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THIOSULFONATES: SYNTHESIS, REACTIONS AND PRACTICAL APPLICATIONS

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The present review covers basic work on the synthesis, chemical reactions and practical application of organic thiosulfonates published before 1969, and gives more detailed attention to papers which appeared in the literature during the last 20 years. Three approaches to the synthesis of thiosulfonates, namely, (i) oxidation-reduction techniques, (ii) nucleophilic and, (iii) electrophilic introduction of an RSO_2S moiety into an organic substrate, are presented in this review. (The synthetic part is divided into two subchapters: the synthesis of "symmetric" thiosulfonates and of "unsymmetric" ones). Nucleophilic substitution, electrophilic reactions, thermolysis and photolysis of thiosulfonates are also described. A special chapter serves as a brief summary of some practical applications of thiosulfonates.

Key words: Thiosulfonates, symmetric and unsymmetric, -synthesis of, -reactions of; sulfides; sulfenic and sulfinic acid derivatives

CONTENTS

1. INTRODUCTION

The thiosulfonates[1] are a large class of organosulfur compounds of the general formula $RS\text{-}SO_2R'$, where R and R′ is aryl or alkyl. They can be referred to

either as *S*-esters of thiosulfonic acid or as derivatives of sulfenic acids. The present authors have no intention to cover fully the large amount of experimental data available on this particular topic. This review is rather an attempt to highlight some interesting results which are being by-passed in some more "fundamental" reviews on thiosulfonate chemistry.

2. SYNTHESIS OF THIOSULFONATES

There have been reported a large number of synthetic methods for the preparation of thiosulfonates. Some of these methods are well developed general techniques, whereas some have quite limited use. For the reader's convenience we have divided them into the two following subgroups: the synthesis of "symmetric" thiosulfonates (R = R′) and the synthesis of "unsymmetric" thiosulfonates (R ≠ R′).

2.1 *Synthesis of "Symmetric" Thiosulfonates*

2.1.1. *From S(II) Derivatives.* The most common method for the synthesis of thiosulfonates bearing the same groups R at S(II) and S(VI) is the oxidation of the corresponding disulfides. There have been proposed a wide range of oxidating reagents for this reaction, but *m*-chloroperbenzoic acid (MCPBA) is used most frequently. Oxidation by MCPBA proceeds under mild conditions ($CHCl_3$, 0 °C[2,3,4,5]) to furnish the corresponding thiosulfonates in very high yield (up to 95%). It is important to stress that the oxidation can be carried out stepwise, allowing the isolation of the intermediate monooxidation product, i.e. the thiosulfinate, after reaction with one equivalent of MCPBA.

$$\text{RS-SR} \xrightarrow[30\ \text{min},\ 0\ ^\circ\text{C}]{1\ \text{eq MCPBA}} \text{RS(O)-SR} \xrightarrow{1\ \text{eq MCPBA}} \text{RSO}_2\text{-SR}$$

Oxidation of unsymmetric disulfides RS-SR′ usually leads to a mixture of two thiosulfonates, RS-SO_2R′ and RSO_2-SR′, except in the case of alkyl phenyl disulfides, where the principal products are *S*-phenyl esters of alkanethiosulfonic acids.[2,3]

$$\text{AlkS-SPh} \xrightarrow{\text{MCPBA}} \text{AlkSO}_2\text{-SPh}$$

Alk = Et 84%

Alk = $PhCH_2$ 45%

Another example of an oxidizing system which is used quite frequently for these purposes is chlorine in acetic acid. Aromatic as well as aliphatic thiosulfonates have been obtained in high yield[5,6] with Cl_2/AcOH. For example:

$$\text{PhS-SPh} \xrightarrow[-5\ ^\circ\text{C},\ 1\ \text{h}]{\text{Cl}_2/\text{AcOH}} \text{PhSO}_2\text{-SPh} \quad (84\%)$$

Sulfuryl chloride can be used in this oxidation instead of chlorine.[7]

There is also an oxidative method which employs hydrogen peroxide in acetic acid.[8,9] The active reagent in this case is believed to be peracetic acid.

$$MeS\text{-}SMe \xrightarrow[25\ ^\circ C,\ 1\ h]{H_2O_2/AcOH} MeSO_2\text{-}SMe \quad (81\%, \text{ref.}^9)$$

Triphenylphosphine ozonide has also been utilized as an oxidant.[10] Its application leads to the formation of thiosulfonates and thiosulfinates.

$$Ph_3P\begin{smallmatrix}O\\O\end{smallmatrix}O + RS\text{-}SR \longrightarrow \underset{1}{RS(O)\text{-}SR} + \underset{10}{RSO_2\text{-}SR}$$

However, it is hard to believe that this particular method will find use in the synthesis of thiosulfonates, considering the large number of simpler and less "exotic" techniques.

Other reagents, such as $NaIO_4$,[5] V_2O_5, and HNO_3,[11] etc., have been used in the oxidation of disulfides, but only infrequently.

