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Preface

The present monograph is devoted to one of the developing topical areas of the organosulfur compounds chemistry, i.e. to the synthesis, reactivity, and fundamental physical properties of aromatic thiols and their derivatives (aryl thiols, sulfides, sulfones, sulfoxides, their acylated derivatives, and thioacylates).

The necessity and timeliness of the monograph is quite obvious to everyone who is familiar with chemistry and technologies of organosulfur compounds and sulfur chemistry in general. At present, the huge reserves of elemental sulfur, released during hydrodesulfurization of petroleum products, have been accumulated and continue to increase. The need for their utilization is strongly dictated by both technological and environmental problems, the acuteness of which is steadily growing. Therefore, we believe that the summarizing of publications devoted to aromatic organosulfur derivatives is timely and useful. Of course, the authors do not in any way consider that the use of organosulfur compounds, such as aryl thiols and their derivatives can solve all the problems associated with the utilization of million tons of elemental sulfur.

Note that in the world scientific literature the flow of publications (original papers and reviews) on the chemistry of aromatic thiols increases year by year. However, a monograph summarizing the main achievements in this field, especially over the last decades, was lacking before the publication of this book.

The monograph covers, along with traditional (classical) methods for the synthesis of aromatic thiols and their derivatives, the newest approaches to the formation of the carbon-sulfur bonds based on the application of transition metals and their complexes. The examples of the synthesis of the most important and available representatives of aromatic thiol derivatives are given at the end of each chapter.

Over the last decades, the attention of researchers has attracted such an important property of thiols (especially aromatic ones), as the ease of their addition to the double and triple bonds. Such reactions, as a rule, occur in the presence of cheap radical initiators or under the action of ultraviolet irradiation and do not require sophisticated and expensive metal complex catalysts. Now, these reactions have found wide practical applications. No wonder that recently several reviews and dozens of original papers and patents have been dedicated to this issue. To this extensively developing research direction, which is now referred to as “ene-thiol chemistry,” is given a significant place in the monograph.

The authors tried to focus their presentation on large series of aromatic thiols and their derivatives bearing different substitutes, which has allowed a correct comparative analysis of both reactivity and various physicochemical properties of the corresponding compounds. For this purpose, the relevant publications were chosen, in which the correlation analysis with reliable statistical processing was systematically and correctly applied. Accordingly, the monograph contains tables of physical and chemical properties of large series of compounds studied. These tables already in themselves represent a factual value and, naturally, increase the importance of the monograph as a reference manual.

The monograph consists of seven chapters. The first five of them cover various aspects of the synthesis and reactivity of the studied objects. In Chap. 1, methods for the synthesis of aryl thiols are discussed. The Chap. 2 is devoted to aromatic sulfides and general approaches to their synthesis. Also, the issues related to the direct preparation of individual representatives of these compounds are analyzed. These representatives were needed to expand the scope of the series, which were subsequently used for the correlation analysis of the relationship between the reactivity, physical properties, and structure of the molecules studied. In particular, the nontrivial problem of aryl thiols alkylation with tertiary alkyl halides is considered in this chapter.

The Chap. 3 covers the methods for the synthesis of aromatic disulfides, sulfoxides, sulfones, and some other derivatives of aromatic thiols. In our opinion, the usage of selenium analogs of the studied derivatives, namely arylselenoacylates, for comparative analysis, is of particular value.

The Chap. 4 deals with the reactions of aromatic sulfides: the electrochemical oxidation of aryl thiols and their derivatives, the bromination of alkyl aryl and alkyl benzyl sulfides, the acylation of alkyl aryl sulfides, and some other reactions involving aromatic thiols and their derivatives.

Chapter 5 of the monograph is dedicated to the application of acylated aromatic sulfides in organic synthesis. In this chapter, the reader should pay attention to the original and simple synthesis of pyrroles and N-vinylpyrroles based on oximes of acylated aromatic sulfides and acetylene in superbasic catalytic systems such as alkali metal hydroxide/DMSO by the Trofimov reaction. In some cases, instead of free acetylene, its synthetic equivalents are used: vinyl chloride and dihaloalkanes, which increases the safety and technological feasibility of the method, and hence the availability of the compounds obtained.

“Of a special scientific significance is the chapter devoted to theoretical issues related to the interaction of the sulfur atom in various degrees of oxidation with neighboring aromatic systems. In this chapter, the ^{1}H, ^{13}C, ^{17}O, ^{19}F, NMR, NQR, IR, UV spectra, as well as X-ray fluorescence data are analyzed at a high professional level, often with correct employment of the correlation analysis. All these data represent a unique material for understanding the main problems of the electronic and conformational structure of aromatic sulfides that allows predicting their reactivity and possible directions of their practical application” (From the review of Academician O. N. Chupakhin on this monograph).

The last Chap. 7 of the monograph is devoted to practical applications of aromatic thiols and their derivatives. Naturally, it was difficult for the authors to encompass in sufficient detail in one chapter all areas, in which these compounds are applied or could be applied. But it seems to us that the above examples convincingly illustrate the almost inexhaustible possibilities of the organosulfur compounds of these series.

The authors hope that the synthetic methods and main reactions involving aromatic thiols and their derivatives summarized in the monograph, the formulated regularities and correlation dependences of the reactivity on their structure, as well as the above experimental procedures, will be of help to the experts working in the field of chemistry and technology of organosulfur compounds.

In general, the monograph can be useful not only to narrow specialists, i.e. synthetic chemists and physical chemists, but also to petrochemists, engineers, pharmacologists, biochemists, photochemists, and photophysicists, who create materials for high technologies, new drugs, and agricultural preparations. The book may be of interest to researchers, faculty staff, graduate students, and students of the chemical faculties of various universities. For many of them, the book can be a desk reference and a source of new ideas.

We express our sincere gratitude to the scientific editor of this monograph, Academician M. P. Yegorov, and to reviewers, Academician O. N. Chupakhin, Profs. N. K. Gusarova and S. V. Amosova for their useful constructive advice and comments. The authors are deeply grateful also to I. G. Grushin and D. N. Tomilin for their valuable help in preparing the manuscript. Any criticism and comments on the book will be accepted with gratitude.

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Introduction

The targeted search for synthetic routes to novel organosulfur compounds and investigations of their properties remain an urgent challenge in organic chemistry [1–8]. Interest in the structure and reactivity of organosulfur compounds, especially aromatic thiols and their derivatives, is due to their wide application in various fields of modern medicine and technology (pharmaceuticals [9–12], stimulators of biochemical processes [13–16], electroconductive complex-forming polymers [17], anticorrosion coatings [18], additives to lubricating oils and fuels [19], analytical reagents [20–22], agricultural pest control agents [23–24], etc.). Aromatic thiols and their derivatives also attract attention as models for theoretical studies. For example, the kinetics of the enzymatic oxidation of aryl thiols has been studied to better understand the metabolism of numerous drugs containing the thiol function [25].

Polyphenylene(arylene)sulfides are important high-temperature engineering thermoplastics possessing increased mechanical strength and elasticity, as well as useful electrical characteristics [26–27]. The method for their production (developed as back as 1948) by high-temperature condensation of polyhalobenzenes in the presence of sulfur and alkali metal carbonates did not find wide industrial application, and therefore, interest in these compounds is not faded to the date. Various reactions of aromatic thiols, sulfides, and disulfides are employed for the synthesis of such compounds. For instance, polyphenylene sulfides are prepared via the reaction of electron transfer involving diphenyl disulfide [28]. Polyphenylene disulfide is also obtained from diphenyl sulfide and sulfur chloride [29]. Catalytic oxidation of aromatic dithiols affords aromatic cyclic disulfide oligomers possessing good solubility and high glass transition temperature [30]. Cyclic disulfide oligomers are used for the construction of polythioarylenes having high thermostability [31]. High-molecular electrically conductive polyphenylene sulfide-phenyleneamine is utilized as a soluble model of polyaniline [32]. The synthesis and functionalization of soluble derivatives of bromomethylated polyphenylene sulfides have been implemented [33]. Macrocyclic arylthioesters (simple and complex oligomers) are synthesized from phthaloyldichloride and diatomic thiophenols [34]. In recent years, transition metals-catalyzed reactions are increasingly being used to prepare polyarylene sulfides. Thus, an approach to phenylene sulfide-sulfoxide oligomers via palladium-catalyzed cross-coupling of aryl iodides with bromothiophenol is described. Further growth of the polymer molecule occurs due to the addition of bromothiophenol to the obtained sulfide after copper-catalyzed substitution of bromine by iodine [35]. Monodisperse *para*-phenylene sulfide oligomers with a high degree of crystallinity are prepared by the Cu-catalyzed cross-coupling of Ar–S and the aromatic substitution of fluorine by aryl thiolates [36]. Oxidative polymerization of diphenyl disulfides in the presence of a vanadium complex has been realized [37].

Synthesis and functionalization of the closest derivatives of aromatic thiols (sulfides, disulfides, sulfoxides, sulfones) continue to command the research interest. The search for new reactions with the participation of these compounds and investigations of their valuable properties are progressing rapidly. The obtained chemical and biochemical data stimulate a comprehensive study of the electronic and spatial structure of organosulfur compounds, especially aromatic thiols and their derivatives. This is necessary to develop more rational, environmentally benign, energy saving, and atom-economical approaches for the synthesis of these important class of compounds.

The peculiarities of the electronic, conformational, and other spatial characteristics of aromatic thiols, sulfides, and their closest derivatives as a whole and their individual fragments, the localization of electron density on atoms and bonds, and the ease of its redistribution, symmetry, and molecular orbitals enable to correctly understand the participation of these molecules in chemical processes, to predict the direction, rate, and other physical-chemical characteristics of organic and bioorganic reactions involving the studied compounds.

Aromatic sulfur derivatives in II, IV, and VI valence states represent convenient objects for establishing the fundamental relationships between the physical-chemical properties of the most important organosulfur compounds, especially aromatic thiols and their derivatives, their structure, and reactivity. Much attention is paid to the conjugation in the series of sulfur compounds with different valencies, to the nature of the interaction between sulfur atom and π- or p-electrons of the substituents, to the rationalization of duality (π-donor or π-acceptor effect) of its electronic influence.

For a long time, the common point of view on the nature of the acceptor properties of the sulfur atom was based on the hypothesis of its participation in 3d–π-interaction. Later, it became clear that this effect had a much more complex character [38–42], since the conclusions about the manifestation of 3d-π-conjugation were often contradictory, and some results could not be explained at all using this hypothesis. A more correct understanding of this effect was hindered by the absence of systematic studies of compounds with a regularly changing structure, which began to appear only in the late 1980s [43–57]. In the present monograph, the analysis of these studies occupies a significant place.

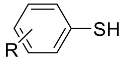
The main sections of the monograph are devoted to the following issues:

- Directed synthesis of aryl thiols, their derivatives; comprehensive physical-chemical study of properties of these compounds;
- Critical analysis of theoretical representations on the electronic structure and reactivity of aromatic thiols, sulfides, and their derivatives on the basis of available experimental data;
- Supplementing the scientific foundations of rational control of technological processes with the participation of the most practically important organosulfur compounds.

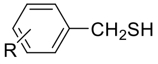
Also, the following issues are discussed in detail:

1. Methods for the synthesis of aromatic sulfur derivatives in II, IV, and VI valence states and (for comparison) their selenium analogs.
2. An original approach to the synthesis of (organylthio)phenylpyrroles by the Trofimov reaction [58–60].
3. Reactivity of aromatic sulfides on the basis of the results of chemical and physical-chemical studies.
4. Spatial and electronic structure, mutual effects of molecular fragments in the series of substituted aryl and benzyl sulfides, aryl sulfoxides, sulfones, and their oxygen and selenium analogs.
5. π-Donor and π-acceptor properties of sulfur, selenium, and oxygen compounds in the ground and excited electronic states and the substituents effect.
6. Some little-known areas of practical application of aromatic thiols, sulfides, and their derivatives.

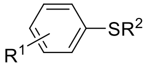
Specifically, the authors focused their attention on the following objects:



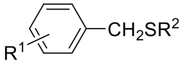
Substituted
aromatic thiols



Substituted benzyl thiols



Substituted
aromatic sulfides



Substituted
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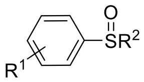
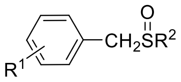
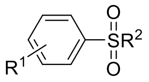


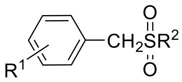
Substituted
aromatic sulfoxides



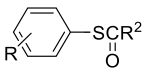
Substituted
benzyl sulfoxides



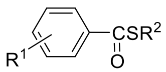
Substituted
aromatic sulfones



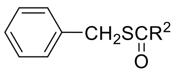
Substituted
benzyl sulfones



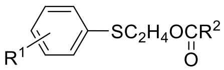
S-aryl thioacylates



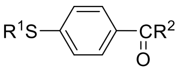
S-Organyl thiobenzoates



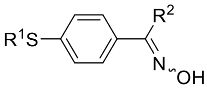
S-Benzyl thioacylates



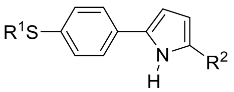
2-(Arylthio)ethyl carboxylates



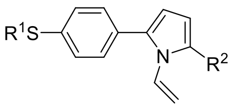
Alkyl 4-(organylthio)phenyl ketones



(Alkylthio)aryl ketoximes



(Organylthio)phenylpyrroles



(Organylthio)phenyl-*N*-vinylpyrroles

A number of monographs on chemistry [2–4, 8, 61–66], biochemistry [13, 67–69], and analysis of organosulfur compounds are known. The works by Prilezhaeva [70–71], Oae [2], Mangini [72–73], Voronkov [62], Chmutova [74], Trofimov [63, 65, 75], Guryanova [76], Kalabin [77], and others [64, 78] have given an insight into the character and strength of intramolecular electronic interactions in the ground and excited states of aromatic thiols, sulfides, and their derivatives. The total and partial effects of element-containing substituents relative to the aromatic ring, depending on the nature and the valence state of the heteroatom, the character of the non-aromatic radical, the nature and position of the secondary substituents in the aromatic nucleus, have been analyzed at both the empirical level and within the framework of correlation equations. These questions are briefly considered in this monograph.

The attention of researchers to these issues is not weakened. Temperature effects upon photolysis of aryl vinyl sulfides in comparison with aryl vinyl ethers are studied [79]. The behavior of aryl vinyl sulfides in reactions of tandem photocyclization and intramolecular addition is investigated [80]. It is assumed and confirmed by the data of *ab initio* calculations that the sulfonic cation acts as an active intermediate in the oxidative polymerization of diphenyl disulfide [81]. The photochemical study of aryl vinyl sulfides and aryl vinyl ethers proves the formation of thiocarbonyl and carbonyl ylides [82]. The investigation into non-oxidative Pummerer reaction, on the example of (*R*)-ethyl-*p*-tolylsulfoxide as an equivalent of chiral α-hydroxyethyl anion, evidences the stereoselectivity of S_N2 type. The mechanism for the formation of enantiomerically pure products, L-α-trifluoromethyltreoninate, and D-α-trifluoromethylallothreoninate is given [83]. It is reported on the unusual effect of the transition metal complexes on the catalytic formation of the C–S and C–Se bonds [84]. Zinc-promoted palladium catalysts are proposed for the formation of a carbon-sulfur bond [85]. Catalytic adaptive recognition of thiol and selenol groups in the synthesis of functionalized vinyl monomers is found [86]. Recently, the participation of transition metals in the activation and conversions of the C–S bond has also been considered [87]. Under the action of a silver catalyst, direct thiylation of quinones with aryl disulfide is implemented [88].

The interest in various aspects of chemistry and physical chemistry of aromatic thiols and their derivatives continues to increase, as evidenced by the publication of numerous relevant reviews. For instance, the review [89] covers the C–S bond forming reactions, including the addition of aromatic thiols to unsaturated compounds catalyzed by metal complexes. Similar reactions of thiols and selenols are also summarized [90]. In a later review [91], the formation of aryl–S bond under the action of copper compounds is surveyed. The reactions of fluorine-containing alkyl (aryl)vinyl sulfides and their interaction with electrophilic and nucleophilic reagents are systematically analyzed [92]. The problems of carbon-sulfur bond formation, including transition metals-catalyzed syntheses of aryl sulfides, continue to be the focus of the researchers [87, 93–97]. Particular attention is paid to these issues in the comprehensive reviews of Beletskaya et al. [95–96]. A chapter in the monograph is devoted to transition metals-catalyzed addition of S–H compounds, including aromatic thiols, to alkynes and allenes and related compounds [97]. Regular coverage of achievements in the synthesis of aryl alkyl- and dialkyl sulfides continues even now [98–99].

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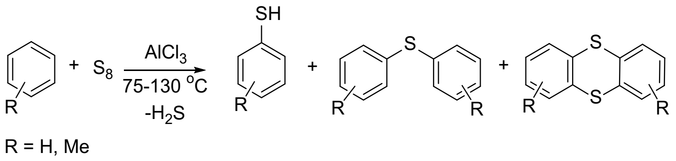
1

Synthesis of Aromatic Thiols

1.1 Reactions of Aromatic Compounds with Elemental Sulfur and its Inorganic Compounds

Synthesis of aromatic thiols and their derivatives is a rather poorly explored area of organosulfur chemistry. Meanwhile, with the rapid progress in industrial organic synthesis, aromatic thiols and their derivatives attract an ever-increasing attention from wide circles of chemical community.

Classical methods for the introduction of the SH-groups into various aromatic compounds are based on the interaction of arenes with sulfur or its inorganic derivatives and are described in the fundamental monograph of Houben-Weyl [1]. It is shown [2] that thiophenol can be obtained using elemental sulfur and anhydrous aluminum chloride, which react with benzene at 75–80 °C. The reaction of toluene with S_8 (115–130 °C) in the presence of $AlCl_3$ affords thiocresols [3]. However, these methods for the synthesis of aromatic thiols are not widely spread, since, along with thiols, which are the major products of the reaction, diarylsulfides and thianthrenes are also formed. The yields of the products depend on the reactants ratio and catalyst amount.

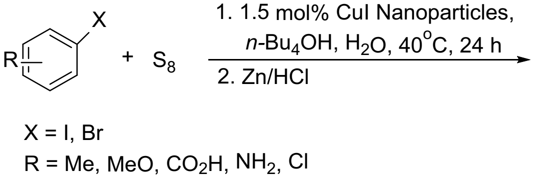


Aryl thiols are also synthesized by the interaction of aryl magnesium halides with elemental sulfur followed by decomposition of the resulting halothiolates with diluted acids or water [4–6]

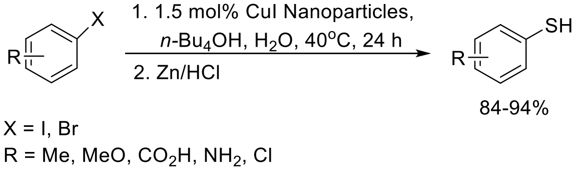
$$\mathrm{ArMgX} \xrightarrow{S_8} \mathrm{ArSMgX} \xrightarrow{H^+/H_2O} \mathrm{ArSH}$$

I. A. Aliyev et al., *Aromatic Thiols and Their Derivatives*,
https://doi.org/10.1007/978-3-030-69621-4_1

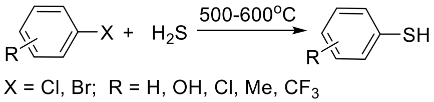
Various bases and Lewis acids are employed to activate elemental sulfur. For instance, aryl iodides upon heating (90 °C) in the presence of K_2CO_3 undergo a CuI-catalyzed cross-coupling reaction with elemental sulfur to deliver, after subsequent treatment with $NaBH_4$ or triphenylphosphine, aromatic thiols with a high yield [7]. A wide range of functional groups including methoxy, hydroxy, acyl, carboxy, amide, bromo, and trifluoromethyl were tolerated in this process.



Aryl thiols were also synthesized by the coupling of aryl halides and sulfur powder in the presence of CuI-nanoparticles followed by the reduction with Zn/HCl [8]. The reaction is implemented in water and *n*-Bu_4NOH that makes the process green. Both aryl iodides and activated aryl bromides are formed in moderate to excellent yields.



Academician M.G. Voronkov et al. have developed promising methods for the synthesis of aryl thiols via high-temperature reactions of halogenated aromatic hydrocarbons with hydrogen sulfide [9–12].



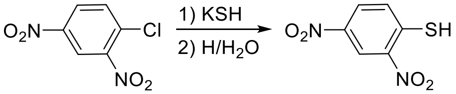
The methods of high-temperature synthesis are also suitable for the preparation of heteroaromatic thiols [10, 12].

Direct nucleophilic substitution of a halogen atom in organohalogen compounds by hydrosulfide anion has become a paradigmatic case in the synthesis of organic thiols [13, 14]. In order to avoid the formation of sulfides due to the equilibrium characteristic of hydrosulfides.

$$2NaSH \xrightleftharpoons{H_2O} Na_2S + H_2S$$

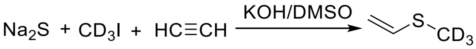
the reaction is carried out in an anhydrous solvent or in an excess of hydrogen sulfide, which limits its scope. Under these conditions, the yields of organic thiols range 36–74% [15].

This method is often used for the synthesis of *ortho*- and *para*-nitro and amino-substituted aryl thiols from the corresponding nitrohaloaromatic compounds [16].



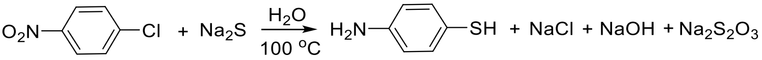
A kinetic study of the reaction between phenylacetylene and sodium hydrosulfide in aqueous DMSO [17] has shown that NaSH is quite stable in DMSO, i.e. the above equilibrium is actually shifted to the left. It turns out [18] that due to the ability of DMSO of extracting sodium hydrosulfide from hydrated Na_2S, it is possible to easily and simply prepare a stable solution of NaSH in DMSO. In the case of $Na_2S{\bullet}4H_2O$, up to 90% of sodium hydrosulfide is transferred to a solution of DMSO [19]. The purity of NaSH solution in DMSO thus obtained reaches 98%. According to the data [17], such a solution is stable and does not undergo hydrolysis, as it occurs with aqueous or alcohol solutions of NaSH, the hydrosulfide being almost completely dissociated [20]. Upon slow addition of an organic halide to a solution of NaSH in DMSO at room temperature, the corresponding thiols are formed in almost quantitative yields [14]. The method has been implemented using a series of aliphatic bromides (C_2-C_{12}).

It is shown that in the system M_2S/organic halide (M = Na, K), acetylene behaves as an efficient trap of the organic thioanion, which leads to the formation of vinyl organosulfides. Using this new highly effective carrier of hydrosulfide anion, namely a solution of NaSH in DMSO, the deuterated vinyl methyl sulfide has been synthesized with a yield of 95% from CD_3I, Na_2S, and acetylene in DMSO in one preparative stage under very mild conditions (room temperature and atmospheric pressure) [19].

