

ULLMANN'S ENCYCLOPEDIA
OF INDUSTRIAL
CHEMISTRY

ULLMANN'S ENCYCLOPEDIA OF INDUSTRIAL CHEMISTRY

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34

Steel
to
or Halides

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2003
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Ullmann's Encyclopedia of Industrial Chemistry

Sixth, Completely Revised Edition

Volume 34

Steel
to
Sulfur Halides

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Vol. 3

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Sulfones and Sulfoxides

KATHRIN-MARIA ROY, Langenfeld, Federal Republic of Germany

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The author would like to thank Bayer AG for undertaking the literature research for this article

IR spectrum. Physical properties of industrially important sulfones are listed in Table 1.

1. Sulfones

1.1. Physical and Chemical Properties

Sulfones are described by the following general structural formula, in which the groups R^1 and R^2 can be hydrocarbon substituents, including cyclic ones, of any combination:



Typical sulfones are colorless and odorless in the pure state and are very stable both thermally and chemically. They are protonated only by the strongest acid systems. Unlike sulfoxides, sulfones form relatively weak hydrogen bonds.

The presence of a sulfonyl group in the molecule is shown by strong absorptions at $1300 - 1320 \text{ cm}^{-1}$ and $1140 - 1160 \text{ cm}^{-1}$ in the

1.2. Synthesis [1, pp. 223, 1129], [2], [3, p. 171]

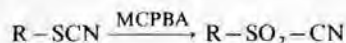
1.2.1. Oxidation of Thioethers (Sulfides)

Sulfones are generally synthesized by oxidation of sulfides via sulfoxides as intermediates. A common oxidizing agent in the laboratory is hydrogen peroxide in acetic acid. It is also often used in industry, but requires reaction temperatures of 70°C up to reflux in many cases [4], [5]. In the presence of various metal catalysts, oxidation with hydrogen peroxide proceeds under milder conditions. Thus, β -hydroxy sulfides can be oxidized selectively and in good yield to the corresponding sulfones by using titanium, vanadium, molybdenum, or tungsten salts [6], as well as selenium dioxide [7], as catalysts. A very effective oxidizing agent, which gives high-purity products in high yield, is *m*-chloroperbenzoic acid (MCPBA). This reagent can often be used if the molecule contains other sensitive groups,

Table 1. Physical data and molecular formulae for some industrially important sulfones

Sulfone	mp, °C (bp, °C/kPa)	Molecular formula (molecular mass)
	(285/101.3)	C ₄ H ₈ O ₂ S (120.16)
4-CH ₃ -C ₆ H ₄ -SO ₂ -C ₆ H ₄ -4-CH ₃	158	C ₁₄ H ₁₄ O ₂ S (246.33)
4-Br-C ₆ H ₄ -SO ₂ -C ₆ H ₄ -4-Br	172	C ₁₂ H ₈ Br ₂ O ₂ S (376.08)
CH ₃ -(CH ₂) ₃ -SO ₂ -(CH ₂) ₃ -CH ₃	46	C ₈ H ₁₈ O ₂ S (178.30)
HO-CH ₂ -CH ₂ -SO ₂ -CH ₂ -CH ₂ -OH	58	C ₄ H ₁₀ O ₄ S (154.19)
C ₆ H ₅ -CH ₂ -SO ₂ -CH ₂ -C ₆ H ₅	149-153	C ₁₄ H ₁₄ O ₂ S (246.33)
C ₂ H ₅ -SO ₂ -CH ₂ -CONH ₂	99	C ₄ H ₉ NO ₃ S (151.19)
CH ₃ -(CH ₂) ₂ -SO ₂ -CH ₂ -CONH ₂	104	C ₅ H ₁₁ NO ₃ S (165.21)
C ₆ H ₅ -SO ₂ -CH ₂ -CH ₂ -OH	(184/19)	C ₈ H ₁₀ O ₃ S (186.23)
CO ₂ H-CH ₂ -CH ₂ -SO ₂ -CH ₂ -CH ₂ -CO ₂ H	222-224	C ₆ H ₁₀ O ₆ S (210.21)
C ₂ H ₅ -SO ₂ -(CH ₂) ₂ -CH ₃	25	C ₅ H ₁₂ O ₂ S (136.21)
(CH ₃) ₂ CH-SO ₂ -CH(CH ₃) ₂	35-36	C ₆ H ₁₄ O ₂ S (150.24)
CH ₃ -SO ₂ -CH ₃	109	C ₂ H ₆ O ₂ S (94.13)
CH ₃ -(CH ₂) ₂ -SO ₂ -(CH ₂) ₂ -CH ₃	26	C ₆ H ₁₄ O ₂ S (150.24)
CH ₃ -(CH ₂) ₇ -SO ₂ -(CH ₂) ₇ -CH ₃	73	C ₁₆ H ₃₄ O ₂ S (290.51)
CH ₃ -SO ₂ -CH ₂ -C ₆ H ₅	126-127	C ₈ H ₁₀ O ₂ S (170.23)
CH ₃ -SO ₂ -(CH ₂) ₃ -CH ₃	28-30	C ₅ H ₁₂ O ₂ S (136.21)
CH ₃ -SO ₂ -C ₆ H ₄ -4-CH ₃	88-89	C ₈ H ₁₀ O ₂ S (170.23)
4-Cl-C ₆ H ₄ -CH ₂ -SO ₂ -C ₆ H ₄ -4-CH ₃	167-168	C ₁₄ H ₁₃ ClO ₂ S (280.78)
CH ₂ =CH-CH ₂ -SO ₂ -C ₆ H ₄ -4-CH ₃	50-52	C ₁₀ H ₁₂ O ₂ S (196.27)
C ₂ H ₅ CO ₂ -CH ₂ -SO ₂ -C ₆ H ₄ -4-CH ₃	91-93	C ₁₁ H ₁₄ O ₄ S (242.30)
4-CH ₃ -C ₆ H ₄ -SO ₂ -C ₆ H ₅	125-126	C ₁₃ H ₁₂ O ₂ S (232.30)
2,2',4-(CH ₃) ₃ -C ₆ H ₂ -SO ₂ -C ₆ H ₄ -4-OCH ₃	136	C ₁₆ H ₁₈ O ₃ S (290.38)
4-CH ₃ -C ₆ H ₄ -SO ₂ -C ₆ H ₃ -2,4-(CH ₃) ₂	51-52	C ₁₅ H ₁₆ O ₂ S (260.36)
C ₆ H ₅ -SO ₂ -C ₆ H ₄ -4-C ₂ H ₅	92-93	C ₁₄ H ₁₄ O ₂ S (246.33)
4-CH ₃ O-C ₆ H ₄ -SO ₂ -CH ₃	120	C ₈ H ₁₀ O ₃ S (186.23)
2,4-(CH ₃) ₂ -C ₆ H ₃ -SO ₂ -CH ₃	56	C ₉ H ₁₂ O ₂ S (184.26)
C ₆ H ₅ -SO ₂ -C ₆ H ₅	121	C ₁₂ H ₁₀ O ₂ S (218.28)
4-CH ₃ -C ₆ H ₄ -SO ₂ -C ₆ H ₅		C ₁₃ H ₁₂ O ₂ S (232.30)
4-CH ₃ -C ₆ H ₄ -CH-SO ₂ -C ₆ H ₄ -4-NHCOCH ₃ CH ₂ -NO ₂	185-187	C ₁₇ H ₁₈ N ₂ O ₅ S (362.41)
C ₆ H ₅ -CH-SO ₂ -C ₆ H ₅ CH ₂ -NO ₂	186-187	C ₁₄ H ₁₃ NO ₄ S (291.33)
4-CH ₃ O-C ₆ H ₄ -CH-SO ₂ -C ₆ H ₄ -4-Cl CH ₂ -CO-C ₆ H ₄ -4-CH ₃	158	C ₂₃ H ₂₁ ClO ₄ S (428.94)
C ₆ H ₅ -CH-SO ₂ -C ₆ H ₄ -4-N(CH ₃) ₂ CH ₂ -CO-C ₆ H ₅	191-192	C ₂₃ H ₂₃ NO ₃ S (393.51)
C ₆ H ₅ -SO ₂ -CH ₂ -OH	57-60	C ₇ H ₈ O ₃ S (172.20)
4-CH ₃ -C ₆ H ₄ -SO ₂ -CH(OH)-(CH ₂) ₂ -CH ₃	78	C ₁₁ H ₁₆ O ₃ S (228.31)
CH ₃ -(CH ₂) ₁₁ -SO ₂ -CH ₂ -OH	64-66	C ₁₃ H ₂₈ O ₃ S (264.43)