Thiols, thionitrates, thionitrites and some other S(II) derivatives have been used in oxidation reactions affording thiosulfonates. The first step of these reactions is S-S bond formation and then further oxidation to the thiosulfonate. For example, oxidation of thiols with chlorine[12] or bromine[13] was found to be a good preparative method for the synthesis of aromatic thiosulfonates.

$$ArSH \xrightarrow[\text{pet. ether, } 25\ ^\circ C]{Cl_2,\ Na_2CO_3} ArSO_2\text{-}SAr$$

$$Ar = p\text{-}X\text{-}C_6H_4,$$

$$X = H,\ Cl,\ MeO,\ CH_3C(O)NH$$

Cyclic thiosulfonates have been obtained by oxidation of α,ω-alkanedithiols with hydrogen peroxide.[14]

$$HS\text{-}(CH_2)_n\text{-}SH \xrightarrow{H_2O_2} (CH_2)_n\begin{smallmatrix}SO_2\\|\\S\end{smallmatrix} \qquad n = 4\ (28\%)$$

$$n = 3\ (26\%)$$

Dinitrogen tetroxide has been found to be a smooth and effective oxidant for thiols. The reactions were carried out in CCl_4 or Et_2O at −20 °C in the dark. A maximum yield was reached in the case of *t*-butanethiol.[15]

$$RSH \xrightarrow[-20\ ^\circ C]{4\ eq.\ N_2O_4} RSO_2\text{-}SR$$

$$R = Ar \text{ or } Alk$$

The reaction of a thiol with N_2O_4 takes place via the formation of a thionitrite, RS-NO.[16,17] This product has been isolated in the pure state, and its reactions with nucleophiles (e.g. with alcohols and amines) have also been studied.

$$RS\text{-}NO + Me(CH_2)_nOH \longrightarrow Me(CH_2)_nONO \quad n = 5\ (18\%)$$

$$RS\text{-}NO + HN(CH_2)_5 \longrightarrow ON\text{-}N(CH_2)_5$$

Introduction of a sulfinic acid after the reaction of the thiol with N_2O_4 leads to the formation of unsymmetric thiosulfonates.[16]

$$RS\text{-}NO \xrightarrow[CCl_4 \text{ or } Et_2O]{R'SO_2H} R'SO_2SR$$

R	R′
Ph	Tol
Bu	Tol
Tol	Ph
n-$C_{12}H_{25}$	*n*-$C_{12}H_{25}$
n-C_8H_{17}	Ph

Thionitrites can also be synthesized by reaction of thiols with $NaNO_2$ in HCl and then made to react with benzenesulfinic acid[18,19] (R = amino acid residue, yields ~ 60%):

$$RSH \xrightarrow[HCl]{NaNO_2} RS\text{-}NO \xrightarrow{PhSO_2H} RS\text{-}SO_2Ph$$

There is an example of the formation of a thiosulfonate from a thionitrate, generated by reaction of a sulfenyl chloride with silver nitrate.[20] The reaction involves the formation of sulfinyl radicals:

$$ArS\text{-}Cl + AgNO_3 \xrightarrow[-\ AgCl]{MeCN,\ -78\ ^\circ C} ArS\text{-}ONO_2 \xrightarrow{EtOH}$$

$$\longrightarrow [ArSO\cdot + NO_2] \xrightarrow[-\ NO_2]{} ArSO_2\text{-}SAr$$

2.1.2. *From S(IV) Derivatives.* Oxidation of thiosulfinates with *m*-chloroperbenzoic acid (MCPBA)[2,21,22,23] gives thiosulfonates.

$$RS(O)\text{-}SR' \xrightarrow[CHCl_3,\ 0\ ^\circ C]{MCPBA} RSO_2\text{-}SR'$$

R	R′
n-Alk	Ph
t-Bu	Ph
t-$BuCH_2$	*t*-$BuCH_2$
4-FC_6H_4	4-FC_6H_4

Sodium periodate ($NaIO_4$) is also capable of selective oxidation of unsymmetric thiosulfinates. However, the isolated yields in the case of symmetric compounds are much higher than with unsymmetric ones.[5,24]

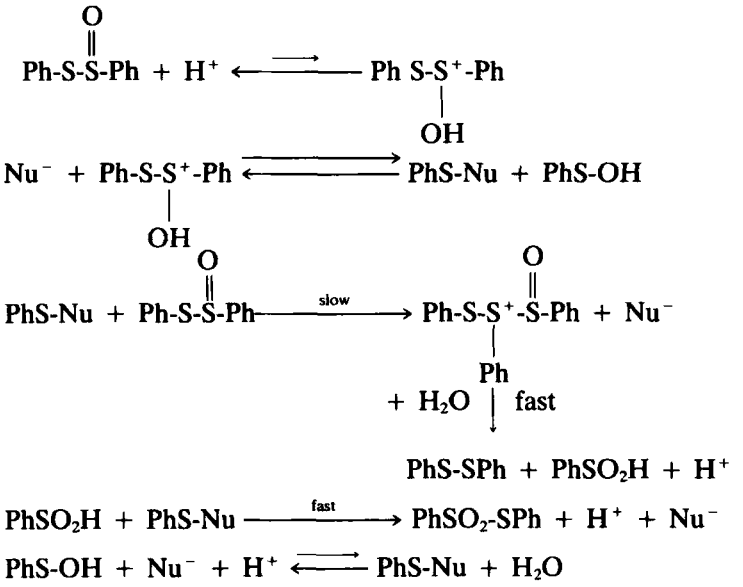
$$RS(O)\text{-}SR \xrightarrow[H_2O/H+]{NaIO_4} RSO_2\text{-}SR$$

R = Ar or Alk

It is also known from the literature that thiosulfinates on standing disproportionate to thiosulfonates and disulfides. The reaction is catalyzed by acids and nucleophiles.[25,26,27,28]

$$RS(O)\text{-}SR \longrightarrow RSO_2\text{-}SR + RS\text{-}SR$$

Sulfides or chloride (bromide) anion can serve as the nucleophilic catalyst. This reaction has been studied in detail by Kice and co-workers;[26,27] the following mechanism was suggested:



$$PhSO_2H + PhS\text{-}Nu \xrightarrow{\text{fast}} PhSO_2\text{-}SPh + H^+ + Nu^-$$

$$PhS\text{-}OH + Nu^- + H^+ \rightleftharpoons PhS\text{-}Nu + H_2O$$

While the disproportionation of thiosulfinates has been studied in depth, its synthetic application is restricted by the fact that half of the starting compound is practically wasted by disulfide formation.