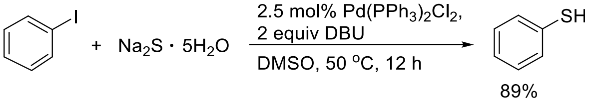


Despite the obvious efficiency, simplicity, and availability of the system Na_2S/H_2O/DMSO, which allows introducing the thiol function into organic compounds via the nucleophilic substitution of the halogen by the SH-group, this reagent is underestimated by organic chemists. In particular, the potential of this reagent for obtaining aromatic thiols from aromatic halides is still obscure. It can be predicted with a high probability that this system will also be very effective for the above purpose. Eventually, the preparative significance of the existing methods for the synthesis of aromatic thiols will be revisited.

The heating of *para*-nitrochlorobenzene with an excess of Na_2S in an aqueous solution is accompanied by the reduction of the nitro group to furnish *para*-aminothiophenol [21, 22].



Formation of thiophenol (89% yield) was observed in $Pd(PPh_3)Cl_2$/dppb-catalyzed coupling reaction of iodobenzene and $Na_2S{\cdot}5H_2O$ in the presence of DBU [23].



1.2 Reactions with Other Sulfur-containing Nucleophiles

The direct nucleophilic substitution of aryl halides with sodium alkylthiolates was considered a simple strategy for the synthesis of aryl thiols. Non-activated aryl halides (chlorides and bromides), as a rule, hardly participate in nucleophilic substitution reactions. The employment of polar non-hydroxyl solvents has significantly expanded the scope of this method. For instance, aryl thiols can be obtained by the reaction of aryl halides with a 2–threefold excess of primary or secondary sodium alkylthiolates in HMPA [24–26], DMF [27], and N-methylpyrrolidone [28]. The one-pot synthesis involves two consecutive stages: the formation of alkyl aryl sulfide via nucleophilic aromatic substitution of the halogen atom by an alkylthiolate anion and the subsequent cleavage of the sulfide across the S − Alkyl bond (dealkylation) to give aromatic thiols [24–28].

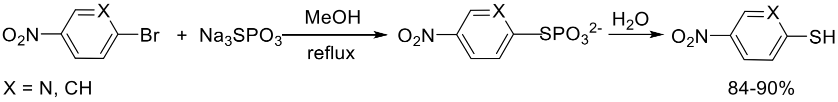
$$\mathrm{ArX} + \mathrm{RSNa} \xrightarrow[-\mathrm{NaX}]{} \left[\mathrm{ArSR}\right] \xrightarrow[-\mathrm{RSR}]{} \mathrm{ArSNa} \xrightarrow{\mathrm{H^+/H_2O}} \mathrm{ArSH}$$

Usually, the reaction proceeds at 100–160 °C. In addition, the dealkylation of sulfides can be executed under the action of alkali metal alkoxides and amides as well as using metal sodium in DMF [27].

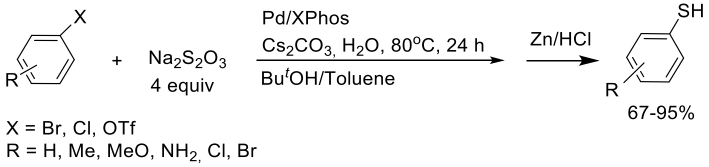
This approach is also suitable for the synthesis of hetaryl thiols such as 2-mercaptothiophene [24], mercaptopyridines [27], and thioquinolines [24, 27].

The methods based on the usage of such *S*-nucleophiles as thiourea, dithiocarbamates, xanthogenates, as well as thioamides and thiophosphates, appear to be more expedient for the preparation of aryl thiols. These one-pot two-step syntheses permit to avoid side processes, which often accompany the direct reactions.

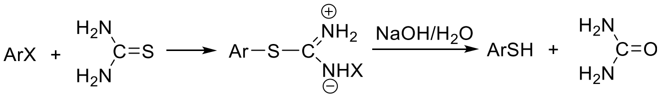
The interaction of activated electron-withdrawing groups of aryl halides with two equivalents of sodium thiophosphate upon boiling in methanol affords arylthiophosphate, which, after treatment with water, is converted into the corresponding thiol in a high yield [29].



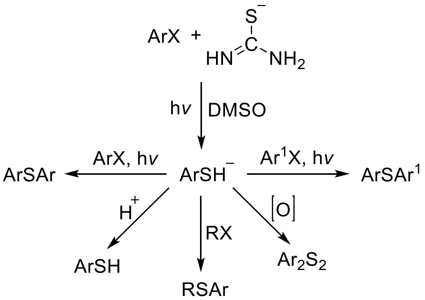
The development of transition-metal-catalyzed C−S coupling reactions has stimulated the emergence of new protocols for the synthesis of thiols. $Pd(OAc)_2$/X-Phos-catalyzed thiolation of aryl halides and trifluomethanesulfonates with sodium thiosulfate as a thiol source proceeds in *tert*-butanol/toluene in the presence of Cs_2CO_3 to give aryl thiosulfate, which is further reduced by Zn/HCl delivering aryl thiols [30]. Water in the system improves the solubility of the sodium thiosulfate.



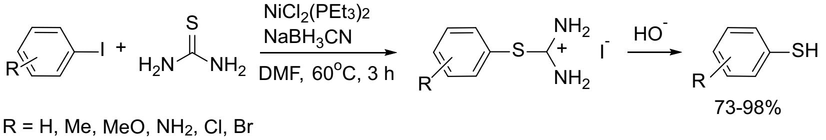
Aryl halides react with thiourea upon heating in alcohol to produce arylisothiuronium salts, the hydrolysis of which leads to the formation of the corresponding thiols [1].



This reaction easily proceeds with aryl halides activated for a nucleophilic attack. Aryl halides with donor substituents in the ring (amino-, alkoxy groups) are activated by UV irradiation [28]. In the photoinduced reactions with thiourea in DMSO (20 °C, 3 h), aryl(benzyl, naphthyl)- and hetaryl(pyridine, quinoline, pyrazine, pyrimidine) halides with OMe, SMe, CN, NO_2, PhCO-substituents successfully generate arylthiolate ions, which, without isolation, can undergo protonation, nucleophilic aliphatic substitution or oxidation to deliver aryl thiols, aryl methyl sulfides, diaryl sulfides or diaryl disulfides in 50–80% yields [31].

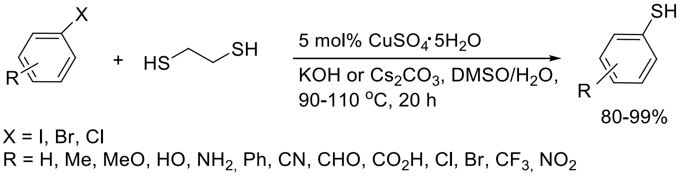


Transition metal catalysts are often exploited to facilitate aromatic nucleophilic substitution in aryl halides. In the presence of catalytic amounts of Ni(0), generated in situ from $[NiCl_2(PPh_3)_2]$, and BH_4CN as a reducing agent, aryl iodides react with thiourea (60 °C, 3–25 h) to give rise to, after the decomposition of isothiouronium iodide and acidification with hydrochloric acid, aryl thiols in quantitative yields [32].

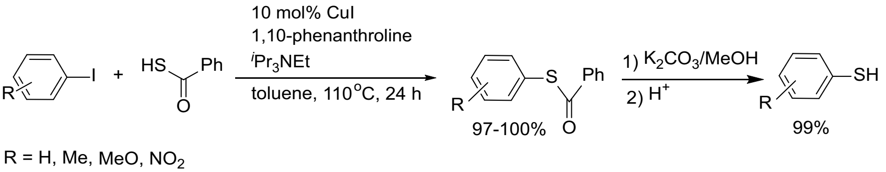


The reaction is successfully implemented in DMF, MeCN, acetone, and dioxane. Electron-donating substituents (amino and alkoxy groups) do not reduce the reactivity of aryl iodides. Under similar conditions, aryl bromides and chlorides do not react with thiourea. The CuI/L-proline-catalyzed coupling of aryl iodides and thiourea occurs in the presence of $NaOBu^t$ in DMSO (90 °C, 24 h) [33].

A highly efficient transition metal-catalyzed one-step synthesis of aryl thiols from aryl halides has been developed [34]. The protocol employs $CuSO_4{\cdot}5H_2O$ as a catalyst and KOH or Cs_2CO_3 as bases, and allows converting aryl iodides, bromides, and chlorides bearing electron-withdrawing groups to the corresponding aryl thiols in good to excellent yields. During the reaction, neither disulfide nor sulfide is formed. It is shown that aryl halides are first coupled with 1, 2-ethanedithiol and the coupled product is transformed in situ to aryl thiols through the C−S bond cleavage via an intramolecular nucleophilic substitution. The protocol tolerates a broad range of functional groups such as amino, hydroxy, trifluoromethyl, ester, carboxy, and formyl.

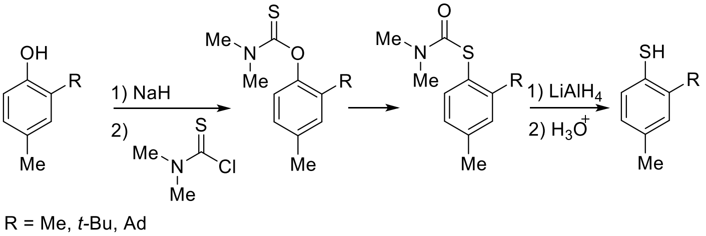


Also, aryl iodides react with thiobenzoic acid in the presence of a copper catalyst and 1,10-phenanthroline to furnish *S*-aryl thiocarboxylates in excellent yields [35]. The coupled product is converted to aryl thiols in quantitative yields upon treatment with K_2CO_3.



This method is applicable to both electron-deficient and electron-rich aryl iodides, and even to sterically hindered substrates.

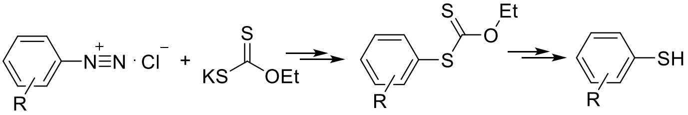
Phenols can also be used as the starting compounds for the synthesis of aromatic thiols. The phenols are converted to *O*-arylthiocarbamates or thiocarboxylic acid esters and then subjected to thermal rearrangement and hydrolysis [36, 37]. The synthesis of 2,4-disubstituted thiophenols from the corresponding phenols has been described [37]. Deprotonation of the starting phenols followed by the treatment with dimethylcarbamoyl chloride (NaH, dimethoxyethane, boiling, 24 h) furnishes *O*-arylthiocarbamates, which undergo thermolysis (250–310 °C) and rearrangement into *S*-arylthiocarbamates. Reduction of the latter with $LiAlH_4$ in THF and acid hydrolysis give thiophenols in 55–68% yields.



A mild conversion of mono- and bicyclic phenols into aryl thiols by palladium-catalyzed coupling reaction of the corresponding triflate with sodium triisopropylsilanethiolate (NaSTIPS) (THF, reflux, 4 h) and subsequent deprotection of the silyl function with tetrabutylammonium fluoride has been published [38].

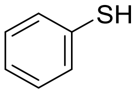
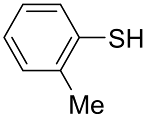
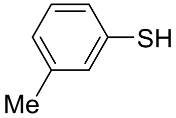
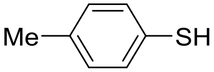
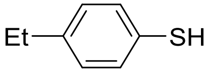
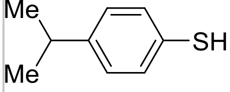
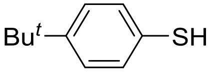
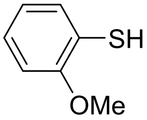
$$\mathrm{ArOH} \xrightarrow{\mathrm{Tf_2O}} \mathrm{ArOTf} \xrightarrow[\text{THF, reflux, 4 h}]{\text{NaSTIPS}} \underset{40\text{-}86\%}{\mathrm{ArS{-}SiPr^{\mathit{i}}_3}} \xrightarrow[0^{\circ}\mathrm{C}]{\mathrm{Bu_4NF}} \underset{43\text{-}72\%}{\mathrm{ArSH}}$$

Substitution of the amino group involving the formation of the C–S bond proceeds through diazonium salt, which is readily obtained from primary aromatic amines [13]. Thiourea [39], thiocarboxylates [40], and alkali metal xanthagentes can act as *S*-nucleophiles. Direct reaction with potassium hydrosulfide is not performed, since the latter is a strong reducing agent and under the process conditions is oxidized to molecular sulfur. The Leuckart method comprises the treatment of an aqueous solution of aryldiazonium salts with potassium ethylxanthagenate on moderate heating (40–45 °C). Subsequent alkaline hydrolysis (KOH/EtOH) of the formed *S*-aryl *O*-ethyl xantagenates gives the corresponding aryl thiols.



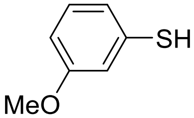
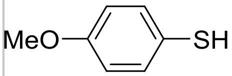
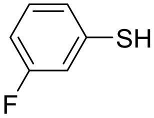
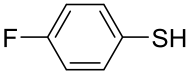
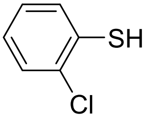
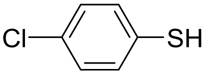
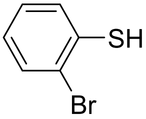
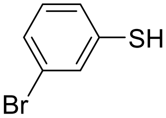
This approach has been used to synthesize a large series of 2- and 3-substituted aryl thiols (Table 1) [41].

Table 1 Aromatic thiols

No.	Structure	Yield, %	B.p., °C/torr (m.p., °C)	n_D^{20}	d_4^{20}
1	2	3	4	5	6
1		72	167–170	1.5870	1.0740
2		45	90–91/25	1.5733	1.0427
3		75	103–104/40	1.5715	1.0446
4		82	195 (43)		
5		65	94–95/16	1.5715	1.0365
6		75	112/20	1.5538	1.0085
7		66	110–111/12	1.5510	0.9888
8		67	100–101/8	1.5926	

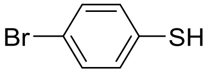
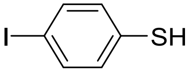
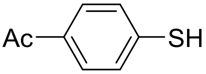
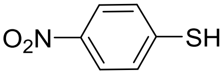
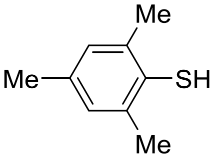
(continued)

Table 1 (continued)

No.	Structure	Yield, %	B.p., °C/torr (m.p., °C)	n_D^{20}	d_4^{20}
9		62	87–88/4		
10		80	69–70/3	1.5812	1.1385
11		58	49/10	15466	1.1921
12		75	64-65/12 48/6	1.5522	1.1986
13		57	100/26	1.5985	1.2783
14		76	80–90/16 (53–54)		
15		55	99–100/11		
16		51	107–108/6	1.6330	

(continued)

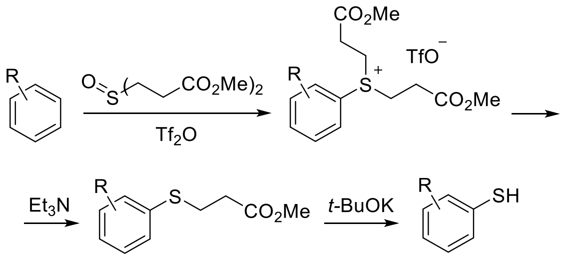
Table 1 (continued)

No.	Structure	Yield, %	B.p., °C/torr (m.p., °C)	n_D^{20}	d_4^{20}
17		76	98–99/10 (74–74)		
18		48	(85–86)		
19		58	(28)	1.6182	
20		65	(76)		
21		52	66/1		

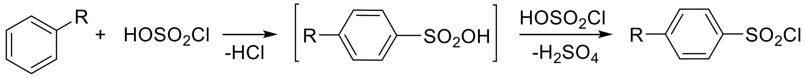
1.3 Reactions with Sulfur-containing Electrophiles

Methods for the synthesis of aryl thiols from aromatic compounds and sulfur-containing electrophiles are multistage. Nevertheless, they are widely used in laboratory practice.

Thus, aryl thiols (12 examples) have been obtained by a one-pot protocol involving the formation of the arylsulfonium salt via the interaction of arenes with activated sulfoxides [42]. Subsequent base-catalyzed double dealkylation leads to aryl thiols in moderate to high yields (46–98%).

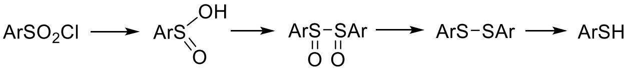


The most common sulfur-containing electrophile is chlorosulfonic acid, which is usually prepared according to Bender [43]. The reaction of chlorosulfonic acid with the substituted arenes gives rise to various sulfonyl chlorides [13, 44, 45].



In industry, sulfonyl chlorides are also obtained by direct sulfonation of arenes with 4–5 equivalents of chlorosulfonic acid.

The reduction of aromatic sulfonyl chlorides with various reducing agents [46–53] is a popular approach to the synthesis of aryl thiols.

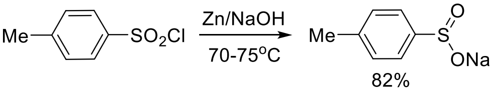


$$ArSO_2Cl \longrightarrow ArS(=O)OH \longrightarrow ArS(=O){-}S(=O)Ar \longrightarrow ArS{-}SAr \longrightarrow ArSH$$

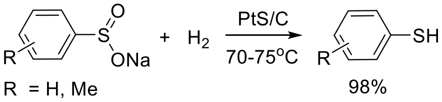
The intermediate products of the reaction are sulfinic acid, disulfoxides, and disulfides.

Hydrogen [48, 53], metals (Zn, Sn, Fe) in combination with acids [46, 54–57] or alkalis [52], hydrogen sulfide [50], and some other reagents [51, 58–60] are used as reducing agents. The choice of a reducing agent strongly depends on the reactivity of the starting sulfonyl chloride.

When 4-methylphenylsulfonyl chloride is reduced in an aqueous-alkaline solution in the presence of zinc (70–75 °C), sodium sulfinate is formed in a high yield [52].



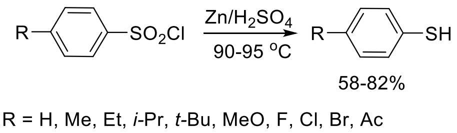
It is shown [42] that hydrogenation of aryl sulfinates in the presence of PtS (170–175 °C, initial hydrogen pressure 60–80 atm) results in the corresponding aryl thiols with almost quantitative yields.



The reduction of aromatic sulfonyl chlorides to thiols has been affected for the first time by Vogt in 1861 [47]. He has synthesized thiophenol from benzenesulfonyl chloride under the action of zinc dust in hydrochloric acid medium.

It is usually assumed that hydrogen behaves as an active reagent in the reduction of organic compounds with metals. It is reported [61] that the activity of hydrogen, released in the system metal/hydrochloric acid, is different and depends on the position of a metal in the periodic table. In each group, it increases as the atomic weight of elements grows. The comparison of different group metals indicates that the activity of the released hydrogen augments in the following order: alkali metals of copper subgroup, alkaline-earth metals of zinc subgroup, aluminum subgroup, etc. According to the work [62], the hydrogen released by these metals is, as a rule, a weak reducing agent. It is believed that the adsorption of organic compounds on the surface of a metal plays a decisive role in their reduction [63–65]. At the same time, the adsorption of acids in the form of molecules or ions occurs, and the hydrogen contained in their composition thus activated [64] interacts with a molecule of organic compound to produce a hydrogenated substrate.

In order to understand the effect of various derivatives of aromatic thiols on the performance characteristics of lubricating oils, the systematic studies on the synthesis of aryl thiols by reduction of aryl sulfonyl chlorides have been carried out in the Institute of Additives Chemistry, the Azerbaijan Academy of Sciences [54, 55]. It is demonstrated that 4-substituted aryl thiols are formed in good yields (58–82%) upon heating the corresponding aryl sulphonyl chlorides (90–95 °C) in diluted sulfuric acid in the presence of 6 equivalents of zinc dust [41].

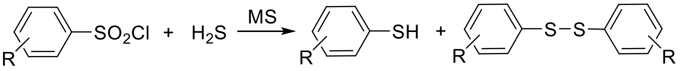


The catalytic hydrogenation of aryl sulfonyl chlorides with noble metals and bases represents an efficient method for the preparation of aryl thiols [53]. The process is executed in aprotic solvents, such as toluene, at 100 °C and a hydrogen pressure of 55 atm. Alkali metal acetates, carbonates or hydroxides, and tertiary amines are employed as bases for binding the released HCl.

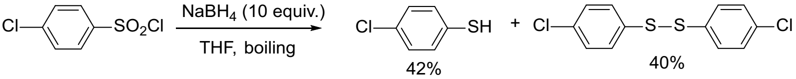
$$ArSO_2Cl + 3H_2 \xrightarrow[100\ ^\circ C,\ 55\ atm]{Pd/C} ArSH + 2H_2O + HCl$$

This method enables to obtain unsubstituted and substituted mono- and polynuclear aromatic and heteroaromatic thiols with high selectivity. Indisputable advantages of the method are high selectivity and ease of the product isolation. Unfortunately, the protocol is not deprived of the drawbacks. These are the fire and explosion hazards of hydrogen handling and the need to use special equipment (autoclaves).

The reduction of aryl sulfonyl chlorides with hydrogen sulfide [50] is not so selective: along with thiols, the corresponding disulfides are formed. The process is realized in the medium of aromatic hydrocarbons under the pressure of H_2S (5 atm, 90–130 °C) or in a flow of hydrogen sulfide (300 °C) and catalyzed by sulfides of Co, Mo, Ni, W, Cu, Fe, Ru, Rh, Ir, obtained in situ from metal oxides and H_2S.

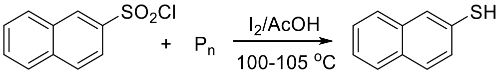


Sulfinic acids or aryl thiols can be synthesized by the reduction of aryl sulfonyl chlorides with metal hydrides. For example, aryl sulfonyl chlorides are reduced with $NaBH_4$ in THF at 0 °C to the corresponding sulfinic acids in 70–85% yields [51]. Using 4-chlorophenylsulfonyl chloride as an example, it is shown that when the reaction is performed upon boiling in THF (10 equivalents of $NaBH_4$), 4-chlorothiophenol (yield 42%) and disulfide (yield 40%) is formed [51].

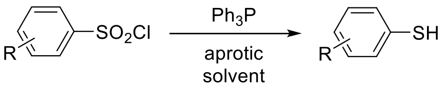


The addition of equimolar amounts of $AlCl_3$ to $NaBH_4$ increases the reducing properties of the latter [58].

Reduction of 4-substituted benzylsulfonyl chlorides and 2-naphthylsulfonyl chloride with red phosphorus in the boiling glacial acetic acid in the presence of a catalytic amount of iodine also affords the corresponding aryl thiols and 2-thionaphthol [59].