as in many pharmaceutically active substances [8]. Alkyl thiocyanates are converted to sulfonyl cyanides by MCPBA [9]



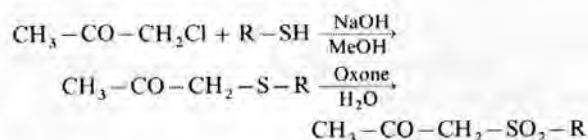
Other oxidizing agents used include potassium permanganate [10], sodium perborate [11], and dimethyldioxirane [12]. An extremely simple, rapid process is sulfide oxidation with periodic acid in the presence of ruthenium tetroxide as catalyst. This reaction is carried out in a two-phase solvent mixture and is, therefore, also suitable for the synthesis of water-soluble sulfones [13]. A related method using osmium tetroxide in the presence of a tertiary amine *N*-oxide gives good yields [14]. In industrial processes, gaseous chlorine is also used as the oxidizing agent (see, for example [15]). The potassium peroxomonosulfate complex Oxone has also gained importance [16]. With this reagent, allyl sulfoxides, for example, can be converted into the corresponding sulfones [17]. In the presence of wet clays such as kaolin or montmorillonite, the oxidation of various sulfides in dichloromethane gives the sulfone almost quantitatively [18].

Oxidation of Phenyl Vinyl Sulfide with H_2O_2 in Glacial Acetic Acid [4]. To a solution of 19.7 g (0.145 mol) of phenyl vinyl sulfide in 70 mL of glacial acetic acid, 56 mL (0.5 mol) of 30 % hydrogen peroxide is added dropwise in such a way that the reaction temperature becomes 70 °C. The reaction mixture is subsequently heated for 20 min under reflux. After cooling, 150 mL of diethylether and 200 mL of water are added, and the organic phase is separated. The organic phase is subsequently washed with water (50 mL) and sodium chloride solution (50 mL) and evaporated, giving 18–19 g (74–78 %) of phenyl vinyl sulfone as a colorless solid, *mp* 64–65 °C.

Oxidation of Sulfides with Oxone in the Presence of Wet Montmorillonite [18]. Commercial clay (montmorillonite or kaolin; 10 g) is treated with 2 g of distilled water in eight portions. After each addition the mixture is shaken vigorously for several minutes, until a loose powder is formed. Then 1.2 g of this catalyst is suspended in 6 mL of dichloromethane (7 mL

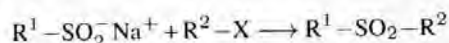
for the kaolin catalyst) and treated with Oxone (2.5 equivalents based on the sulfide). After addition of 1 mmol sulfide the reaction vessel is purged with argon, closed, and stirred for 2 h at room temperature. After filtration of the catalyst on a glass frit, washing with ca. 100 mL of dichloromethane, and evaporation of the solvent, the pure sulfone (> 98 % purity) is obtained almost quantitatively.

A particularly simple and rapid process allows the synthesis of sulfonyl-substituted propanones on a large scale [19]. Here, chloroacetone is reacted with various sulfides. The intermediate β -keto sulfide is not isolated but is oxidized directly with Oxone to the sulfone.



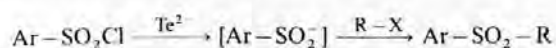
1.2.2. Alkylation of Sulfinic Acid Derivatives

Alkylation of the ambidentate sulfinic acid ion with soft alkylating agents, such as alkyl halides, is a widely used method for synthesis of sulfones:

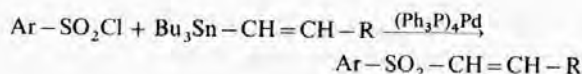


Aryl sulfones, in particular, in which the second sulfonyl substituent can be an alkyl [20], an alkynyl [21], a β -keto [22], or an allyl [23] group, can be produced by this process. These reactions are catalyzed, for example, by copper(I) bromide [24], phase-transfer catalysts [20], [21], [25], or ultrasound [26].