Barnard reported a reaction of sulfinyl chlorides with zinc furnishing thiosulfonates.[29]

$$RS(O)Cl + Zn \xrightarrow{Et_2O} RSO_2\text{-}SR$$

R = Ph (96%), Bu (73%), Pr (68%), Pentyl (78%), Oct (78%)

The mechanism for this reaction, suggested by Freeman and Keindl,[30] implies the formation of a sulfenyl anion:

$$RS(O)Cl + Zn \longrightarrow R\text{-}S^-{=}O + ZnCl^+$$

$$RS(O)Cl + RS^-{=}O \longrightarrow [RS(O)\text{-}S(O)R \text{ or } RS(O)\text{-}O\text{-}SR] \longrightarrow RSO_2SR$$

2.1.3. *From S(VI) derivatives.* The reduction of alkane- or arenesulfonyl chlorides with potassium iodide in acetone gives the desired thiosulfonates in high yields.[31]

$$2\ RSO_2Cl \xrightarrow[\text{acetone, 25 °C}]{KI/Py} RSO_2\text{-}SR$$

R = CH_3, Ph, Tol, 4-$CH_3OC_6H_4$, etc. (60–85%)

The isolated yields increased when the reactants used were predried. The reac-

tion is believed to occur via a thiol generated *in situ*. This thiol then reacts with the sulfonyl chloride to give the thiosulfonate as the principal product. The contribution of a possible side reaction, i.e. reaction of the thiol with the thiosulfonate, is negligible.

Thermolysis of arenesulfonylhydrazines is also used for the synthesis of "symmetric" aromatic thiosulfonates.[8]

$$RC_6H_4SO_2\text{-}NH\text{-}NH_2 \xrightarrow[-N_2,\ -H_2O]{} RC_6H_4SO_2\text{-}SC_6H_4R$$

The thiosulfonate forms in this reaction along with sizable amounts of contaminants, mainly disulfides and a sulfonamide, and the isolated yields do not exceed 55%. This makes the reaction interesting primarily from a theoretical point of view rather than as a preparative method.

2.2 *Synthesis of "Unsymmetric" Thiosulfonates*

2.2.1. *By reaction of S(II) with S(IV) compounds.* The most important procedure for the synthesis of thiosulfonates possessing different substituents at the S(II) and the S(VI) atom is reaction between sulfenic and sulfinic acids derivatives, based on the thiophilicity of the sulfinate anion toward electrophilic sulfenylating species such as sulfenyl chlorides,[32] sulfenamides,[33] disulfides,[34] and thiosulfinates.[35]

$$R\text{-}SO_2^- \xrightarrow[-X^-]{R'SX} RSO_2\text{-}SR'$$

$$X = Hal, NR''_2, SR, S(O)R''$$

Thus, reaction of trichloromethanesulfenyl chloride and sodium sulfinates proceeds smoothly at room temperature to give the corresponding thiosulfonates.[32] The yields of aliphatic as well as aromatic thiosulfonates are moderate, 35–60%.

Thiosulfonates have also been obtained by reaction of heterocyclic sulfinic acids with aliphatic sulfenamides.[33]

$$RSO_2H + R'S\text{-}NEt_2 \longrightarrow RSO_2SR' \quad (38\text{–}57\%)$$

$$R = \text{hetaryl};\ R' = Me, Et, Pr, Bu$$

Bentley and co-workers[34] used disulfides as sulfenylating reagents. The reactions were carried out in the presence of $AgNO_3$.

$$MeSO_2Na + RSSR + ArNO_2 \longrightarrow MeSO_2SR + RSAg + NaNO_3$$

$$R = Me, Et, i\text{-}Pr$$

Thiosulfinates can also serve as the source of the sulfenylating agent, due to the fact that the rate of nucleophilic substitution at $-S(O)R$ is much slower than that at an RS center and, therefore, the nucleophile usually attacks S(II).[35]

$$ArSO_2H + PhS(O)\text{-}SPh \longrightarrow ArSO_2\text{-}SPh + H_2O$$

2.2.2. *By reaction of S(II) with S(VI) compounds.* The only method which fits this classification is the reaction of sulfonyl halides with thiolate anions.[36]

$$RSO_2Hal + R'S^-M^+ \xrightarrow[-\ MHal]{\text{acetone}} RSO_2\text{-}SR'$$

$$R = Ar$$

The isolated yields of thiosulfonates in this reaction leave much to be desired (< 40%) and there is a persistent by-product, the disulfide R'S-SR' formed as a result of reaction between thiosulfonate and excess thiol. This problem is the main reason why this reaction is not used as a *preparative* method for thiosulfonate synthesis.

