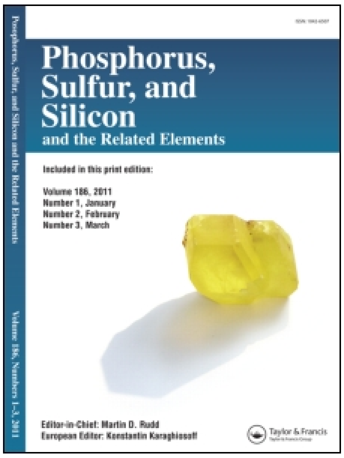

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SOME INDUSTRIAL SULFUR COMPOUNDS ; NOVELTIES IN THEIR MANUFACTURE, MAIN USES AND POTENTIAL DEVELOPMENTS

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ABSTRACT

Much progess has been made in recent years in the manufacture of the main basic sulfur compounds.

Emphasis has been placed on improvement of the quality and consistency of industrial sulfur compounds ; reducing by-products, residual organic chlorides and catalyst impurities ; and dealing with environmental problems tied to odor and the toxicity of most of these products. This explains the tendancy to look for synthetic routes which avoid chlorine-containing raw materials and to select solid catalysts which are easier to separate.

In the mercaptan series, methyl mercaptan, which is the major product by virtue of its use in methionine production, is now experiencing the increasing development of carbamates as insecticides. The main uses of other mercaptans involve manufacture of agrochemicals in the thiocarbamate and thiophosphate series.

The mercaptocarboxylic acids are commonly used as plastic additives, in heat-stabilizers for PVC and as antioxidants for polyolefins. However, thioglycolic acid is experiencing promising developments in the field of thiophenic derivatives.

We must mention the specific and important developments of dimethyldisulfide as a safe sulfur donor in the refining industry and as a thiomethylating agent. Dimethylsulfoxide is becoming increasingly important as a solvent for organic synthesis and as a reactant in the pharmaceutical industry.

Other versatile reactants are methanesulfonyl chloride, a convenient building block for synthesis of pharmaceutical and agrochemical intermediates, and methanesulfonic acid which is experiencing strong growth as an acid catalyst, an electrolyte, a solvent and a reagent for pharmaceutical and agrochemical syntheses.

1. INTRODUCTION

This survey covers a range of topics showing the potential development and the main actual uses of the most important basic industrial organic sulfur compounds.

Our background in sulfur chemistry, in the ELF ATOCHEM GROUP, began in the fifties with the discovery of many sour gas fields in the Southwest of FRANCE, and the launch of a major program to manufacture and develop a full line of sulfur compounds based on H2S chemistry, including mercaptans, sulfides, polysulfides, sulfoxides, mercaptoacids and esters and sulfonic acids and chlorides. In the USA, other sources of H2S were used to build the same line of products, nowadays within the framework of ELF ATOCHEM N.A.

Many thousands of organic sulfur compounds have been synthesized, but only some hundreds have reached the industrial scale. However, sulfur chemicals play a vital role in the formulation of a wide range of products including cosmetics, lubricants, polymers, agricultural and pharmaceutical chemicals, animal feeds, oil and plastic additives and refining and gas production additives. New developments of sulfur compounds are tied to many complementary actions :

- Fundamental research concerning new synthetic routes more convenient to scale up,
- Applied research concerning properties of the sulfur compounds.

2. MANUFACTURE OF SULFUR COMPOUNDS

Numerous routes could be applied to synthesize sulfur-containing molecules. It will be necessary to select the best way regarding :

- the more economical raw material,
- the potential to produce a purer product free of by-products or catalysts traces,
- the handling of odorous or toxic products under safe conditions,
- the more convenient waste treatment.

The sulfur could be introduced by many sources :

- CS_2 is used for specific reactions leading to thiocarbonates, thiocarbamates, thiurames or thioureas.
- Sulfur chlorides are used to react with olefinic and phenolic compounds. Residual chlorine species must be avoided.
- Sulfur itself can react with unsaturated compounds, but this reaction is not selective. Sulfur is a convenient and cheap reagent to obtain polysulfides from mercaptans.
- H_2S is the more convenient reagent to produce mercaptans and derivatives (1).

H_2S is separated from sour gas by well-tested sweetening processes applying a chemical absorption (amines, carbonates) or a physical absorption by solvents. H_2S is available at a purity of greater than 99 %.

H_2S is produced industrially by reaction of hydrogen and sulfur :

$$H_2 + S \text{ -------> } H_2S \qquad \text{(Girdler process (450°C))}$$

or by reaction of sulfur and methane :

$$CH_4 + 4S \text{ ------> } 2H_2S + CS_2 \quad \text{(Folkins process)}$$

2.1. MERCAPTANS and SULFIDES MANUFACTURE

Many routes can be used to obtain mercaptans, starting from H_2S or its salts.

2.1.1. Heterogeneous catalysis on n-Alcohols

In the thiolation of alcohols, H_2S acts as a nucleophilic reactant with basic or acidic catalysts. The nucleophilic substitution of alcohols by H_2S occurs at 300°C on an alumina type catalyst impregnated with alkaline agents (Na_2O, K_2O) or transition metal oxide (WO_3). Phosphotungstate alkaline salts on alumina have also been used. Mercaptans can react with alcohols, under the same conditions, to produce sulfides. The H_2S/ROH ratio must be increased to improve mercaptan selectivity over sulfide selectivity. The temperature, in the range 300-400°C, must be decreased as the molecular weight of the alcohol increases to avoid alcohol dehydration(2).