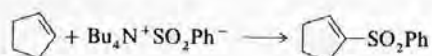
A related reaction is that of arylsulfonyl chlorides with alkyl iodides or benzyl chlorides in the presence of telluride. The reaction is based on a reactivity inversion, where the original electrophilic sulfonyl group is converted to the nucleophilic sulfinic acid ion by electron transfer from the telluride ion [27]:



Substituted vinyl and allyl sulfones are obtained in good yield by palladium-catalyzed coupling of arylsulfonyl chlorides with organotin compounds [28].



The sulfonylation of various organometallic reagents with arylsulfonyl fluorides is a one-step sulfone synthesis, which gives alkyl, trimethylsilylmethyl, and allyl sulfones in good yield [29]. Cycloalkenes can be converted particularly easily into the corresponding vinyl sulfones by reaction with tetrabutylammonium sulfinate [30].



1.2.3. Addition of Sulfinic Acid Derivatives to Multiple Bonds

Isolated double bonds do not generally react with sulfinic acids or their salts to give sulfones. Iodosulfonylation and sulfonylmercuration, which both take place regioselectively [31], are exceptions. The adducts formed initially are converted by dehydrohalogenation or demercuration into the corresponding vinyl sulfones (see Figure 1).

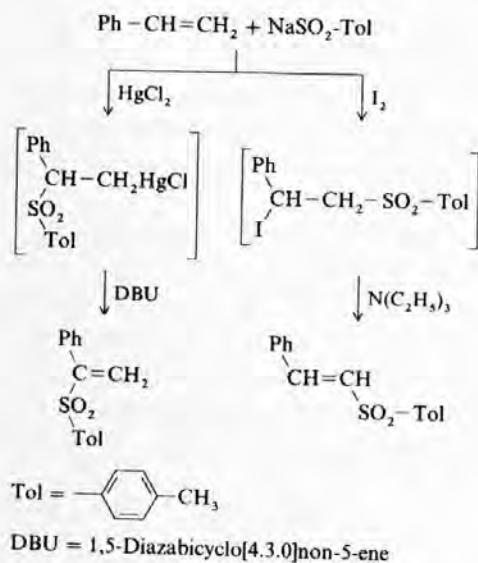
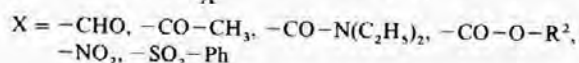


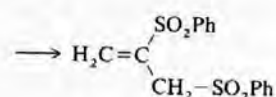
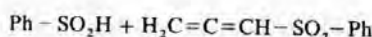
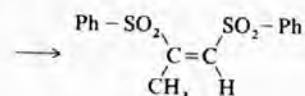
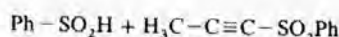
Figure 1.

Conjugated dienes [32] and α,β -unsaturated carbonyl compounds [33] can also be converted regioselectively into unsaturated sulfones by using iodosulfonylation.

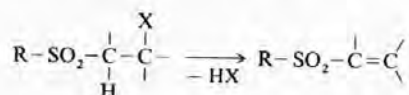
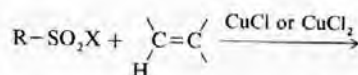
The addition of sulfinic acids to polarized double or triple bonds is an excellent method of synthesizing sulfones [34]. A large number of olefins, such as vinyl aldehydes [35] and ketones [36], nitroolefins [37], acrylic acid derivatives [38], vinyl sulfones [39], quinones [40], and quinonimines [41] have been used successfully as acceptor compounds.



Sulfinic acid also adds readily to sulfonyl-substituted allenes and acetylenes to give disulfonyl derivatives [42].

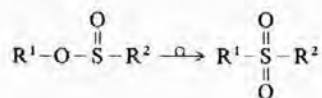


Unlike sulfinic acids, the addition of sulfonyl halides to unsaturated C-C systems is a radical reaction in which mixtures of isomers can be formed. To suppress competing polymerization reactions, the addition is carried out in the presence of copper(I) or copper(II) salts. The β -halo sulfones formed initially can be converted into vinyl sulfones by elimination of hydrogen halide [43].



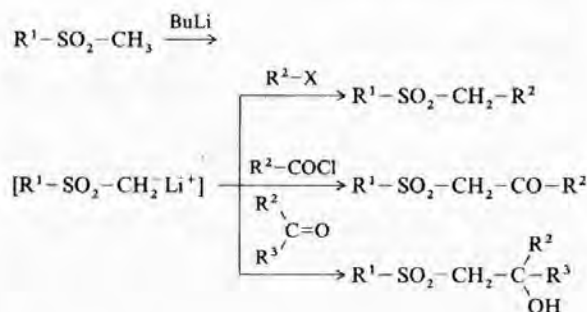
1.2.4. Rearrangement of Sulfinates

Sulfinates rearrange to sulfones under various conditions. Acids [44], tertiary amines [45], or palladium(0) complexes [46] are examples of suitable catalysts. Allyl-substituted sulfinic acid esters can also be isomerized thermally [46], [47].



1.2.5. Sulfones from Sulfonyl Carbanions

α -Sulfonyl carbanions are formed from sulfones containing α -hydrogens by the action of bases, such as Grignard reagents, alkali-metal amides, sodium hydride, or butyllithium. These carbanions can be converted into a variety of new sulfones by alkylation, acylation, or addition to unsaturated systems.



Treatment of α -sulfonyl carbanions with acid chlorides [48] or esters [49] gives β -keto sulfones, which can rearrange with allyl bromide to give α -allyl-substituted β -keto sulfones [50].

The Knoevenagel condensation of aryl sulfones with aldehydes or ketones is also frequently used. The intermediate products eliminate water to form vinyl sulfones [51] (see Figure 2).

The Knoevenagel condensation, with subsequent allyl sulfoxide-sulfenic acid ester rearrangement, is of synthetic importance in the production of γ -hydroxy- α,β -unsaturated sulfones. Here piperidine is used as the base [52] (see Figure 3).

