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ADVENTURES IN ORGANOSULFUR CHEMISTRY

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Irwin Douglass was born in 1904 in Des Moines, Iowa and was educated in the public schools of Nebraska, Illinois and Iowa. He received a B.S. degree from Monmouth College, Illinois in 1926 and a Ph.D. in chemistry from the University of Kansas in 1932. In his forty-six year career as a teacher of chemistry he has taught at Monmouth, Illinois High School (1926–1928), the Junior College of Kansas City, Missouri (1930–1931), North Dakota Agricultural College (1932–1933), Northern Montana College (1933–1940) and the University of Maine (1940–1972). He conducted post-doctoral research at Yale University during 1937–1938, served as a Ranger-Naturalist in Yellowstone National Park during the summers of 1936–1940 and was a visiting scholar at the University of California in Los Angeles 1962–1963. He became Professor of Chemistry, Emeritus at the University of Maine in 1972 and was a member of the State of Maine Board of Environmental Protection during 1974–1977. His research explored both the fundamental and applied chemistry of organosulfur chemistry and is presented here along with an autobiographical account of his journey. Because of Irwin's failing eyesight, his daughter Miriam has prepared this account of his research. She started her career in chemistry chlorinating disulfides in Irwin's laboratory. She obtained her B.A. in chemistry in 1960 from Oberlin College and a Ph.D. in organic chemistry from Northwestern University in 1965. Since then she has explored the applied chemistry of organosulfur compounds, inorganic and organic oxidants, nitrosamines and enzymes at the Colgate-Palmolive Research Laboratories. She was Adjunct Associate Professor of Chemistry at Rutgers, the State University of New Jersey, during 1970–1980.

Key words: Acyl isoselenocyanates, acyl isothiocyanates; alkylsulfur trichlorides; chlorination of organosulfur compounds; nuclear magnetic resonance; oxazolidines, thiazines and thiazolidines; sulfenamides; sulfenyl, sulfinyl and sulfonyl chlorides; sulfinic acids; sulfinate esters; thiolsulfonate esters; thioureas.

CONTENTS

1. BIOGRAPHY

My adventures with organosulfur compounds began when I was in the eighth grade in Biggsville, a small town in western Illinois. In late October I skinned a skunk and before disposing of the carcass I removed the scent gland from the base of the tail and saved it. On Halloween a group of friends and I used it to liberally anoint the school house door. The next day the stench in the building was so strong that classes were dismissed for two days. When classes resumed the school was visited by a member of the school board who issued a dire warning. No punitive action was taken and I continued my education in Biggsville through two years of high school.

In 1920 the family moved to Ames, Iowa where I finished high school. After graduation from Monmouth College in Monmouth, Illinois in 1926 and teaching chemistry and physics in Monmouth High School for two years I began graduate study in chemistry at the University of Kansas. I interrupted my graduate study in 1930–31 to teach chemistry in the Junior College of Kansas City, Missouri and then returned to Kansas and was granted the Ph.D. degree in 1932.

In that year the nation was in the depths of the Great Depression and at commencement time I was the only one of four doctorate candidates in chemistry who was employed for the next year. I had obtained a one-year appointment at North Dakota Agricultural College (NDAC). At NDAC there were three chemistry majors from the previous year's class who had been unable to find employment and had returned to work on Master's degrees. I was assigned to develop graduate courses for them and to direct their theses. This was a challenging and exciting experience for a young Ph.D. and led to a publication on nicotinyl isothiocyanate and derivatives.[1]

During the year at NDAC I had written many letters trying to locate work for the next year, but without success. I was not sorry that I could not stay at NDAC because the State of North Dakota was nearly bankrupt and the legislature drastically cut all salaries at NDAC. The man I had replaced had received $2800 a year before he left and had to return at $1500.

In early September I was hired to teach chemistry *and* to coach basketball at Northern Montana College (NMC) in Havre, Montana. I had experience in athletics, but basketball was the only intercollegiate sport at NMC and I had never played basketball except in a few intramural games.

Northern Montana College was a new school with the college office and some classrooms in the Havre High School building. President Vande Bogart had a Ph.D. in chemistry and had supervised the construction of a science building out of materials salvaged from an abandoned army fort near Havre.

Pershing Hall was not finished when I arrived and I spent Thanksgiving recess moving chemical supplies and equipment from the high school laboratory. The shelves for chemicals were built during the Christmas holidays by ten carpenters on a relief program.

NMC had no gymnasium but was permitted to use the high school facilities in the evening. My teaching schedule included two courses in General Chemistry and either Quantitative Analysis or Organic Chemistry in different quarters. I supervised all laboratories. This made a heavy schedule and it gave no promise of providing the stimulation of the experience at NDAC. The basketball proved to be reasonably successful because the boys, including some Sioux Indians, knew more about the game than I did and I tried to interfere as little as possible.

Each year I dismissed my chemistry classes for a week while I took the basketball team on a trip across the state to play the other teams on the schedule. I planned for an extra day on the trip to be used for something of educational value. One year the team went down a copper mine in Butte, another year they visited the smelter in Anaconda and another the electrolytic refinery in Great Falls. At the latter place I learned that the element selenium is a by-product of the electrolytic refining of copper.

Because the element selenium is closely related to sulfur I wondered if selenium compounds analogous to the sulfur compounds in my thesis could be prepared. With selenium obtained from the Anaconda Copper Company I conducted experiments described in Section 2 below. I sent a reprint of the publication[2] to Dr. Treat B. Johnson at Yale University and asked about a post-doctorate research assistantship. It happened that Dr. Johnson's assistant was leaving and I received an appointment for 1937–1938.

During the summers of 1936–1940 I was employed as a seasonal Ranger-Naturalist in Yellowstone National Park. I found there that the Carnegie Geophysical Laboratory had made an exhaustive study of the hot springs in Yellowstone and I thought the story should be made more available. I summarized the findings of Allen and Day in a paper, "Some Chemical Features of Yellowstone National Park" which was published in the Journal of Chemical Education.[3]

During my summers in the Park I had opportunity to meet several prominent chemists. Dr. W. E. Bradt, with whom I had corresponded on organoselenium compounds, passed through the Park on his way to the University of Maine where he had been hired as Head of the Department of Chemistry and Chemical Engineering. We continued to correspond and in 1940 Dr. Bradt offered me a full time position in his Department at the University of Maine. I readily accepted.

Upon my arrival in Maine, I was told that Dr. Bradt was being called to active military service with the Maine National Guard and that I was to serve as Acting Head of the Department. Fortunately, he did not have to leave for several months, allowing me time to become familiar with departmental administration. Wartime adjustments came as male students crowded the enrollment in the hope that college men would be deferred in the draft. Many readjustments were necessary with the disappearance of these men as they were drafted. The wave after wave of Army Specialized Training Program (ASTP) trainees

who were shipped to the campus kept administrators busy adjusting teaching loads and searching for additional instructors.

During the war the Maine State Police asked me to prepare "sniff sets" to use in Civil Defense exercises to identify war gases in the event of enemy attack. Mustard "gas", actually an oily liquid, was readily prepared from the commercial solvent bis-(2-hydroxyethyl) sulfide by treatment with hydrochloric acid. I got some between my fingers and for several days nursed large blisters.

The gas phosgene was to be identified by the odor of a liquid known as triphosgene. When I sought its identity from a faculty member on leave with the War Department in Washington, I received a single-worded telegram "hexachlorodimethyl carbonate". During its preparation by chlorination I monitored the course of reaction by noting the disappearance of the sweet odor of dimethyl carbonate and the formation of the unpleasant musty-smelling triphosgene. This incautious analytical method sent me to bed with gurgling lungs. The State Police were provided with 20 sets of small bottles containing charcoal and enough toxic material to give a perceptible odor. There were no enemy gas attacks in Maine and to my knowledge I was the only gas casualty during that period.