Mercaptans ranging from methylmercaptan to dodecylmercaptan have been industrially synthesized by thiolation of primary alcohols.

- Thiolation of secondary alcohols is not the preferred route to synthesize secondary mercaptans, because of competing dehydration of the alcohols. In this case the preferred route is H_2S addition to olefinic compounds.

- H_2S can also react with aliphatic or cyclic oxides to produce sulfides. This is one way to synthesize tetrahydrothiophene or thiophene(3).

2.1.2. H_2S addition to olefins

The catalytic addition of H_2S to olefins follows the Markovnikov rule, the SH species attacks the less hydrogen-containing carbon on the double bond.

With linear olefins, having terminal or internal double bonds and acidic catalysts (zeolites, cation exchange resins, silica alumina) secondary mercaptans are obtained(4). With branched olefins, we can obtain tertiary mercaptans. Heavy molecular weight tertiary mercaptans are manufactured starting from propylene oligomers and using the acid-catalysed addition of H_2S. Many processes have been successively applied using numerous kinds of catalysts : $AlCl_3$, BF_3, silica alumina (filtrol), zeolites or acidic cation exchange resins(5).

Solid catalysts are nowadays the preferred solution. Lewis acids that were formerly used had many disadvantages correlated to washing, corrosion and high catalyst consumption. The new catalysts give products with good consistency, required by their application as chain transfer agents in polymerization. Tertiary mercaptans such as tert-butyl, octyl, nonyl or dodecyl mercaptan are manufactured by this technique.

- H_2S can also react with the double bond of acrylic derivatives (nitrile, acid, ester) with basic catalysts (amines, Na or K alcoholates, magnesium oxide). Under these conditions nucleophilic addition of H_2S takes place in the position ß to the carbonyl group(6).

- H_2S can also be used as a radical reagent. Addition then follows the anti-Markovnikov rule and produces primary mercaptans when starting from α-olefins.

According to the nature of emitted photons, the reaction proceeds by direct photolysis or by intermediate photoradical initiators. The best initiators under UV light are azo derivatives, acetophenone or aromatic carboxylated derivatives associated to organic phosphites(7).

The optimal conditions require a large excess of H_2S under pressure to avoid sulfide production.

Primary mercaptans ranging from C_3 to C_{12} have been industrially manufactured by a photochemical process starting from α-olefins.

A very selective route leading to primary mercaptans starting from linear olefins has been claimed. In a first step, a tertiary mercaptan reacts with an α-olefin to produce an unsymmetrical sulfide, which is then cleaved by H_2S over a resin catalyst into a primary mercaptan and a recovered tertiary mercaptan which can be recycled.(8).

. Photoradical process

$$(CH_3)_3C{-}SH + CH_2{=}CH{-}R \longrightarrow (CH_3)_3C{-}S{-}CH_2{-}CH_2{-}R$$

. Sulfhydrolysis

$$(CH_3)_3C{-}S{-}CH_2{-}CH_2{-}R \xrightarrow[\text{Sulfonic resin}]{H_2S} R{-}CH_2{-}CH_2{-}SH + (CH_3)_3C{-}SH$$

2.1.3. Nucleophilic substitution of halogenated compounds

Alkaline salts of H_2S are also used to realize nucleophilic substitution of halogenated derivatives. The most convenient salts are Na and ammonium hydrosulfides. To work at complete conversion of the halogenated raw materials, it is necessary to use an over pressure of H_2S. The most important product manufactured by this technique is thioglycolic acid or mercaptoacetic acid.

2.2. POLYSULFIDE, SULFOXIDE, SULFONYL CHLORIDE AND SULFONIC ACID MANUFACTURE

2.2.1. Polysulfides

The most convenient route to manufacture polysulfides is the reaction of sulfur and a mercaptan, using a basic catalyst. However, this reaction is not simple, and interchange reactions between mercaptan and polysulfide groups occur.

Numerous kinds of catalysts have been used(9) :

- liquid catalysts such as amines or Na or K ethoxylate,
- solid catalysts such as zeolite (aluminosilicate), heteropolyacids and their alkali or alkaline earth metal salts on a metal oxide support and basic resins.

By this process, dimethyldisulfide and tertiary polysulfides are manufactured.

Other routes can be applied to produce a large variety of polysulfides :

- Air oxidation of mercaptans contained in petroleum fractions, giving a mixture of alkyl disulfides (trade name Merox®).
- Reaction of sulfur chloride with olefins to give chlorosulfurized compounds, where the chlorine group is substituted by alkaline sulfide or polysulfide (trade name Anglamol® in E.P. applications).
- Reaction of sulfur with unsaturated fatty oils to produce sulfurized fatty oil additives for E.P. applications.
- Other sulfurized compositions useful as multipurpose lubricating oil additives have been extensively claimed in the patent literature. They are synthesized by reacting olefinic compounds, sulfur and H_2S in the presence of basic catalysts(10).
- Some activated halogenated compounds can be easily reacted with alkali disulfide to produce alkyl disulfide. It is a convenient route to produce pure disulfides.
- Pure disulfides can also be produced by reacting mercaptans with hydrogen peroxide.