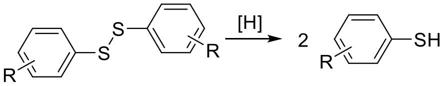
A convenient and straightforward method for the synthesis of aryl thiols (71–94% yields) via the reaction of aryl sulfonyl chlorides with triphenylphosphine has been described [60]. The reaction proceeds in aprotic solvents (toluene, xylene, benzene, chloroform, dichloromethane) with self-heating and is completed in 10–20 min.



The generality of this reaction is demonstrated in 16 examples. A shortcoming of this method is the use of three equivalents of triphenylphosphine.

1.4 Reduction of Diaryl Disulfides

The reduction of disulfides to thiols is a common process in organic chemistry. Numerous methods for the preparation of aromatic thiols described in manuals and reference books are based on the reduction of diaryl disulfides with various reagents or reducing processes.



Various hydride reducing agents has been used including $NaBH_4$ [66, 67], LiAl (Bu^{t}O)$_3$H [68], dithiothreitol [69], phosphines [70, 71].

Usually, the hydrogenation of disulfides occurs under the hydrogen pressure in the presence of catalysts (for example, MoS_2 [72] or VIII group metals [73] on supports). A method for the hydrogenation of diaryl disulfides in the presence of bases (hydroxides, carbonates or alcoholates of alkali and alkaline-earth metals) has been claimed [73]. The reaction proceeds in MeOH, EtOH or *i*-PrOH (80° C, hydrogen pressure at room temperature 10 atm) and is catalyzed by Ni.

To reduce disulfides, metals in an acidic medium, for example, zinc or iron powder in glacial acetic [74–76], hydrochloric [6, 77, 78] or diluted sulfuric acid [6, 79, 80], hydrogen sulfide [81] and alkali metal sulfides [82, 83] in aqueous or aqueous alcohol solutions are often employed. The reduction of disulfides with alkaline solutions (NaOH or Na_2CO_3) to give thiophenols proceeds even more easily [83, 84].

$$2\mathrm{ArSSAr} + 4\mathrm{HO}^- \longrightarrow 3\mathrm{ArSH} + \mathrm{ArSO}_2^- + 2\mathrm{H_2O}$$

Diaryl disulfides with electron-donating substituents are relatively easily reduced with the systems Et_3SiH/CF_3CO_2H [85], $Et_3SiH/BF_3{\bullet}H_2O$ [86]. It is assumed that the cleavage of the S–S bond occurs through the formation of sulfonium cation.

$$\begin{array}{c}
\mathrm{ArSSAr} + \mathrm{H}^+ \rightleftharpoons \mathrm{ArSH} + \mathrm{ArS}^+ \\
\mathrm{ArS}^+ + \mathrm{HSiEt_3} \longrightarrow \mathrm{ArSH} + \mathrm{Et_3Si}^+ \\
\hline
\mathrm{ArSSAr} + \mathrm{HSiEt_3} + \mathrm{CF_3CO_2H} \longrightarrow 2\mathrm{ArSH} + \mathrm{CF_3CO_2SiEt_3}
\end{array}$$

In the reducing system $N_2H_4{\bullet}H_2O/KOH$, dianorganic disulfides form potassium organylthiolates, a mild acidification of which leads to thiols [87, 88]. Also, such thiolates can be used in situ in the synthesis of organosulfur compounds. For example, it is found that vinyl methyl sulfide can be synthesized in a yield of 80% by vinylation of dimethyl disulfide with acetylene at atmospheric pressure (45–50 °C) in the presence of highly basic reducing system $N_2H_4{\bullet}H_2O$/KOH/N-methylpyrrolidone [89].

The physical constants of aryl thiols synthesized by various methods to establish the relationship between structure, physical–chemical properties, and reactivity are given in Table 1.

1.5 Examples of Syntheses

1.5.1 Synthesis of 2- and 3-substituted Aryl Thiols from Diazonium Chlorides and Potassium Ethylxanthogenate

3-Methylthiophenol (No. 3, Table 1). Into a 1-L flask, equipped with a mechanical stirrer and a thermometer, immersed in an ice bath, were placed 150 ml of conc. HCl ($d_4^{\mathbf{20}}$ 1.18) and 150 g of crushed ice. 3-methylaniline (80.0 g, 0.75 mol) was slowly added to the flask upon stirring. The mixture was then cooled to 0 °C and a cold solution of $NaNO_2$ (51.8 g, 0.75 mol) in water (125 mL) was slowly added, keeping the temperature below 4 °C.

Into a 2-L flask, equipped with thermometer, dropping funnel, and stirrer, an aqueous solution of potassium ethylxanthogenate (140 g) was placed. The mixture was heated to 40–45 °C and then an aqueous cold solution of diazonium was slowly added at this temperature for 2 h. Afterwards the stirring was continued for ~ 0.5 h. The red oily layer of *meta*-tolylethylxanthogenate was separated, and the aqueous layer was extracted twice with ether. The oily layer and the ether extracts were combined, washed with 10% NaOH solution (100 mL), and then with water until neutral reaction, dried over $CaCl_2$ and the ether was distilled off. The residue was dissolved in 95% EtOH (500 mL), the solution was boiled, and granulated KOH (175 g) was slowly added to the hot solution so that the solution boiled continuously. The mixture was boiled until the sample was completely soluble in water (about 8 h).

Afterwards, EtOH (400 mL) was distilled off, and the residue was dissolved in a minimum amount of water (about 50 mL). The solution was extracted with Et_2O (3×100 mL), the aqueous layer was acidified with 6N H_2SO_4 (625–650 mL) until strongly acidic reaction (pH 1–2). To the acidified solution, was added zinc dust (2 g) and 3-methylthiophenol was distilled off with water vapor. Lower layer of the distillate (3-methylthiophenol) was separated, the aqueous layer was extracted with Et_2O (3–100 mL), the extract was combined with the main mass of 3-methylthiophenol. The solution was dried over anhydrous $CaSO_4$, the solvent was distilled off, and the oily residue was distilled in vacuum. Yield 69 g (75%), b. p. 103–104 °C/40 torr.

2- and 3-Substituted aryl thiols (2, 8, 9, 11, 13, 15, 16, Table 1) were synthesized analogously.

1.5.2 Synthesis of 4-substituted Aryl Thiols via Reduction of Aromatic Sulfonyl Chlorides

4-Fluorothiophenol (No. 12, Table 1). Into a three-necked flask, equipped with mechanical stirrer, thermometer, dropping funnel, and reflux condenser, was placed 4-fluorobenzenesulfonyl chloride (194.5 g, 1 mol), twice recrystallized from

Et_2O and 20% H_2SO_4 (3 kg). Zinc dust (390 g, 6 g-atom) was gradually added to the mixture at 0–5 °C. After completion of zinc addition, the reaction mixture was stirred at the same temperature for another 1 h, and then the temperature of the reaction mixture was raised to 90–95 °C and the mixture was heated for 7–10 h until a transparent liquid was formed. The mixture thus obtained was cooled to room temperature, extracted with benzene (5 × 100 mL), the extract was washed with water until the neutral reaction and dried over Na_2SO_4. Distillation in vacuo gave 95.9 g (75%) of 4-fluorothiophenol, b.p. 64–65 °C/12 torr.

Thiophenol (1) and 4-substituted aryl thiols (4–7, 10, 14, 17–19, 21, Table 1) were obtained similarly.

1.5.3 Synthesis of Aryl Thiols via Reduction of Diaryl Disulfides

4-Nitrothiophenol (No. 20, Table 1). To a solution of 4-nitrochlorobenzene (157.5 g, 1 mol) in 250 ml of boiling EtOH. Then an alcohol solution of NaOH (40 g, 1.0 mol) was added dropwise. The reaction mixture was cooled and poured onto a mixture of ice (1 kg) and water (1500 mL). The residue was filtered off, the filtrate was acidified with HCl, 4-nitrothiophenol was separated, washed with water (500 mL), and dried; then dissolved in EtOH (150 mL), a solution of NaOH (40 g) in water (1500 mL) was added and filtered. After precipitation with hydrochloric acid, 4-nitrothiophenol was filtered off, washed, and dried in a vacuum desiccator. The yield was 100.9 g (65%), m.p. 76 °C.

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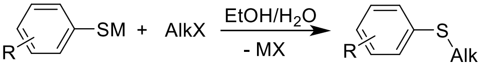
Aromatic Sulfides

2

Aromatic sulfides are valuable synthetic intermediates, which are frequently met in biologically and pharmaceutically active molecules or in polymeric materials. In particular, diaryl- and aryl/heteroaryl sulfides are essential components of numerous drugs efficient against inflammation, cancer, human immunodeficiency virus (HIV), asthma, Alzheimer's, and Parkinson's diseases (See Sect. 7.2). Furthermore, diaryl sulfides are precursors to the corresponding sulfoxides and sulfones that also exhibit important biological activities and are contained in antifungal and anticancer agents, as well as in drug candidates, for the treatment of Alzheimer's disease or HIV. Classical and modern methods for the synthesis of aryl sulfides are described in monographs [1–9] and reviews [10–20]. This chapter briefly summarizes the main approaches to the synthesis of aromatic sulfides from a variety of reagents.

2.1 General Approaches to the Synthesis of Aryl Sulfides

The traditional methods for the preparation of alkyl aryl sulfides are based on the reactions of nucleophilic substitution involving alkyl halides. Usually, these sulfides are synthesized by the treatment of alkyl halides with sodium or potassium aryl thiolates in alcohol, aqueous-alcohol or aqueous solutions.



However, this route is unsuitable for *tert*-alkyl halides, since under these conditions, as a rule, they undergo dehydrohalogenation [21, 22]. *tert*-Alkyl aryl sulfides can be synthesized by alkylation of aryl thiols with olefins at 280–300 °C and 200 atm in the presence of aluminum chips [23] or at 135–160 °C on a KU-2 cation-exchange resin (35–40% by weight of the starting aryl thiol) as a catalyst [24].

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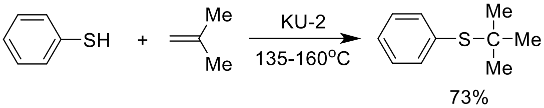
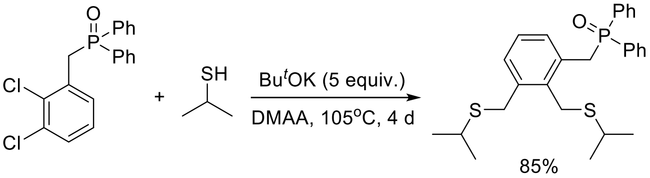
https://doi.org/10.1007/978-3-030-69621-4_2

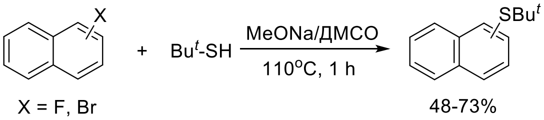


There are known methods for the preparation of *tert*-alkyl aryl sulfides in a low yield by alkylation of aryl thiols with olefins or alcohols in the presence of AlX_3 (X = Cl, Br) [25, 26] or various acidic or basic catalysts [10]. These methods involve the neutralization of acid catalysts, which limits their feasibility.

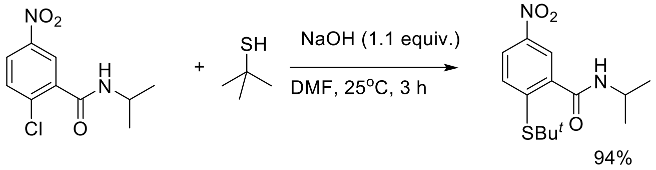
Another approach to the synthesis of alkyl aryl sulfides is the nucleophilic aromatic substitution of aryl halides with alkyl thiols. Given the lower reactivity of alkyl thiols as compared to thiophenols, more basic compounds are usually required for these reactions. Nonactivated aryl halides (chlorides and bromides) interact with thiolate anions only in the presence of strong bases, for example, alkali metal amides in liquid ammonia [27]. The employment of aprotic solvents (HMPTA, DMF, DMSO, DMAA, etc.) in combination with alkali metal alkoxides significantly facilitates the arylation of thiols [28–31]. Polyglymes are proposed as alternative solvents for the thiolation of aryl halides [32]. 3-[(Diphenylphosphoryl) methyl]-1,2-bis(isopropylthio)benzene is obtained with 85% yield via the reaction between 2-propanethiol and 3-[(diphenylphosphoryl)methyl]-1,2-dichlorobenzene (Bu^tOK, DMAA, 105 °C, 4 d) [33].



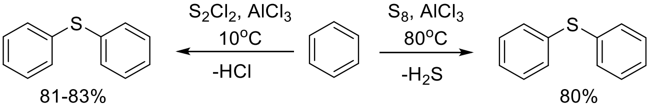
tert-Alkylaryl sulfides can also be obtained by the reactions of aryl halides with *tert*-alkylthiolates in aprotic polar solvents [28, 29]. Fluoro- and bromonaphthalenes interact with Bu^tSNa in DMSO (110 °C, 1 h) to afford *tert*-butylnaphthyl sulfides with 48–73% yields [28].



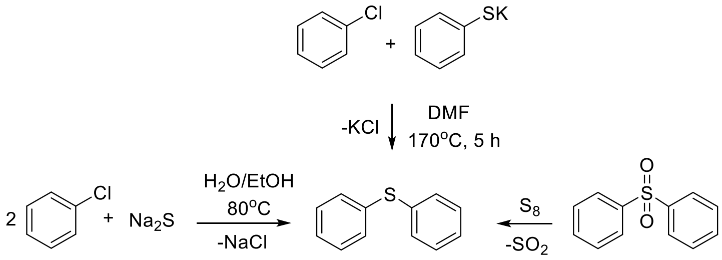
Nonactivated aryl halides also successfully react with *tert*-alkylthiolates in HMPA (80 °C, 7 h) [29]. The interaction of aryl halides bearing activated electron-withdrawing groups with alkyl thiols is much easier. When *tert*-butyl thiol reacts with 2-chloro-N-isopropyl-5-nitrobenzamide (NaOH/DMF, 25 °C, 3 h) under argon, 2-(*tert*-butylthio)-N-isopropyl-5-nitrobenzamide is formed with 94% yield [34].



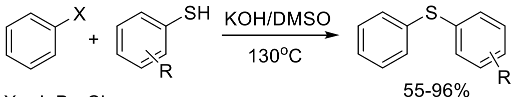
Diphenyl sulfide has been synthesized as early as the beginning of the twentieth century by the treatment of benzene with sulfur chloride [35] or elemental sulfur [36] in the presence of aluminum chloride.



Diphenyl sulfide can also be obtained by the reaction of chlorobenzene with phenylthiolate in amide solvents (170–175 °C, 5–10 h) [37], sodium sulfide or hydrosulfide upon boiling in an aqueous alcohol solution [28]. Diphenyl sulfide is synthesized by the reduction of diphenyl sulfone with sulfur [38].



Transition metal-free methods are also employed in the reactions of aryl thiols with aryl halides. The use of the KOH/DMSO system (superbase) essentially expedites the synthesis of aryl sulfides [39, 40]. Iodo-, bromo-, and chlorobenzenes with electron-donating and electron-withdrawing substituents react with thiophenol upon heating in DMSO (130 °C, 6–24 h) in the presence of 2 equivalents of KOH to furnish sulfides with 55–96% yields [39].

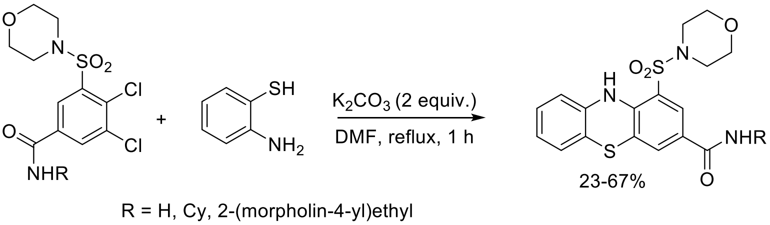


X = I, Br, Cl

R = H, 2-Me, 4-Me, 3-MeO, 4-MeO, 2-NO_2, 4-NO_2

In the case of 2- and 4-substituted aryl halides, a mixture of 3- and 4-arylphenylsulfides (~1:1) is formed, which indicates that the reaction proceeds via benzyne (elimination-addition) mechanism. The same mechanism has been proposed in [40].

The reaction of dichlorobenzene, containing electron-withdrawing carboxamide and sulfonamide groups, with 2-aminobenzenethiol (K_2CO_3/DMF, reflux, 1 h) produces phenothiazine-3-carboxamide with 23–67% yields [41].

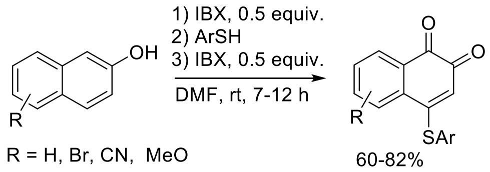


4,5-Bis((4-hydroxyphenyl)thio)phthalonitrile has been synthesized with high yield from 4,5-dichlorophtalonitrile and 4-hydroxythiophenol using the above system (K_2CO_3/DMF, 80 °C, 24 h) [42]. Potassium carbonate, easily available and handled base, is commonly selected to implement thioetherification of aryl fluorides with thiophenols. For example, an aromatic nucleophilic substitution of 3-fluoro-4-nirtobenzoic acid with 4-mercaptophenol using K_2CO_3 as a base in DMF (25 °C, 12 h) gives the corresponding diaryl sulfide with 72% yield [43]. Other popular catalytic systems of the above reaction are K_2CO_3/DMSO, Et_3N/DMSO, K_2CO_3/NMP/toluene, NaH/NMP/toluene [20].

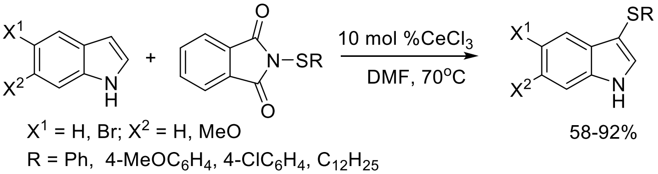
It is shown that the reactions of aryl halides with thiols proceed more easily under the conditions of phase-transfer catalysis. The process can be catalyzed by crown ethers, quaternary ammonium or phosphonium salts. Aryl halides activated by the nitro group interact with thiophenol in aqueous alkali/toluene medium in the presence of R_4NCl at room temperature to give rise to diaryl sulfides with 80–97% yields [44]. The reactions of dichlorobenzenes with primary and secondary alkyl thiols are performed upon vigorous stirring (KOH/H_2O, dicyclohexano-18-crown-6 as a catalyst, 110 °C, 14–48 h) in an inert atmosphere to deliver sulfides with 65–89% yields [45]. Under these conditions, dichlorobenzenes do not react with aryl thiols.

In recent decades, much attention has been paid to the development of new concepts for the C–S bond formation, namely direct oxidative coupling through the selective functionalization of the C–H bond. Such processes are endowed with high yields and impressive regio- and stereo-selectivity and are thus becoming a part of an ever-growing armory of useful synthetic tools available to organic chemists today. An oxidizing agent is usually required. Silver salts, organic acids, DDQ, sulfuric acid have shown favorable effects as oxidants in promoting the cleavage of C−H bonds to varying degrees [20].

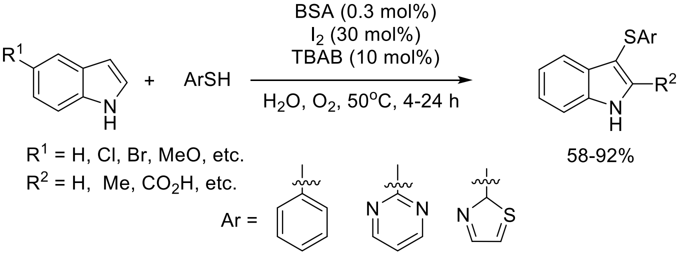
Oxidation and *S*-arylation of various substituted 2-naphthols through one-pot synthesis protocol using *orto*-iodoxybenzoic acid (IBX) as an oxidant and aryl thiols as sulfur source (DMF, 20–25 °C, 7–12 h) give 4-arylthionaphthalene-1,2-diones with 60–82% yields [46].



Anhydrous $CeCl_3$ is successfully used as a catalyst for the synthesis of several 3-sulfenyl indoles in good to excellent yields through the reaction of indole with *N*-(alkylthio) and *N*-(arylthio)phthalimides in DMF [47].



Bovine serum albumin (BSA)–I_2 as a highly efficient cooperative cascade catalyst allows for direct sulfenylation of indole with readily available aromatic and heteroaromatic thiols via in situ generation/cleavage of a disulfide (S–S) bond followed by the C–S bond formation, in one-pot in aqueous medium using oxygen [48].

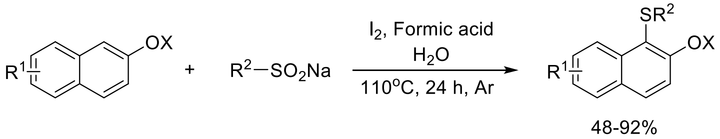


Various substrates (substituted indoles, 2-naphthol and 4-hydroxycoumarin) tolerate this protocol. Only 0.3 mol% BSA, 10 mol% tetrabutylammonium bromide, and 30 mol% iodine are needed for the reaction, which proceeds without any metal or base.

Besides, the above thiophenols, sodium sulfinates and sulfonyl hydrazides have been applied as environmentally friendly sulfenylation reagents that are stable, readily accessible, and odor-free.

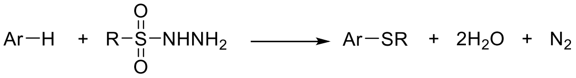
An efficient procedure for the formation of C–S bonds via direct C–H functionalization has been developed under aqueous conditions. In this process, various sodium sulfinates are used as the sulfur source to smoothly couple with 2-naphthols providing aryl sulfides with good to excellent yields [49]. Iodine is employed as an effective additive in this transformation. Functional groups such as halogens, trifluoromethyl, and trifluoromethoxy well tolerate the reaction. Apart from

2-naphthol, this reaction system could also be applied to the direct sulfenylation of phenol derivatives and methoxybenzenes with sodium benzenesulfinate.