When World War II ended I looked forward to Dr. Bradt's return, but this was not to be. After serving with distinction as an artillery officer in the South Pacific Campaign, he was wounded and returned to the Walter Reed Hospital in Washington. He died before he could return to Orono.

This tragedy forced readjustments in the University of Maine's Department of Chemistry and Chemical Engineering. Chemistry and Chemical Engineering were made separate departments and I was made Head of Chemistry. Pulp and Paper Technology was absorbed into Chemical Engineering and Professor Lyle Jenness became Head of that Department.

For more than fifty years the University of Maine had trained men for the pulp and paper industry. The reputation of the university in that field extended overseas, and when the war ended a number of Chinese students enrolled to study Pulp and Paper. I developed a graduate course, "The Chemistry of Cellulose and Wood."[4]

In 1952 the Maine Potato Starch Manufacturers came to the Department of Industrial Cooperation at the university to ask for technical assistance and I took a year's leave to work on their problems.[5,6]

After the great difficulty in hiring graduate assistants during the war years it became easier to get qualified applicants. I had a capable series of students working with me on the chemistry of sulfenyl chlorides, alkylsulfur trichlorides, sulfinyl chlorides, sulfinate esters and thiolsulfonate esters. This chemistry is reviewed below.

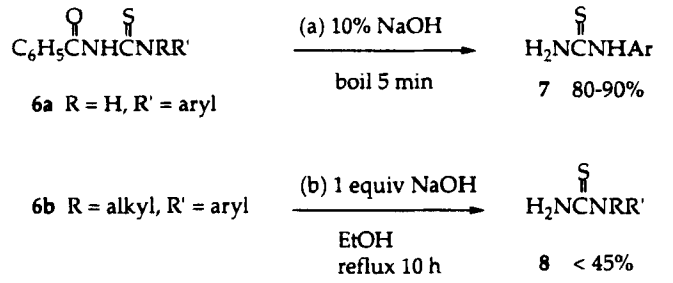
In 1960 a paper mill three miles east of the university converted its pulping method to the Kraft process which produces the malodorous gases methanethiol and dimethyl sulfide. With my background in wood chemistry and organosulfur compounds, I took sabbatical leave in 1962–1963 at the University of California in Los Angeles where I studied everything I could find in the literature on the Kraft odor problem. When I returned to Maine I obtained a generous grant from the Air Pollution Control Administration in Washington. In collaboration with Lawrence Price, a chemist with the S. D. Warren Paper Company, I studied the factors influencing odor production. These results and those from later research were presented at national and international symposia and were published over a six-year period.[7–14]

I retired from the university in 1972 but continued to work independently in my laboratory until I was elected to the Orono, Maine Town Council and appointed to the State Board of Environmental Protection. In 1977 Mrs. Douglass and I moved to Vermont to a home on the western slope of the Green Mountains where we enjoy the view across the Champlain Valley and Lake Champlain to the Adirondack Mountains in New York State.

2. ACYL ISOTHIOCYANATES AND ACYL ISOSELENOCYANATES

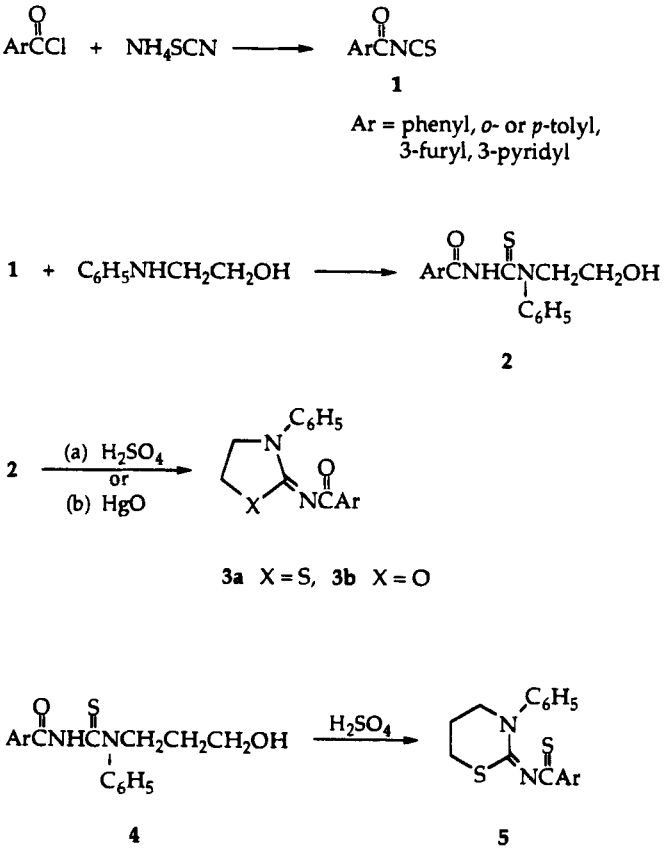
Irwin's thesis at the University of Kansas, carried out under the supervision of Dr. F. B. Dains, was concerned with the preparation of acyl isothiocyanates and their conversion to thioureas and certain heterocyclic compounds.[1,15,16] When an acetone solution of an inorganic thiocyanate is treated with an acid chloride a solution of the acyl isothiocyanate **1** forms, as illustrated in Scheme 1. Treatment of **1** with an amine produces a thiourea. If the amine has an hydroxyethyl group, the resulting thiourea (**2**) can be cyclized with acid to a thiazolidine (**3a**). Treatment of 2 with mercuric oxide produces the corresponding oxazolidine (**3b**). The thiourea **4**, produced from condensation of 3-aminopropanol with acyl isothiocyanates, can be cyclized to thiazines (**5**).

When the benzoylthiourea **6a** is derived from a primary amine, the acyl group can be removed readily by hydrolysis, leaving the corresponding monosubstituted thiourea **7**. Since benzoyl isothiocyanate and acylthioureas are easily made, the procedure affords methods for both the identification of amines and the rapid preparation of monosubstituted thioureas. The hydrolysis of benzoylthioureas **6b** derived from secondary amines is slower and lower yields of the 1,1-disubstituted thioureas **8** are obtained.[16]



Acyl isoselenocyanates are formed when aromatic or aliphatic acid chlorides are mixed with acetone solutions of potassium selenocyanate. Subsequent reactions with amines produce a variety of acyl selenoureas **9**.[2]

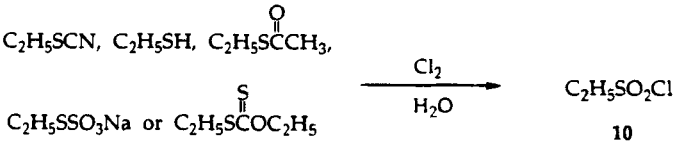
9



SCHEME 1 Conversion of acylthioureas to thiazolidines, oxazolidines and thiazines.

3. AQUEOUS CHLORINATION OF ORGANIC SULFUR COMPOUNDS

Useful syntheses of sulfonyl chlorides were discovered when a variety of thiols and their derivatives were chlorinated in cold water.[17,18] Excellent yields of ethanesulfonyl chloride (**10**) are obtained from ethyl thiocyanate, ethanethiol, ethyl thiolacetate, sodium ethylthiosulfate and ethyl ethylxanthate.