All these process are actually applied, and the choice of the route depends on the availability of raw materials, the scale of the production and the required quality.

2.2.2. Sulfoxides

Dimethyl sulfoxide (DMSO) is manufactured from dimethyl sulfide, which is obtained either by processing spent liquors from the kraft pulping process or by the methanol H_2S reaction.

Many catalysts have been claimed to make the oxidation of the sulfide easier(11):

- oxidation by organic peroxides,
- oxidation by air and nitrogen oxide catalysis.

2.2.3. Alkanesulfonyl chlorides and Alkanesulfonic acids

Many routes have been claimed to synthesize methanesulfonyl chloride (MSC) and methanesulfonic acid (MSA). The sulfochlorination of alkanes and the chlorine-oxidation of MeSH or CH_3-S-S-CH_3 are particularly attractive to produce very pure products, required for pharmaceutical and electrolytic applications.

Process	**Raw materials**	**Products**
AIR OXIDATION	R-S-S-R, O_2, NO_2 catalyst	MSA
	R-S-S-R, Cl_2, Air, NO_2 catalyst	MSA - MSC
	R-SH, Air, NO_2 catalyst	MSA
DIRECT OXIDATION	R-SH, R-S-S-R, H_2O_2	MSA
	R-SH, R-S-S-R, HCl, H_2O_2	MSA - MSC
	R-S-S-R, H_2O_2, Electricity	MSA
CHLORINE OXIDATION	R-SH, R-S-S-R, Cl_2, H_2O	MSA or MSC
	R-S-CO-S-R, Cl_2, H_2O	
SUBSTITUTION	R-Cl, Na_2SO_3, HCl	MSC
SULFOCHLORINATION	CH_4, SO_2, Cl_2, hν	MSA and MSC
SULFOXIDATION	R-H, SO_2, O_2, metal catalyst	MSA

3. APPLICATIONS OF SULFUR COMPOUNDS

3.1. MERCAPTANS AND ALKYLPOLYSULFIDES

Mercaptans are used to introduce the sulfur group into various molecules having biological properties in the agrochemical and pharmaceutical industries or having antioxidant properties in polymer additives. Heavy mercaptans are mainly used as chain transfer agents in polymerization.

The disulfides and polysulfides are used as sulfur donors in Extreme Pressure Additives for lubricants or in sulfiding of metal oxide catalysts in petrochemistry.

Another typical use of mercaptans and sulfides is the odorization of natural gas.

3.1.1. Methyl mercaptan

Methyl mercaptan is the most important mercaptan produced nowadays.

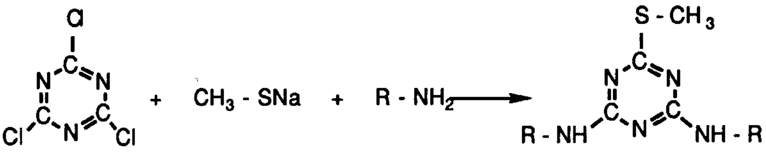
Methyl mercaptan is principally used in the manufacture of methionine.

Methyl mercaptan is a toxic liquified gas and must be handle with care. It has to be carried in bulk, and that is a disadvantage for new development. However, other industrial products easy to handle and transport are proposed : aqueous Na or K methyl thiolate solutions, dimethyldisulfide and dimethylsufoxide.

Methyl mercaptan and its mercaptide derivatives are used as nucleophilic agents for chlorine substitution, allowing the synthesis of intermediates for agrochemical and pharmaceutical industries.

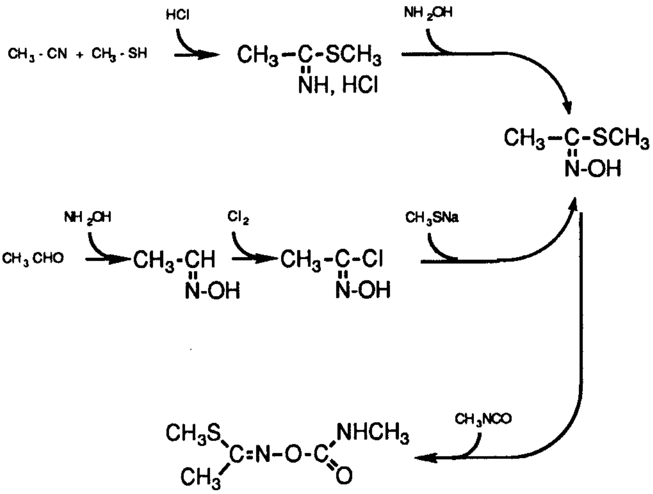
- Symmetrical triazines are produced by reaction of methylthiolates and amines with cyanuryl chloride. They are well-known herbicides(13).

SYMMETRICAL TRIAZINES : HERBICIDES (Terbutryn)

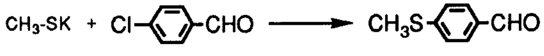


- Carbamoyl oximes can be produced by the acetonitrile and the acetaldoxime routes. They form the Methomyl insecticides (14).

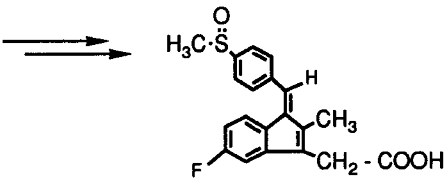
CARBAMATES : INSECTICIDES (Methomyl)



- Alkali metal thiolates are used to react with chlorobenzaldehyde to produce 4-methylthiobenzaldehyde, an intermediate for the synthesis of many drugs(15).