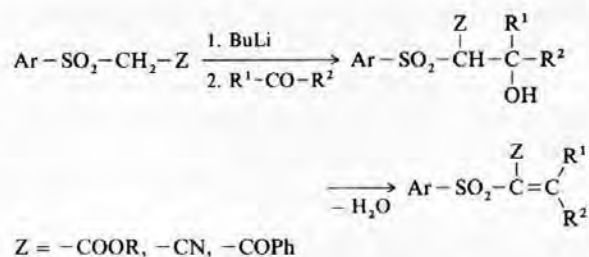


Figure 2.

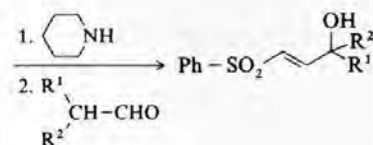
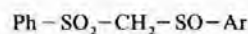
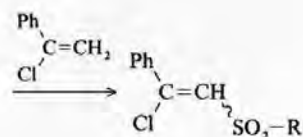
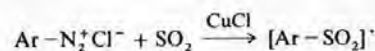


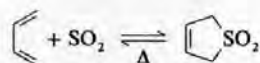
Figure 3.

1.2.6. Addition of Sulfur Dioxide

By addition of sulfur dioxide to aryldiazonium salts, aryl sulfonyl radicals are formed, which can react with olefins to give alkyl aryl sulfones [53].



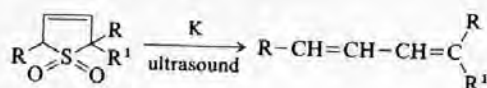
1,3-Dienes undergo stereoselective cycloaddition with sulfur dioxide to give sulfolenes. This reaction is reversible [54].



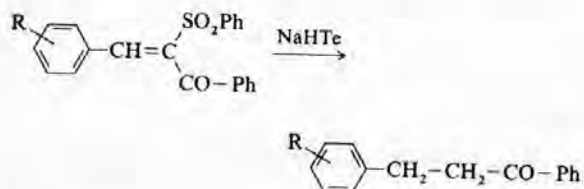
1.3. Reactions

Reductive Elimination of the Sulfonyl Group. Reductive elimination of the sulfonyl group is of great synthetic importance because sulfones are used as intermediates in many syntheses. Alkali metals in ammonia or low molar

mass amines [55], sodium amalgam [56], and aluminum amalgam [57] have been described as reducing agents. Sulfur dioxide is eliminated from unsaturated, cyclic sulfones by potassium dispersed with ultrasound [58].

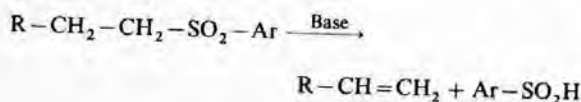


The simultaneous reduction and desulfonylation of α -alkylidene β -keto sulfones is effected under mild conditions by using sodium hydrogentelluride [59].

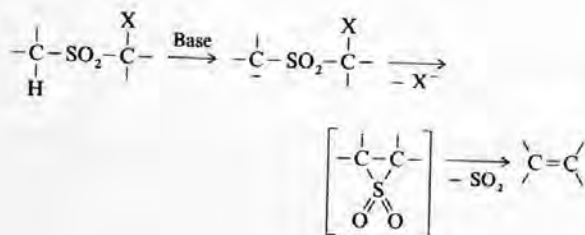


The sulfonyl group can be eliminated photochemically from β -keto sulfones by using a β -keto ester in the presence of a ruthenium(II) salt, so that many other functional groups are not attacked [60].

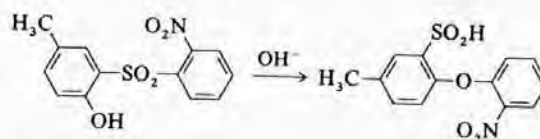
Elimination of Sulfinate. The base-catalyzed elimination of organic sulfinate groups from sulfones is often used preparatively. Arylsulfonyl [61] and, in particular, trifluoromethanesulfonyl groups are good leaving groups [62]:



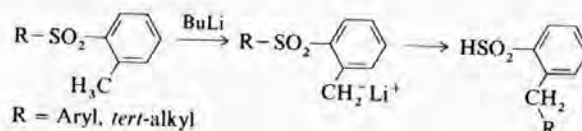
Ramberg-Bäcklund Reaction. Bases effect the elimination of sulfur dioxide from α -halo sulfones with α -hydrogens via an episulfone intermediate, to give olefins [63].



Smiles and Truce-Smiles Rearrangement. Diaryl and aralkyl sulfones undergo base-catalyzed rearrangement to form sulfinic acids [64]. In the *Smiles rearrangement* the migrating aryl group must be activated by an electron-withdrawing group.



In the related *Truce-Smiles rearrangement* a nonactivated aryl or tertiary alkyl group migrates to a carbanion formed by lithiation of an *o*-methyl group [65].



1.4. Industrial Uses

Unsaturated sulfones can be used as intermediates for pharmaceuticals and pesticides and for modification of polymers [66]. Many reactive dyes also contain unsaturated sulfonyl groups, (e.g., see [67]). The possible uses of sulfones described below are taken from the extensive patent literature. For uses of sulfolane, see $\rightarrow$ Benzene, Chap. 6.3.; $\rightarrow$ Gas Production.

Uses in Crop Protection. 1,1-Diiodomethyl sulfone [68], heterocyclic sulfones [69], and α -sulfonyloximes [70] have been described as *plant fungicides*. Certain sulfones are effective *herbicides* [71]. Others act as *insecticides* and *acaricides* [72].

Pharmaceutical Uses. Dihydropyridine sulfone derivatives are *calcium antagonists*, which are said to have a longer period of activity and fewer side effects than nifedipine [73]. Alkylsulfonyl-substituted steroid pyrazoles and thiazoles exhibit *antiandrogenic activity* [74].