The products isolated and the rate of the reaction depended on the structure of the thiol. Chlorination of benzenethiol proceeds more slowly to benzenesulfonyl chloride (**11**) in a stepwise manner, yielding diphenyl disulfide and benzenesulfenyl chloride as intermediates.

$$C_6H_5SH \xrightarrow[H_2O]{Cl_2} (C_6H_5S)_2 \longrightarrow C_6H_5SCl \longrightarrow \underset{\mathbf{11}}{C_6H_5SO_2Cl}$$

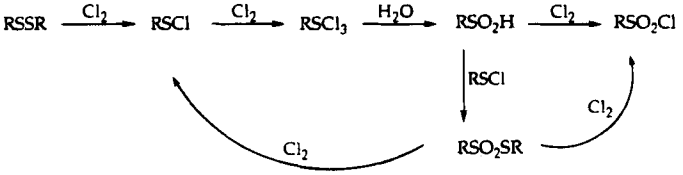
A major product from the aqueous chlorination of phenylmethanethiol is the water-insoluble *S*-benzyl phenylmethanethiosulfonate (**12**) which can be isolated along with the disulfide and the sulfonyl chloride.[17]

$$C_6H_5CH_2SH \xrightarrow[H_2O]{Cl_2} \underset{\mathbf{12}}{C_6H_5CH_2\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{-}SCH_2C_6H_5} + (C_6H_5CH_2S)_2 + C_6H_5CH_2SO_2Cl$$

From benzyl thiocyanate a unique reaction product, phenylmethanesulfinic acid (**13**), is formed.[18]

$$C_6H_5CH_2SCN \xrightarrow[H_2O]{Cl_2} \underset{\mathbf{13}}{C_6H_5CH_2SO_2H}$$

The various reaction products described above along with the chemistry of organosulfur trichlorides discussed below in Section 4.3 are consistent with the mechanism of conversion of thiols to sulfonyl chlorides outlined in Scheme 2.

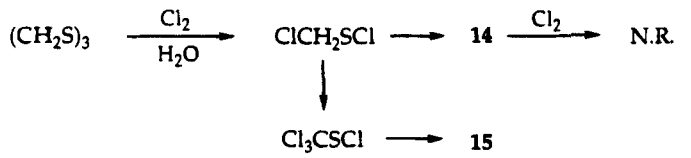


SCHEME 2 A possible mechanism for the conversion of thiols to sulfonyl chlorides.

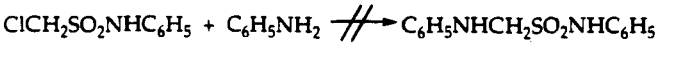
The aqueous chlorination of 1,3,5-trithiane yields chloromethanesulfonyl chloride (**14**),[19] a compound which was of special interest because of its potential as precursor to new therapeutic sulfonamides. Major by-products are sulfate, bis(chloromethyl) sulfide, sulfur dichloride, carbon tetrachloride and trichloromethanesulfonyl chloride (**15**).

$$(CH_2S)_3 \xrightarrow[H_2O]{Cl_2} \underset{\mathbf{14}}{ClCH_2SO_2Cl} + SO_4^{2-} + (ClCH_2)_2S + SCl_2 + CCl_4 + \underset{\mathbf{15}}{Cl_3CSO_2Cl}$$

The latter is not derived from **14**, which is inert to further chlorination. Both sulfonyl chlorides apparently originate from sulfenyl chloride precursors.

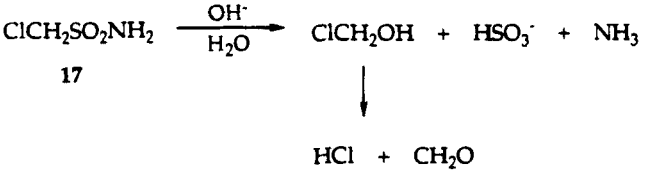


Chloromethanesulfonanilide (**16**) was prepared from the sulfonyl chloride with the intent of replacing the chlorine with various other groups to produce sulfonamides with pharmacological activity. However, the chlorine in **16** is inert to displacement by boiling aniline or hot sodium phenoxide.[20]



16

It is possible to hydrolyse chloride from chloromethanesulfonamide (**17**) with boiling 5% NaOH, but only after first cleaving the carbon-sulfur bond.



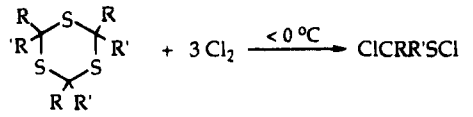
17

4. SULFENYL CHLORIDES

4.1 *Anhydrous Chlorination of 1,3,5-Trithianes*

The intermediacy of sulfenyl chlorides in the formation of sulfonyl chlorides by aqueous chlorination of 1,3,5-trithiane was suggested in Section 3 above. Anhydrous chlorination of both unsubstituted and alkyl substituted 1,3,5-trithianes (**18a**) leads to the formation of α-chloro sulfenyl chlorides (Scheme 3).[21] To avoid overchlorination and decomposition of the unstable monosubstituted chlorosulfenyl chlorides, the temperature has to be maintained below 0 °C. Disubstituted derivatives can be prepared with relative ease.

Chlorination of phenyl substituted trithianes **18b** leads to elimination of sulfur and the formation of 1,1-dichloro compounds. An improved synthetic procedure for the substituted

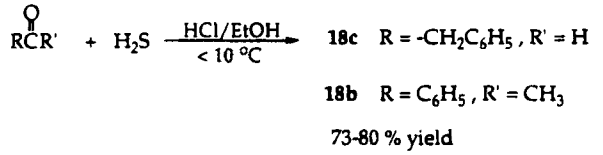


18a

R = H or CH_3 ; R' = H, CH_3 , C_2H_5 , C_4H_9

18b ⟶ $C_6H_5RCCl_2$ + S + S_2Cl_2 or SCl_2

R = C_6H_5 , R' = H or CH_3



SCHEME 3 Preparation of substituted 1,3,5-trithianes and their anhydrous chlorination.

trithianes was developed.[22] The *cis,cis,cis*- and *cis,cis,trans*-isomers of **18c** were isolated in a 4:1 ratio.

Chloromethanesulfenyl chloride (**19**) and several of its derivatives are unstable.[23] Unsymmetrical disulfides (**20**), formed from reaction of a sulfenyl chloride and a thiol, disproportionate to the symmetrical disulfides. In contrast, the analogous di- and trichloro compounds **21** and **22** are stable to distillation conditions.

$ClCH_2SCl$ + RSH ⟶ $ClCH_2SSR$ ⟶ $(ClCH_2S)_2$ + $(RS)_2$

19 **20**

R = C_2H_5 and C_6H_5

Cl_2CHSCl + C_2H_5SH ⟶ $Cl_2CHSSC_2H_5$

21

Cl_3CSCl + C_2H_5SH ⟶ $Cl_3CSSC_2H_5$

22

The unsymmetrical sulfide **23** formed from reaction of the electrophilic sulfenyl chloride with ethylene is somewhat more stable than other derivatives, but less stable than the dichloro analog **24.**

$$ClCH_2SCl \quad CH_2{=}CH_2 \longrightarrow ClCH_2SCH_2CH_2Cl$$

23

$$Cl_2CHSCl + CH_2{=}CH_2 \longrightarrow Cl_2CHSCH_2CH_2Cl$$

24

Trichloromethanesulfenyl chloride is unreactive toward ethylene under the same conditions, which provides further evidence of its unusual properties, first observed with its stability toward hydrolysis.