2.2.3. *From alkali metal thiosulfonates.* Reaction of alkali metal thiosulfonates with alkyl or aryl halides[37,38] is a much more selective method for the synthesis of organic thiosulfonates compared with the method just mentioned above.

$$RSO_2S^-M^+ \xrightarrow[-\ MHal]{R'Hal,\ acetone/H_2O} RSO_2\text{-}SR'$$

$$R = XC_6H_4\ (X = H, Cl, Br, MeO, AcNH, NO_2, CH_3)$$

$$R' = Et, Pr, i\text{-}Pr, Bu, i\text{-}Bu, Ph_2CH$$

The only problem which restricts the general application of this method is the complexity of the synthesis of the starting $RSO_2S^-M^+$ which involves the reaction of freshly prepared hydrosulfide with a sulfonyl chloride:[39,40]

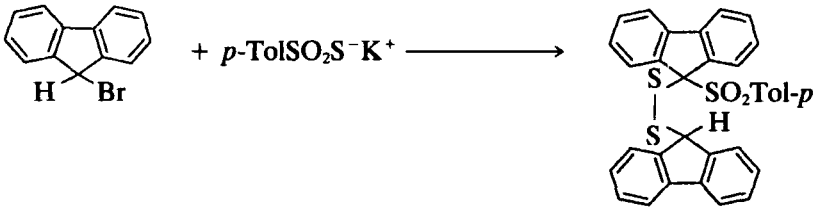
$$MOH + H_2S \xrightarrow[-H_2O]{} MSH \xrightarrow[-HCl]{RSO_2Cl} RSO_2S^-M^+\ (M = K, Na)$$

There have been reported, however, good alternative methods for the synthesis of thiosulfonates of alkali metals employing reaction of elemental sulfur with sulfinate in amine as a solvent[41] or the same reaction in the presence of an anion exchange resin.[42]

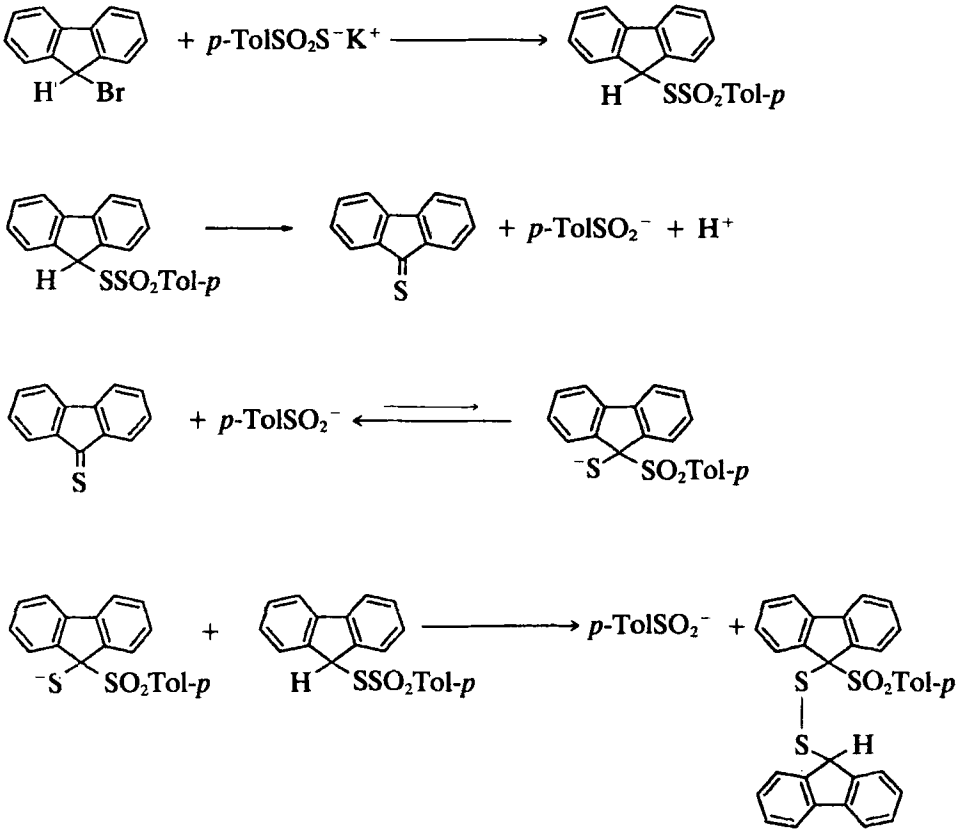
$$R\text{-}C_6H_4\text{-}SO_2^-Na^+ + S_8 \xrightarrow[20\ ^\circ C]{\text{amine or } NH_3} R\text{-}C_6H_4\text{-}SO_2S^-Na^+\ (\text{ref. } ^{41})$$

amine = Et_2NH, Et_3N, morpholine, piperidine

Reaction of potassium *p*-toluenethiosulfonate with a diarylmethyl bromide normally leads to the formation of a diarylmethyl *p*-toluenethiosulfonate.[38,43,44] However, an attempt to obtain 9-fluorenyl thiosulfonate by this reaction failed. Instead of the desired thiosulfonate, the authors[45] isolated a difluorenyl disulfide derivative containing a *p*-toluenesulfonyl group:



This disulfide with its unusual structure is assumed to arise as a result of the reaction sequence shown below, the key step being facile elimination from the initially formed "normal" 9-fluorenyl thiosulfonate due to the acidity of the proton in the 9-position.

