl component, two diastereoisomers were produced. It is of interest that a thermodynamically unstable isomer, **5** or **7**, was predominantly formed as described above. This tendency was also reported by Tavares and his co-workers. They stated that chloromethyl *p*-tolyl sulfoxide reacted with benzaldehyde to yield mainly *cis*-2-phenyl-3-(*p*-tolylsulfinyl)oxirane whose structure was assigned tentatively from the NMR coupling constant between the methine protons in the oxirane ring. They explained that their result can be attributed to precipitation of a less soluble *cis* isomer. This does not hold in our observation because the reaction condition is homogeneous. We would like to propose a plausible mechanism for the formation of a thermodynamically unstable isomer in the Darzens-type reaction of chloromethyl methyl sulfoxide with an unsymmetrical ketone. The carbanion (**12**) derived from chloromethyl methyl sulfoxide attacks a carbonyl compound to form an intermediate (**13**) in the first step of the reaction. We assume that this step is not reversible. The formation of **13a** proceeds through a less hindered transition state than the formation of **13b**, owing to the difference in bulkiness between M and L (M<L). If the oxy anion in **13a** attacks the carbon atom bearing chlorine atom from behind, as in the usual ring-closure reaction of chlorohydrins, the thermodynamically unstable isomer (**14a**) will be formed from the kinetically preferred intermediate (**13a**).

It is interesting to compare this result with that of Darzens-type condensation of α-halosulfones studied by Vogt and Tavares.[11] According to their report, a thermodynamically stable isomer, *i.e. trans* isomer, was produced exclusively. They assume that the initial nucleophilic attack upon a carbonyl compound is rapidly reversible and the product determining step is the ring closure (**16**→**17**). The thermodynamically stable isomer was formed predominantly, passing through the preferred transition state, from the dynamic equilibrium between two diastereoisomers of **16**.



Scheme 4



We believe that the conflicting behaviors in α-halosulfoxides and α-halosulfones can be ascribed to the difference of stability in anions **12** and **15**. Anion **15** is much more stable than anion **12**.

Experimental

Reaction of Chloromethyl Methyl Sulfoxide with Benzophenone. To a solution containing 550 mg of chloromethyl methyl sulfoxide and 970 mg of benzophenone in 5 m*l* of *t*-butanol, 10 m*l* of potassium *t*-butoxide solution (0.77N) in *t*-butanol was added and the resulting solution was stirred for 6 hr at room temperature. The solid deposited by the addition of methylene chloride (50 m*l*) was filtered off and the filtrate was evaporated under reduced pressure. The residue was crystallized from carbon tetrachloride to give 780 mg of 2,2-diphenyl-3-methylsulfinyloxirane **1** as colorless crystals.

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11) P. F. Vogt and D. F. Tavares, *Can. J. Chem.*, **47**, 2875 (1969).

An analytical sample was obtained by recrystallization from methylene chloride-carbon tetrachloride (mp 109—110°C); IR (neat): 1034 cm^{-1}, NMR ($CDCl_3$): δ 7.37 (s, 5H), 7.35 (s, 5H), 4.58 (s, 1H), and 2.57 (s, 3H).

Found: C, 69.61; H, 5.43; S, 12.45%. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.39%.

Reduction of 1 with Lithium Aluminum Hydride. To a solution containing 200 mg of **1** in 10 m*l* of ether, 150 mg of lithium aluminum hydride was added and the reaction mixture was stirred for 40 hr at room temperature. After the addition of 3N sulfuric acid (3 m*l*), the mixture was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column-chromatography (on silica gel, elution with benzene) to afford 96 mg of a colorless oil. This oil was identical with the product obtained by the reduction of 1,1-diphenyl-2-methylsulfinylethanol[9] with lithium aluminum hydride; bp 120°C/0.2 mmHg, NMR (CCl_4): δ 7.5—7.0 (m, 10H), 3.54 (s, 1H, OH), 3.29 (s, 2H), and 1.98 (s, 3H).

Found: C, 73.97; H, 6.47; S, 13.15%. Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60; S, 13.12%.

Oxidation of 1 with m-Chloroperbenzoic Acid. *m*-Chloroperbenzoic acid (175 mg) was added to a solution containing 208 mg of **1** in 15 m*l* of methylene chloride and the mixture was stirred for 1 hr under cooling with ice water. After the addition of sodium carbonate (200 mg) to the mixture and stirring for 1 hr at room temperature, insoluble material was filtered off and the filtrate was evaporated under reduced pressure. The residual crystals were recrystallized from carbon tetrachloride-*n*-hexane to yield 100 mg of the aldehyde **4** as colorless crystals; mp 125—126°C, IR (KBr): 1715, 1303, and 1136 cm^{-1}, NMR (CCl_4): δ 9.94 (s, 1H), 7.7—7.2 (m, 10H), and 2.74 (s, 3H), MS (70 eV): *m/e* 274 (M^+), 195 (base peak), 167 (69%), 166 (20%), 165 (51%), and 152 (18%).

Found: C, 65.39; H, 5.17; S, 11.67%. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69%.

Reaction of Chloromethyl Methyl Sulfoxide with Acetone. To a solution containing 815 mg of chloromethyl methyl sulfoxide in 2.5 m*l* of acetone, 12 m*l* of potassium *t*-butoxide (0.77N) in *t*-butanol was added and the solution was stirred for 11 hr at room temperature. After the addition of methylene chloride (50 m*l*), the deposited solid was filtered off and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (elution with methylene chloride and methanol-ethyl acetate (1:5)) to afford 924 mg (95%) of pale yellow crystals which were recrystallized from carbon tetrachloride to give **2** as colorless crystals; mp 88—89°C, IR (KBr): 1039 cm^{-1}, NMR (CCl_4): δ 3.80 (s, 1H), 2.66 (s, 3H), 1.48 (s, 3H), and 1.45 (s, 3H).