4.2 *Electrophilic Reactions of Methanesulfenyl Chloride*

Methanesulfenyl chloride, readily prepared by the anhydrous chlorination of methanethiol or dimethyl disulfide,[24] is highly unstable and undergoes spontaneous decomposition at ambient temperatures to CH_3Cl, CH_3SSCl, CH_3SSCH_3, CH_3SSSCH_3, $CH_3S_4CH_3$, HCl and other products.[25,26] If the compound is freshly prepared, however, and kept at the temperature of solid carbon dioxide until used, it enters into a wide variety of easily controlled reactions.

The array of products formed when methanesulfenyl chloride reacts with various types of esters is best explained by electrophilic attack by sulfenyl sulfur at the atom designated by (→) in Scheme 4.[27]

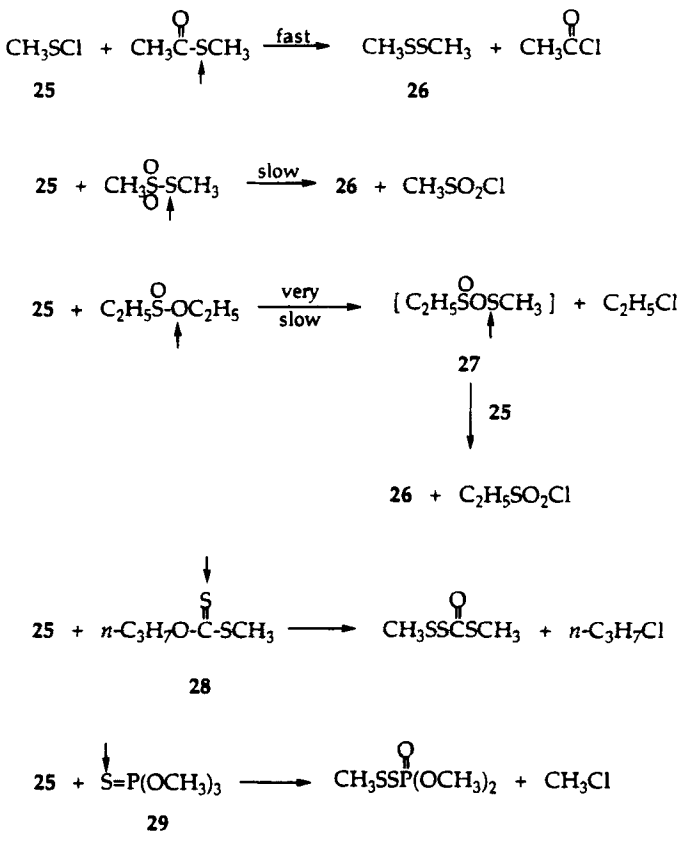
Methanesulfenyl chloride (**25**) reacts readily by electrophilic attack on the sulfur of *S*-methyl thioacetate to form dimethyl disulfide (**26**) and acetyl chloride.[28] A much slower, but analogous reaction occurs between **25** and *S*-methyl methanethiosulfonate to form **26** and methanesulfonyl chloride.

With ethyl ethanesulfinate, electrophilic attack of **25** occurs on the ester oxygen rather than the sulfur to form the reactive sulfinic-sulfenic anhydride (**27**) and ethyl chloride. Attack of **25** on the sulfur atom of **27** produces disulfide **26** and ethanesulfonyl chloride.

In the reaction of **25** with the dialkyl xanthate **28** electrophilic attack occurs at the thiono sulfur, rather than at the thiol sulfur or alkoxy oxygen, to form 2,3,5-trithia-4-hexanone and propyl chloride.[29] Benzenesulfenyl chloride and trichloromethanesulfenyl chloride react with **28** in an analogous manner. In the reaction of **25** with trimethyl thionophosphate (**29**) electrophilic attack also occurs at the thiono sulfur to yield methyl chloride and *O,O*-dimethyl *S*-methylsulfenyl thiolphosphate.

Hydrolysis of **25** depicted in Scheme 5 is slow.[28] Subsequent electrophilic attack of **25** on the sulfur atom of methanesulfenic acid produces *S*-methyl methanethiosulfinate (**30**), which disproportionates by the pathway shown to *S*-methyl methanethiosulfonate (**31**) in 72% yield and dimethyl disulfide (**26**).

Reaction of **25** with methanol (Scheme 6) is faster[28,30,31] and leads to final products whose formation can be explained by reaction of **25** with intermediate products. Subsequent reaction of **25** with methyl methanesulfenate (**32**) produces unstable **30**, which disproportionates to **31** and **26**. Electrophilic attack of **25** on the thiol sulfur of **30** produces **26** and methanesulfinyl chloride (**33**), which is rapidly converted to the methyl ester **34**.

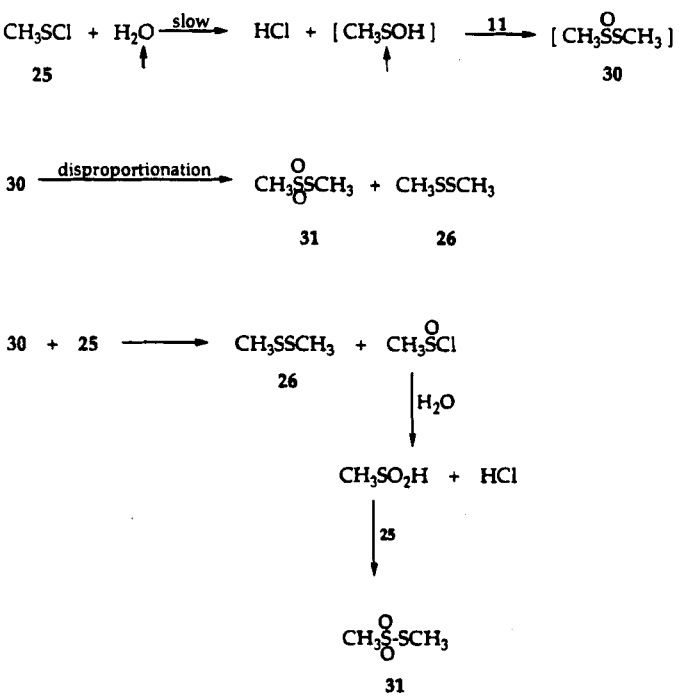


SCHEME 4 Electrophilicity of methanesulfenyl chloride.

Various products are formed by electrophilic attack by **25** at three sites on **34**—the sulfinyl sulfur (Path a), the sulfinyl oxygen (Path b) or the alkoxide oxygen (Path c). Replacing the ester methyl group of **34** with more bulky R groups alters the proportion of attack by **25** at the various positions.[27] The data in Table 1 demonstrate that whereas Path c dominates with the small R = CH_3, no attack on the alkoxide oxygen by this path occurs with the bulky R = 2-C_8H_{17}. As the size of R increases, attack at sulfur (Path a) increases.

The stereochemistry of the reaction by which alkyl chlorides are formed from **25** and alcohols was studied using optically active 2-butanol and 2-octanol and several derivatives.[32] Inversion of configuration predominates in the formation of 2-butyl or 2-octyl chloride, presumably by the mechanism outlined in Scheme 7.

Reaction of methanesulfenyl chloride (**25**) with ethylene oxide produces 2-chloroethyl methanesulfinate (**36**) in 84 % yield.[33] This and other products are readily explained by electrophilic attack of **25** first on the oxide oxygen to form the sulfenate ester **35** (Scheme 8). Reaction of **25** at the sulfur atom of **35** produces ethylene dichloride and *S*-methyl methanethiosulfinate, which undergoes further reaction with **25** as shown.



SCHEME 5 Reaction of methanesulfenyl chloride with water.