Sulfonylnitromethane derivatives are aldose reductase inhibitors and can be used for the treatment of certain secondary effects of *diabetes* and *galactosemia* [75]. A range of sulfonyl-substituted benzazepines and imidazoles have

been patented as agents for the treatment of *gastrointestinal disorders* [76]. Fluoro sulfones are said to be very effective leukotriene antagonists with *antiallergic* and *anti-inflammatory activity* [77]. Aryl- or heteroaryl-substituted sulfones exhibit activity against *picornaviruses* [5] and *retroviruses* [78]. Sulfonylcyclopentenones are *antitumor agents* and promote *bone formation* [79].

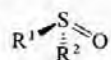
Others. Piperidinyl sulfones are used as light stabilizers in polymers, particularly polyolefins [80]. Certain heterocyclic sulfones can be used as *corrosion protection agents* for metals [81]. Sulfones are used as hardeners [82] and couplers [83] in *photographic materials*. Diazodisulfones can be used in the production of *semiconductors* and as photosensitive reagents for *printing plate materials* [84]. Certain fluorinated sulfones have *nonlinear optical properties* [85]. Sulfone percarboxylic acids are *bleaching agents* with little damaging effect on colors and good storage stability [86]. *Fabric softeners* contain esters or ethers of thiodiglycol sulfones [87].

2. Sulfoxides

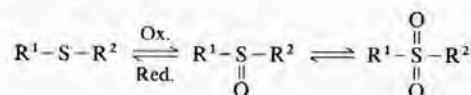
2.1. Physical and Chemical Properties

Sulfoxides are colorless, hygroscopic liquids or solids. They dissolve readily in protic solvents to form strong hydrogen bonds. Because of the polar nature of the S—O bond, sulfoxides form adducts with salts of most metals.

Because of the pyramidal structure of sulfoxides, unsymmetrically substituted compounds of this series form enantiomers, with the sulfur atom as the chiral center.



In sulfoxides, sulfur has the intermediate oxidation state of +4. Sulfoxides can therefore be reduced to form sulfides (thioethers) and oxidized to form sulfones by reversible redox reactions.



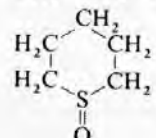
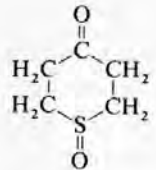
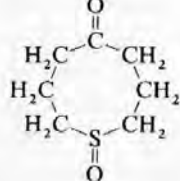
Physical properties of important sulfoxides are listed in Table 2.

2.2. Synthesis

2.2.1. Oxidation of Sulfides [1, pp. 207, 665], [2], [3, p. 121], [88], [89]

The oldest and most frequently used method for the production of sulfoxides is by oxidation of sulfides. Since further oxidation to the corresponding sulfones can occur, a range of selective reagents and methods has been developed. Oxidation with hydrogen peroxide, which has long been known, can be carried out in the presence of various catalysts. Acids, such as acetic [90], [91], perchloric [92], and sulfuric acids [93], [94] are suitable. A more recent industrial process uses 50 % sulfuric acid and an organic acid, such as formic or acetic acid, in a 1 : 1 ratio as the catalyst [93]. Similarly, sterically hindered sulfides can be oxidized selectively and in high yield with hydrogen peroxide in the presence of a catalyst mixture of sulfuric acid and a secondary or tertiary alcohol [94]. Other suitable catalysts are titanium trichloride [95], selenium dioxide [96], tellurium dioxide [97], and vanadium pentoxide [98], which can act simultaneously as an indicator of excess hydrogen peroxide. Good yields of sulfoxide are obtained by using the complex from urea and hydrogen peroxide (UHP complex) together with half an equivalent of phthalic anhydride [99]. The use of organic peroxides, such as cyclohexyl or *tert*-butyl hydroperoxide has also been known for a long time [100]. Sulfide oxidation takes place quantitatively at -78°C using 2-methoxy-2-hydroperoxypropane produced in situ from 2,3-dimethyl-2-butene and ozone [101]. Among the organic peroxycarboxylic acids, peracetic [102], perbenzoic [103], and monoperoxyphthalic acids [104], in particular, are effective oxidizing agents. One of the best selective oxidizing agents is *m*-chloroperoxybenzoic acid, which not only gives sulfone-free sulfoxides [105], but also reacts with a broad range of substrates [106] including unstable unsaturated thioethers [4], multifunctional heterocyclic thioesters [107], thioacetals [108], disulfides [109], and penicillins [110].

Table 2. Physical data and molecular formulas for some industrially important sulfoxides

Sulfoxide	mp, °C (bp, °C/kPa)	Molecular formula (molecular mass)
$C_6H_5-CH_2-SO-CH_2-C_6H_5$	134–135	$C_{14}H_{14}OS$ (230.33)
$C_6H_5-SO-CH_3$	33–34	C_7H_8OS (140.21)
$C_6H_5-SO-C_6H_5$	69–71	$C_{12}H_{10}OS$ (202.28)
$C_6H_5-SO-CH_2-COOH$	118–119	$C_8H_8O_3S$ (184.21)
$CH_3-CH_2-SO-CH_2-CH_3$	(45–47/0.015)	$C_4H_{10}OS$ (106.19)
	67–68	$C_5H_{10}OS$ (118.20)
	109–110	$C_5H_8O_2S$ (132.18)
	91–92	$C_7H_{12}O_2S$ (160.24)
$C_6H_5-SO-CH_2-CH_3$	(68–70/0.005)	$C_8H_{10}OS$ (154.23)
$CH_3-(CH_2)_3-SO-(CH_2)_3-CH_3$	(105/0.3)	$C_8H_{18}OS$ (162.30)
$4-H_3C-C_6H_4-SO-CH_3$	38–39	$C_8H_{10}OS$ (154.23)
$C_6H_5-CH_2-SO-CH_2-CH_3$	51–52	$C_9H_{12}OS$ (168.26)
$C_6H_5-SO-CH_2-C_6H_5$	122–123	$C_{13}H_{12}OS$ (216.30)
$CH_3-(CH_2)_2-SO-(CH_2)_2-CH_3$	(73–75/0.1)	$C_6H_{14}OS$ (134.24)
$C_6H_5-CH_2-SO-CH_3$	53–54	$C_8H_{10}OS$ (154.23)
$C_6H_5-SO-CH=CH_2$	(105–110/0.15)	C_8H_8OS (152.22)
$4-H_3CO-C_6H_4-SO-CH_3$		$C_8H_{10}O_2S$ (170.23)
$C_6H_5-SO-CH_2-CH=CH_2$		$C_9H_{10}OS$ (166.24)
$C_6H_5-CO-CH_2-SO-C_6H_4-4-CH_3$	83–84	$C_{15}H_{14}O_2S$ (258.34)
$4-CH_3-C_6H_4-SO_2-CH_2-SO-C_6H_4-4-CH_3$	117–118	$C_{15}H_{16}O_3S_2$ (308.42)