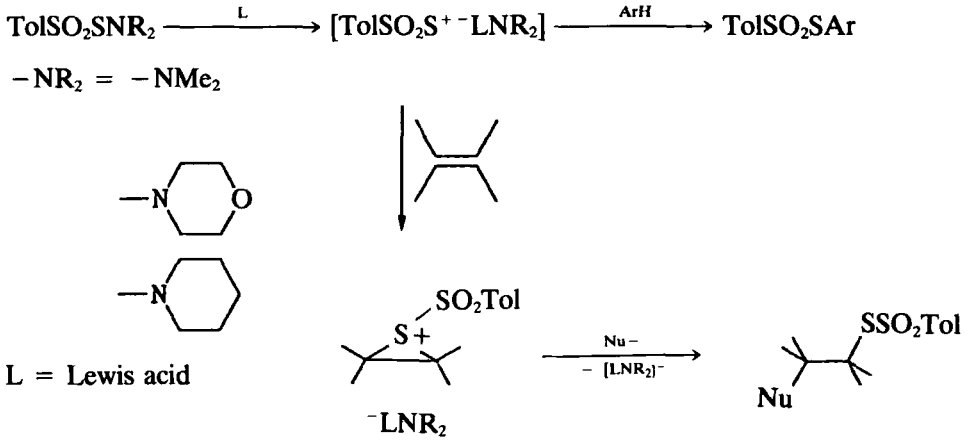


Apparently, acidic α-hydrogens in alkyl halides can cause problems for the synthesis of thiosulfonates. Weidner and Block[46] attempted a synthesis of 4-bromophenacyl *p*-toluenethiosulfonate by reaction of *p*-$TolSO_2S^-K^+$ with 4-bromophenacyl bromide (4-$BrC_6H_4C(O)CH_2Br$). Along with the desired thiosulfonate they isolated a by-product, believed to be the sulfide thiosulfonate 4-$BrC_6H_4C(O)CH(SSO_2Tol\text{-}p)SCH_2C(O)C_6H_4Br$-4. The authors explain its formation by sulfenylation of the anion 4-$BrC_6H_4C(O)\text{-}CH^-\text{-}SSO_2C_6H_4Br$-4 by the thiosulfonate 4-$BrC_6H_4C(O)\text{-}CH_2SSO_2C_6H_4Br$-4. This, however, is not in keeping with the previously mentioned reaction of potassium *p*-toluenethiosulfonate with 9-bromofluorene.

2.2.4. *From derivatives of thiopersulfonic acids.* The thiosulfonate synthesis described in 2.2.3 is based on the direct *nucleophilic* introduction of a thiosulfonate group at an electron-deficient site. Recently there has been developed an

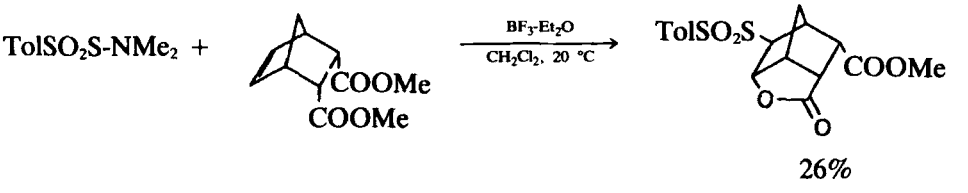
opposite approach, i.e. the *electrophilic* introduction of an RSO_2S moiety into a nucleophilic molecule which makes it possible to extend considerably the range of substrates useful for the synthesis of thiosulfonates. *S*-Sulfonylsulfenamides ($RSO_2SNR'_2$), *S*-sulfonylthio-sulfenamides ($RSO_2SSNR'_2$) and *S*-sulfonylsulfenyl chlorides (RSO_2SCl) have been used as synthetic equivalents of the RSO_2S^+ species.[47,48,49,50]

S-Sulfonylsulfenamides (or aminothiosulfonates) have been known since the 1970's[51] and *S*-sulfonylthio-sulfenamides since the 1980's[52], but their reactions were not studied until recently. It has been found that, upon activation with Lewis acids (BF_3-Et_2O, SO_3, or Py-SO_3), *S*-tosylsulfenamides react as synthetic equivalents of the electrophilic species *p*-$TolSO_2S^+$ and are capable of adding to the olefinic double bond as well as of initiating electrophilic aromatic substitution.



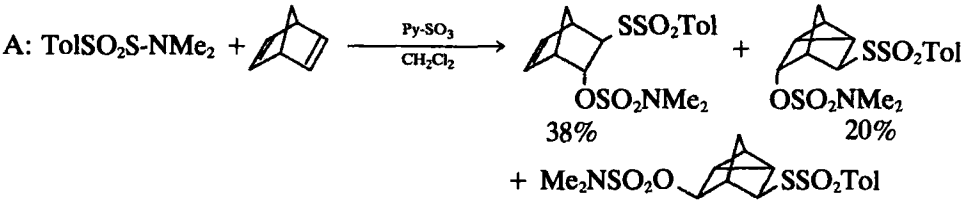
Depending on the type of olefin there are two products which can be formed: either (i) sulfamato-thiosulfonates of type A in the case of conformationally rigid olefins (e.g. norbornene or norbornadiene), or (ii) betaines B in the case of conformationally flexible olefins. These two types of reaction products, however, are not unusual for SO_3-mediated additions of "standard" sulfenamides to olefins (cf.[53,54,55,56]).

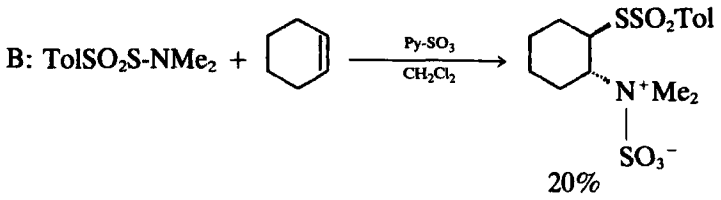
In some cases products of conjugated addition have been obtained.