4.3 *Further Chlorination to Alkylsulfur Trichlorides*

Symmetrical dialkyl disulfides are chlorinated under cold anhydrous conditions first to the alkanesulfenyl chloride, where the reaction can be terminated after the addition of one mol-equivalent of chlorine, and subsequently to the alkylsulfur trichloride (**37**).[24,31,34,35]

TABLE 1 The Reaction of CH_3SCl (0.02 mol) with $CH_3S(O)OR$ (0.01 mol)

	% Attack by Path		
R	a	b	c
CH_3	36	20	43
C_2H_5	28	46	26
2-C_3H_7	58	32	9
2-C_4H_9	61	36	3
2-C_8H_{17}	61	49	0

$$RSSR \xrightarrow{Cl_2} 2\,RSCl \xrightarrow{2\,Cl_2} 2\,RSCl_3$$

37

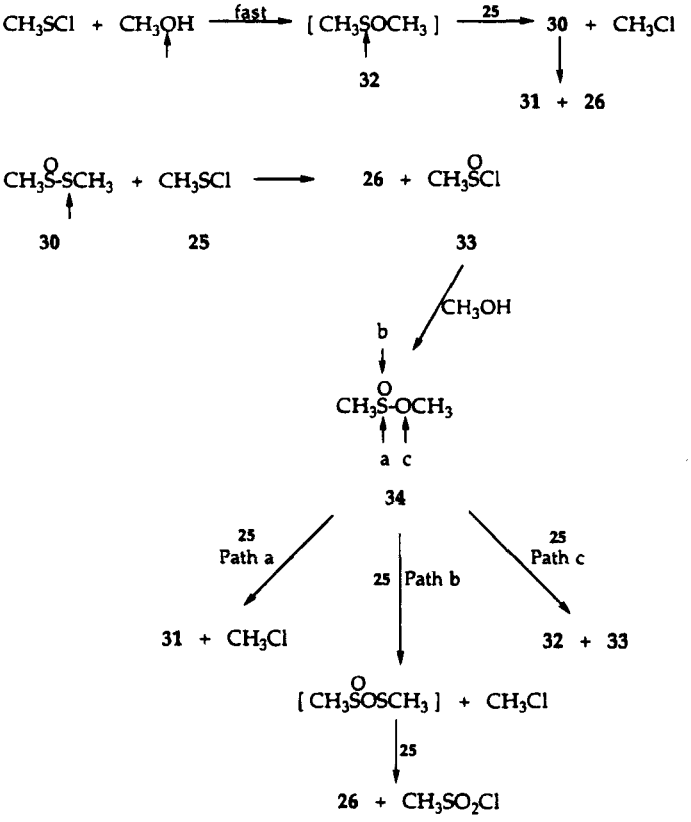
R = CH_3, $ClCH_2$, C_2H_5, *n*- and *i*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, C_6H_5

Chlorination of acylated and sulfonated thiols (thiol esters **38** and thiolsulfonates **39**, respectively) cleaves the acyl-sulfur bond to form the acyl chloride and the alkylsulfur trichloride (Scheme 9). Interestingly, chlorination of the thiono analogs, the dithio esters **40** and the xanthates **41**, produces α,α-dichloro sulfenyl chlorides[36,37] and alkylsulfur trichlorides.[38]

The alkylsulfur trichlorides decompose at ambient temperatures to the 1-chloroalkanesulfenyl chlorides **42**.[25,34]

$$R'CH_2SCl_3 \longrightarrow R'CHClSCl + HCl$$

42

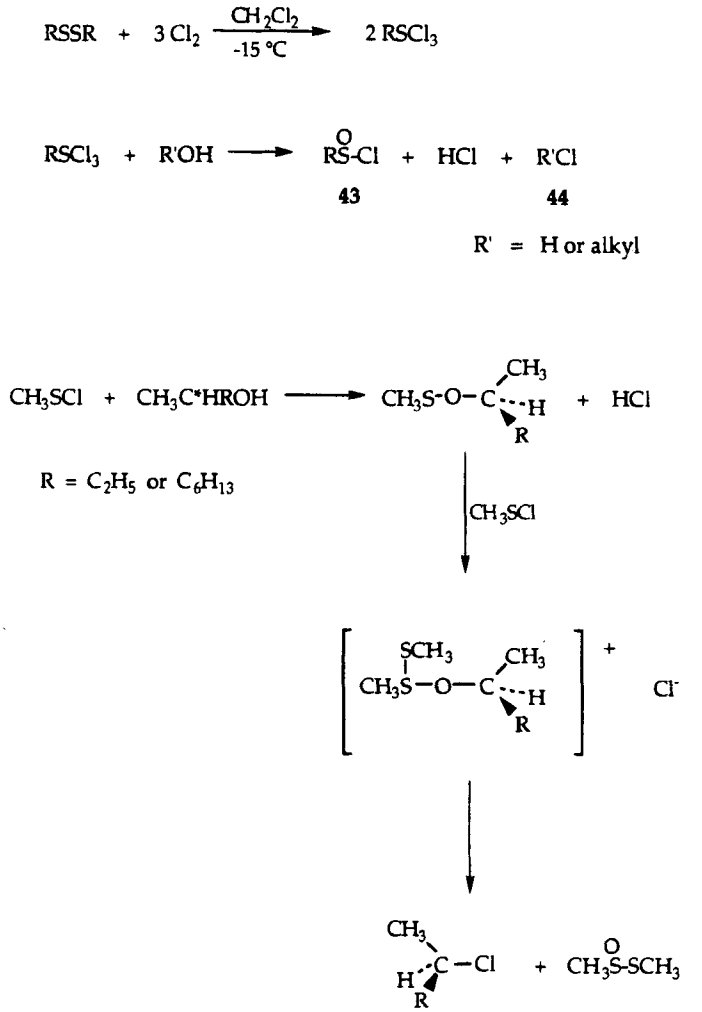


SCHEME 6 Reaction of methanesulfenyl chloride with methanol.

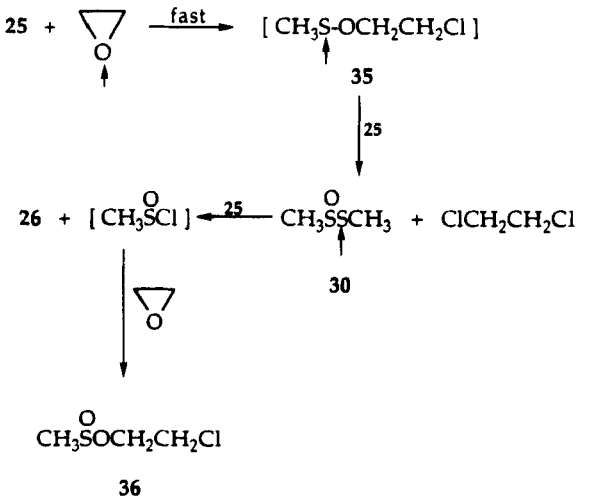
5. SULFINYL CHLORIDES

5.1 *Preparation*

Solvolyses of organosulfur trichlorides with water or alcohols produce sulfinyl chlorides **43** in high yields.[39] The reaction is especially useful for preparing the lower alkanesulfinyl chlorides from the corresponding thiols or disulfides. The complete formation of organosulfur trichloride before addition of water or alcohol is necessary to avoid the predominance of other reaction pathways.[40]



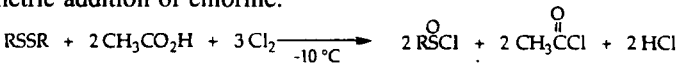
SCHEME 7 The stereochemistry of alkyl chloride formation in the reaction of CH_3SCl with alcohols.