X = H, Me, Et
R^1 = H, Br, OH
R^2 = Alk, Ph, 4-AlkC_6H_4, 4-MeOC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-CF_3O

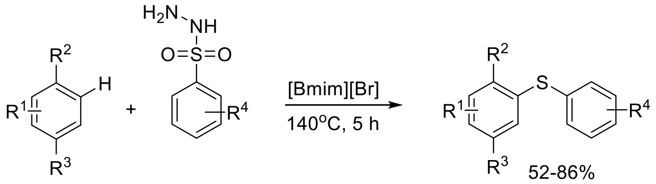
Hydrazide is another preferable sulfur source, which permits to accomplish *S*-alkylation or *S*-arylation wherein water and molecular nitrogen are generated as environmentally benign by-products.



$$Ar-H + R-\underset{O}{\overset{O}{\overset{\|}{\underset{\|}{S}}}}-NHNH_2 \longrightarrow Ar-SR + 2H_2O + N_2$$

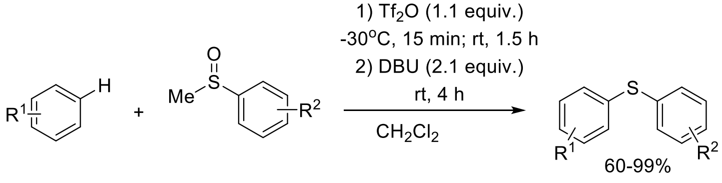
In the presence of 5–10 mol % iodine, a range of aryl-, heteroaryl-, and alkyl-sulfonyl hydrazides smoothly underwent sulfenylation with indoles [50], electron-rich aromatics [51], heteroaromatics [52–54], flavonoids [55] to give structurally diverse unsymmetrical sulfides with moderate to excellent yields with extremely high regioselectivity. The reactions proceed through the cleavage of sulfur–oxygen and sulfur–nitrogen bonds.

A convenient approach to the synthesis of unsymmetrical diaryl sulfides by the reaction of sulfonyl hydrazides with phenols using a [Bmim][Br] ionic liquid through the formation of C–S bonds has been elaborated [56]. The reaction has further been extended to indole, *β*-naphthol, and aromatic amine moieties. This protocol offers a new, versatile, and greener approach for the thiolation of natural phenols (monoterpenes)/aromatic phenols/*β*-naphthols/aromatic amines and indoles without any catalyst. A broad range of functional groups well tolerates this reaction.



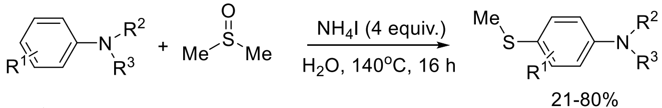
R^1 = OH, OMe, NH_2
R^2, R^3 = H, Me, Pr^i; R^4 = H, Me, Bu^t, CF_3, NO_2

Metal-free C–H thioarylation of arenes using methyl sulfoxides constitutes a general procedure for the synthesis of highly valuable diaryl sulfides with high yields [57]. The method exploits the reactivity of activated sulfoxides (sulfoxonium salts), which are excellent electrophiles. The coupling of arenes and heteroarenes with in situ activated sulfoxides is regioselective, uses readily available starting materials, is operationally simple, and tolerates a wide range of functional groups. The method allows the incorporation of a variety of functional groups (bromo, chloro, acetal, alkenyl, ester, ketone and aldehyde, nitro, sulfone) in either coupling partner. Heteroaromatics, such as indole, dibenzothiophene, benzothiophene, thiophene, and furan are also successfully involved in the reaction.



R^1 = H, 2-Br, 4-Cl, 4-MeO, 2,5-Me_2, 2-CF_3, 4-CF_3, 4-NO_2, 4-$MeSO_2$, 4-MeCO
R^2 = H, 4-Me, 4-I, 4-Br, 3-MeO, 4-MeO, 3-CO_2Me, 4-CHO

In the last years, DMSO is also explored as a powerful methylthio source in the synthesis of aryl methyl sulfides via regioselective $C_{sp}{}^2$–H bond functionalization. Aryl methyl sulfides are synthesized through highly regioselective *para*-methylthiolation of arylamines using DMSO as the methylthio source in the presence of NH_4I under metal-free conditions [58]. For the substrates with both electron-donating and electron-withdrawing substituents, the reaction proceeds smoothly and ensures moderate to good yields of the products.

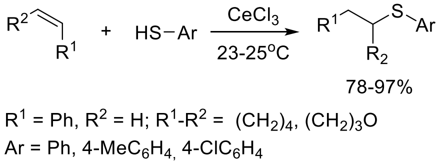


R^1 = H, 2-Me, 2-MeO, 3-Me, 3-MeO, 3-Pr^i, 3-Bu^t,3-F,
3,5-Me_2, 2,6-Me_2, 2,6-$(Pr^i)_2$, 2-F,3-Me, 2-Ph
R^2, R^3 = H, Me, Et, Bu^n
NR^2R^3 = morpholine, piperidine

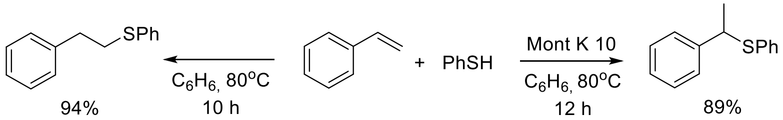
Analogously, the regioselective sulfenylation of imidazo[1,2-*a*]pyridines at the 3-position in the presence of *p*-tosyl chloride in dichloroethane/DMSO (100 °C, 8 h) [59] or in iodine and acetone (100 °C, 12 h) [60] under air has been described. The control experiments confirm that the reaction occurs through a radical mechanism to deliver methylthiyl radicals (MeS$^{\cdot}$).

A rational and atom-economical route to alkyl aryl sulfides is the addition of aryl thiols to unsaturated compounds [3, 9, 10, 61]. The addition of thiols to multiple carbon–carbon bonds is realized as either an ionic or free radical process. The literature discloses various protocols including the use of catalysts (Brønsted or Lewis acids [62–65], metal complexes, bases, radical initiators), ultrasonic or microwave irradiation, ionic liquids, etc. It is found [66] that alkyl and aryl thiols are added to the substituted styrenes and alkyl vinyl ethers in water (room temperature, 1.5–4.5 h) without any additives to form anti-Markovnikov adducts with 71–90% yields.

In the presence of anhydrous $CeCl_3$ (5 mol%) without a solvent, thiols react with alkenes to give adducts according to (in the case of cyclic vinyl ethers) or against (for styrenes, cyclic and acyclic alkenes) Markovnikov rule [67].

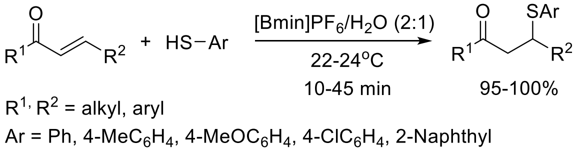


Thiols are added to alkenes in an electrophilic manner in the presence of $AlCl_3$ (in cyclohexane at room temperature) [63] or montmorillonite clay (Mont K 10, boiling in benzene) [68], producing adducts with high selectivity according to the Markovnikov rule. In the absence of a catalyst, the reaction proceeds via a radical mechanism and leads to anti-Markovnikov adducts with almost quantitative yields [68].

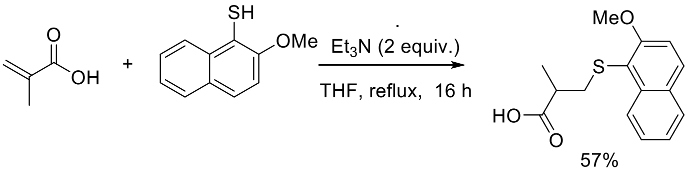


Terminal, internal, cyclic, acyclic, and branched alkenes react with aromatic and aliphatic thiols upon boiling in hexane (5–12 h) in the presence of H-Pro zeolites against the Markovnikov rule delivering sulfides with 53–98% yields [69]. An exception, like in the case of $CeCl_3$ [67], is cyclic vinyl ethers that form *α*-adducts.

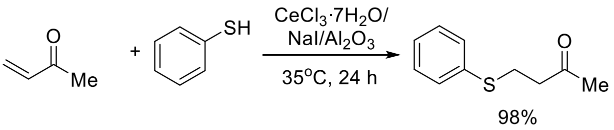
To alkenes, activated by electron-withdrawing substituents, thiols are added through nucleophilic or radical mechanisms with the formation of *β*-adducts. Ionic liquids can be exploited as an alternative to organic solvents. It is shown [70] that *α,β*-unsaturated ketones readily add thiols in a hydrophobic ionic liquid $[Bmin]PF_6/H_2O$ without acidic catalysts to afford Michael adducts with high yields and with excellent 1,4-selectivity.



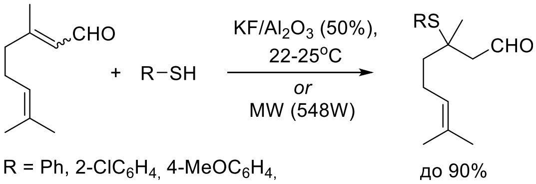
Besides, Et_3N is used as a base in conjugate addition with methacrylic acid and 2-methoxynaphthalene-1-thiol (Et_3N/THF, reflux, 16 h) [71].



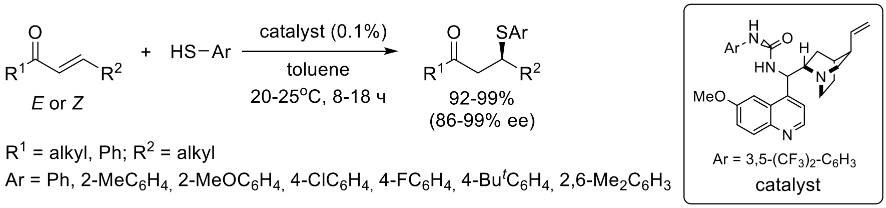
A solid-phase reaction of thiophenol with 3-buten-2-one in the presence of the system supported on neutral alumina is considered highly efficient [72].



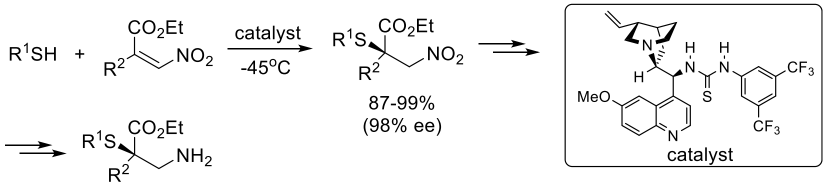
In the presence of KF/Al_2O_3 from citral and aryl thiols (without solvent, room temperature, 3–9 h), sulfides are obtained with 65–90% yields [73]. The additional microwave radiation (548 W) shortens the interaction time to 1–6 min, the yield of sulfides ranging 35–90%. The catalyst can be employed up to three times without loss of the activity. In the absence of a catalyst, chemoselectivity is violated and 1,4- and 1,2-adducts are formed.



Recently, much attention has been paid to enantioselective reactions of the conjugate addition of thiols to Michael acceptors using organic catalysts. Quinine derivatives appear to be highly efficient in the synthesis of optically active sulfides [74, 75]. The interaction of substituted aryl thiols with cyclic and acyclic enones (toluene, room temperature, 8–18 h) in the presence of quinine-derived urea (0.1 mol%) leads to the formation of aryl sulfides with high isolated yields (92–99%) and enantioselectivity (ee 86–99%) [74].

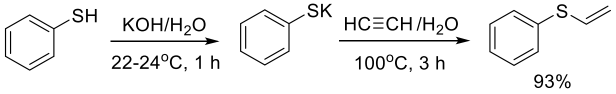


The addition of thiols through the conjugated double bond of *α,β,β*-trisubstituted nitroalkenes (–25° C, benzene/ether, 1:1 or –45° C, toluene) proceeds smoothly in the presence of 0.3 mol% of an organic catalyst, quinine-functionalized thiourea, to furnish sulfides with up to 100% yield (ee 98%) [75]. The forming adducts are used in the synthesis of new $\beta^{2,2}$-amino acids and *β*-peptides.



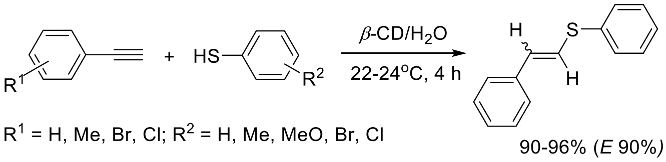
The addition of thiols to acetylenes, including base-catalyzed vinylation, is a convenient and atom-economical approach to the synthesis of vinyl sulfides [9, 10, 61, 76–81]. Vinylation of thiols with acetylenes in most cases occurs in the presence of bases [10, 76, 78, 80, 81] or metal complex catalysts [9, 61]. Under classical conditions, the addition of thiols to acetylene is carried out without solvent or in dioxane at 70–130 °C and proceeds easier than the vinylation of alcohols owing to a higher nucleophilicity of thiols. The reaction of thiols with acetylenes in polar non-hydroxyl solvents significantly accelerates nucleophilic processes and permits to decrease the temperature by 70–100 °C (up to ambient) [77, 78].

In search of an alternative to organic solvents, a highly efficient version of base-catalyzed vinylination of thiols with acetylene in water has been developed [80, 82]. The reaction proceeds in the presence of a twofold molar excess of KOH with respect to thiophenol under acetylene pressure (initial pressure 11–14 atm) at 100 °C for 3 h.



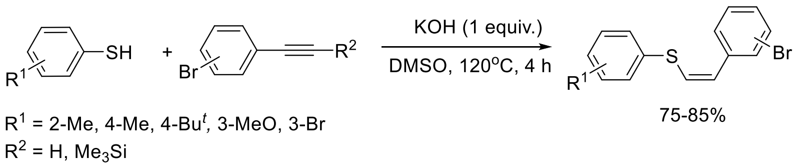
Obviously, in this case, not free thiol, but the corresponding potassium thiolate, which is easily generated by treatment of thiols with potassium hydroxide in water (room temperature, 1 h), undergoes vinylation.

Aromatic acetylenes are found to regio- and stereoselectively interact with thiophenols in the β-cyclodextrin/water system [83]. The reaction is realized at room temperature to give *E*-2-aryl vinyl sulfides with 90–96% yields.



Implementation of this reaction in aqueous DMSO in the presence of a catalytic pair CuI/K_2CO_3 (room temperature, 16 h) leads to the selective formation of *Z*-isomers of 2-aryl vinyl sulfides with 58–91% yields [84].

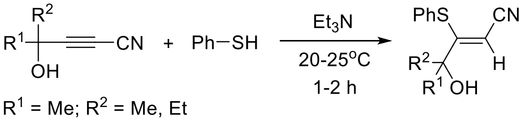
Hydrothiolation of bromo-substituted arylacetylenes with thiophenols (KOH/DMSO, 120 °C, 4 h) proceeds with high chemo-, regio- and stereoselectivity to afford only *Z*-aryl styryl sulfides with up to 85% yield [81]. The alternative reaction of *S*-arylation of bromarylacetylenes under these conditions is not realized.



R^1 = 2-Me, 4-Me, 4-Bu^t, 3-MeO, 3-Br
R^2 = H, Me_3Si

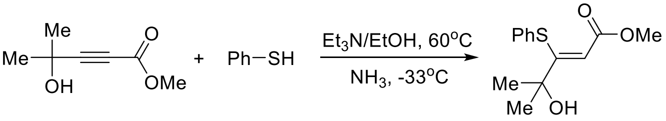
Under similar conditions, the reaction of aryl thiols with 3-ethynylthiophene also occurs regio- and stereoselectively (yield of *Z*-adducts is 75–79%). In the case of ethyl propiolate, the corresponding arylthioacrylates are formed with 70–75% yields, the ratio of the *Z:E* isomers being varied from 2:1 to 1:1 [81].

Thiophenol reacts with acetylenic hydroxynitriles regio- and stereospecifically in proton (alcohols) and aprotic (dioxane) solvents (Et_3N, 20–25 °C, 1–2 h) giving *Z*-3-phenylthio-2-alkeneonitriles with quantitative yields [85].

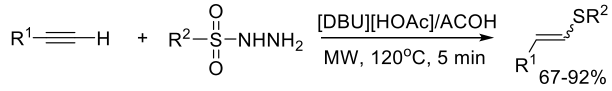


R^1 = Me; R^2 = Me, Et

Selective hydrothiolation of methyl-2-pentenoate with thiophenol occurs in liquid ammonia or in EtOH (Et_3N, 60 °C) to deliver *Z*-3-phenylthio-2-pentenoate with a quantitative yield [86].

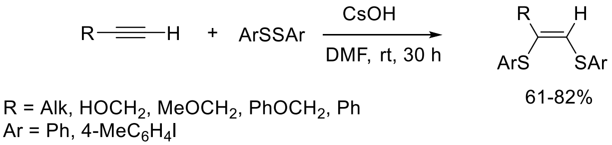


Not only thiphenols, but also sulfonyl hydrazides can transform alkynes into aryl vinyl sulfides. It is reported that vinyl sulfides are synthesized by MW-assisted reaction of sulfonyl hydrazides with aryl/heteroarylacetylenes using a DBU-based ionic liquid [87]. Due to high conversion, excellent regioselectivity, short reaction time (120 °C, 5 min), and use of a recyclable ionic liquid, this protocol promises to be a practical and greener alternative to the existing methods.



R^1 = Ph, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-FC_6H_4, 2-Pyridyl
R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$Bu^tC_6H_4$, 4-$NO_2C_6H_4$, Benzyl

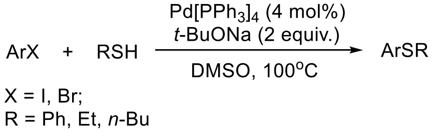
Functionalized aliphatic and aromatic terminal alkynes react well with diaryl disulfides under very mild conditions (CsOH/DMF, 20–25 °C, 30 h) under a nitrogen atmosphere to exclusively afford *Z*-isomers in 61–82% yields [88].



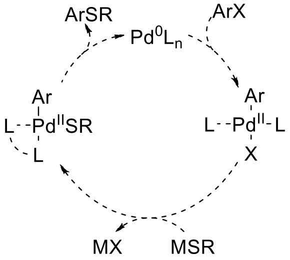
2.2 Transition Metal-Catalyzed Methods of the C–S Bond Formation

Over the last 30 years, the number of publications devoted to the catalytic nucleophilic substitution of halogens in aryl halides by the arylthio groups under the action of the corresponding aliphatic and aromatic thiols was growing in avalanche-like progression. These reactions, which are referred to as cross-coupling, proceed in the presence of metal complex catalysts (most often, Cu, Pd, Fe, less often Co, Rh, In, and Ni, even less often Ag, Mg).

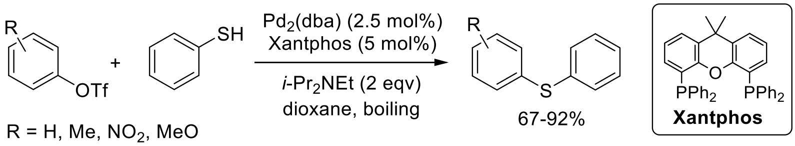
The metal complex-catalyzed nucleophilic substitution of aryl halides by thiolates has been first described in 1978 [89]. Diaryl and alkyl aryl sulfides are synthesized in the presence of Pd $[PPh_3]_4$ and *t*-BuONa (DMSO, 100 °C).



Numerous studies on the palladium-catalyzed synthesis of aryl sulfides are summarized in reviews [13, 14, 90]. All reactions, as a rule, occur via the standard mechanism of Pd-catalyzed formation of a carbon-heteroatom bond through oxidative addition ($Pd^0 \rightarrow Pd^{II}$) and reductive elimination ($Pd^{II} \rightarrow Pd^0$) [90].

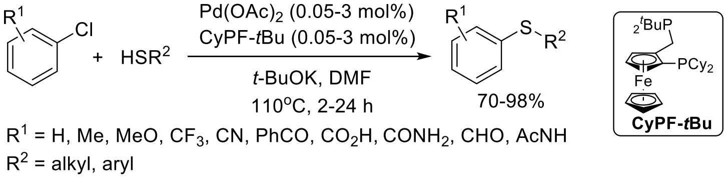


The employment of a palladium catalyst allows implementing the cross-coupling of thiols not only with aryl bromides [89, 91], but also with aryl triflates [91–93] and activated aryl chlorides [91, 94]. Aromatic and aliphatic thiols easily undergo the cross-coupling with aryl bromides, chlorides, and triflates in the presence of the catalytic system $Pd_2(dba)_3$/Xantphos [91, 92]. The use of a homogeneous catalyst, tris(dibenzylideneacetone)dipalladium(0), and chelating diphosphine ligand enable to synthesize diaryl sulfides bearing electron-donating and electron-withdrawing substituents with high yields (67–92%) [91].



Unlike aryl bromides and triflates, aryl chlorides tolerate the cross-coupling in the presence of a stronger base Cs_2CO_3. Similar reactions with K_2CO_3 in xylene are realized upon boiling for 24 h [92].

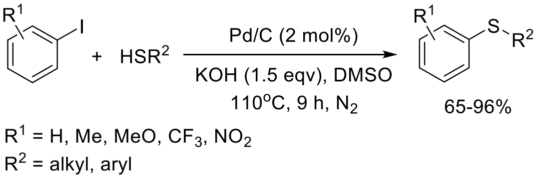
A very efficient palladium complex for the cross-coupling of aromatic and aliphatic thiols with aryl chlorides has been proposed [94, 95]. The complex, formed in situ from $Pd(OAc)_2$ or $Pd(dba)_2$ and 1-dicyclohexinephosphino-2-di-*tert*-butylphosphinoethylferrocene (Josiphos ligand CyPF-*t*Bu) catalyzes the arylation of thiols with aryl chlorides having nitrile, keto-, amido-, amino-, and hydroxyl groups.



Sterically unhindered aryl chlorides react with thiols selectively, while the reactions of *o*-substituted aryl chlorides are accompanied by the formation of side symmetric diaryl sulfides [94].

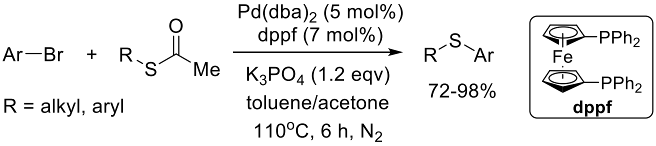
The cross-coupling of aliphatic and aromatic thiols with aryl bromides and iodides under the action of this palladium complex (0.005 mol%) takes less than 2 h to afford the corresponding aromatic sulfides bearing different functional groups with high yields [95].

It has been shown that the reactions of thiophenols, thionaphthols, and aliphatic thiols with aryl and hetaryl halides can successfully proceed using the ligand-free palladium on activated carbon [96]. These reactions occur easily with aryl iodides and aryl bromides bearing acceptor substituents, unlike nonactivated aryl bromides. Nonactivated aryl chlorides could not be involved in this reaction.



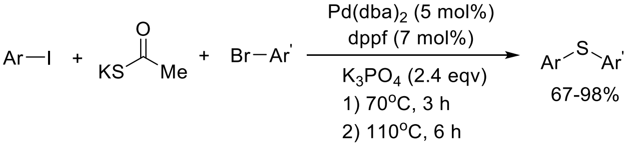
An important condition for the successful formation of sulfides is the application of the KOH/DMSO system. In the presence of weaker bases (K_2CO_3, K_3PO_4), as well as in non-polar solvents, the reaction does not take place.