ANTI INFLAMMATORY :



Sulindac

3.1.2. Alkyl mercaptans

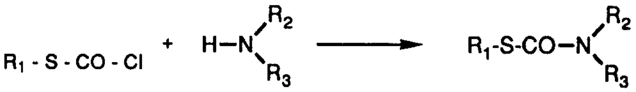
A field where various mercaptans are widely used is the pesticide industry and, on a smaller scale, in the pharmaceutical industry.

In the pesticide area, most of the products actually applied are very old products. Maybe the tendancy will be to find more sophisticated, more selective and less toxic products. The sulfonyl ureas are promising new herbicides under development.

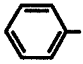
In the pesticide industry, sulfur compounds are involved in two main classes of products :

- the thiocarbamates, most of which are herbicides⁽¹⁶⁾,

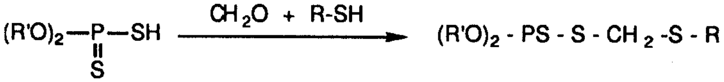
$$R_1-SH \quad + \quad Cl-CO-Cl \longrightarrow R_1-S-CO-Cl$$



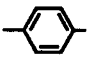
$$R_1-S-CO-Cl + H-N\begin{smallmatrix}R_2\\R_3\end{smallmatrix} \longrightarrow R_1\text{-}S\text{-}CO-N\begin{smallmatrix}R_2\\R_3\end{smallmatrix}$$

R_1 - SH	R_2 - R_3	PRODUCT
C_2H_5 - SH	Cycloheptaméthylène	*Molinate*
C_2H_5 - SH	i-Butyl	*Butylate*
$-CH_2SH$	sec-Butyl	*Thiocarbazil*
C_3H_7 - SH	Propyl	*Vernolate*

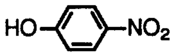
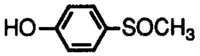
- the thiophosphates, most of which are insecticides⁽¹⁷⁾.



$$(R'O)_2-\underset{\underset{S}{\|}}{P}-SH \xrightarrow{CH_2O\ +\ R\text{-}SH} (R'O)_2-PS-S-CH_2-S-R$$

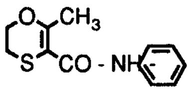
REAGENT	EXAMPLE	PRODUCT
R - SH	Cl––SH	*Carbophenothion*
	C_2H_5 - SH	*Phorate*
	$(CH_3)_3$- C - SH	*Terbuphos*

$$(R'O)_2-\underset{\overset{\Vert}{S}}{P}-Cl \quad + \quad R\text{-}OH \longrightarrow (R'O)_2-PS-R$$

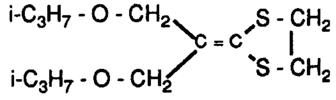
REAGENT	EXAMPLE	PRODUCT
R - OH		*Parathion*
		*Fensulfothion*
	$HO-CH_2-CH_2-S-C_2H_5$	*Demeton*

Sulfur has been introduced into many other agrochemicals by various processes including reaction of a mercaptan with an unsaturated group to obtain the 3-Ethylthiobutanal intermediate in the oximes herbicides, formation of the thioester linkage in pyridate herbicide(18) and building of heterocyclic moieties with 2-mercaptoethanol and ethane dithiol (19).

HETEROCYCLIC DERIVATIVES :

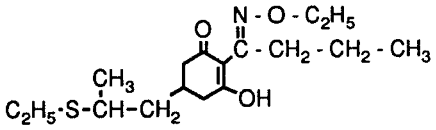


Vitavax (fungicide)



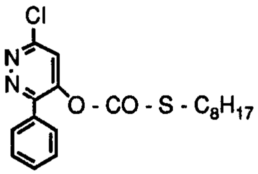
Isoprothiolan (fungicide)

OXIME DERIVATIVES :



Sethoxydim (herbicide)

MISCELLANEAOUS



Pyridate (herbicide)

Other mercaptan applications

The sulfur group is selected in polymer addtives for its antioxidant properties. In this area heavy linear mercaptans, such as dodecylmercaptan as esters of dodecylthiodipropionic acid and pentaerythritol, are extensively used as stabilizers for polyolefins.

A typical use of mercaptans and sulfides is their application to odorize natural gas. Pure products such as tetrahydrothiophene, tert-butyl mercaptan, or a mixture of these products and others such as isopropyl mercaptan, diethyl sulfide, dimethyl sulfide, ethyl mercaptan and n-propyl mercaptan are applied worldwide.

3.1.3. Tertiary mercaptans

Most of these products are manufactured by the acid-catalysed addition of H_2S to oligomers of propylene and isobutylene.

Their polysulfides are manufactured by reacting the tertiary mercaptan and sulfur under basic conditions.

Numerous applications are developing for polysulfides in the areas of drilling muds, wire drawing for steel and copper wire production, metalworking fluids and gear oils.

The more applied mercaptans are C_4-C_8-C_9-C_{12}. They are essentially used as modifiers in emulsion polymerization of Styrene-Butadiene-Acrylonitrile copolymers (SBR, ABS, SAN, NBR). Tertiododecyl mercaptan is used as chain transfert agent, instead of carbon tetrachloride in latex SB carboxylique copolymers for environmental reasons.