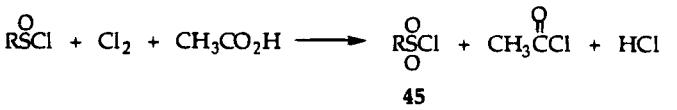
SCHEME 8 Reaction of methanesulfenyl chloride with ethylene oxide.

High degrees of inversion of configuration in the alkyl chlorides **44** produced by alcoholysis of methylsulfur trichloride were observed (2-butyl, 92% and 2-octyl, 61–73%).[39] The proposed mechanism[32] was similar to that depicted in Scheme 7.

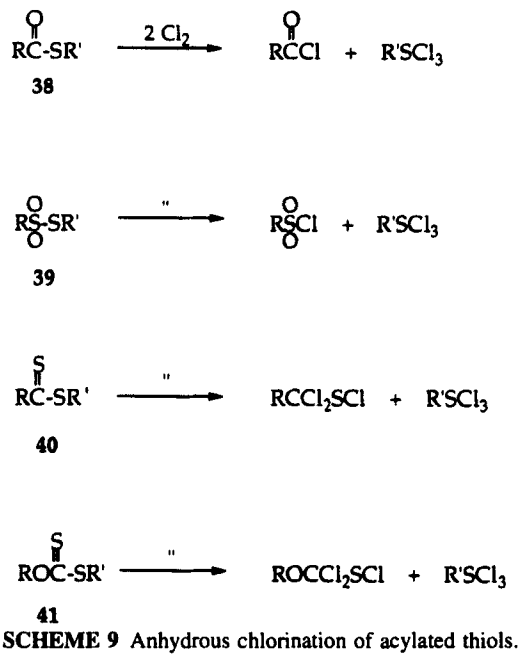
Replacing water or alcohol by acetic acid, used as both solvent and reactant, provides the advantages of fluidity and avoidance of overchlorination by the ready detection of the stoichiometric addition of chlorine.[41–43]



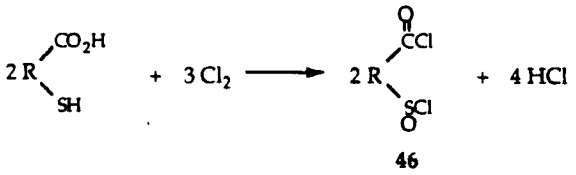
In the presence of excess chlorine and acetic acid the sulfinyl chloride is converted into sulfonyl chloride.[43]



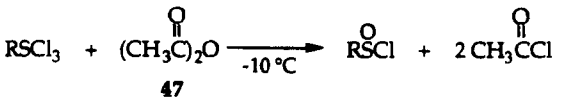
When mercapto acids or their corresponding disulfides, with the carboxyl group in an appropriate geometrical position, are chlorinated under anhydrous conditions, chlorosulfinyl acyl chlorides **46** are formed by an intramolecular solvolysis process.[44] Chlorination of both an aromatic mercapto acid, thiosalicylic acid, and the aliphatic 3-mercaptopropanoic and 4-mercaptobutanoic acids in methylene chloride proceeded smoothly to the corresponding chlorosulfinyl acyl chlorides.



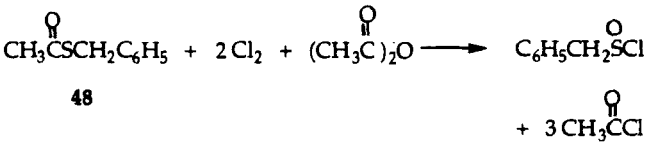
SCHEME 9 Anhydrous chlorination of acylated thiols.



When water, alcohol or acetic acid is used as reactant, the evolution of the reaction product hydrogen chloride presents disposal problems and can lead to loss of chlorine. These are avoided when acetic anhydride (**47**) is used as reactant.[26,45]



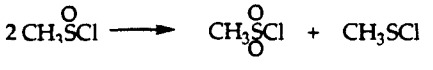
Use of thiolesters as reactants leads to higher yields. Whereas a poor yield of phenylmethanesulfinyl chloride was obtained from dibenzyl disulfide, nearly quantitative yields were produced by chlorination of *S*-benzyl thioacetate (**48**) in acetic anhydride.[40]



48

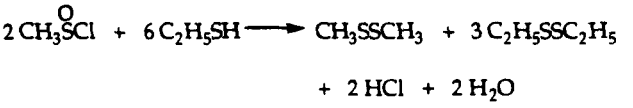
5.2 *Properties of Methanesulfinyl Chloride*

Methanesulfinyl chloride is unstable, decomposing by disproportionation to methanesulfonyl chloride (**49**) and methanesulfenyl chloride (**25**).[46] The latter is unstable and decomposes to hydrogen chloride and other products (see Section 4.2). Pressure build-up in sealed containers of alkanesulfinyl chlorides stored at room temperature has led to explosions.[45,46]

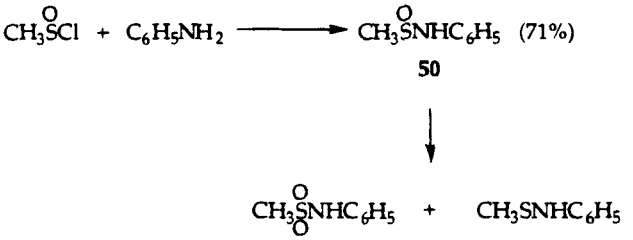


49 **25**

Reaction of methanesulfinyl chloride with ethanethiol did not lead to the expected alkanethiolsulfinate ester, but instead to a mixture of the symmetrical dimethyl and diethyl disulfides.[47]

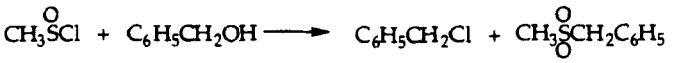


In cold ether solutions methanesulfinyl chloride readily reacts with aniline.[47] The methanesulfinamide **50** disproportionates to the sulfonamide and sulfenamide at room temperature.



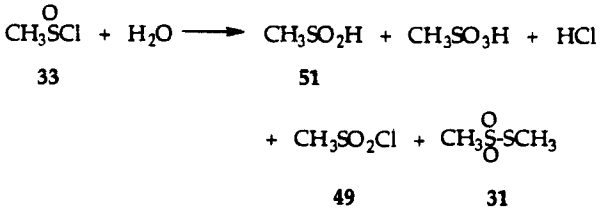
50

When an alcohol and methanesulfinyl chloride are refluxed together the alcohol is converted in high yield to the alkyl chloride. In the case of benzyl alcohol an 83% yield of benzyl chloride was isolated along with 8.3% of methyl benzyl sulfone.[47]



Along with the expected hydrolysis product methanesulfinic acid (**51**), reaction of meth-

anesulfinyl chloride (**33**) with water produces methanesulfonyl chloride (**49**), its acid and *S*-methyl methanethiosulfonate (**31**).[26,48]

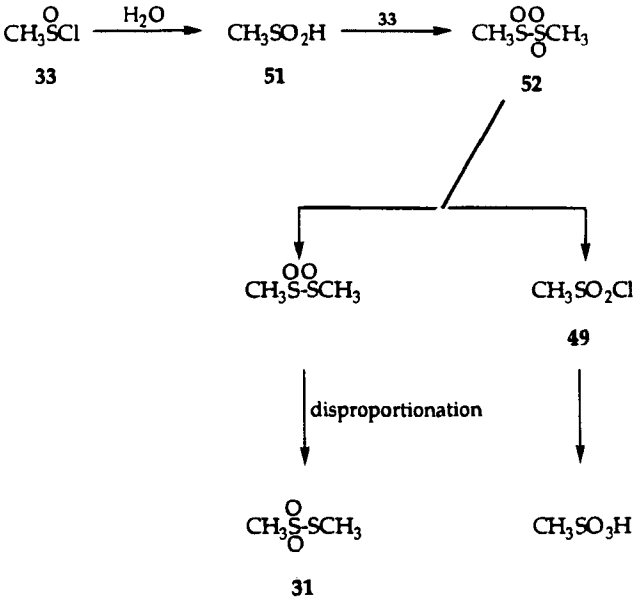


A proposed mechanism of this reaction is depicted in Scheme 10. NMR evidence was found for the existence of the transient sulfinyl sulfone intermediate **52**.