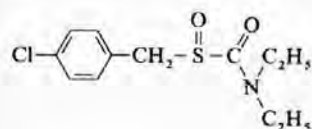
The longest-known oxidizing agent, used for sulfide oxidation as early as 1865, is nitric acid [111]. In the presence of gold(III) salts and by phase-transfer catalysis, oxidation with aqueous nitric acid in nitromethane is selective; oxidizable groups such as vinyl, tertiary amino, hydroxy, and diol groups are not attacked [112]. Very good yields of sulfoxide are also obtained with acetyl and benzoyl nitrates [113], and with the inorganic oxidants thallium(III) nitrate [114] and ceric ammonium nitrate (CAN). Oxidation with CAN alone is limited to diaryl sulfides, since in the presence of an α -hy-

drogen in the substrate molecule, the sulfoxide formed undergoes a Pummerer rearrangement under reaction conditions [115]. When CAN oxidation is carried out with sodium bromate as a co-oxidizing agent [116] or by phase-transfer catalysis [117], dialkyl and aryl alkyl sulfides can also be oxidized selectively. One of the most frequently used methods for effecting the sulfide–sulfoxide transformation is oxidation with sodium metaperiodate in aqueous methanol at 0 °C [118]. Modified processes employ sodium metaperiodate on an alumina carrier [119] or water-insoluble tetrabutylammoni-

um metaperiodate in boiling chloroform [120]. Iodosobenzene [121] and *o*-iodosylbenzoic acid [122] are also effective oxidizing agents. Selective oxidation with halogen compounds, such as sodium bromite [123], benzyltrimethylammonium tribromide [124], and particularly sodium hypochlorite has been described. The latter can be used in alkaline media at pH > 10 for the production of pharmacologically active compounds [125].

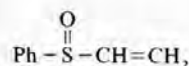
In addition to sulfones, sulfoxides are also obtained by reaction of sulfides with Oxone [16]. In the presence of wet alumina, phenyl alkyl sulfides are converted to either sulfone-free sulfoxides or sulfones, depending on the quantity of Oxone used [126]. Diastereoselective oxidation with Oxone has also been described [127].

Synthesis of 4-Chlorobenzyl-*N,N*-Diethylcarbamoyl Sulfoxide [94]



10 mol (2.575 kg) 4-chlorobenzyl-*N,N*-diethylthiocarbamate are dissolved in 1.5 L of toluene and treated with 0.4 L of formic acid and 0.4 L of 50 % sulfuric acid. Then 1.07 kg of 35 % hydrogen peroxide (11 mol) is added dropwise with stirring and ice-cooling in such a way that the temperature of the reaction mixture does not exceed that of the surroundings. After the mixture has been stirred for 4 h at room temperature, the organic phase is separated and neutralized with 20 % aqueous NaOH. The toluene phase is washed with water and evaporated to give the sulfoxide in 95 % yield (purity 95 %).

Synthesis of Phenyl Vinyl Sulfoxide [4]

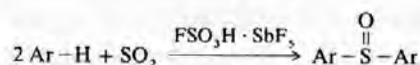


A solution of 20 g (0.147 mol) phenyl vinyl sulfide in 250 mL of dichloromethane, is cooled to -78°C , and a solution of 25.4 g (1.0 equivalent) of *m*-chloroperoxybenzoic acid in 200 mL of dichloromethane is added dropwise with stirring over 30 min. The reaction mixture is then warmed for 1 h in a water bath at 30°C

and poured into 300 mL of saturated hydrogencarbonate solution. The organic phase is separated, and the aqueous phase is extracted with 3×250 mL of dichloromethane. The combined organic phases are dried over magnesium sulfate, and after evaporation of the solvent, the residue is distilled. About 15–16 g (68–70 %) of the sulfoxide is obtained as a colorless liquid, *bp* 98°C (80 Pa).

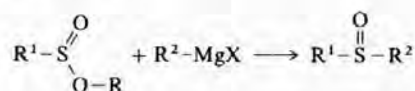
2.2.2. Reaction of Sulfur Dioxide with Aromatics

Simple aromatic compounds can be converted into the corresponding sulfoxides in good yield with sulfur dioxide and an equimolar quantity of Magic Acid ($\text{FSO}_3\text{H} \cdot \text{SbF}_5$). Unsymmetrical sulfoxides are also accessible by this route [128].

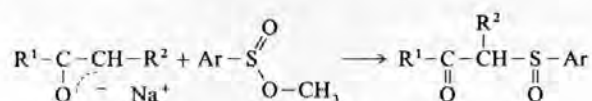


2.2.3. Sulfoxides from Sulfinates

Reaction of sulfinates with organometallic compounds, such as Grignard reagents and organocopper or organolithium reagents, is important for the production of optically active sulfoxides.

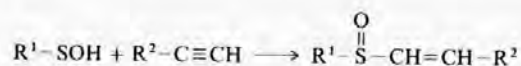


An extension of this reaction is the Claisen condensation of enolate anions with methyl arylsulfinates, giving α -keto sulfoxides [129].



2.2.4. α,β -Unsaturated Sulfoxides

A range of vinyl sulfoxides is accessible through trapping reactions of thermally produced sulfenic acids with alkenes [130].