As polysulfides they are also largely used as extreme-pressure oil additives in lubricants and as presulfiding agents in petrochemistry and refining industry to transform the NiMo, CoMo/Al_2O_3 oxide catalyst into sulfides(20).

3.1.4. Functionalized mercaptans

a) Mercaptoethanol

Mercaptoethanol 2-ME is synthetised by reaction of H_2S and ethylene oxide.

The main uses of 2-ME are (21) :

- Heat stabilizers in polyvinylchloride. It is used as the so-called reverse ester from oleic acid, useful as an ingredient for direct formulation in PVC lubricants and stabilizers or for further complexing with alkyl tin derivatives.

  These esters possess cost and efficiency advantages over thioglycolate esters but they are more odorous.

- Chain transfer agents in polymerization. Mercaptoradical is a hydrogen donor that controls molecular weight during aqueous polymerization of acrylics.

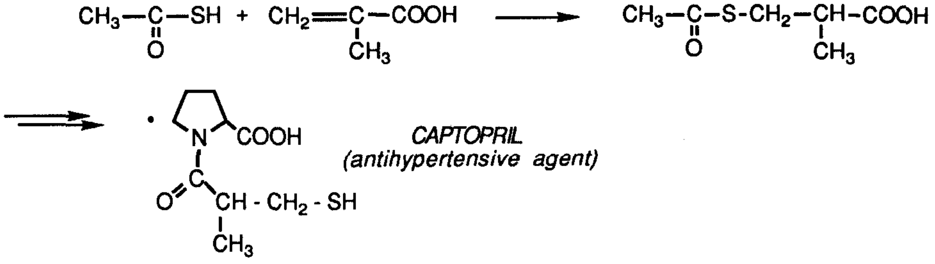
- In the agrochemical industry, 2-ME is used to introduce the oxathiene moiety and, for example, to produce VITAVAX fungicide and homologs.

- In the pharmaceutical industry 2-ME is used as a building block in many drugs. Its reductive properties are applied to reactivate Interferon(22).

- 2-ME has other miscellaneous uses(23) :
  - the mercapto group is useful as an ore flotation depressant in mining recovery,
  - producing glycols with a thio ether linkage for polyurethane elastomers,
  - as thiodiglycol it is used as a carrier for dyes in the textile industry,
  - extreme-pressure water soluble additives as disulfides.

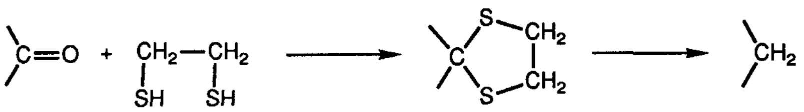
b) Miscellaneous

- **Thioacetic acid,** which is synthetized from acetic anhydride and H2S, is used in the pharmaceutical industry to introduce the thioacetyl group (CH_3-CO-S) or the mercapto group into molecules. This property is applied to synthesize CAPTOPRIL, an anti-hypertensive drug (24).



- **Ethanedithiol,** which can be obtained from raw materials such as ethane dichloride or mercaptoethanol, is used in pharmaceutical applications as a ketone group protector(25).

  It can also be utilized to introduce the dithiane moiety into drugs and pesticides.



- Many **other dithiols and polythiols** are now industrially available, such as :
  - triethylene glycol dimercaptan ($HS\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}SH$)
  - dimercaptoethyl sulfide ($HS\text{-}CH_2\text{-}CH_2\text{-}S\text{-}CH_2\text{-}CH_2\text{-}SH$)
  - ethylcyclohexane dimercaptan ($HS\text{-}C_6H_{10}$ - $CH_2\text{-}CH_2\text{-}SH$)
  - trimercaptopropane ($HS\text{-}CH_2\text{-}CH$ $(SH)\text{-}CH_2\text{-}SH$)

They have promising potential development as polymer modifiers.

3.2. MERCAPTOCARBOXYLIC ACIDS

Thioglycolic acid (TGA) was first developed in the early 1940's in the field of cosmetology as an active material for cold wave permanents and depilatories.

With the strong rise of the PVC industry in the 1950's TGA found a major application as a raw material in the manufacture of organotin stabilizers, to improve thermal stability and prevent discoloration during PVC processing.

With the arrival of large scale commercial production, TGA began to be used more and more as a raw material in the manufacture of other fine or specialty chemicals, notably in the pharmaceutical and agricultural areas.

3.2.1. Mercaptocarboxylic acids as plastic additives

The most important development of mercaptocarboxylic acids and derivatives, especially thioglycolic acid and its 2-ethylhexyl ester, concerns its use as a raw material for tin stabilizers for PVC, to prevent discoloration during PVC processing.

These tin derivatives serve the following functions :

- avoid the thermal dehydrochlorination of PVC,
- assure good compatibility and good diffusion of the stabilizers through the resin.

It is the nucleophilic character of the S towards halogen that is utilized here, and the TGA derivatives are largely preferred to other mercaptan derivatives. A similar range of additives is formed with antimony and has been used as stabilizers and pesticides.