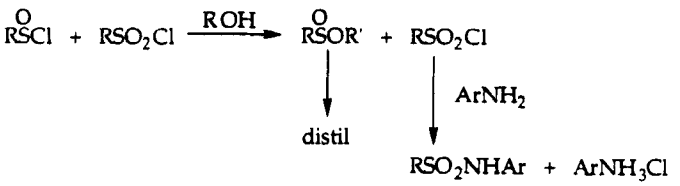
6. Sulfinate Esters

6.1 *Preparation*

Pure alkane- and arenesulfinate esters can be conveniently prepared in high yields by reaction of alcohols and sulfinyl chlorides, prepared by chlorination of aliphatic or aromatic thiols or disulfides in acetic anhydride as described in Section 5.1.[49] After removal of the acetyl chloride by-product the crude sulfinyl chloride reacts rapidly with added alcohol. The much more slowly reacting sulfonyl chloride contaminant is removed as its amide **53** by treatment with a high boiling primary amine, such as *p*-toluidine.

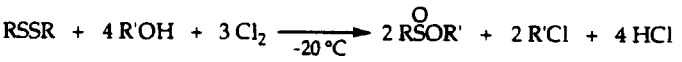


SCHEME 10 Mechanism of the hydrolysis of methanesulfinyl chloride.



53

Sulfinate esters may also be synthesized directly by the low-temperature chlorination of disulfides in alcohols.[50]



6.2 *Reactions of Sulfinate Esters*

Halogenation of a sulfinate ester by chlorine or bromine produces the sulfonyl halide and alkyl halide. The same products are formed when methylsulfur trichloride is the chlorinating agent, along with other products resulting from the secondary reaction of methanesulfenyl chloride with the ester.[49] These and other reactions are illustrated in Scheme 11.

n-Butyl methanesulfinate (**54**) can be formed in excellent yield by the reaction of 1-butanol with methyl methanesulfinate, in the presence of catalytic amounts of either sulfuric acid or sodium methoxide.[51] No ester interchange occurred with bulky *t*-butyl alcohol.

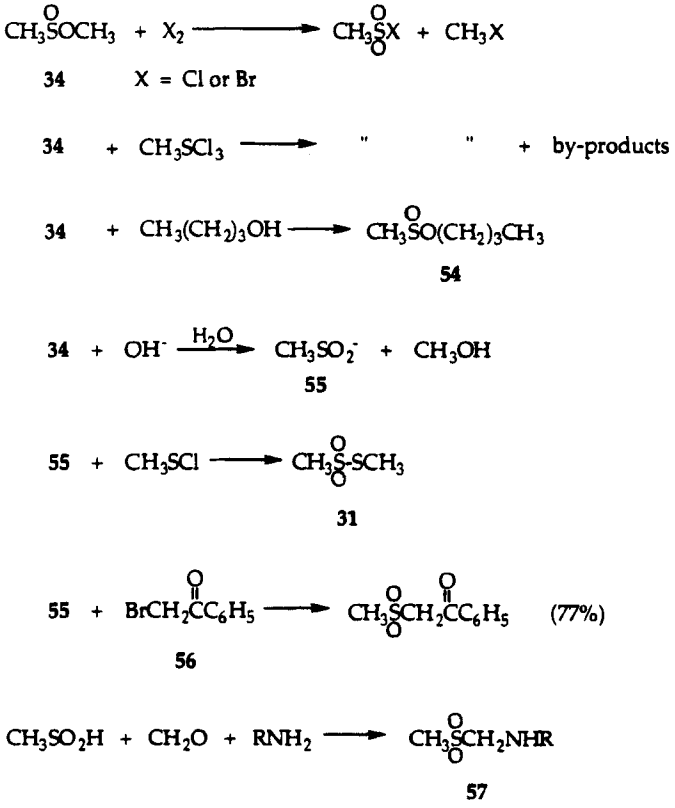
Methyl methanesulfinate is slowly hydrolysed by hot water, more rapidly in acid solution and with great speed in the presence of alkali.[49] The methanesulfinate anion **55** produced under the latter conditions has synthetic utility. When treated with methanesulfenyl chloride, *S*-methyl methanethiosulfonate (**31**) forms.[51] Good yields of sulfones are produced by reaction of **55** with compounds containing active halogen, such as benzyl chloride, *n*-butyl bromide, chloroacetone, phenacyl bromide (**56**) and 2,4-dinitrophenyl chloride. Products of Mannich-type reactions are formed when a solution of **55** is acidified with formic acid and mixed with formaldehyde and an amine or amide. Methysulfonylmethyl derivatives **57** were prepared from urea, benzamide, acetamide, methanesulfonamide and *p*-toluidine.[51]

7. THIOLSULFONATE ESTERS AND SULFENAMIDES

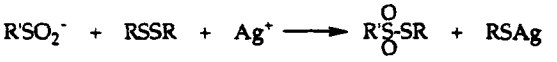
The preparation of *S*-methyl methanethiosulfonate (**31**) from reaction of methanesulfinic acid and methanesulfenyl chloride, each formed separately, was described in Section 6.2. Symmetrical thiolsulfonate esters, such as **31**, can be prepared in one reaction mixture by taking advantage of the more rapid hydrolysis of sulfinyl chlorides than that of sulfenyl chlorides (Scheme 12).[52] A mixture of symmetrical disulfide in 1 mol-equivalent of acetic acid is first chlorinated and then hydrolysed.

Unsymmetrical thiosulfonate esters **39** can also be prepared in one reaction mixture using a three-step process. Chlorination of the first disulfide in 2 mol-equivalents of acetic acid produces the sulfinyl chloride and acetyl chloride. Addition of a second disulfide and chlorination in the same reaction flask produces sulfenyl chloride. Addition of four mol-equivalents of water converts the sulfinyl chloride to sulfinic acid which reacts *in situ* with the sulfenyl chloride to form **39**.

Both symmetrical and unsymmetrical thiolsulfonate esters can be prepared in high yield by the cleavage of disulfides by thiosulfinate anions in the presence of silver ion.[53]

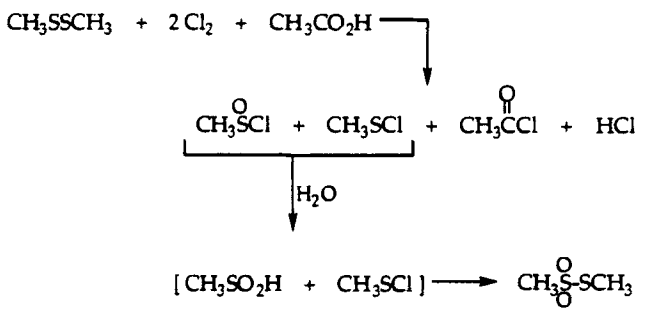


SCHEME 11 Reactions of methyl methanesulfinate.