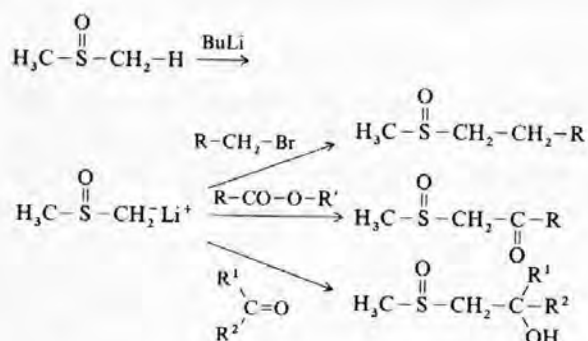
2.2.5. Optically Active Sulfoxides

Chiral sulfoxides, which play an important role in asymmetric synthesis, are produced by asymmetric synthesis, optical and kinetic separation of enantiomers, and stereospecific synthesis; for reviews, see [3], [131].

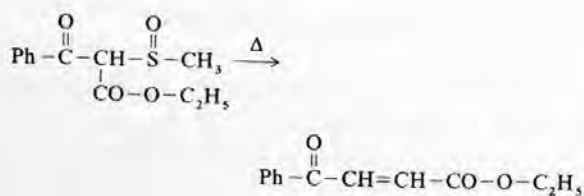
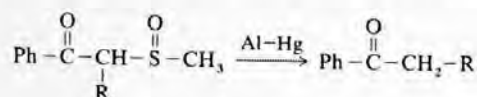
2.3. Reactions

2.3.1. Reactions of α -Sulfinyl Carbanions

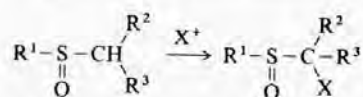
Strong bases, such as butyllithium, sodium hydride, or lithium dialkylamide, deprotonate sulfoxides with α -hydrogens to give α -sulfinyl carbanions. The latter react stereoselectively with organic electrophiles to form C-C bonds [1], [2, p. 583].



Subsequent reactions consist of reductive cleavage of the sulfinyl group to a ketone and elimination with the formation of a double bond. These processes have been used for the synthesis of various ketones and carboxylic acids [132].



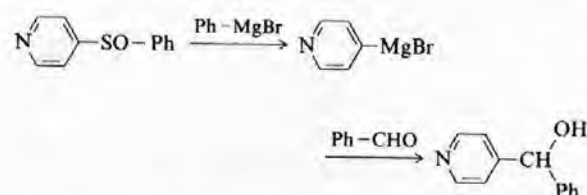
For α -halogenation of sulfoxides, which also proceeds via sulfinyl carbanions, various reagents have been described [1], [3].



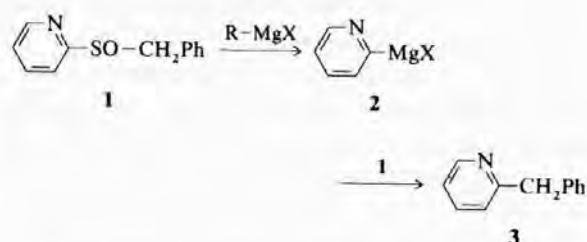
Halogenation with *N*-halosuccinimides [133] and chlorination with *N,N*-dichloro-*p*-toluenesulfonamide [134] give good yields.

2.3.2. Reactions with Grignard Reagents

Ligand exchange reactions between heterocyclic sulfoxides and Grignard reagents are used for production of the corresponding heterocyclic Grignard reagents. Subsequent reaction of these organometallic derivatives with carbonyl compounds provides a route to new heterocyclic compounds [135], [136].



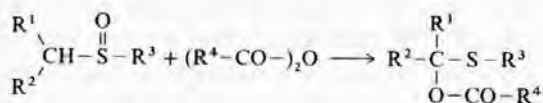
A variant of this reaction is ligand coupling. The heterocyclic Grignard compound (2) formed initially reacts with the educt sulfoxide (1) to give the coupling product 3 [137].



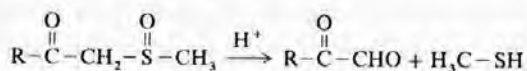
This reaction is used mainly for the synthesis of bisaryls [138], [139].

2.3.3. Pummerer Rearrangement

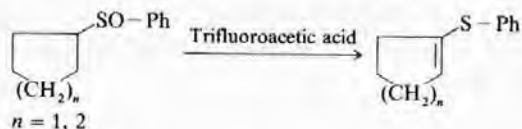
In the Pummerer rearrangement, sulfoxides having at least one α -hydrogen are treated with acids or strong electrophiles such as carboxylic acid anhydrides or chlorides to form α -substituted sulfides as the primary products.



The Pummerer rearrangement is used widely in synthesis [1], [3]. For example, α -dicarbonyl compounds are formed from β -keto sulfoxides on acidic workup.



Cycloalkyl phenyl sulfoxides are converted into vinyl sulfides under conditions of the Pummerer rearrangement [140].



2.3.4. Oxidation and Reduction

Oxidation of sulfoxides to sulfones not only is a frequently occurring side reaction in the production of sulfoxides, but is also used for the synthesis of sulfones (see Section 2.2.1).

Reduction of sulfoxides to sulfides is achieved with hydrogen in ethanol on Pd-C catalysts [141] or selectively with dichloroborane [142] even in the presence of acid chloride, ester, nitrile, or nitro groups. Deoxygenation of sulfoxides with zinc-dichlorodimethylsilane under very mild conditions [143] and with polystyryldiphenylphosphine [144] has also been described. These reactions have no effect on a wide variety of functional groups and permit a cleaner product isolation.

2.4. Uses

Many sulfoxides are used as intermediates in the production of pharmaceuticals, plant protection agents, and other physiologically active substances.

Sulfoxides also play an important role in the synthesis of optically active substances. A selection of patents on the use of sulfoxides is given below.

Crop Protection and Veterinary Drugs

Insecticides and acaricides [145].

Bactericides and fungicides [146].

Plant growth regulators [147].

Anthelmintics in veterinary medicine [148].

Pharmaceuticals

Agents for treating gastrointestinal disorders [149].

Enantiomerically pure sulfoxides as cardiovascular medicines [150].

Sulfoxide derivatives of 5-thiaprostaglandin E_1 act as vasodilators and inhibit thrombocyte aggregation [151].

Thiocarbamoylsulfoxide derivatives exhibit antihypertensive action [152].

Imidazolyl sulfoxides are anti-inflammatory and are also said to be suitable for treating asthma and skin diseases such as psoriasis [153].

Trichlororuthenium complexes with a sulfoxide group have antitumor activity [154].