Apart from thiols, other sulfur-containing nucleophiles can participate in the formation of the C–S bonds. For example, symmetrical and unsymmetrical aryl sulfides are obtained by cross-coupling of *S*-aryl (or *S*-alkyl)thioacetates and aryl halides in the presence of the catalytic system $Pd(dba)_2$/dppf [bis(dibenzylideneacetone)palladium(0)/[1,1′-bis(diphenylphosphino)ferrocene] upon heating in a mixture of toluene/acetone, 2: 1 [97]. In these reactions, K_3PO_4 is used as a base.

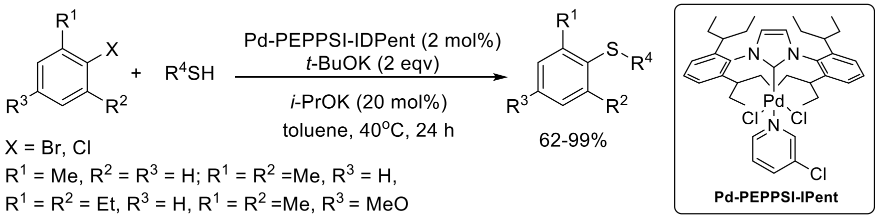


The role of acetone is still obscure. However, its addition to toluene dramatically affects the yield of sulfides. The authors suggest that acetone facilitates deprotonation of *S*-arylthioacetates.

Potassium thioacetate can be employed instead of arylthioacetates in the synthesis of diaryl sulfides. The reaction of two equivalents of aryl bromide with potassium thioacetate under optimal conditions [$Pd(dba)_2$/dppf, K_3PO_4 (2.4 eq.), 110 °C, 6 h) furnishes symmetrical diaryl sulfides with 64–97% yields [97]. Asymmetrical diaryl sulfides are obtained selectively via a modified one-pot two-stage process comprising the preliminary preparation of *S*-arylthioacetate from aryl iodide and potassium thioacetate (70 °C, 3 h) followed by its subsequent interaction (110 °C, 6 h) with aryl bromide.



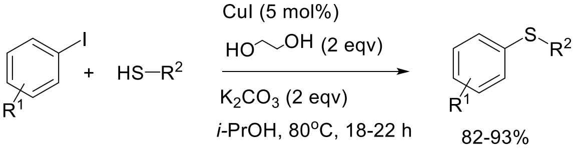
A bulky catalyst based on palladium and a sterically hindered ligand, di(2,6-*iso*pentylphenyl)imidazole, has been developed. The catalyst is effective in the cross-coupling of *ortho*-substituted deactivated aryl halides with alkyl, aryl, and silyl thiols [98]. The reactions successfully proceed with 2 mol% Pd-PEPPSI-IPent in the presence of *t*-BuOK as a base in toluene at 40 °C.



X = Br, Cl
R^1 = Me, R^2 = R^3 = H; R^1 = R^2 =Me, R^3 = H,
R^1 = R^2 = Et, R^3 = H, R^1 = R^2 =Me, R^3 = MeO
R^4 = Ph, 4-FC_6H_4, 2-MeC_6H_4, 2,6-$Me_2C_6H_3$, 1-Naphthyl, CH_2Ph, t-Bu, n-C_8H_{17}, Cy, Si(i-Pr)$_3$

Halothiophenes, benzothiophenes, imidazoles, quinolines, and pyridazines react with aryl thiols similarly at room temperature or low heating (23–40 °C).

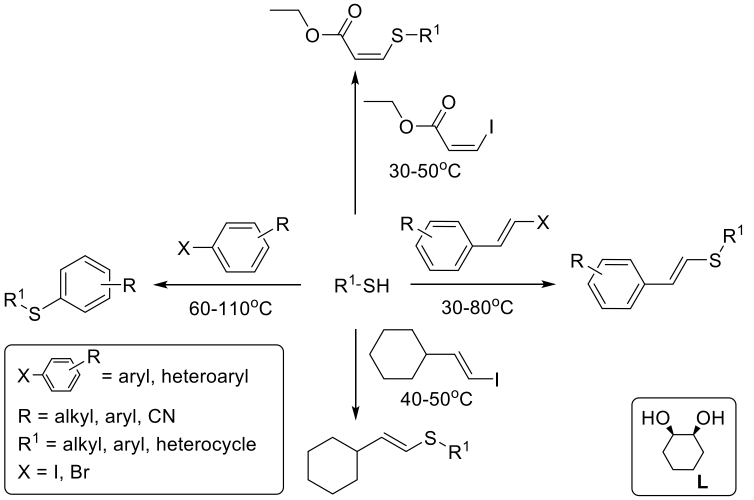
In the last decade, the progress in the synthesis of diaryl sulfides via the cross-coupling of aryl halides and thiols is mainly associated with the use of copper salts in combination with ligands such as diols [99–101], triols [102], phenols [103], diamines [104], pyridines [105], benzotriazole [106], etc. The available catalytic system CuI/$HOCH_2CH_2OH/K_2CO_3$/*i*-PrOH allows one to synthesize aromatic sulfides from thiols and aryl iodides while preserving various functional groups [99].



R^1 = Me, MeO, Br, CN, NO_2, NH_2, OH, CO_2H, CO_2Et, CHO
R^2 = aryl, alkyl

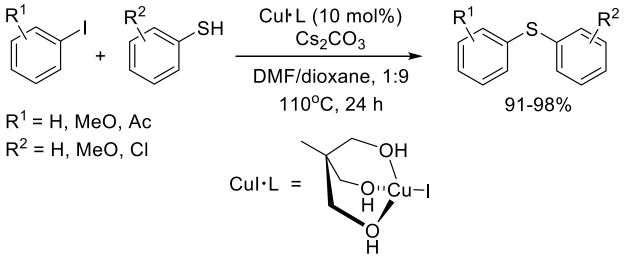
A similar reaction involving the CuI/*trans*-1,2-cyclohexanediol complex is implemented using microwave irradiation (K_2CO_3, *i*-PrOH, 120 °C) [101].

The catalytic system CuI/*cis*-1,2-cyclohexanediol turns out to be very efficient for the synthesis of aryl, heteroaryl, and vinyl sulfides [100]. The proposed bidentate *O*-donor ligand, according to the authors, is more active than *trans*-1,2-cyclohexanediol and ethylene glycol. This universal catalytic system is tolerant with respect to various functional groups and permits to obtain different aryl and vinyl sulfides under mild conditions.



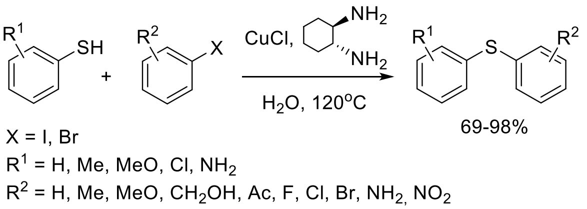
Conditions: CuI (10 mol%), L (20 mol%), K_3PO_4 (1.5 eqv), DMF, 0.5-15 h, 75-98% yields

Tris(hydroxymethyl)ethane is proposed as an effective tripodal ligand relative to CuI in the formation of C–S bond in the reaction of thiols with aryl iodides, while Cs_2CO_3 is used for HI binding [107].



A natural phenolic compound, hematoxylin, isolated from sandalwood, has been proposed as an effective CuBr ligand in the synthesis of aromatic sulfides from thiols and aryl halides (K_3PO_4, DMF/H_2O, 90 °C, 6 h) [103]. This catalyst is moisture- and air-resistant, tolerant to various substituents and allows preparing diaryl sulfides with 67–91% yields.

A simple and efficient method for the synthesis of diaryl sulfides from thiophenols and aryl iodides and aryl bromides using a copper catalyst in an aqueous medium has been documented [104].



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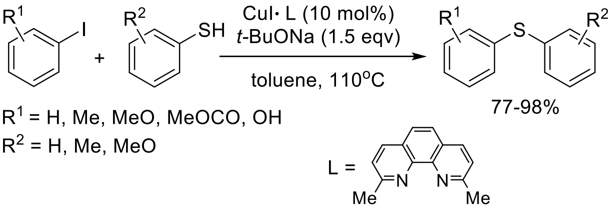
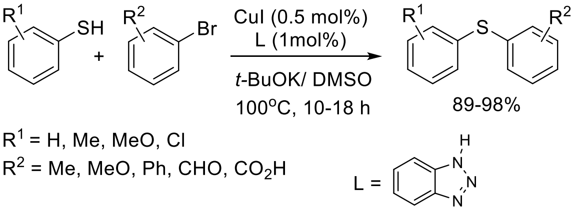
trans-1,2-Diaminocyclohexane acts as a ligand and base. The authors emphasize that an aqueous solution of the catalytic complex can be reusable in this synthesis.

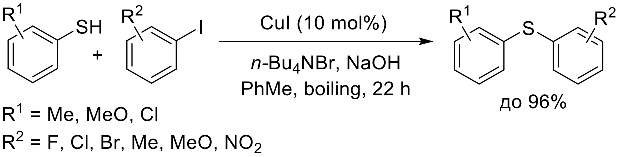
An interesting version of CuI/2,9-dimethyl-1,10-phenanthroline (necuproin)-catalyzed cross-coupling of thiols with aryl halides using *t*-BuONa as a base (toluene, 110 °C) has been elaborated [105].



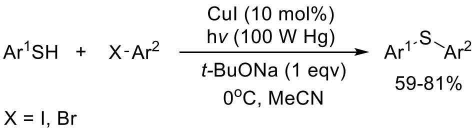
An effective general protocol for the cross-coupling of thiols with aryl halides is based on the use of the CuI/benzotriazole catalytic system [106].



It has been reported on CuI-catalyzed nucleophilic substitution reactions between aryl thiols and aryl halides occurring without ligands [108, 109]. In the presence of catalytic amounts of CuI, aromatic thiols interact with aryl iodides upon boiling in toluene to form diaryl sulfides with high yields [108].

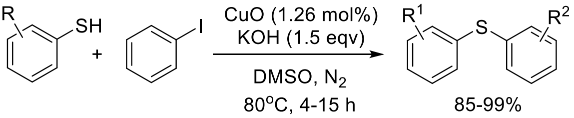


A similar photoinduced reaction between aryl thiols and aryl halides (10 mol% CuI, acetonitrile) proceeds efficiently at 0 °C and involves one-electron transfer [109].



X = I, Br
Ar^1 = Ph, 2-FC_6H_4, 2,6-$Me_2C_6H_3$, 3-$MeOC_6H_4$, 3-Py, 2-thiophene
Ar^2 = Ph, 1-Naphthyl, 3,5-$Me_2C_6H_3$, 2-FC_6H_4

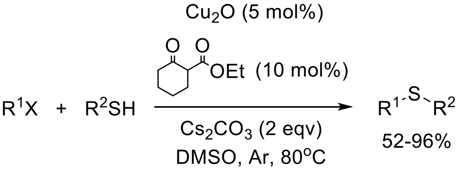
Other popular copper compounds for catalysis of the above reaction are copper oxides. Thus, CuO nanoparticles appear to be efficient catalytic species for the cross-coupling of thiols with iodobenzene [110].



R = H, Me, MeO, NO_2, Br
R^2 = F, Cl, Br, Me, MeO, NO_2

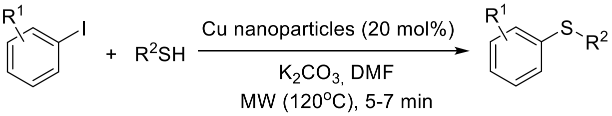
Other salts [$CuSO_4 \cdot 5H_2O$ and $Cu(OAc)_2 \cdot 2H_2O$], as well as ordinary CuO, are ineffective in this reaction. Also, an important prerequisite for successful implementation of the cross-coupling is the application of DMSO as a solvent.

A cross-coupling of aryl, alkyl, and hetaryl thiols with aryl and hetaryl halides catalyzed by copper (I) oxide in DMSO has been disclosed [111].



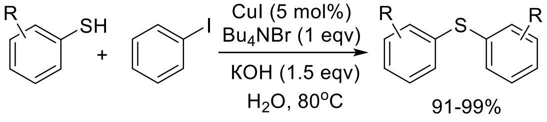
R^1 = Ar, Hetar
R^2 = Alk, Ar, Hetar
X = I, Br, Cl

The synthesis of a catalyst consisting of copper(II) oxide on mesoporous SiO_2 is described. This ligand-free catalyst effectively catalyzes the cross-coupling of thiols with aryl iodides in DMSO at 110 °C [102]. Among the studied catalysts, the formation of the Ar–S bond is most efficiently catalyzed by copper nanoparticles in the absence of ligands under the action of microwave irradiation [112].



R^1 = H, Me, MeO, OH, Cl, Br, NH_2, NO_2
R^2 = Ar, Alk

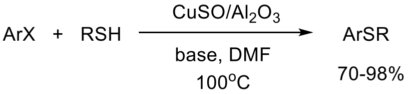
Cu-catalyzed C–S cross-coupling between thiols and aryl iodides in an aqueous medium has been implemented [113]. The reaction proceeds under the action of CuI/Bu_4NBr system and does not require an inert atmosphere.



R = H, Me, MeO, NO_2, Br, Cl

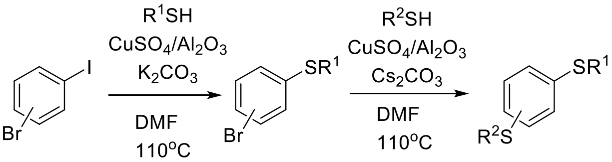
2-Naphthylthiol and benzyl thiol react with iodobenzene in the same fashion. In the absence of tetrabutylammonium bromide, which, as the authors believe [113], ensures the dissolution of organic substrates in water, diaryl sulfides are not formed.

A cheap, air-stable, environmentally friendly, and recyclable heterogeneous catalyst, $CuSO_4/A_2O_3$, is used for cross-coupling of aromatic thiols with aryl halides [114].

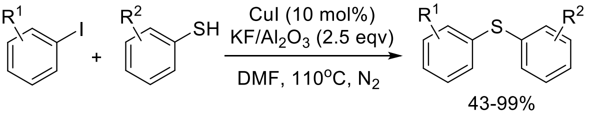


$$ArX + RSH \xrightarrow[\text{base, DMF}\ 100^{\circ}C]{CuSO/Al_2O_3} \underset{70\text{-}98\%}{ArSR}$$

The catalytic cross-coupling of aryl iodides occurs in the presence of K_2CO_3, whereas polarization of the Ar–Br bond requires a stronger Cs_2CO_3 base. Such a selective base-controlled coupling of aryl thiols with iodo- and bromarenes leads to the formation of unsymmetrical *bis*-sulfides [114].



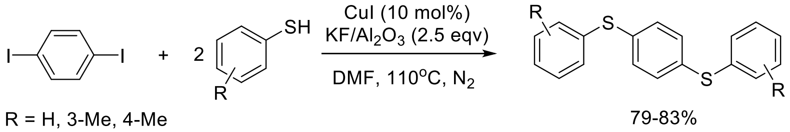
Copper(I) iodide in combination with KF/Al_2O_3 base effectively (without ligands and other additives) catalyzes the reaction of cross-coupling between thiols and aryl iodides (DMF, 110 °C, 8 h) [115].



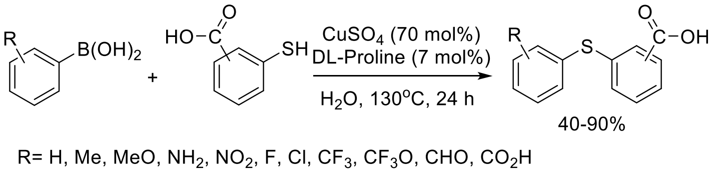
R^1 = H, 2-, 3-, 4-Me; 4-MeO, 4-NH_2, 4-NO_2, 4-F, 4-Br, 4-Ac
R^1 = H, 2-, 3-, 4-Me; 4-NO_2, 4-F, 4-Cl

The KF/Al_2O_3 solid base, first used for the formation of the C–S bond, proves to be effective for a wide range of substrates. Various diaryl sulfides, including those containing alkyl, alkoxy, halogen, nitro, amino, and acyl groups in the aromatic core, have been obtained with moderate to high yields.

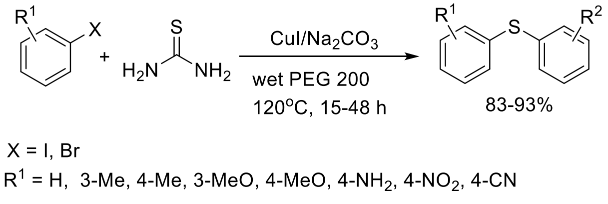
A similar protocol is employed to synthesize bissulfides from 1,4-diiodobenzenes [115].



An efficient, practical, highly selective, and environmentally benign method for the synthesis of aryl sulfides has been disclosed. The available catalytic system, $CuSO_4$/DL-proline/NaOH, allows obtaining unsymmetrical diaryl sulfides from thiols and aryl boronic acids using water as a green solvent (130 °C, 24 h) [116]. The products are formed with moderate to excellent yields. A broad range of aryl boronic acids and scalable processes make this methodology appropriate for the synthesis of diverse aryl sulfides.

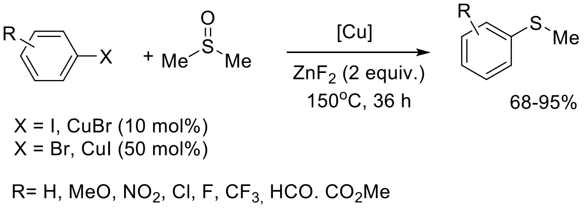


Various sulfur transfer reagents have been applied instead of free thiols for the formation of diaryl sulfides. An improved protocol has been developed for the one-pot CuI-catalyzed preparation of symmetrical diaryl sulfides from available aryl halides in the presence of thiourea as sulfur transfer agent under ligand-free conditions in wet poly(ethylene glycol) and in the absence of an inert atmosphere [117].



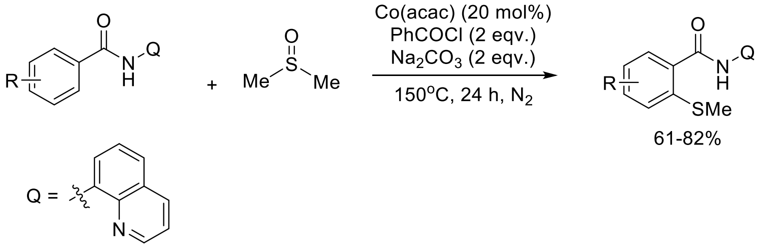
Also, aryl iodides, aryl bromides bearing electron-withdrawing and electron-donating groups are utilized for the synthesis of symmetrical diaryl sulfides with high yields. However, this catalytic system turns out to be inapplicable for chloroarenes. Other efficient catalyst of the above reaction is tris-(dibenzylideneacetone)dipalladium(0) ($[Pd_2dba_3]$) [118].

Apart from thiols and thiourea, other sulfur reagents such as xanthate [119], thioacetate, thiocyanate [120], and metal sulfides can participate in the transition metal-catalyzed synthesis of diaryl sulfides. DMSO is also employed as a powerful methylthio source in the transition metal-catalyzed reactions with aryl halides. In the copper-catalyzed reaction of aryl halides with DMSO, a variety of aryl methyl sulfides is obtained with good to excellent yield (68–95%) in the presence of ZnF_2 (150 °C, 36 h) [121]. The procedure tolerates a series of functional groups such as methoxy, nitro, chloro, fluoro, trifluoromethyl, formyl, and methoxycarbonyl (24 examples).

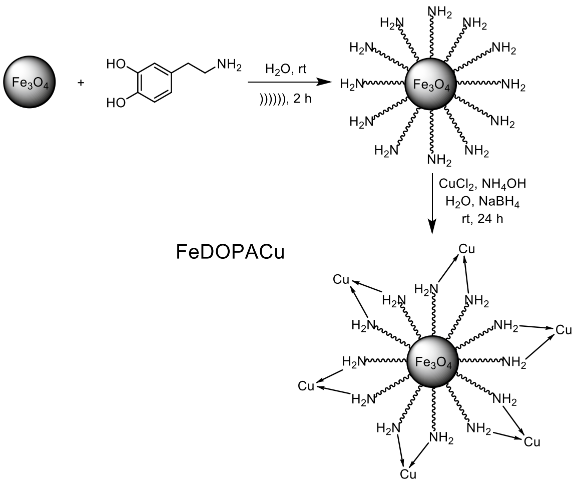


A similar thiomethylation of haloarenes with DMSO in the presence of CuI and DABCO (130 °C, 12–24 h) has been implemented [122]. Thus, these protocols are feasible and low-costing alternatives to the traditional methods for the preparation of aryl methyl sulfides.

The first example of Co-catalyzed highly mono-selective *ortho*-methylthiolation of $C_{sp}{}^2$–H bonds using DMSO as the methylthiolation source with the assistance of an 8-aminoquinoline directing group has been reported [123]. Simple Co-salt Co $(acac)_3$ is used as a catalyst and DMSO is utilized as a methylthiolation source. It is found that the reaction strongly depends on the addition of PhCOCl (two equiv.) as an additive. The reaction tolerates various functional groups to afford a number of *ortho*-methylthiolated benzamides with 61–82% yields.

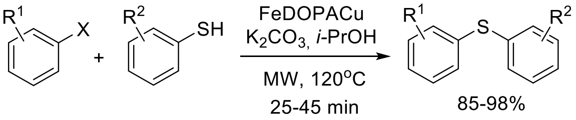


In recent years, special attention is focused on the development of metal catalysts on a heterogeneous support. The advantages of such catalysts are easy separation from the product and reusability. For instance, functional magnetic ferrite nanoparticles are claimed as heterogeneous support for a copper catalyst [124]. The active catalyst is formed under the action of ultrasound on nanoferrite and 3,4-dihydroxyphenylalanine hydrochloride (DOPA) in water and the subsequent addition of $CuCl_2$ in an alkaline medium.

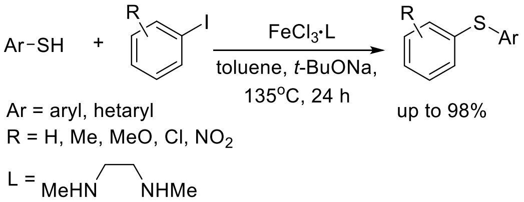


FeDOPACu

This complex nano-sized catalyst contains only 0.82% copper and catalyzes the reaction of cross-coupling of thiols not only with aryl iodides, but also with less active aryl bromides. It is easily separated from the reaction mixture under the action of an external magnet and can operate during 3 cycles without loss of the activity [124].



A while ago, iron-based complexes have been proposed for the arylation of thiols. The employment of the catalytic system $FeCl_3$/N,N'-dimethylethylenediamine and *t*-BuONa as a base allows obtaining diaryl sulfides from aryl thiols and aryl iodides with moderate to high yields [125].



Despite such advantages of this catalytic system as cheapness and lower toxicity in comparison with other transition metals, it has certain shortcomings. First, iron-catalyzed reactions of aryl thiols and aryl iodides proceed at higher temperatures, and secondly, the reaction with less active aryl bromides and aryl chlorides, as well as aliphatic thiols, does not take place.