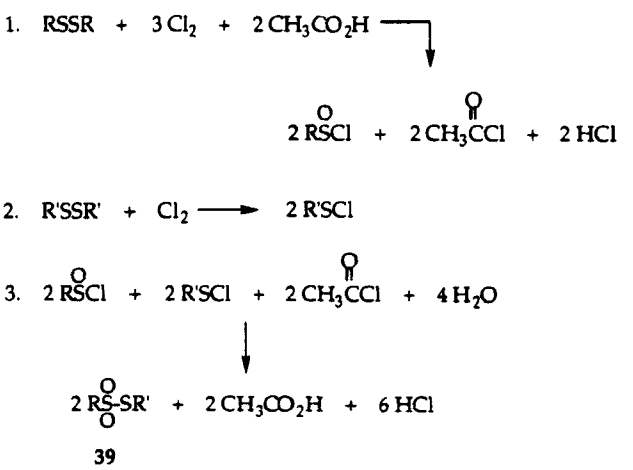
The proposed mechanism (Scheme 13) suggests that the transformation is initiated by formation of a silver ion-disulfide complex followed by nucleophilic displacement on sulfur by the sulfinate anion.

Symmetrical



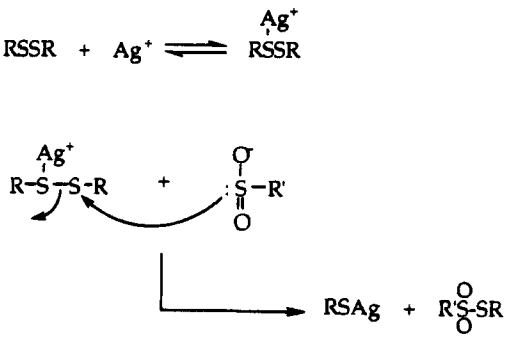
31

Unsymmetrical



39

SCHEME 12 Synthesis of symmetrical and unsymmetrical thiolsulfonate esters by chlorination and hydrolysis of disulfides.



SCHEME 13 Silver ion-assisted displacement on sulfur.

TABLE 2 ^1H Chemical Shifts (ppm) of Some Divalent Sulfur Compounds

Compound	δ	Compound	δ
CH_3SH	1.0	$CH_3SSSSSSCH_3$	2.66
CH_3SH	2.05	$CH_3SSO_2CH_3$	2.69
$CH_3SCH_2SCH_3$	2.05	CH_3SSCl	2.75
CH_3SCH_3	2.08	CH_3SSCCl_3	2.78
$CH_3C(O)SCH_3$	2.24	CH_3SCl	2.91
CH_3SCH_2Cl	2.28	$CH_3SCH_2SCH_3$	3.45
$CH_3SC(O)SSCH_3$	2.35	$CH_3SC(S)OCH_3$	4.05
CH_3SSCH_3	2.41	$CH_3C(O)SH$	4.47
CH_3SSH	2.42	CH_3SCH_2Cl	4.68
$CH_3SC(S)OCH_3$	2.46	CH_3SSCH_2Cl	4.78
CH_3SCHCl_2	2.47	$ClCH_2SSCH_2Cl$	4.84
$CH_3SSC(O)SCH_3$	2.48	$ClCH_2SCH_2Cl$	4.86
CH_3SCN	2.51	$ClCH_2SCHCl_2$	4.86
CH_3S_4Cl	2.51	$ClCH_2SO_2CHCl_2$	4.92
CH_3SSSCH_3	2.56	$ClCH_2SCl$	5.08
CH_3SSCH_2Cl	2.60	$ClCH_2SCCl_3$	5.10
$CH_3SS(O)CH_3$	2.62	$(Cl_2CH)_2S$	6.75
$CH_3SSSSCH_3$	2.64	CH_3SCHCl_2	6.75
$CH_3SSSSSCH_3$	2.64	Cl_2CHSCl	6.83
CH_3S_3Cl	2.65	$ClCH_2SCHCl_2$	6.85
CH_3SCCl_3	2.66	$Cl_2CHSCCl_3$	7.05

A high-yield, one-step synthesis of sulfenamides **58** from dialkyl or diaryl disulfides was developed using a similar pathway.[54]

$$RSSR + AgX + 2\,R'_2NH \longrightarrow RSNR'_2 + RSAg + R'_2NH_2X$$

58

8. NUCLEAR MAGNETIC RESONANCE OF ORGANOSULFUR COMPOUNDS

The wide variety of organosulfur compounds prepared in the studies reviewed in this account provides an opportunity to compile useful chemical shift data from their proton

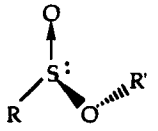
TABLE 3 ^1H Chemical Shifts (ppm) of Some Trivalent Sulfur Compounds

Compound	δ	Compound	δ
$CH_3SO_2^-$	2.34	$CH_3S(O)SCH_3$	2.94
$CH_3S(O)CH_3$	2.43	$CH_3S(O)Cl$	3.37
$CH_3S(O)OCH_3$	2.52	$CH_3S(O)OCH_3$	3.65
$CH_3SOSO_2CH_3$	2.87	$ClCH_2S(O)OCH_3$	4.09
CH_3SO_2H	2.93	$ClCH_2S(O)Cl$	4.78

TABLE 4 ^1H Chemical Shifts (ppm) of Some Tetravalent Sulfur Compounds

Compound	δ	Compound	δ
$CH_3SO_2CH_3$	2.98	$ClCH_2SO_2NH_2$	4.48
$CH_3SO_2CH_2Cl$	3.05	$ClCH_2SO_2CH_2Cl$	4.67
CH_3SO_3H	3.15	$ClCH_2SO_2Cl$	4.93
$CH_3SO_2CHCl_2$	3.17	$ClCH_2SO_2CCl_3$	5.13
$CH_3SO_2S(O)CH_3$	3.22	$CH_3SO_2CHCl_2$	6.18
$CH_3SO_2SCH_3$	3.31	$ClCH_2SO_2CHCl_2$	6.68
$CH_3SO_2CCl_3$	3.34	$(Cl_2CH)_2SO_2$	6.90
$(CH_3SO_2)_2O$	3.42	$Cl_2CHSO_2CCl_3$	7.18
CH_3SO_2Cl	3.63		

magnetic resonance spectra.[25,40,51,54] This is done for protons in compounds with divalent, trivalent and tetravalent sulfur in Tables 2, 3 and 4, respectively. The chemical shift data, measured on carbon tetrachloride solutions, are arranged in increasing downfield shift from the internal standard tetramethylsilane.



59

59a R = CH_3, R' = $(CH_3)_2CH$

59b R = $(CH_3)_2CH$, R' = CH_3

Sulfinate esters exhibit chemical shift nonequivalence in the heterosteric groups R and R′ in **59** caused by the magnetically anisotropic sulfinate center.[56] The intrinsic nonequivalence of methyl protons in the isopropyl group of **59a** was evident by chemical shifts of δ = 1.28 and 1.32 (CCl_4, 35°C). This nonequivalence was insensitive to temperature changes. The methyl substituents α to the sulfinyl sulfur in **59b** have little intrinsic nonequivalence. The use of anisotropic benzene as solvent enhanced the nonequivalence which was not evident in CCl_4.

9. ACKNOWLEDGMENTS

The senior author is indebted to his mentors, Dr. F. B. Dains of the University of Kansas and Dr. Treat B. Johnson of Yale University, who introduced him to the satisfaction enjoyed when one discovers a new compound or new reaction in organosulfur chemistry. He also wishes to acknowledge the assistance of fellow faculty members at various stages of his research. Much credit is also due to the graduate students who labored over their Master's or doctoral theses to reveal the chemistry described above. He expresses his gratitude to his daughter Miriam, who as co-author has summarized forty years of exploration in the field of organosulfur chemistry.

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