Agents for treating allergic reactions, particularly asthma [155].

Methionine sulfoxide lowers the liver toxicity of acetaminophen in humans [156].

Tetrahydrothiophen-1-oxide and its derivatives are inhibitors of alcohol dehydrogenase and therefore act as antidotes for alcohol poisoning [157].

Various sulfoxides are enzyme inhibitors [158].

Thiocarbamate sulfoxides have been described as agents for combating alcohol addiction [159].

Agents for treating sun-damaged skin [160].

Sulfoxides support the percutaneous absorption of a range of pharmaceuticals [161].

Others

Bis(2-hydroxyethyl) sulfoxide is used to treat oily hair [162].

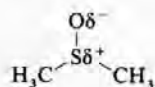
Sulfoxides act as stabilizers for polymers and lubricating agents against heat, light, and oxygen [163].

Polyalkoxylated thioglycol sulfoxides are used as fabric softeners [164].

Use in refrigerating liquids for refrigerators and air-conditioning equipment [165].

Coupling agents in silver halide color films [166].

2.5. Dimethyl Sulfoxide



Dimethyl sulfoxide (DMSO) is a colorless, odorless, strongly hygroscopic liquid. It is readily miscible with water and other protic solvents such as alcohols. This property can be attributed to the formation of strong hydrogen bonds between the polarized S–O bond and water molecules. The strong polarity of the S–O bond, with a partial negative charge on oxygen (see formula) is shown by the high dipole moment (4.3 ± 0.1 D at 20 °C) and basicity ($\text{p}K_{\text{B}} = -2.7$) of dimethyl sulfoxide. Pure DMSO forms chain-like polymeric association complexes at room temperature. This gives rise to considerably higher melting and boiling points compared to dimethyl sulfide (see Table 3).

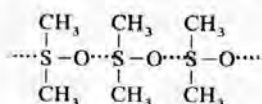


Table 3. Comparison of physical properties of dimethyl sulfide and dimethyl sulfoxide

	Dimethyl sulfide	Dimethyl sulfoxide
<i>mp.</i> , °C	–98	18.5
<i>bp.</i> , °C	38	189
<i>d.</i> , g/mL	0.846	1.101

2.5.1. Production

In principle, DMSO can be produced by oxidation of dimethyl sulfide as described in Section 2.3.1. These methods are, however, often suitable only for small quantities. In industry, DMSO is produced by catalytic oxidation of dimethyl sulfide with oxygen or by oxidation with nitrogen dioxide [167]. The oxidation of dimethyl sulfide with oxygen at 7.2 MPa and 105 °C gives good yields of DMSO [168].

2.5.2. Uses

Dimethyl sulfoxide is an excellent solvent [169] that is widely used for reactions in modern chem-

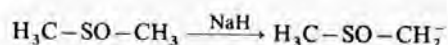
istry. Because of its high polarity and good solvation of cations, DMSO dissolves not only a large number of organic compounds, but also many metal salts, particularly those of alkali and alkaline-earth metals. DMSO is also a good solvent for many polymers.

A range of different pharmacological properties and effects have been described for DMSO [170]. For example, it increases the capacity of the skin to absorb drugs, and exhibits both analgesic and bacteriostatic activity. It can be used for the treatment of infection by retroviruses [171] and as an anti-inflammatory agent. Furthermore, DMSO has been described as a preservative and cryo-protective agent for organ and tissue transplants [172].

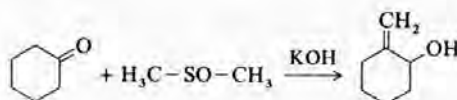
In plant protection, DMSO can be used to ward off mammals (e.g., deer [173]) and as a growth stimulant [174].

2.5.3. Reactions

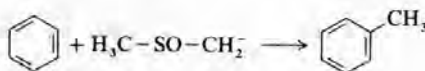
The so-called dimsyl anion, formed on treatment of dimethyl sulfoxide with base, can react further like other sulfinyl carbanions (see Section 2.3.1).



Cyclic ketones react with DMSO in the presence of KOH to give 2-methylenecycloalkanols [175].



The methylation of various aromatic systems by the dimsyl anion is also of interest [176].



3. Toxicology

3.1. Sulfones [177–181]

The toxicity of sulfones is generally low. The sulfonyl group is relatively stable metabolically.

However, for some compounds, enzymatic reduction to the sulfide has been discussed. For the solvent *sulfolane* (tetramethylene sulfone), on oral administration to rats, an average lethal dose of 1.8–2.5 g/kg has been found. Various mammals show neurotoxic symptoms after oral administration, injection, inhalation, or dermal absorption of sulfolane. No information is available on the carcinogenic or teratogenic activity of sulfolane. *p*-Chlorophenyl phenyl sulfone, used as an insecticide, is a skin irritant; in animal experiments, liver and kidney damage occurs. For 2,4,5,4'-tetrachlorodiphenyl sulfone (tetradifon, an acaricide), very low toxicity has been found in animal experiments.

3.2. Dimethyl Sulfoxide [178], [181–184]

Dimethyl sulfoxide has very low *acute toxicity*, and chronic effects are observable only at high doses. The lethal dose for humans is estimated to be ca. 10–12 mL/kg [177]. The toxic effects of DMSO, such as skin rash and itching after dermal application, hemolysis after intravenous infusion, and gastrointestinal disorders after swallowing, depend strongly on the concentration. DMSO–water mixtures have an irritant effect only at concentrations > 70 % DMSO.

In the mammalian organism, sulfoxides can be reduced to sulfides by tissue or microbial enzyme systems. Enzymatic oxidation to sulfones has also been described, therefore the toxic effect of sulfoxides can arise from both of these redox states.

Teratogenic and mutagenic activity has been described for DMSO. DMSO strengthens the action of other toxic substances due to absorption through the skin.

In handling DMSO, attention should be paid to the fact that hazardous chemical reactions can occur in some cases. Explosions have been reported as a result of thermal decomposition and on reaction with organic acid chlorides, non-metal halides, perchloric acid, perchlorates, nitrates, and sodium hydride.

Only limited data can be found in the literature on the toxicity of other sulfoxides.

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