These organic compounds, especially derivatives of mercaptopropionic acid, are used as secondary antioxidants in polyolefins and in styrene-butadiene latex resin (SBR). The thioesters antioxidant family consists of a number of higher alkyl (C12-C18) diesters of 3,3'-dithiodipropionic acid. They are used in combination with hindered phenols. It is the ability of the sulfur group to reduce peroxides associated with the synergistic effect of hindered phenols as free radical scavangers which makes this combination effective.

Other derivatives of mercaptocarboxylic acids have been claimed and used as plastic additives or polymer modifiers. One of the more promising developments concerns the utilization of polymercaptans (esters of polyglycols) as modifiers for polyurethanes applied in the optical glass industry. In this case the sulfur is useful to improve the refractive index towards the mineral glass index(26).

3.2.2. Cosmetic/hair keratin structurants

TGA and its salts, like ammonium, ethanolamine and calcium, are widely used in hair keratin structurants in waving, straightening or removing in depilatories.

TGA is a powerful reducing agent in neutral or alkaline solutions. The hair treatment is based on the cleavage of the cysteine disulfide link of keratine into the cystine moiety that provides the flexibility required for the hair to assume the new wave or curl desired. This cleavage is followed by an oxidative treatment by various oxidizing agents that fixes the hair in its new shape.

The kinetics of the thiol disulfide interchange has been investigated, and the reacting species is the mercaptan anion.

3.2.3. Pharmaceutical/Agrochemical

TGA is presently used in low volume in this area (less than 5 % of the total production). However, it is the most promising way to develop this versatile reactant.

TGA's unique properties make it an ideal candidate for a variety of chemical reactions including addition, elimination and cyclisation reactions. This is due to the acidic nature of the thiol group located in the alpha-position relative to the carboxylic function.

The methyl and ethyl esters of TGA have shown promise as raw materials in several fine chemical fields. The blocking of the carboxylic group as the ester leaves the HS group free to react.

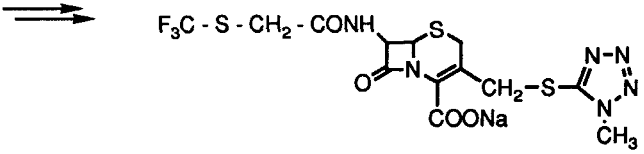
a) Reactions involving the mercaptan group

In the presence of bases, the mercaptan group of TGA becomes a strong nucleophile, able to react with halogenated compounds by a substitution reaction.

- This property is applied to the manufacture of many valuable pharmaceutical and agrochemical intermediates(27).

CEPHALOSPORINE

$$HS-CH_2-CO_2C_2H_5 + F_3-C-Cl \longrightarrow F_3C-S-CH_2-CO_2C_2H_5$$



Cefazaflur

- Base-catalysed displacement of aliphatic halogen by TGA esters can be achieved as easily as by TGA itself.

- Addition of TGA esters to activated double bonds is possible via a classical base-catalysed procedure.

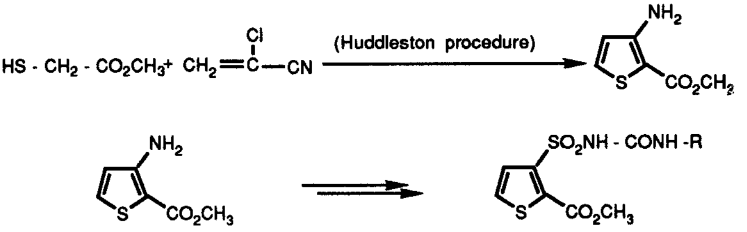
- Moreover, the reactivity of TGA esters extends towards activated aromatic halogen, which can be substituted by a nucleophilic mechanism permitted in polar solvents.

b) Synthesis of heterocyclic compounds

The methylene group of TGA esters, with its remarkable position between a mercaptan and an ester function, displays a significant ability to react.

Under alkaline conditions, where the electron withdrawing effect of both functions is enhanced, interesting routes to a great variety of heterocyclic compounds are available depending on the nature of the coreactant.

A diversity of structures, resulting from the reactivity of either the methylene group or the ester group, can be obtained such as thiophene, thiazole and other N-S heterocyclic compounds(28). Methylthioglycolate could be the starting material to sulfonylureas and many other biologically active compounds.



3.3. *DIMETHYLDISULFIDE*

DMDS is a very versatile product experiencing broad growth.

As a thiomethylation agent, it is used to produce methylthiophenols which have found use as pesticide, pharmaceutical and antioxidant intermediates.

The most attractive synthesis method is the electrophilic substitution on phenol with dialkyl disulfide, but the reaction is not regiospecific. Many attempts to improve the selectivity to the ortho- or para-positions have been made with phenol and DMDS(29).

With its lower odor and safer use it can be an alternative to methyl mercaptan in many applications.

DMDS has recently found many important outlets in the refining industry. It is more efficient and easier to handle than competing products such as CS_2 and H_2S. It is used as sulfur carrier in stream-cracker feedstock to produce ethylene and propylene.

In the refining industry, it is largely used for the sulfidation of metal oxide catalysts to metal sulfides for their activation in various treatments such as hydrodesulfurization, hydrotreatment and hydrocracking of crude petroleum. DMDS is also used to modify the selectivity of platinum-based catalysts in reforming and to prevent coke formation in hydrodealkylation(30).