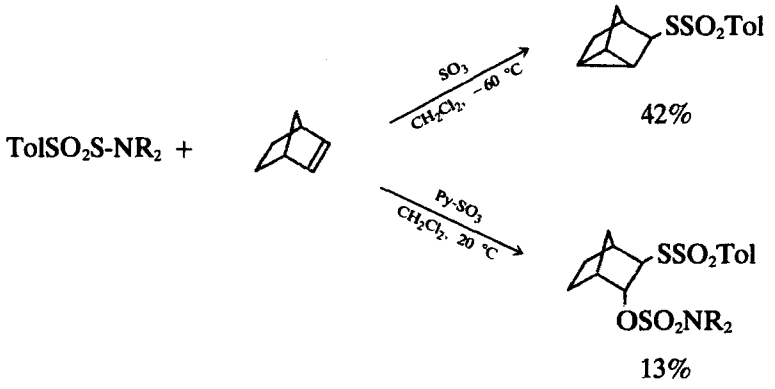
26%

A study of reactions of *S*-tosylsulfenamides activated by sulfur trioxide





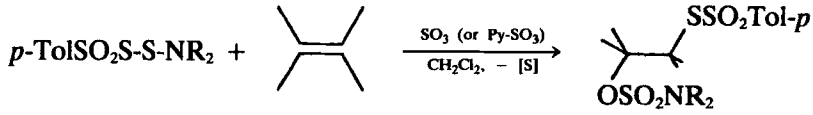
shows that the outcome of these reactions with norbornene depends on whether neat sulfur trioxide or its complex with pyridine is used as the activating reagent. Thus, in the case of neat sulfur trioxide, the formation of a 3-tricyclo[2.2.1.$0^{2,6}$]heptyl thiosulfonate by addition-elimination was observed, whereas the reaction with Py-SO_3 gave the normal 1,2-adduct. The author assumes[50] that this result implies the involvement of two different electrophilic species.

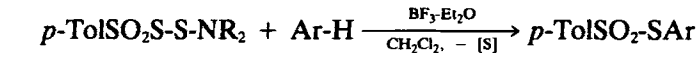


Aromatic substitutions (e.g. with anisole or phenetole) take place upon activation by BF_3-Et_2O. The isolated yields here as well as in the above-mentioned electrophilic additions to olefins are moderate, 25 to 50%.

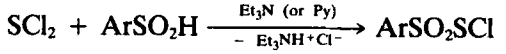
The same products have been obtained from similar activated additions of *S*-sulfonylthiosulfenamides to unsaturated substrates. The experimental procedure does not differ from that for *S*-sulfonylsulfenamides. However, the isolated yields

of the target thiosulfonates were increased 2- to 3-fold compared to those with *S*-sulfonylsulfenamides.

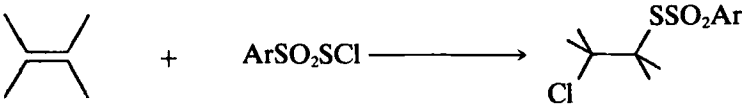


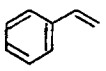


In spite of the fact that *S*-acyl sulfenyl chlorides [RC(O)SCl] as well as aryl- and alkyloxycarbonyl sulfenyl chlorides [ROC(O)SCl] have been known since the 1950's,[57,58,59] and that the chemistry of the analogous phosphorus-containing sulfenyl chlorides [$R_2P(O)SCl$] has been under detailed investigation for quite a long time,[60] their sulfur analogs, the *S*-sulfonyl sulfenyl chlorides [RSO_2SCl] were unknown until recently. They have now been obtained by reaction of sulfur dichloride with arenesulfinic acids in the presence of a tertiary amine.[49] Diethyl ether or methylene chloride served as solvent.



Apparently, *S*-sulfonylsulfenyl chlorides are synthetic equivalents of the RSO_2S^+ species. Indeed, their reactions with olefins proceed smoothly at room temperature without any additional activation.



Olefin	Ar	isolated yield of addition product, %	
	Ph	10	
	p-Tol	76	
	o-$NO_2C_6H_4$	24	
	Ph	51	mixture of regioisomers
	p-Tol	64	
	o-$NO_2C_6H_4$	17	
	Ph	47	*trans*-1,2-adduct
	p-Tol	45	
	*p*-Tol	23	Markovnikov adducts
	*p*-Tol	40	

Thus, *S*-sulfonylsulfenyl chlorides are of great importance for the electrophilic introduction of thiosulfonate groups which makes it possible to draw on the large number of readily available olefins and arenes as possible starting materials for the synthesis of thiosulfonates.

To summarize briefly part 2 of this review:

The most frequently employed method for the synthesis of "symmetric" thiosulfonates is the oxidation of disulfides (2.1.1).

$$RS\text{-}SR \xrightarrow{[O]} RSO_2\text{-}SR$$

"Unsymmetric" thiosulfonates can be synthesized by nucleophilic substitution with sodium or potassium thiosulfonates (2.2.3)

$$RSO_2S^-M^+ + R'Hal \longrightarrow RSO_2SR'$$

However, the most frequently employed method for the synthesis of "unsymmetric" thiosulfonates is the reaction of sulfinate anions with sulfenyl halides or their analogs (2.2.1)

$$R\text{-}SO_2^- + R'S\text{-}X \xrightarrow[-X]{} RSO_2SR'$$

$$X = Hal, NR''_2, SR'', S(O)R''$$

Electrophilic introduction of the thiosulfonate group, sulfosulfenylation of alkenes with *S*-sulfonylsulfenyl chloride, appears to be another good preparative method for thiosulfonates (2.2.4).

3. CHEMICAL PROPERTIES OF THIOSULFONATES

The reactions of thiosulfonates are somewhat similar to the reactions of sulfenyl chlorides and some other derivatives of sulfenic acids. This is why Hogg called them "moderated" sulfenyl chlorides in sulfenylation reactions.[1] However, in some radical reactions and oxidation-reduction processes thiosulfonates behave quite differently.