A similar reaction in the presence of a water-soluble catalytic system $FeCl_3$•$6H_2O$/cationic 2,2′-dipyridyl ligand occurs under aerobic conditions upon boiling in water to give aryl sulfides with high yields [126].

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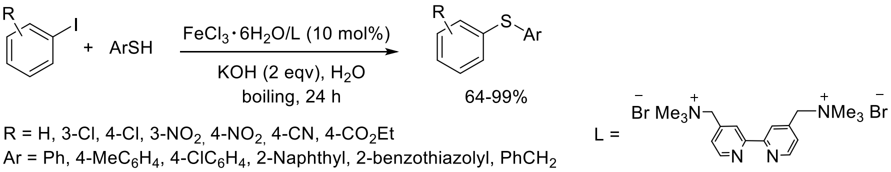
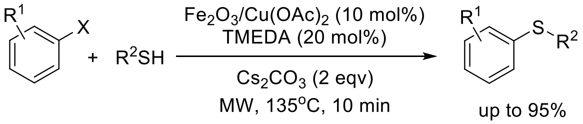


R = H, 3-Cl, 4-Cl, 3-NO_2, 4-NO_2, 4-CN, 4-CO_2Et
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 2-Naphthyl, 2-benzothiazolyl, $PhCH_2$

An important benefit of this catalytic system is the possibility of its repeated usage. After separation of the organic products by extraction with hexane, the aqueous solution containing the catalyst can be exploited in a new cycle without any treatment. A possibility of using a catalyst solution for 6 cycles with a slight decrease in activity has been confirmed experimentally.

Under the action of a combined Fe/Cu catalyst and microwave radiation (DMF, 135 °C, 10 min), the *S*-arylation of aromatic, aliphatic, and cyclic thiols with aryl halides is efficiently performed [127].

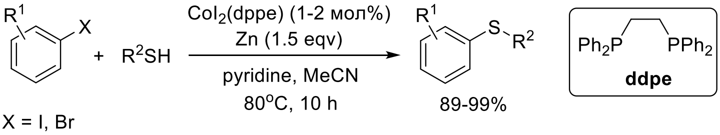


X = I, Br, Cl
R^1 = H, 3-Cl, 4-Cl, 3-NO_2, 4-NO_2, 4-CN, 4-CO_2Et
R^2 = Ph, 4-MeC_6H_4, 2,6-$Me_2C_6H_3$, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 2-Py, 2-thiazolyl, 2-benzothiazolyl, $PhCH_2$, *n*-Bu, Cy

Iron oxide in combination with copper salts and tetramethylethylenediamine (TMEDA) catalyzes the cross-coupling of thiols not only with aryl iodides, but also with aryl bromides and aryl chlorides.

$FeCl_3$ together with effective diphosphine ligands, such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) or 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos), successfully promotes the coupling of thiols and aryl iodides upon heating (135 °C, 24 h) in toluene [128]. Among bases, sodium and potassium *tert*-butylates have shown the best properties.

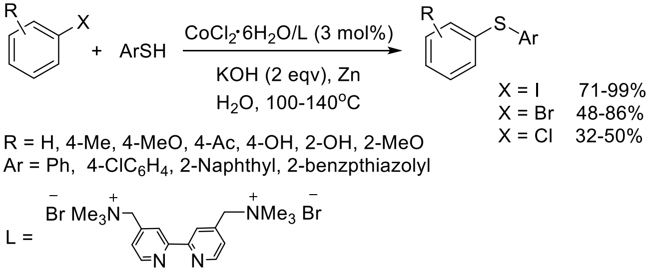
An alternative cobalt complex-catalyzed cross-coupling of aryl halides with aromatic and aliphatic thiols using zinc has been elaborated [129].



X = I, Br
R^1 = H, 4-Me, 4-MeO, 4-Ac, 4-CN, 4-OH, 4-NH_2, 4-CHO, 2-MeO, 2-CH_2OH, 2,4,6-Me

Zinc in this reaction reduces Co(II) to Co(I), thus activating the catalyst. Aryl halides with electron-donating and electron-withdrawing groups in *ortho*- and *para*-position as well as hetaryl (pyridyl, furyl, indolyl) halides form the corresponding sulfides with high yields (89–99%).

An efficient, reusable catalytic system $CoCl_2{\bullet}6H_2O$/cationic 2,2′-bipyridyl ligand has been developed for the cross-coupling of thiols with aryl halides in water [130].

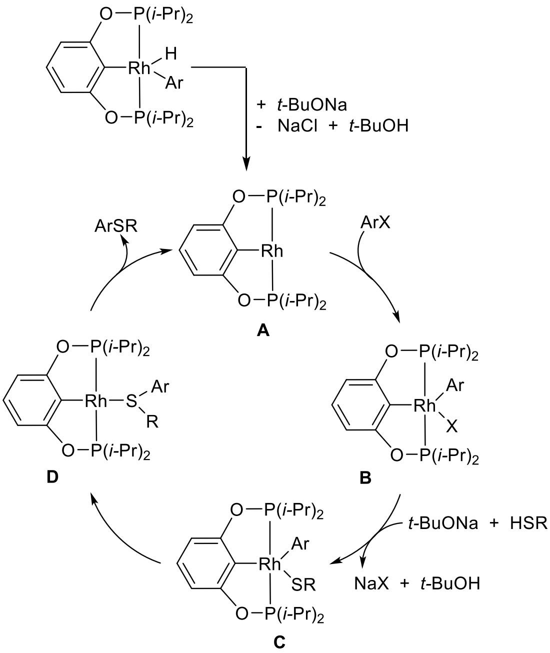


As in [129], zinc reduces the catalyst precursor to Co(I) and, probably, forms zinc thiolate, which undergoes the cross-coupling with RC_6H_4X. Aryl iodides react with aryl thiols in an aqueous catalytic system (100 °C, 24 h, KOH as a base), giving rise to the cross-coupling products with high yields (71–99%). In this case, cationic ligand plays also an important role. In the reaction with less active aryl bromides and aryl chlorides, this catalytic system is more active than a similar complex based on $FeCl_3{\bullet}6H_2O$ [126], in the presence of which the products are almost not formed. To obtain diaryl sulfides, here it is necessary to increase the reaction temperature to 140 °C and prolong its duration to 48 h. An undisputable advantage of this catalytic system is its repeated use. The yield of sulfides synthesized in the presence of this catalytic system decreases from 99 (1st cycle) to 88 (4th cycle) and 60% (7th cycle).

The investigations into aromatic nucleophilic substitution under the action of thiols are also focused on rhodium-assisted catalysis. Thus, a general procedure for the synthesis of aromatic sulfides by a cross-coupling of thiols with aryl iodides in the presence of the rhodium complex $[RhCl(cod)]_2$ and PPh_3 as a ligand has been developed [131]. Aryl iodides with electron-donating and electron-withdrawing groups, as well as sterically hindered ones, interact with aryl and alkyl thiols (toluene, *t*-BuONa as a base, 100 °C, 24 h) to deliver aryl sulfides with high yields. The presence of phosphine ligand is mandatory here.

The rhodium complex $(POCOP^{i}Pr)Rh(H)(Cl)$, formed by a pincer ligand, is an active precatalyst for the formation of the carbon–sulfur bond in the arylation of thiols not only by aryl iodides, but also by bromides and chlorides [132]. The cross-coupling occurs in the presence of 3 mol% of the catalyst (toluene, *t*-BuONa, 110 °C, 2–24 h) to afford aryl sulfides with up to 98% yield. The catalytic cycle of the reaction includes dehydrochlorination of the complex to generate a coordination-unsaturated rhodium fragment **A** followed by subsequent oxidative addition of the aryl halide [Rh(I) → Rh(III)]. The organyl rhodium intermediate

B undergoes transmetalation with NaSR forming a complex (POCOP)(Rh)(Ar)(SR) **C**, which then is subjected to a reductive coupling and gives adduct (POCOP)(Rh) (ArSR) **D**. The latter stage leads to the formation of sulfide and regeneration of active coordination-unsaturated forms of the rhodium catalyst.

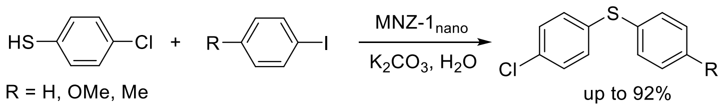


Indium compounds turn out to be efficient catalysts for the cross-coupling of aryl and alkane thiols with aryl halides [133, 134]. Arylation of thiols with aryl iodides and aryl bromides in DMSO (KOH as a base, 135 °C, 24 h) in the presence of 10 mol% of the complex $In(OTf)_3$/TMEDA ($Me_2NCH_2CH_2NMe_2$) ensures high yields of aryl sulfides [134]. An exception is aryl halides with electron-donating substituents. In this case, the yield decreases to 15–79%. The reaction mandatorily requires catalyst and ligand, as well DMSO.

A more efficient catalyst for this reaction is nano-sized In_2O_3 [133]. Indium oxide is active in the absence of a ligand and provides a high yield of aryl sulfides at a concentration of 3 mol%.

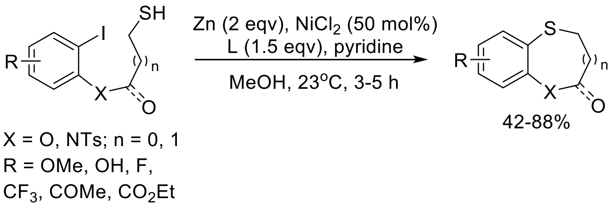
The efficacy of manganese-catalyzed cross-coupling of thiols with aryl iodides is determined by the nature of the ligand. Using $MnCl_2$ in combination with 1,1-phenanthroline (20 mol%) and Cs_2CO_3 (toluene, 135 °C, 48 h), various diaryl- and alkyl aryl sulfides are obtained with 63–99% yields[135].

Mild arylation of 4-chlorothiophenol with aryl iodides is promoted by a catalyst based on NiO-ZrO_2 (MNZ-1) nanocrystals prepared via self-assembly after acidic treatment of $Ni(NO_3)_2$ и $Zr(OBu)_4$ and calcination at 400 °C [136]. The reaction proceeds at room temperature in an aqueous medium.



After the reaction, the catalyst can be regenerated by calcination at 400 °C in air and returned to the cycle. The yield of sulfide on the second cycle decreases insignificantly (from 89 to 87%).

Intra- and intermolecular C–S cross-coupling of various functionalized thiols and thioacetates with aryl iodides in the presence of the Ni(0)/ethyl crotonate/pyridine complex takes place at room temperature [137].



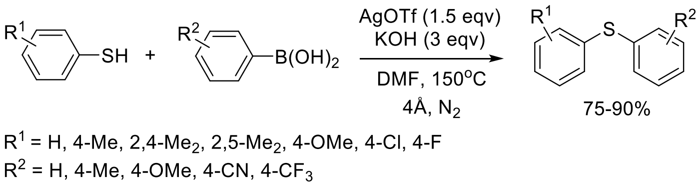
The catalyst is easily generated in situ from a mixture of Zn/NiCl$_2$/pyridine / ethyl crotonate by reduction of Ni(II) to Ni(0) with zinc. 2,2′-Bipyridine can be used as a ligand instead of ethyl crotonate.

An electrochemical method for the synthesis of aryl phenyl sulfides from thiophenol and halobenzenes in the presence of a 2,2′-bipyridine complex of a zero-valent nickel, Ni(bipy)$_2$, has been elaborated [138].

$$\mathrm{ArX} + \mathrm{PhSH} + e^- \xrightarrow[\mathrm{Ni(bipy)_2}]{\mathrm{NMP},\ 22\text{-}24^\circ\mathrm{C}} \mathrm{ArSPh} + X^- + 1/2\mathrm{H_2}$$

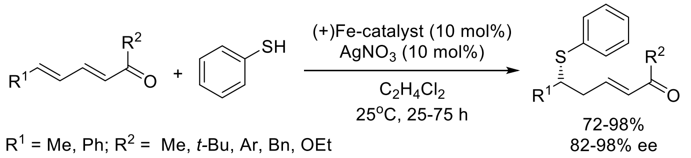
X = Br, I 70-90%

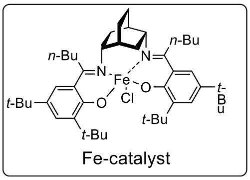
Aryl boronic acids [139] can act as partners of thiols in the Ag(I)-catalyzed cross-coupling.



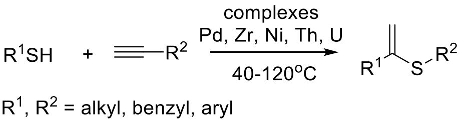
The effectiveness of this version of the reaction in the synthesis of aryl sulfides has been established for a wide range of substituted thiols and aryl boronic acids.

The reaction of thiols with acyclic $\alpha,\beta,\gamma,\delta$-unsaturated dienones, catalyzed by a chiral salen-iron(III) complex based on *cis*-2,5-diaminobicyclo[2.2.2] octane, gives δ-thia-α,β-unsaturated ketones with an enantiomeric excess of up to 98% [140].

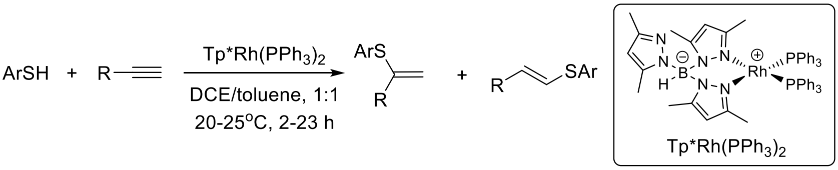




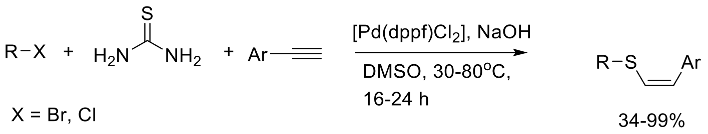
The application of transition metal complexes allows changing regioselectivity of the addition of thiols to substituted acetylenes, depending on the nature of the catalyst. It has been established that in the presence of palladium [141, 142], zirconium [143], nickel [144], actinoid (Th and U) [145] complexes, the addition of thiols to terminal alkynes is selectively directed to the formation of adducts according to the Markovnikov rule.



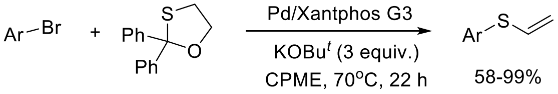
In the presence of rhodium complexes, the direction of the reaction changes depending on ligand surrounding and the nature of a thiol. The addition of thiophenol to acetylenes, catalyzed by $RhCl(PPh_3)_3$ (1–3 mol%), proceeds regio and stereoselectively to produce the *E*-isomers of anti-Markovnikov adducts [142]. When replacing the Williamson catalyst with rhodium-pyrazole-borate complex, $Tp^*Rh(PPh_3)_2$ (3 mol%), the reaction takes other directions: in dichloroethane/toluene (1:1) medium at room temperature, alkyl and arylacetylenes form adducts with alkane thiols according to the Markovnikov rule, while aryl thiols give a mixture of Markovnikov and anti-Markovnikov adducts in the ratio from 6:1 to 1.4:1 [142].



Organyl styryl sulfides have been synthesized through Pd-catalyzed one-pot, three component reaction of organohalides, thiourea, and arylalkynes [146]. The process is carried out under mild conditions to give anti-Markovnikov products of the Z-configuration in moderate to excellent yields and high selectivity.



A nontraditional approach to the synthesis of aryl vinyl sulfides is described [147]. 2,2-Diphenyl-1,3-oxathiolane slowly liberates vinyl sulfide anion under basic conditions. Using a Pd/Xantphos catalyst system to activate a wide range of aryl bromides, this transient sulfide species can be effectively trapped and fed into a traditional Pd0/PdII catalytic cycle. This reaction is amenable to a wide range of electronically diverse aryl bromides.



Ar = Ph, 2-, 3-, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-Bu^tC_6H_4, 2-, 3-MeOC_6H_4; 3-, 4-$CF_3C_6H_4$; 4-NMe_2, 2-naphthyl, 6-MeO-2-naphthyl, etc.

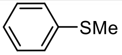
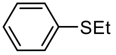
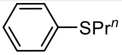
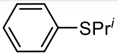
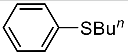
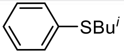
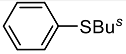
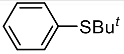
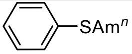
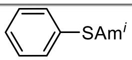
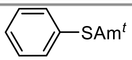
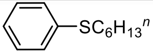
2.3 Directed Synthesis of Substituted Aromatic Sulfides

For systematic synthetic and physical–chemical investigations, summarized in this monograph, a series of various alkyl aryl and diaryl sulfides with a regularly changing structure has been synthesized. The compounds obtained bear both electron-donating and electron-withdrawing substituents [148]. The structure and the main physical–chemical characteristics of these compounds are given in Table 2.1.

The interest in these sulfides is due to the possibility of their application as models for theoretical studies, e.g. to investigate the interaction between an aromatic fragment and sulfide sulfur atom, to elucidate the dependence of this interaction on the conformational structure of the molecule, and to evaluate the ability of sulfur atom to transfer electronic effects.

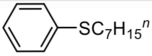
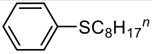
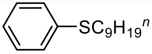
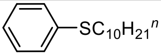
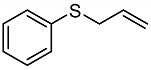
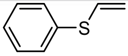
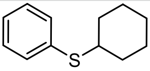
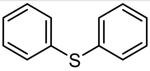
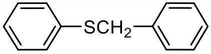
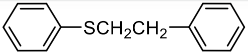
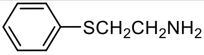
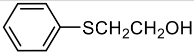
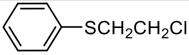
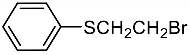
3- and 4-Halo-substituted aryl sulfides, and especially 4-fluorine derivatives, poorly studied before the publication of Aliev's works [148] invoke a great interest for the applied and theoretical research. A complete series of alkyl derivatives of 4-chloroaryl sulfides and 4-bromoaryl sulfides has been first described in [149, 150].

Table 2.1 Aryl organyl sulfides

No.	Structure	Yield, %	B.p., °C/torr (m.p., °C)	n_D^{20}	d_4^{20}
1	2	3	4	5	6
1		90	193	1.5862	1.0578
2		93	60/3	1.5668	1.0210
3		95	107/17	1.5570 1.5571 1.5530	0.9985 0.9995 0.9979
4		86	66/4	1.5462	0.9855
5		84	80/2	1.5444	0.9836
6		92	85/4	1.5532	0.9589
7		96	82/5	1.5412	0.9771
8		54	55-56/2	1.5320	0.9658
9		90	99/2	1.5394	0.9708
10		89	102/4	1.5417	0.9698
11		68	75/1	1.5372	0.9637
12		88	107/2	1.5328	0.9555

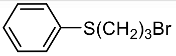
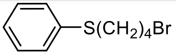
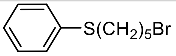
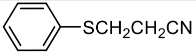
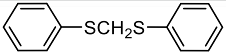
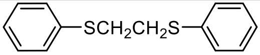
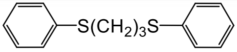
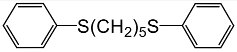
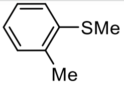
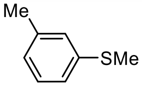
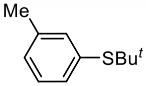
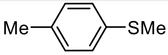
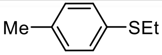
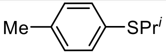
(continued)

Table 2.1 (continued)

13		86	120/2	1.5280	0.9476
14		85	132/1	1.5232	0.9437
15		85	146/2	1.5229	0.9358
16		84	157/2	1.5218^{25}	0.9336
17		80	75/2	1.5756	1.0254
18		61	52/3	1.5894	1.0395
19		80	110/6	1.5660	1.0302
20		84	295	1.6320	1.1104
21		91	(41-42)		
22		76	156/2	1.6098	1.0826
23		92	120/6	1.5927	1.0929
24		81	121/2	1.5928	1.1439
25		83	95/3	1.5815	1.1674
26		66	121/5	1.6084	1.4414

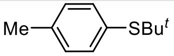
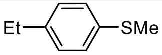
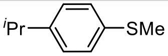
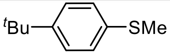
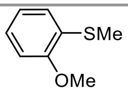
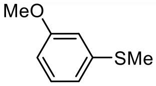
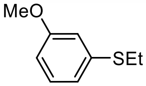
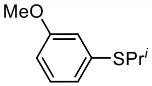
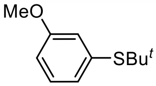
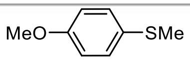
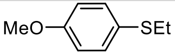
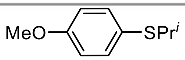
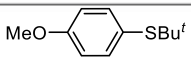
(continued)

Table 2.1 (continued)

27		70	115/1	1.5950	1.3925
28		76	142/3	1.5966	1.3163
29		62	134/1	1.5778	1.2996
30		91	130/3	1.5740	1.1074
31		83	176/2 (40)	1.6513	1.1718
32		23	68/5		
33		29	178/1 (82)	1.6204	1.1584
34		32	198/1	1.6085	1.1024
35		87	53/1	1.5800	1.0348
36		89	73/2	1.5741	1.0295
37		30	83/4	1.5309	0.9514
38		93	70/3	1.5725	1.0261
39		91	66/2	1.5577	0.9904
40		89	73-74/3	1.5392	0.9698

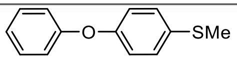
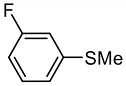
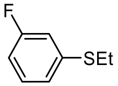
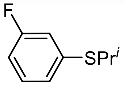
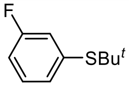
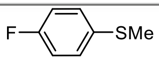
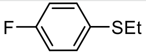
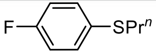
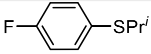
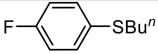
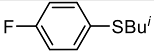
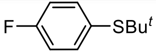
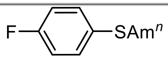
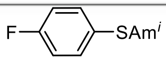
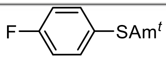
(continued)

Table 2.1 (continued)

41		90	84/3.5	1.5300	0.9507
42		95	68/2	1.5646	1.0104
43		92	88/3	1.5549	0.9925
44		90	89/2	1.5471	0.9844
45		89	142/25	1.5960	1.1189
46		85	91/2	1.5836	1.0874
47		84	100/2	1.5668	1.0707
48		88	106/5	1.5508	1.0459
49		31	108/5	1.5384	1.0175
50		90	89/2	1.5792	1.1060
51		93	96/2.5	1.5630	1.0650
52		92	105/3	1.5488	1.0379
53		36	101/3	1.5414	1.0178