Found: C, 44.82; H, 7.50; S, 23.77%. Calcd for $C_5H_{10}O_2S$: C, 44.75; H, 7.51; S, 23.89%.

Oxidation of **2** by *m*-chloroperbenzoic acid was carried out in methylene chloride to yield the corresponding sulfone **3** as a colorless oil; IR (neat): 1317 and 1150 cm^{-1}, NMR ($CDCl_3$): δ 3.85 (s, 1H), 3.00 (s, 3H), 1.72 (s, 3H) and 1.46 (s, 3H).

Found: C, 39.38; H, 6.74; S, 21.10%. Calcd for $C_5H_{10}O_3S$: C, 39.98; H, 6.71; S, 21.35%.

Reaction of Chloromethyl Methyl Sulfoxide with Pinacolone. To a mixture containing 580 mg of chloromethyl methyl sulfoxide and 1.65 g of pinacolone, 10 m*l* of 0.77N potassium *t*-butoxide solution in *t*-butanol was added and the solution was stirred for 11 hr at room temperature. After the addition of 100 m*l* of methylene chloride and 1 m*l* of water, the mixture was dried over anhydrous sodium sulfate. After filtration, the filtrate was evaporated under reduced pressure. The residue was shown by NMR analysis to contain **5** and **6** in a ratio of 74:26, and was chromatographed on Florisil to give 244 mg of a mixture consisting of **5** and **6** (5:3), and 247 mg of **5**. An analytical sample of **5** was obtained by recrystallization from methylene chloride-*n*-hexane as colorless crystals; mp 79—81°C, IR (KBr): 1034 cm^{-1}, NMR (CCl_4): δ 3.78 (s, 1H), 2.58 (s, 3H), 1.48 (s, 3H), and 1.00 (s, 9H).

Found: C, 54.60; H, 9.09; S, 18.16%. Calcd for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; S, 18.19%.

Although **6** was not isolated, a compound whose NMR signals (CCl_4) appeared at δ 3.44 (s, 1H), 2.88 (s, 3H), 1.40 (s, 3H), and 1.08 (s, 9H) was assigned to be **6**.

Reaction of Chloromethyl Methyl Sulfoxide with Acetophenone. To a solution containing 365 mg of chloromethyl methyl sulfoxide and 412 mg of acetophenone in 5 m*l* of *t*-butanol, 6 m*l* of 0.77N potassium *t*-butoxide in *t*-butanol was added and the reaction mixture was stirred for 1 hr at room temperature. After the addition of 90 m*l* of methylene chloride and a small amount of activated charcoal, the insoluble solid was filtered off. The filtrate was evaporated under reduced pressure, and the residue was crystallized from carbon tetrachloride - *n*-hexane to give 383 mg (60%) of pale yellow crystals which were shown by NMR analysis to consist of **7** and **8** (3:2). An analytical sample was obtained by successive recrystallization from carbon tetrachloride and water as a colorless solid; mp 124—128°C, IR (KBr): 1036 cm^{-1}. The NMR signals ($CDCl_3$) of **7** appeared at δ 7.36 (s, 5H), 3.92 (s, 1H), 2.71 (s, 3H), and 1.87 (s, 3H). The NMR of **8** showed the absorption ($CDCl_3$) at δ 7.36 (s, 5H), 4.16 (s, 1H), 2.40 (s, 3H), and 1.80 (s, 3H).

Found: C, 61.04; H, 6.41; S, 16.37%. Calcd for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.16; S, 16.34%.

Reaction of Chloromethyl Methyl Sulfoxide with Thiobenzophenone. To 3.5 m*l* of potassium *t*-butoxide solution (0.77N) in *t*-butanol, 245 mg of chloromethyl methyl sulfoxide and 310 mg of thiobenzophenone were added and the reaction mixture was stirred for 15 min at room temperature. The solid deposited by the addition of 50 m*l* of methylene chloride was filtered off and the filtrate was evaporated under reduced pressure. Crystallization of the residue from *n*-hexane gave 165 mg of colorless crystals. These crystals were dissolved in methanol-methylene chloride. After separation of insoluble crystals, the mother liquor was evaporated under reduced pressure to give 145 mg (38%) of colorless crystals. An analytical sample was obtained by recrystallization from methylene chloride - *n*-hexane; mp 106—107°C, IR (KBr): 1021 cm^{-1}, NMR (CCl_4): δ 7.28 (broad s, 10H), 6.88 (s, 1H), and 2.59 (s, 3H).

Found: C, 74.53; H, 5.91; S, 13.23%. Calcd for $C_{15}H_{14}OS$: C, 74.34; H, 5.82; S, 13.23%.

Independent Synthesis of 1,1-Diphenyl-2-methylsulfinylethylene. Sodium hydride (185 mg) was added to a solution of 1,1-diphenyl-2-methylsulfinylethanol[9] (1.04 g) in 15 m*l* of tetrahydrofuran and the mixture was stirred for 20 min at room temperature. Methyl iodide (3 m*l*) was added and the solution was kept for 30 min at room temperature with stirring. After the addition of water (10 m*l*), the reaction mixture was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give colorless crystals which were recrystallized from *n*-hexane to give the corresponding methyl ether (**11**), mp 130.5—132.5°C.

A mixture containing 150 mg of **11** and 2 m*l* of 0.77N potassium *t*-butoxide in *t*-butanol was refluxed for 3.5 hr. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (elution with methylene chloride and ethyl acetate) to afford 39 mg of **9** as colorless crystals, mp 107—107.5°C. These crystals were identical with those obtained by the reaction of chloromethyl methyl sulfoxide with thiobenzophenone (by IR and mixture mp).

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