3.1. *Nucleophilic Substitution*

Thiosulfonates react with nucleophiles according to the following scheme:

$$Nu^- + RS\text{-}SO_2R' \longrightarrow NuSR + R'SO_2^-$$

$$Nu = AlkO^-, RS^-, R_2NH, RMgX, PR_3, {}^-CHXY$$

The rate of nucleophilic substitution at $-SO_2R$ is several orders of magnitudes lower than that of substitution at $-SR$ or $-S(O)R$.[61] That is why the attack of a nucleophile usually takes place at the S(II) atom. There are, however, exceptions to this rule: in reactions with amines or thiols, *trichloro* and *trifluoro* derivatives of the type $CHal_3S\text{-}SO_2R$ give sulfonamides and thiosulfonates by nucleophilic attack at the S(VI) atom of the starting thiosulfonate. Weidner and Block[62] believe that electronic factors account for this deviation from the usual chemical

behavior of thiosulfonates. They proved that steric factors are not responsible. For example, p-$TolSO_2SCCl_3$ reacts with morpholine in ethanol to yield a sulfonamide. At the same time the more bulky p-$TolSO_2SCMe_3$ gives a sulfenamide. The authors offer the following explanation based on a consideration of electronic effects: p-$TolSO_2SCMe_3$ has only one electron-withdrawing group at S(II), and the lone electrons at S(II) are shifted toward the p-$TolSO_2$ group. In p-$TolSO_2CCl_3$ there are two electron-withdrawing groups, p-$TolSO_2$ and CCl_3, at the S(II) atom. Thus, the lone electrons are located closer to the S(II) atom, reducing its electrophilicity.

In general, reactions of thiosulfonates with nucleophiles lead to the formation of the same products as the corresponding reactions of sulfenyl chlorides. However, the greater stability of thiosulfonates in comparison with that of sulfenyl chlorides make them more valuable for sulfenylations.

Thiols react with thiosulfonates to yield disulfides. The high rate of this reaction makes it impossible to obtain thiols by basic hydrolysis of thiosulfonates because the thiol, once formed, reacts with the starting thiosulfonate to give the disulfide as the principal product.[63a]

$$4\ RSX + OH^- \longrightarrow 3\ RS^- + 4\ X^- + RSO_2^- + 2\ H_2O$$

for X = Hal, OR, NR_2, S(O)R

$$3\ RSO_2\text{-}SR + 4\ OH^- \longrightarrow RS\text{-}SR + 4\ RSO_2^- + 2\ H_2O$$

for X = SO_2R

The reactions with amines have been found to proceed smoothly in polar solvents such as MeCN, DMF, EtOH and DMSO:

$$RSO_2\text{-}SR' + NH_3 \longrightarrow RSO_2H\cdot NH_3 + R'SNH_2 \quad \text{(ref. 63a)}$$

$$RSO_2\text{-}SR' + H_2NR'' \longrightarrow RSO_2H\cdot H_2NR'' + R'SNHR'' \quad \text{(ref. 63a)}$$

$$RSO_2\text{-}SR' + HNR''_2 \longrightarrow RSO_2H\cdot HNR''_2 + R'SNR''_2 \quad \text{(ref. 63b)}$$

$$RSO_2\text{-}SR' + NR''_3 \longrightarrow R'S\text{-}N^+R''_3\ RSO_2^- \quad \text{(ref. 64)}$$

A quite unusual example of C-S bond cleavage following a nucleophilic attack of morpholine at the S(II) atom of thiosulfonate has been reported by Senning.[65]

$$PhSO_2S\text{-}CH(SO_2Ph)_2 + R_2NH \longrightarrow PhSO_2S\text{-}NR_2 + CH_2(SO_2Ph)_2$$

Reactions of thiosulfonates with CH-acids have been studied in detail by several groups of researchers.[66,67,68,69,70] For example, reaction of arenethiosulfonates with some CH-acids in the presence of base gives the corresponding arylthio derivatives:

$$YCH_2X \xrightarrow[\text{or NaOR}]{Et_3N} YCH^-X \xrightarrow{RSO_2SR'} R'S\text{-}CHXY$$

X = Y = Ac, R = p-$NO_2CH_6H_4$, R' = 2,4-$(NO_2)_2C_6H_3$ (66%)

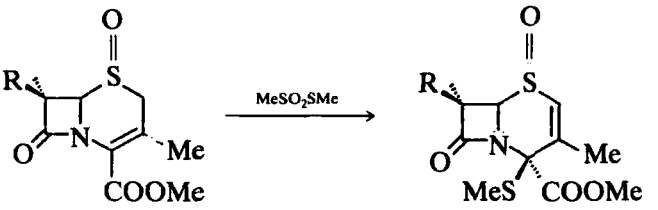
X = Ac, Y = CO_2 Et, R = p-$MeOC_6H_4$, R' = Ph (54%)

It is also possible to synthesize disubstituted compounds $(RS)_2CXY$[69,70] in this way.

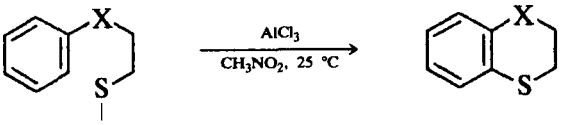
The outcome of thiosulfonate reactions with P(III) derivatives depends strongly on the structure of the reactants.[71]

3.2. *Electrophilic Reactions*

The electrophilic reactions of thiosulfonates resemble the corresponding reactions of sulfenyl chlorides. Thus, reactions of cefalosporins with methyl methanethiosulfonate proceed regio- and stereoselectively to furnish only the β-isomer:[72]



Thiosulfonates react with some aromatic compounds in the presence of Lewis acids such as $AlCl_3$ to give products of electrophilic substitution of the aromatic ring. Benzo-1,4-dithiin and benzo-1,4-oxathiin[73] have been prepared in this manner.