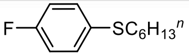
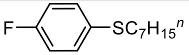
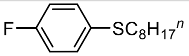
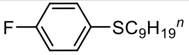
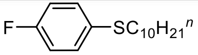
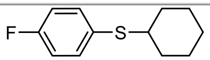
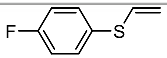
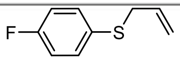
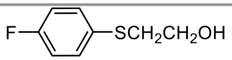
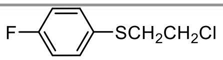
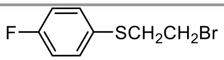
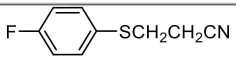
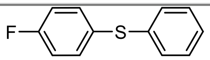
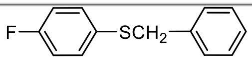
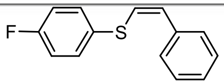
(continued)

Table 2.1 (continued)

54		78	154-155/3	1.6176	1,1692
55		91	51/2	1.5598	1.1513
56		90	55/2	1.5447	1.1128
57		88	62/2	1.5298	1.0525
58		48	69/1	1.5184	1.0278
59		92	55/4	1.5505	1.1614
60		90	61/4	1.5357	1.1098
61		88	76/4	1.5290	1.0803
62		90	68/4	1.5212	1.0658
63		87	88/3.5	1.5239	1.0572
64		88	85/4	1.5207	1.0536
65		65	66/4	1.5122	1.0380
66		81	107/5	1.5176	1.0369
67		86	99/4	1.5174	1.0356
68		70	90/15	1.5533	1.0832

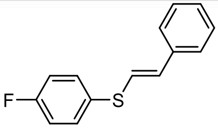
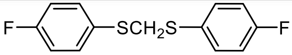
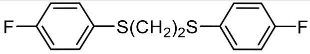
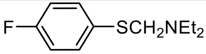
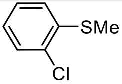
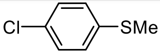
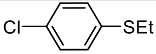
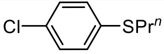
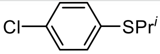
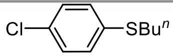
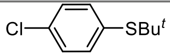
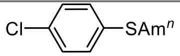
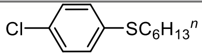
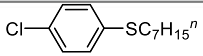
(continued)

Table 2.1 (continued)

69		78	111/3	1.5144	1.0237
70		76	123/3	1.5116	1.0144
71		75	146/3	1.5094	1.0050
72		73	145/3 (22.5)		
73		71	160/3 (24.5)		
74		78	116/3	1.5466	1.1063
75		75	66/6	1.5574	1.1388
76		81	70/3	1.5470	1.1093
77		77	116/3	1.5618	1.2374
78		70	103/5	1.5560	1.2598
79		35	109/3	1.5774	1.5074
80		94	137/3	1.5493	1.2014
81		66	107/2	1.6058	1.1847
82		93	116/1 (32)		
83		84	160-164/4	1.6471	1.1761

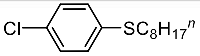
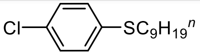
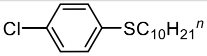
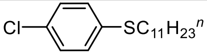
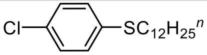
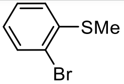
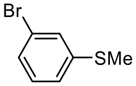
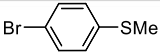
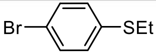
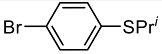
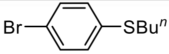
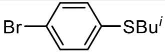
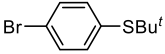
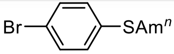
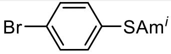
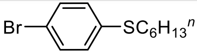
(continued)

Table 2.1 (continued)

84		88	160-165/4 (25-26)		
85		82	156/2.5	1.6066	1.2943
86		64	129/6 (72)		
87		85	99/2	1.5325	1.0660
88		92		1.6022	1.2249
89		92	79/3 (21)	1.6006	1.2145
90		91	89/4 (-25)	1.5812	1.1669
91		88	101/3 (-16)	1.5683	1.1299
92		89	78/1.5	1.5612	1.1154
93		91	116/4 (-2)	1.5608	1.1028
94		85	88/3	1.5475	1.0845
95		85	122/2 (3)	1.5541	1.0887
96		82	149/4 (4)	1.5471	1.0626
97		86	160/4 (13)	1.5402	1.0534

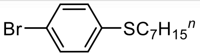
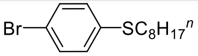
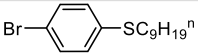
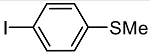
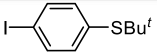
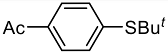
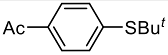
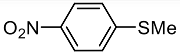
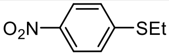
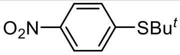
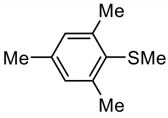
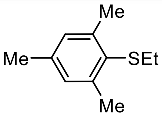
(continued)

Table 2.1 (continued)

98		86	179/4 (19)	1.5376	1.0386
99		85	163/3 (27)		
100		84	160/1 (31)		
101		82	201/3 (38)		
102		88	198/2 (41)		
103		94	88/1	1.6286	1.4982
104		94	98/3	1.6215	1.4743
105		91	75/1 (35)		
106		90	117-118/5	1.6059	1.4482
107		89	106/2	1.5845	1.3550
108		88	140/4	1.5818	1.3376
109		89	114/1.5	1.5792	1.3231
110		88	102/3	1.5666	1.2950
111		86	140/2	1.5727	1.2841
112		85	141/3	1.5712	1.2803
113		83	149/1	1.5653	1.2509

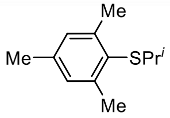
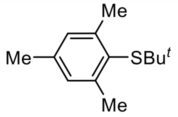
(continued)

Table 2.1 (continued)

114		82	169/1.5	1.5588	1.2232
115		81	174/1	1.5491	1.1959
116		82	185/1	1.5430	1.1627
117		86	(40-41)		
118		76	(68-69)		
119		70	142/3 (29)		
120		27	122/1	1.5575	0.9849
121		92	(71-72)	1.6408	1.2391[80]
122		90	135/1 (40)		
123		92	137-139/1 (45)		
124		45	121/1 (34)		
125		88	93/4	1.5552	1.0000
126		83	97/3	1.5468	0.9839

(continued)

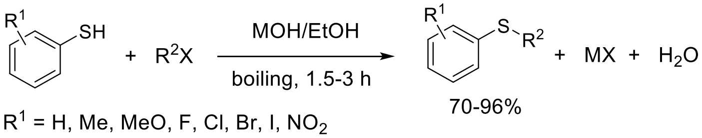
Table 2.1 (continued)

127		82	93/2	1.5398	0.9642
128		42	104/2	1.5408	0.9643

2.3.1 Alkyl Aryl Sulfides

2.3.1.1 Alkylation of Aryl Thiols with Primary and Secondary Alkyl Halides

A series of alkyl aryl sulfides has been synthesized by a classical method for alkylation of aryl thiols with primary and secondary alkyl halides in alkali-alcohol solution.

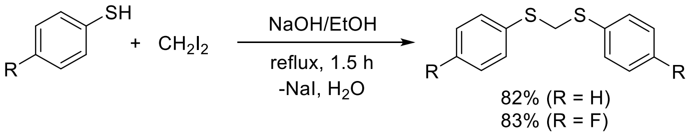


R^1 = H, Me, MeO, F, Cl, Br, I, NO_2
R^2 = *n*-alkyl, *s*-alkyl
X = Cl, Br, I; M = Na, K

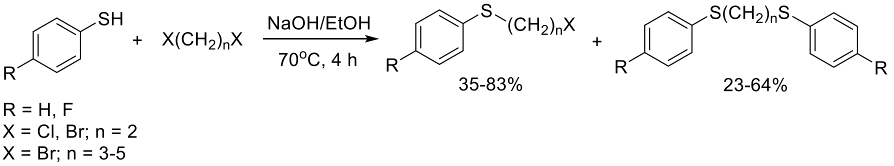
The reaction proceeds for 1.5–3 h upon boiling of aryl thiols with alkyl halides in EtOH in the presence of an equimolar amount of sodium or potassium hydroxide. 2-, 3-, and 4-Substituted aryl thiols readily participate in the process [150–152]. Eventually, organophenyl sulfides, alkyl 2-,3-,4-alkylphenyl sulfides, alkyl 2-,3-,4-methoxyphenyl sulfides, methyl 4-phenoxyphenyl sulfide, alkyl 3-,4-fluorophenyl sulfides, alkyl 2-, 4-chlorophenyl sulfides, alkyl 2-,3-,4-bromophenyl sulfides, 4-iodophenyl methyl sulfide, alkyl 4-nitrophenyl sulfides, and alkyl 2,4,6-trimethylphenyl sulfides (87 compounds) have been prepared with 70–96% yields (Table 2.1).

As seen from Table 2.1, the substituents in aryl thiols do not noticeably affect the yield of the target products.

Disulfides separated by a methylene spacer are obtained under similar conditions by the reaction of thiophenol or 4-fluorothiophenol with methylene iodide.

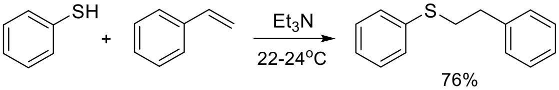


It has been attempted to synthesize monosulfides from 1,2-dichloroethane and dibromoalkanes $Br(CH_2)_nBr$. When the molar ratio of the reactants $X(CH_2)_nX$: ArSH is 2: 1 and the reaction temperature is 70 °C, monosulfide becomes the major product, but the double substitution process cannot be completely suppressed. In all cases, a mixture of two sulfides is formed. In the series of dihalides studied, the highest yield of monosulfide (83%) is reached in the case of dichloroethane and thiophenol, the lowest yield (35%) is observed for dibromoethane and 4-fluorothiophenol.



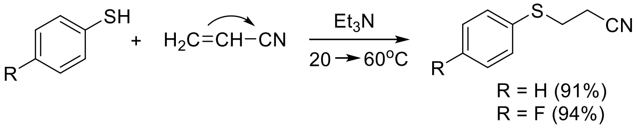
2.3.1.2 Other Methods

(2-Phenylethyl)phenyl sulfide is prepared with 76% yield by the reaction of thiophenol with styrene in the presence of a catalytic amount of Et_3N at room temperature [148].

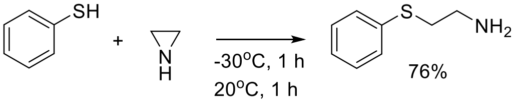


This is a rare example of easy nucleophilic addition of thiols to a weak electrophile, styrene.

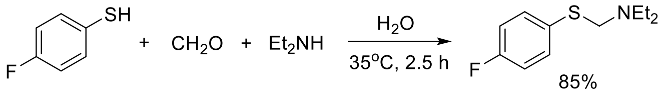
Sulfides with a nitrile group are obtained by nucleophilic addition of aryl thiols to acrylonitrile. Due to the increased electrophilicity of the double bond in acrylonitrile (electron-withdrawing effect of the nitrile group), aryl thiols interact with acrylonitrile even without a catalyst. In the presence of triethylamine, the reaction is accompanied by an exothermic effect and leads to cyanoethylated sulfides with almost quantitative yield [148].



2-Aminoethylphenyl sulfide is synthesized with 92% yield from thiophenol and aziridine by simple mixing of the reactants at − 30 °C.

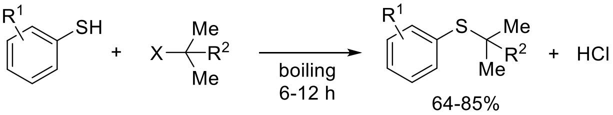


The data on aminomethylation of aryl thiols is almost lacking in the literature. Using 4-fluorothiophenol [148, 151] as an example, it is shown that diethyl amine together with formaldehyde in aqueous media smoothly aminomethylates aryl thiols to form N,N-diethylaminomethyl 4-fluorophenyl sulfide with 85% yield.



2.3.2 *tert*-Alkyl Aryl Sulfides

The method for the synthesis of sulfides by the alkylation of aryl thiols with alkyl halides described in Sect. 2.3.1 is unsuitable for *tert*-alkyl aryl sulfides. It has been established [153] that *tert*-alkyl aryl sulfides are formed upon heating of aryl thiols and *tert*-alkyl halides (50–80 °C, 6–12 h) in the absence of catalysts and solvents, the yield being 64–85%.



R^1 = H, 4-Me, 3-MeO, 4-MeO, 3-F, 4-F, 4-Cl, 4-Br, 4-Ac, 4-NO_2, 2,4,6-Me_3
R^2 = Me, Et; X = Cl, Br

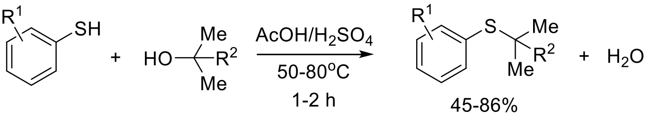
The reaction is realized upon boiling the reactant in an excess haloalkyl and proceeds, apparently, through the intermediate formation of a *tert*-alkyl carbenium ion, which further reacts with aryl thiol, the abstracted proton being bound by a halogen anion.

$$\mathrm{Me_2R^2CX} \rightleftharpoons \mathrm{Me_2R^2C^+} + \mathrm{X^-}$$

$$\mathrm{Me_2R^2C^+} + \mathrm{ArSH} \rightleftharpoons \mathrm{Me_2R^2SAr} + \mathrm{H^+}$$

This reaction opens a route to the development of modern environmentally benign technology for the preparation of previously diffcult to access *tert*-alkyl aryl sulfides, since it requires no catalyst or condensing agent and the released hydrogen halide is a commercial product.

In continuation of this research, a simpler and more convenient method for the synthesis of *tert*-alkyl aryl sulfides from cheap and available raw materials (aryl thiols and tertiary alcohols) in the system AcOH/H_2SO_4 has been elaborated [148].



R^1 = H, 3-Me, 4-Me, 3-MeO, 4-MeO, 3-F, 4-F, 3-Cl, 4-Cl, 4-Br, 4-I, 4-NO_2, 2,4,6-Me_3
R^2 = Me, Et

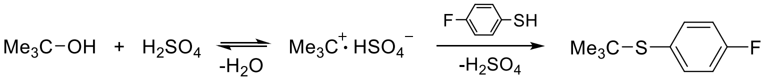
Table 2.2 Alkylation of 4-fluorothiophenol with *tert*-butanol: optimization of the reaction conditions

No	Reactants, mmol			AcOH, ml	Conditions		Yield $4\text{-}FC_6H_4SBu\text{-}t$, %
	$4\text{-}FC_6H_4SH$	*t*-BuOH	H_2SO_4		T, °C	t, h	
1	25	50	25	20	20	2	27
2	50	100	50	25	20	24	74
3	25	50	25	20	50	2	74
4	25	50	25	20	80	2	86
5	25	50	12.5	20	80	2	82
6	25	50	6.25	20	80	2	77
7	25	50	2.5	20	80	2	74
8	12.5	25	0	10	80	2	0
9	25	50	25	20	80	1	83
10	25	37.5	25	20	80	2	84
11	25	25	25	20	80	2	78

The conditions for the synthesis of *tert*-alkyl aryl sulfides have been optimized using the interaction of 4-fluorothiophenol with *t*-BuOH (Table 2.2).

Under the action of sulfuric acid, *t*-BuOH reacts with 4-fluorothiophenol to afford *tert*-butyl-4-fluorophenyl sulfide even at room temperature. However, a longer time (24 h) is required for complete conversion of the thiol. A similar result is attained in 2 h by heating the reactants at 50 °C (Table 2.2, entries 1–3). The highest yield of the sulfide (86%) is reached upon heating 4-fluorothiophenol: *t*-BuOH: H_2SO_4 in a molar ratio of 1:2:1 at 80 °C for 2 h.

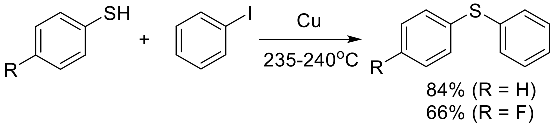
In this case, the mechanism has also a carbocationic character: the *tert*-butyl carbocation, generated owing to the elimination of the hydroxide anion from *t*-BuOH, further substitutes the proton in thiophenol.



The method developed allows synthesizing *tert*-alkyl aryl sulfides with 76–86% yields.

2.3.3 Diaryl Sulfides

Diphenyl and phenyl 4-fluorophenyl sulfides are obtained by the cross-coupling of the corresponding aryl thiols with iodobenzene in the presence of copper bronze at 235–240 °C with 84 and 66% yields, respectively.

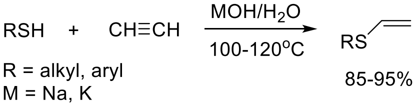


In the light of systematic studies [154–157] indicating an extremely strong increase in the nucleophilicity of *O*- and *S*-centered anions in superbasic systems such as MOH (M = Li, Na, K, Cs)/DMSO, there is reason to believe that the cross-coupling of aryl thiols with halobenzenes, i.e. the classic Ulman reaction, will be realized in these catalytic systems even at a much lower temperature.

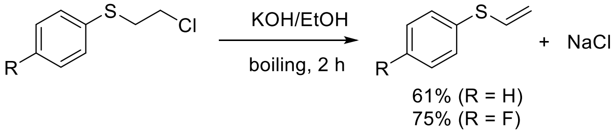
2.3.4 Vinyl Sulfides

Unsaturated sulfides possess a plethora of valuable properties and are intensively studied as promising monomers, comonomers, and building blocks for organic synthesis [6, 158, 159]. Therefore, the search for and development of new convenient approaches to their synthesis represent a challenge.

The nucleophilic addition of alkyl and aryl thiols to acetylenes proceeds easier than the addition of alcohols, which is explained by a higher nucleophilicity of thiols. A new expeditious "green" method for the preparation of vinyl organyl sulfides has been developed. The method comprises the reaction of acetylene with alkali metal thiolates (obtained in situ from thiols and alkali metal hydroxides in water) [80, 82]. The reaction easily occurs upon heating the thiols and 2–3 equivalents of NaOH or KOH in water (100–120 °C, 2–3 h) with acetylene under pressure. The yields of the target products are 85–95%.

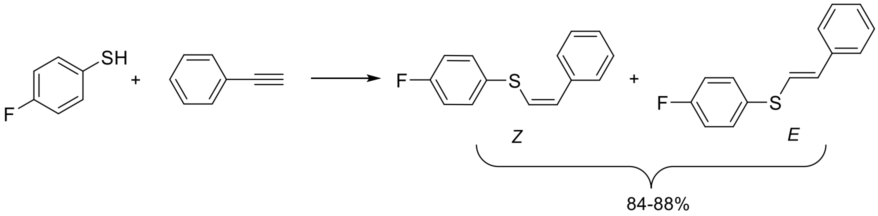


Apart from a general method for the synthesis of vinyl sulfides via direct vinylation of thiols with acetylene, dehydrochlorination of 2-chloroethyl aryl sulfides can be employed for the preparation of some representatives of aryl vinyl sulfides [151]. Vinyl phenyl and vinyl 4-fluorophenyl sulfides are produced by dehydrochlorination of the corresponding aryl 2-chloroethyl sulfides upon boiling in EtOH in the presence of KOH with 61 and 75% yields, respectively.



The reactions of the nucleophilic addition of alkyl thiols to arylacetylenes in the Cs_2CO_3 (10 mol%)/DMSO system proceed at room temperature leading to the corresponding alkyl alkenyl sulfides with good yields and high *Z*-selectivity [160]. Similar reactions with aryl thiols require harsher conditions, namely: the KOH (100 mol%)/DMSO, 120 °C, 4 h [81]. In both cases, the thiol adds against the Markovnikov rule and in accordance with the *trans*-nucleophilic addition rule [77].

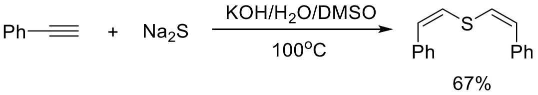
Radical addition of aryl thiols to phenylacetylene in the absence of catalysts, in contrast to alkylthiols, takes place at room and lower temperatures [161]. The *Z*- and *E*-2-styryl 4-fluorophenyl sulfides are synthesized by free radical addition of 4-fluorothiophenol to phenylacetylene. The reaction proceeds upon mixing the reactants without a catalyst and solvent and is accompanied by the exothermic effect. As a result, 2-styryl 4-fluorophenyl sulfide is formed with 84–88% yield as a mixture of two isomers, the ratio of which is determined by the temperature mode of the reaction [151].



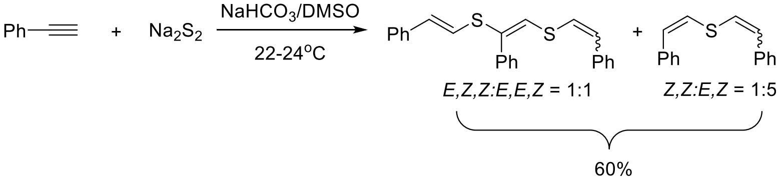
According to ^{1}H NMR data, at room temperature, an adduct enriched by a kinetically controlled *Z*-isomer (Z:E = 70:30) is formed, while at 70 °C the *E*-adduct prevails (Z:E = 20:80).

The reactions of acetylenes with sulfide-anions and sulfur open up new possibilities for the synthesis of substituted divinyl sulfides.

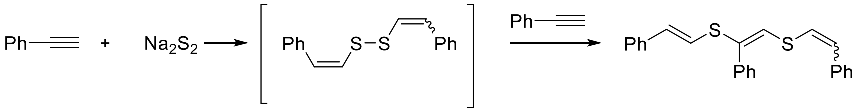
Phenylacetylene easily reacts with hydrated sodium sulfide in the KOH/DMSO system (100 °C) to furnish *Z,Z*-di(2-phenylvinyl) sulfide (yield 67%) [162].



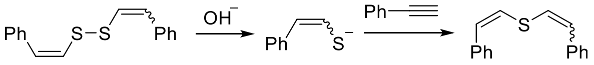
The reaction of arylacetylenes with alkali metal disulfides ensures a facile route to polyunsaturated compounds with two sulfide sulfur atoms. In the system NaHCO$_3$/DMSO, phenylacetylene reacts with sodium disulfide (room temperature, 20 h) giving 1,2-di(2-phenylethenylthio)-1-phenylethene and di(2-phenylethenyl) sulfide in a ratio of ~ 1: 6 with a total yield of 60% [163].



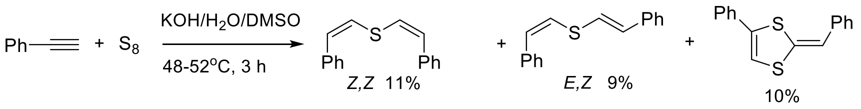
Apparently, the reaction proceeds through the formation of di(2-phenylethenyl) disulfide, across the S–S bond of which the third molecule of phenylacetylene is introduced (according to the known scheme of diganyl disulfides cleavage with acetylenes [164], which leads to the formation of 1,2-di(2-phenylethenyl)-1-phenylethene.