DMDS is also an excellent "solvent" for sulfur(31). In fact, DMDS chemically reacts with sulfur, reversibly, to form dimethylpolysulfide :

$$CH_3 - S - S - CH_3 + S \longrightarrow CH_3 - S_x - CH_3$$

$$CH_3 - S - S - CH_3 + H_2S \underset{\longleftarrow}{\longrightarrow} 2\,CH_3 - SH + S$$

This property is applied to the deplugging of sour gas wells ($H_2S < 60$ %). In the bottom of wells where pressure and temperature are high, sulfur is perfectly soluble, but at the top, where pressure and temperature decrease, the risk of plugging arises, proportional to the H_2S concentration. DMDS can be injected batchwise to unplug sour gas wells.

Unfortunately, DMDS breaks down in the presence of H_2S to methylmercaptan, and cannot be totally recovered. It cannot be used for super sour gas ($H_2S > 60$ %), where higher organic disulfides are proposed.

3.4. DIMETHYL SULFOXIDE

The oxidation of dimethylsulfide to dimethylsulfoxide (DMSO) is realized industrially by air or oxygen with nitrogen oxide catalysis.

The worldwide consumption of DMSO has constantly increased, due essentially to the pharmaceutical and agrochemical industries where it is used as a reaction medium. On a smaller scale, it is also used as a solvent in the polymer industry. The remaining markets involve uses as a carrier of biological substances, the electronic industries and as a selective solvent for BTX in the refining industry.

The major development of DMSO is due to its special place among aprotic polar solvents. Its remarkable properties, such as high polarity and dielectric constant, perfect miscibility with water and intense cation solvation by the oxygen atom, give it a powerful solvent capacity and result in an increased reactivity of anions.

However, I would like to point out some aspects of the interest in using DMSO as a versatile reagent in synthesis.

3.4.1. DMSO as a mild oxidation agent(32)

DMSO must generally be activated by acidic conditions, to dimethylsulfonium ion which reacts :

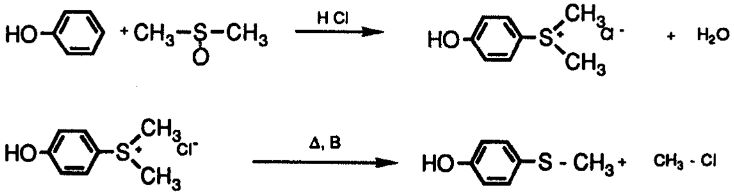
- with alcohols to produce ketones and dimethylsulfide,
- with epoxides to produce α-hydroxyketones,
- with thioketones to produce ketones.

DMSO can also be used to transform sulfides into sulfoxides and mercaptans into disulfides.

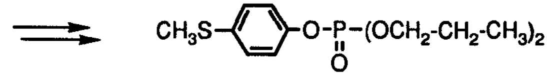
3.4.2. DMSO as a thiomethylation agent(33)

DMSO condenses easily on phenolic or aromatic compounds, activated by electron donor substituents, in the presence of strong protonic acids to produce dimethylsulfonium salts that lead, in basic medium or by heating, to thiomethylated derivatives. This reaction is very selective for the para-position.

As an example of industrial utilization, we can mention manufacture of an insecticide, 4-methylthiophenyl dipropylphosphate.



INSECTICIDE :



3.4.3. DMSO as a methylenation and a methylation agent(34)

DMSO in a strongly basic medium leads to methylides :

- DIMSYL anion ($CH_3 - SO - CH_2^-$) is obtained by the action of sodium hydride or sodium amide on DMSO.
- The ylides of sulfur are obtained by action of a strong base on trialkylsulfoxonium salts. Trimethylsulfoxonium iodide, which is a commercial product, reacts with sodium hydride to produce dimethylsulfoxonium methylide $[(CH_3)_2\text{-}S^+(O)\text{-}CH_2^-]$ and with dimsyl anion to produce dimethylsulfonium methylide $[CH_3)_2\text{-}S^+\text{-}CH_2^-]$

DIMSYL ANION

$$CH_3 - SO - CH_3 + \begin{cases} NaH \longrightarrow CH_3 - SO - {}^-CH_2 \quad {}^+Na + H_2 \\ NaNH_2 \longrightarrow CH_3 - SO - {}^-CH_2 \quad {}^+Na + NH_3 \end{cases}$$

TRIMETHYL SULFOXONIUM IODIDE

$$\longrightarrow (CH_3)_3 \text{-}S^+ = O \quad {}^-I$$

DIMETHYL SULFOXONIUM METHYLIDE - COREY REAGENT

$$(CH_3)_3 \text{-}S^+ = O \quad {}^-I + NaH \longrightarrow (CH_3)_2 - {}^+SO - {}^-CH_2 + NaI + H_2$$

Various applications have been found for these methylides thanks to the work of E.J. COREY.

The dimsyl anion, which is a powerful nucleophile, reacts with non-enolizable carbonyl compounds to produce ß-hydroxysulfoxides and with esters to produce ß-keto sulfoxides.

Dimethyl sulfoxonium methylide reacts selectively with an aldehyde or a ketone to form an epoxide and with alcohols, amines or oximes as a methylation agent.

Trimethylsulfoxonium iodide is a commercial product, convenient for various syntheses in the pharmaceutical industry.