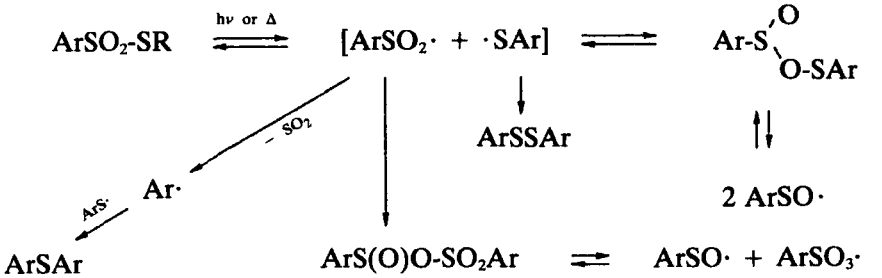


X = S, 73%

X = O, 76%

3.3. *Thermolysis and Photolysis*

The thermolysis and photolysis of thiosulfonates have been studied intensively by ESR. There is certainty about the formation of sulfonyl and sulfinyl radicals. Gilbert and co-workers[74,75] proposed the following mechanism for these reactions.



3.4 *Oxidation and Reduction*

Cautious oxidation of thiosulfonates with MCPBA leads to the formation of α-disulfones.[76,77,78]

$$RSO_2\text{-}SR \xrightarrow{MCPBA} RSO_2SO_2R$$

The oxidation with KO_2/18-crown-6 in pyridine is accompanied by S-S bond breaking and gives both sulfinic and sulfonic acid.[79]

$$PhSO_2SPh \xrightarrow[Py,\ 0\ °C]{KO_2/18\text{-Crown-6}} PhSO_2^- + PhSO_3^-$$

Reduction with Zn in alcohol gives thiol and sulfinic acid, whereas reduction with Zn in acidic media or reduction with sodium amalgam produces two thiols:[1]

$$RSO_2\text{-}SR' \xrightarrow{Zn/alcohol} RSO_2H + R'SH$$

$$RSO_2\text{-}SR' \xrightarrow[or\ Na/Hg]{Zn/H^+} RSH + R'SH$$

It is possible to avoid S-S bond breaking during the reduction of a thiosulfonate. Thus, reaction with iron gives disulfides in high yields:[80]

$$RSO_2\text{-}SR' \xrightarrow[10\ h]{Fe,\ 200\ °C} RS\text{-}SR'$$

R = R′ = Ph, Tol, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, Et or R = Tol, R′ = Ph

If the temperature exceeds 200 °C, the reduction furnishes a mixture of disulfide and sulfide.

Reduction with NaI and trimethylchlorosilane also proceeds without cleavage of the S-S bond to yield the corresponding disulfide.

$$RSO_2\text{-}SR' \xrightarrow{Me_3SiCl/NaI} RS\text{-}SR'\ (R,R' = Ar)$$

The authors[81] proposed a rather complex mechanism for this reaction involving S-S bond cleavage and re-formation. They assume that the actual reactive intermediate is Me_3SiI.

4. PRACTICAL APPLICATION OF THIOSULFONATES

The ready availability of thiosulfonates and their stability make them very valuable for industrial use. There are three principal groups of industrial application of thiosulfonates: (i) as biologically active compounds,[32,37,82,83,84,85] (ii) in polymer production,[86,87] and (iii) in photographic processes.[88,89]

The use of thiosulfonates as biologically active compounds appears to be of great perspective. Their bactericidal and fungicidal activity is evidently due to blocking of the normal metabolism of the microorganisms by sulfenylation of the thiol groups of enzymes.[90] The following aryl and alkyl esters of thiosulfonic acids are being used as preservatives in the storage of fruit and vegetables.

$EtSO_2\text{-}SAlk$, *p*-$NH_2C_6H_4SO_2\text{-}SC_6H_4NH_2$-*p*, $EtOC(O)CH_2S\text{-}SO_2C_6H_4NH_2$-*p*

Several alkyl alkanethiosulfonates (e.g. *c*-C_5H_9S-SO_2Pr or *c*-C_5H_9S-$SO_2C_6H_{11}$-*c*) inhibit the growth of bacteria which cause onion rotting and, at the same time, can stimulate the growth of some plants.

Boldyrev and co-workers mentioned an antimicrobial activity of trichloromethyl and alkyl esters of thiosulfonic acids.

Finally, some thiosulfonates such as $(CH_3)_2N$-$CH(CH_2SSO_2Ph)_2$ have found use as insecticides.[82]

The copolymerization of some unsaturated thiosulfonic acids with styrene or vinyl acetate gave polymers possessing lower viscosity and degree of polymerization. This was possibly due to thiosulfonate participation in the chain transfer step.

A mixture of thiosulfonates of the type $ArSO_2$-SAr′ (Ar and Ar′ = Ph or 4-RC_6H_4) with azodicarboxamide has been used as a blowing agent for thermoplastics.[87]

There is still another area of thiosulfonate applications, i.e. photographic emulsions. Addition of bis-thiosulfonates ($ArSO_2$-$S(CH_2)_nS$-SO_2Ar, Ar = Ph or 4-RC_6H_4) to silver halide emulsions increases the sensitivity by 20–60%. Compounds of the following type RSO_2 $S[(CH_2)_nSSO_2]_mR$ (R = aryl or hetaryl, n = 1–4, m = 0,1) was found to minimize haze.[88] The authors explain these effects by the low hydrophilicity of thiosulfonates and their enhanced ability to be absorbed by the AgHal surface, which increases the quantum yield and decreases haze formation.

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