3.5. METHANESULFONIC ACID/METHANESULFONYL CHLORIDE

3.5.1. Methanesulfonic acid

MSA is a strong, high boiling organic acid. It is a non-oxidizing acid, chemically stable, and, unlike H_2SO_4 and carboxylic acids, MSA does not react with alcohols to form the corresponding mesylate esters (except under severe conditions). MSA is much less corrosive than either H_2SO_4 or HCl.

Because of its characteristics MSA has become the acid catalyst of choice in a variety of applications (35):

- It is preferred for manufacture of various acrylate esters, because it does not catalyze side-reactions at the double bonds, producing products of exceptional color quality,
- it is an effective catalyst for the direct esterification of carboxylic acids by various olefins and
- it is used as a catalyst for various carbonylation reactions.

Because of its high conductivity and the high solubility of many of its salts, MSA has found utility as an electrolyte in a variety of electrochemical applications. The most highly developed is as a replacement for fluoboric acid in tin-lead solder plating.

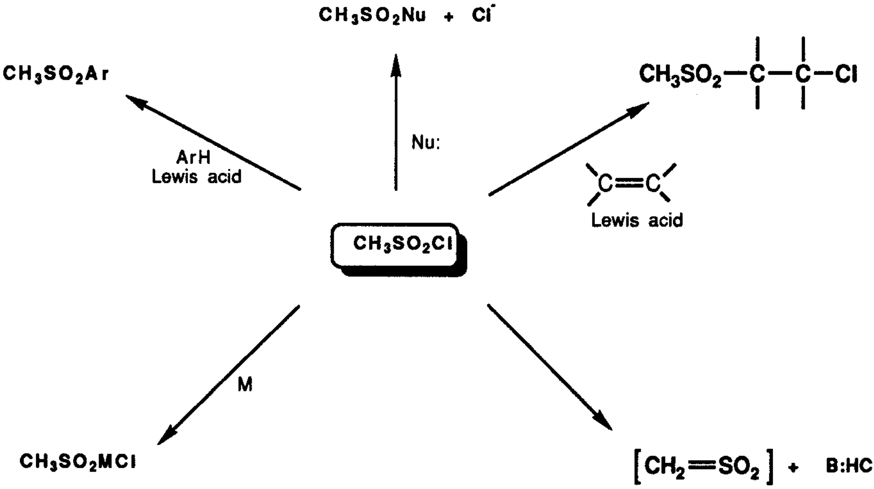
MSA is also finding a growing number of applications as a solvent. For example, for regeneration of ion-exchange resins, to remove heavy metals from effluent streams.

It is also utilized to produce pharmaceutical products such as mesylate classes.

3.5.2. Methanesulfonyl chloride

Methanesulfonyl chloride (MSC) is a highly versatile and useful chemical for synthesis of a variety of commercially important intermediates in the pharmaceutical, photographic and agricultural industries.

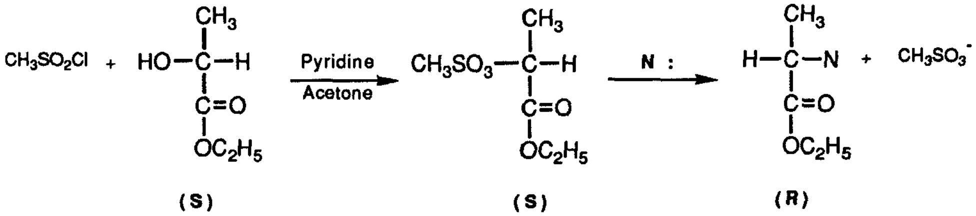
- MSC offers the mesyl group ($MeSO_2^-$) for substitution in a variety of reactions typical of acid chlorides. MSC reacts with nucleophiles to give methylsulfonyl derivatives : for example ; a methanesulfonate ester if the nucleophile is an alcohol, a methanesulfonamide if the nucleophile is an amine and a sulfone if the nucleophile is a carbon radical.
- In the presence of Lewis acids MSC will undergo Friedel-Crafts reactions with aromatics to produce aromatic methyl sulfones.
- MSC reacts with a variety of metals to give methanesulfinate salts.
- MSC reacts with certain bases at low temperature to produce the highly reactive sulfene.
- MSC reacts with olefins in the presence of Lewis acids to produce methyl haloalkylsulfones.



MSC plays an important synthetic role in the pharmaceutical and agrochemical industries, it is used as a building block, a protective or a leaving group.

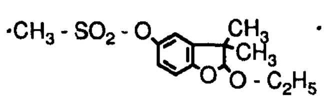
MSC has gained synthetic usefulness because it reacts with optically active alcohols such as the enantiomers of lactic acid esters to give complete retention of configuration in stereospecific synthesis.

This inversion of configuration is useful in manufacture of herbicides where the (R) enantiomers may be more biologically active(36).

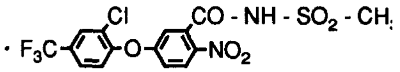


MSC is utilised in the synthesis of an important intermediate in the production of an anti-AIDS drug (AZT), and it is used as a chemical intermediate for the synthesis of various agrochemicals(37) and pharmaceuticals(38).

HERBICIDES

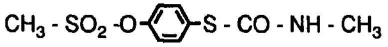


Ethofumesate



Fomesafen

FUNGICIDE



Methasulfocarb

MSC is also used in the synthesis of a wide variety of photographic chemicals such as mesylated glycols for use as photogaphic gelatin hardeners and for the manufacture of color developing agents(39).

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