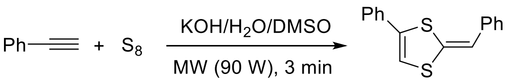
Alkali cleavage of disulfide across the S–S bond and further interaction of the intermediate styrylsulfide anions with phenylacetylene affords di(2-phenylethenyl) sulfide. An increase in the basicity of the medium (performance of the reaction without $NaHCO_3$) promotes such direction of the process: the yield of di (2-phenylethenyl) sulfide augments to 80%, whereas 1,2-di(2-phenylethenylthio)-1-phenylethene is formed only in the trace amounts.



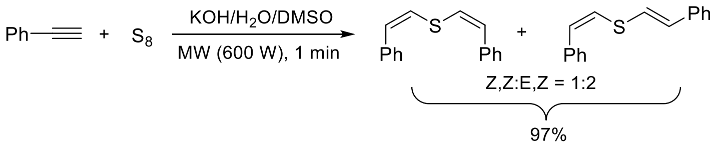
Sulfurization of phenylacetylene with elemental sulfur in the system KOH/DMSO (48–52 °C, 3 h) results in the *E*,*Z*- and *Z*,*Z*-isomers of distyryl sulfide and 4-phenyl-2-[(*Z*)-phenylmethylidene]-1,3-dithiol with 9, 11, and 10% yields, respectively [165].



The use of microwave assistance in this reaction allows its selectivity and efficiency to be controlled. Microwave irradiation (90 W, 2 min) of a mixture, containing elemental sulfur, phenylacetylene, KOH, and H_2O in DMSO, chemoselectively gives 4-phenyl-2-[(*Z*)-phenylmethylidene]-1,3-dithiol, the yield being 100% at 10% conversion of phenylacetylene (GLC data).

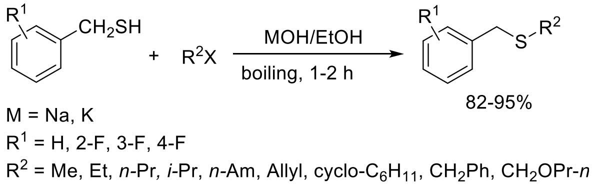


Under the action of microwave irradiation (600 W), *Z*,*Z*- and *E*,*Z*-di (2-vinylphenyl) sulfides are formed for 1 min in a 1: 2 ratio (^{1}H NMR data), the total yield is 97% based on the reacted phenylacetylene (conversion of the latter is 65%).



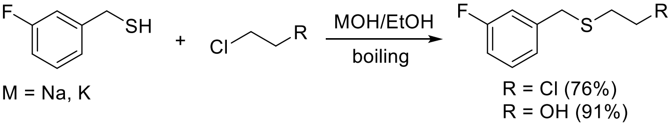
2.3.5 Benzyl Thiols and Benzyl Sulfides

The reaction of benzyl- and fluorine-substituted benzyl thiols with primary and secondary alkyl halides in an alcohol solution of alkali metal hydroxides delivers alkyl benzyl sulfides with a yield of 82–95% (Table 2.3) [148, 166].

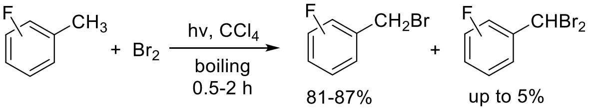


M = Na, K
R^1 = H, 2-F, 3-F, 4-F
R^2 = Me, Et, *n*-Pr, *i*-Pr, *n*-Am, Allyl, cyclo-C_6H_{11}, CH_2Ph, CH_2OPr-*n*

Benzyl thiols interact with functional alkyl halides, for example, dichloroethane and ethylene chlorohydrin, in a similar manner.



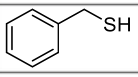
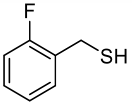
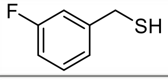
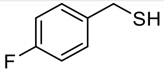
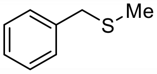
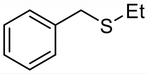
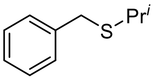
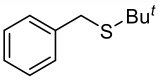
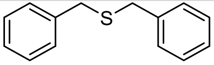
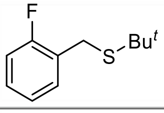
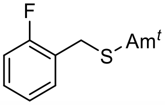
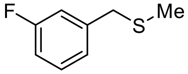
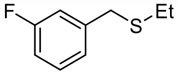
Fluoro-substituted benzyl thiols are synthesized from the corresponding fluorotoluenes in two stages. Initially, bromination of fluorotoluenes with bromine in the light (boiling in CCl_4, 0.5–2 h) gives fluorobenzyl bromides (yield 81–87%) (Table 2.4) [167].



Under these conditions, monobromination proceeds with high selectivity, the yield of dibromo derivatives does not exceed 5% [148].

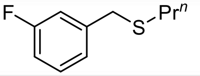
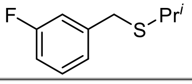
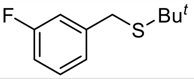
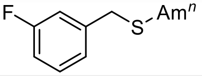
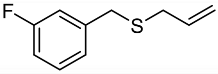
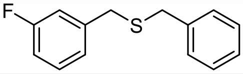
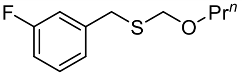
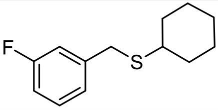
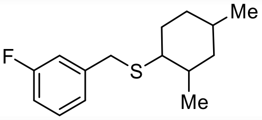
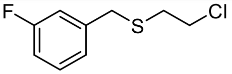
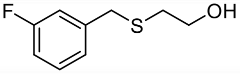
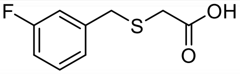
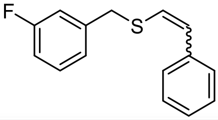
Alkylation of thiourea (EtOH, boiling, 6 h) with the benzyl bromides and the subsequent hydrolysis of thiouronium salt (5 N NaOH, 60 °C, 2 h) [167] furnishes benzyl thiols with 66–82% yields.

Table 2.3 Substituted benzyl thiols and sulfides on their basis

No.	Structure	Yield, %	B.p., °C /torr (m.p., °C)	n_D^{20}	d_4^{20}
1	2	3	4	5	6
1		64	65/4	1.5757	1.0544
2		66	79/11	1.5535	1.1709
3		75	78/10	1.5460	1.1630
4		82	51/1	1.5439	1.1532
5		83	90-91/12	1.5630	1.0274
6		83	81/3	1.5510	0.9826
7		84	86/3	1.5588	0.9690
8		45	81/2	1.5302	0.9626
9		85	(49)		
10		78	90/3	1.5225	1.0414
11		55	123/4	1.5240	1.0352
12		95	66/2	1.5382	1.1249
13		90	75/3	1.5302	1.0931

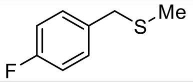
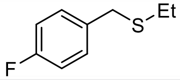
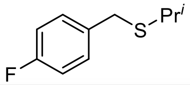
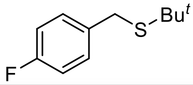
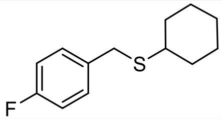
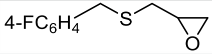
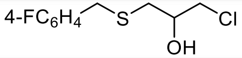
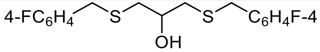
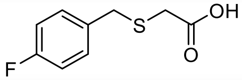
(continued)

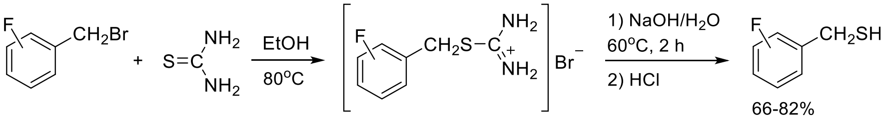
Table 2.3 (continued)

14		90	88/2	1.5238	1.0653
15		91	90/3	1.5210	1.0448
16		78	76/2	1.5148	1.0364
17		88	104/3	1.5160	1.0325
18		89	95/3	1.5780	1.1765
19		87	155/17	1.5180	1.1286
20		83	45/2	1.5450	1.1592
21		85	52/1	1.5462	1.1210
22		78	147/1	1.5706	1.1332
23		76	106/3	1.5502	1.2170
24		91	145/4	1.5536	1.2019
25		86	160/3	1.5400	1.2500
26		96	(22)		

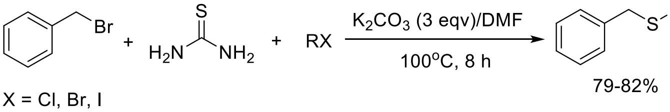
(continued)

Table 2.3 (continued)

27		83	78/6	1.5358	1.1211
28		90	82/3	1.5280	1.0848
29		91	76/1	1.5168	1.0533
30		80	64/1	1.5496	1.1048
31		86	133/1	1.5419	1.0956
32		31	122/1	1.5472	1.1936
33		40	205/1	1.5793	1.2493
34		26	232/1	1.5813	1.2482
35		86	160/3 (48)		



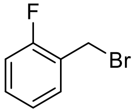
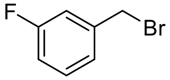
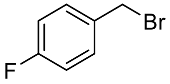
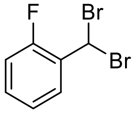
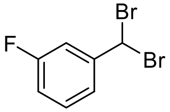
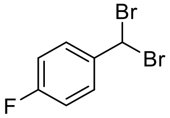
Recently [168], a one-step efficient method for the synthesis of alkyl benzyl sulfides from benzyl bromides, thiourea, and alkyl halides has been elaborated. The reaction takes place in DMF (100 °C, 8 h) in the presence of K_2CO_3 and leads to alkyl benzyl sulfides with a yield of 79–92%.



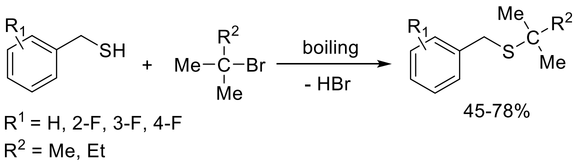
X = Cl, Br, I

R = *i*-Bu, *s*-Bu, *i*-Am, *n*-C_6H_{13}, *n*-C_8H_{17}, *n*-$C_{12}H_{25}$, cyclo-C_5H_9, cyclo-C_6H_{11}

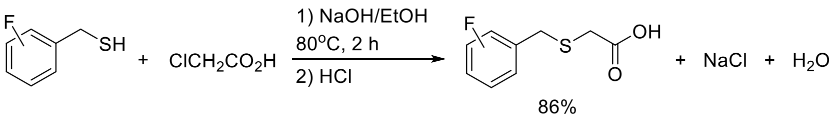
Table 2.4 Fluoro-substituted benzyl bromides

No.	Structure	Yield, %	B.p., °C / torr	n_D^{20}	d_4^{20}
1	2	3	4	5	6
1		82	75/6	1.5594	1.5954
2		81	66/3	1.5520	1.5414
3		87	64/1	1.5520	1.5790
4		4	95/6	1.5900	1.8916
5		4	88/3	1.5851	1.8998
6		5	83/1	1.5894	1.9118

Tertiary alkyl benzyl sulfides are obtained by alkylation of benzyl thiols with *tert*-alkyl bromides without catalysts and condensing agents [166] (Table 2.4).

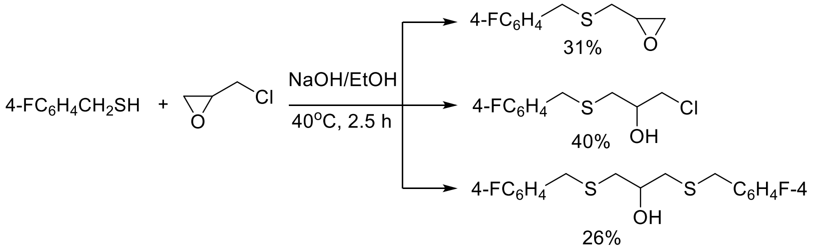


Chloroacetic acid is used as an alkylating agent of 3- and 4-fluorobenzyl thiols. Alkylation proceeds very easily upon boiling the reactants in an alcohol solution of NaOH. After neutralization of the sodium salt with a solution of HCl, the functionalized benzyl sulfides are formed with 86% yield.



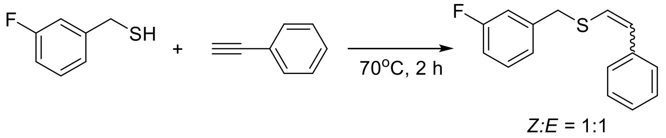
The active carboxyl group provides additional possibilities for further functionalization of benzyl sulfides.

Using 4-fluorobenzyl thiol as an example, it has been shown that interaction with epichlorohydrin in the presence of an equimolar amount of NaOH (40 °C, 2.5 h) occurs in the following directions:



The products of chlorine atom substitution and those of the epoxy ring opening are easily separated by fractional distillation [148]. The ratio of products depends on the amount of alkali in the reaction medium.

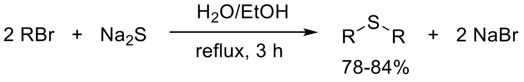
3-Fluorobenzyl thiol is easily added to phenylacetylene via a radical mechanism without a catalyst to produce anti-Markovnikov *Z*- and *E*-adducts with a quantitative yield. The reaction proceeds with an exothermic effect.



2.3.6 Dialkyl Sulfides

To compare the peculiarities of the C_{sp2}–S–C_{sp2}, C_{sp2}–C_{sp3}, and C_{sp3}–S–C_{sp3} bonds formation, it is pertinent to discuss briefly the conditions of dialkyl sulfides synthesis. Table 2.5 shows the yields and physical–chemical characteristics of symmetric and asymmetric dialkyl sulfides, synthesized by the classical approaches.

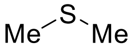
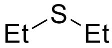
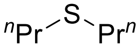
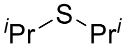
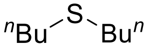
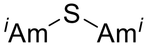
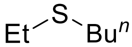
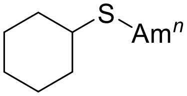
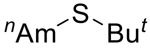
Symmetrical dialkyl sulfides are obtained by the interaction of alkyl halides with sodium sulfide in a water–alcohol solution.



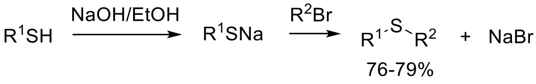
$$2\,RBr + Na_2S \xrightarrow[\text{reflux, 3 h}]{H_2O/EtOH} R{-}S{-}R + 2\,NaBr \quad 78\text{-}84\%$$

R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Am

Table 2.5 Dialkyl sulfides

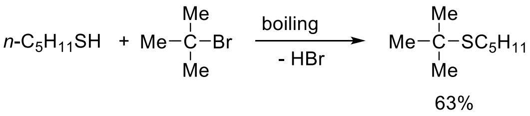
No.	Structure	Yield, %	B.p., °C /torr	n_D^{20}	d_4^{20}
1		80	37-38	1.4352	0.8486
2		78	92-93	1.4435	0.8366
3		82	142-143	1.4480	0.8365
4		83	120-121	1.4385	0.8142
5		84	62/7	1.4506	0.8390
6		72	80/6	1.4518	0.8325
7		76	143-144	1.4495	0.8382
8		79	110/6	1.4857	0.9081
9		63	49/3	1.4546	0.8290

Nonsymmetrical dialkyl sulfides are synthesized from alkyl halides and sodium thiolates in ethanol solution.

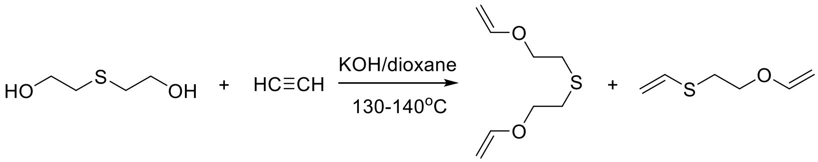


R^1 = *n*-Bu, *n*-Am; R^2 = Et, cyclo-C_6H_{11}

Amyl *tert*-butyl sulfide is prepared with 63% yield according to the original procedure [153] by boiling pentanethiol with *tert*-butyl bromide without a catalyst and condensing agents.

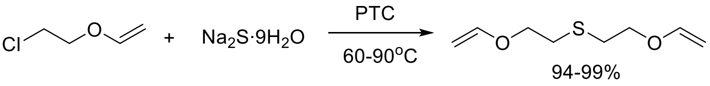


Di(2-vinyloxyethyl) sulfide (23% yield) is obtained by direct vinylation of bis (2-hydroxyethyl) sulfide (thiodiglycol) with acetylene (10 mol% KOH, 130–140 °C) [169].



The vinylation of thiodiglycol is accompanied by cleavage of the C–S bond [169, 170] and/or elimination of vinyl alcohol from di(2-vinyloxyethyl) sulfide that leads to the formation of abnormal products (up to 50%), mercaptoethanol, and its vinyl ethers.

Under the conditions of phase-transfer catalysis (PTC), di-(2-vinyloxyethyl) sulfide is synthesized from vinyl-2-chloroethyl ether and sodium sulfide with a yield close to quantitative (94–99%) [171].



PTC = TEBAC, catamine AB, dibenzo-18-crown-6

These examples confirm a higher easiness of the C_{sp3}–S–C_{sp3} bond formation as compared to the C_{sp2}–S bond during the nucleophilic substitution of a halogen atom by sulfide or alkylthiolate anions.

2.4 Examples of Syntheses

2.4.1 Reactions of Thiols with Primary and Secondary Alkyl Halides

2-((4-Fluorophenyl)thio)ethan-1-ol (No. 77, Table 2.1). To a solution of 4-fluorothiophenol (12.8 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in EtOH (25 mL) heated to 80 °C, ethylene chlorohydrin (8.5 g, 0.1 mol) was added dropwise (~ 30 min) and the mixture was refluxed for 1.5 h upon vigorous stirring. Then ethanol was distilled off, the residue was diluted with water (25 mL) and extracted with benzene (3 × 25 mL). The extract was washed with a saturated solution of $NaHCO_3$, dried over $CaCl_2$, and the solvent was removed. Distillation in vacuum gave 13.20 g (77%) of sulfide, b.p. 116 °C/3 torr, n_D^{20} 1.5618, d_4^{20} 1.2374.

Alkyl aryl sulfides No. 1–7, 9, 10, 12–17, 19, 21, 22, 24, 35, 36, 38–40, 42–48, 50–52, 54–57, 59–64, 66 67, 69–74, 76, 82 (Table 2.1) were obtained analogously.

(2-Chloroethyl)(4-fluorophenyl)sulfide (No. 78, Table 2.1). To a solution of 4-fluorothiophenol (12.82 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in ethanol (25 mL), 1,2-dichloroethane (19.79 g, 0.2 mol) was poured and the reaction mixture was stirred at 70 °C for 4 h. Then ethanol and excess dichloroethane were distilled off, and the residue was extracted with benzene (4 × 25 mL). The extract was washed with an aqueous solution of $NaHCO_3$ and dried over $CaCl_2$. Fractionation gave 13.21 g (70%) of sulfide, b.p. 103 °C/3 torr, n_D^{20} 1.5560, d_4^{20} 1.2598 and 2.58 g (18%) of 1,2-bis-((4-fluorophenyl)thio)ethane, b.p. 129 °C/6 torr, m.p. 72 °C (No. 86, Table 2.1).

Sulfides No. 25–29, 32–34, 79 (Table 2.1) were obtained analogously.

Bis((4-(fluorophenyl)thio)methane (No. 85, Table 2.1). To a solution of 4-fluorothiophenol (12.8 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in ethanol (30 mL), CH_2I_2 (13.4 g, 0.05 mol) was added dropwise at 80 °C for 30 min, and the mixture was stirred for 1.5 h. Then ethanol was distilled off and the residue was extracted with benzene (4 × 25 mL). The extract was washed with an aqueous solution of $NaHCO_3$ and dried over $CaCl_2$. Fractionation gave 11.1 g (82%) of product, b.p. 156 °C/2.5 torr, n_D^{20} 1.6066, d_4^{20} 1.12943.

Di(phenylthio)methane No. 31 (Table 2.1) was obtained analogously.

(4-Chlorophenyl)(dodecyl) sulfide (No. 101, Table 2.1). To a mixture of 4-chlorothiophenol (14.5 g, 0.1 mol) and 20% alcohol solution of NaOH (4.0 g, 0.1 mol), dodecyl bromide (24.7 g, 0.1 mol) was added dropwise at 80 °C. The reaction mixture was stirred for 2 h at the same temperature, the reaction product was extracted with benzene, washed with a solution of $NaHCO_3$ and water up to neutral pH, and then dried over $CaCl_2$. After removal of benzene, the product was distilled in vacuum to give 27.4 g (88%) of sulfide, b.p. 198 °C/2 torr, m.p. 41 °C.

Sulfides No. 88–93, 95–101, 103–109, 111–117, 121–123, 126–128 (Table 2.2), 7, 8 (Table 2.5) were obtained analogously.

(3-Fluorobenzyl)(methyl)sulfide (No. 12, Table 2.3). In a three-necked flask equipped with a stirrer, dropping funnel, reflux condenser, and thermometer, 3-fluorobenzylthiol (10.6 g, 0.075 mol) and a solution of KOH (4.2 g, 0.075 mol) in ethanol (50 mL) were placed. Then CH_3I (12.2 g, 0.1 mol) was added dropwise to the reaction mixture upon vigorous stirring at 40 °C for 30 min. Stirring was continued for another 1.5–2 h at the same temperature. Ethanol was distilled off from the reaction mixture, the residue was diluted with water (50 mL) and extracted with benzene (3 × 50 mL). The benzene was removed and distillation of the residue in vacuum gave 11.0 g (95%) of sulfide, b.p. 66 °C/2 torr, n_D^{20} 1.5382, d_4^{20} 1.1249.

Compounds No. 5–7, 9, 13–15, 17–24, 27–29, 31 (Table 2.3) were obtained analogously.

(Methyl)(4-phenoxyphenyl)sulfide (No. 54, Table 2.1). To a solution of 4-phenoxyphenyl magnesium bromide, obtained from Mg (0.2 g-atom) and 4-phenoxybromobenzene (0.2 mol) in dry diethyl ether (600 mL), finely powdered sulfur (6.4 g, 0.2 mol) was added. Afterwards, the mixture was boiled for 1 h and cooled. Then methyl iodide (28.4 g, 0.2 mol) was added, and the mixture was boiled for 10 h, cooled and NH_4Cl solution was added upon stirring. The ether solution was separated, washed three times with 10% NaOH solution, then with water until neutral pH, and dried over Na_2SO_4. After removing the ether, the residue was distilled in vacuum to give 15.7 g (36%) of sulfide, b.p. 154–155 °C/3 torr, n_D^{20} 1.6176, d_4^{20} 1.1692.

Diisoamylsulfide (No. 6, Table 2.5). In a three-necked flask equipped with a reflux condenser, dropping funnel, and stirrer, $Na_2S \cdot 9H_2O$ (360 g, 1.5 mol) was dissolved in EtOH (250 mL) and isoamyl bromide (302 g, 2 mol) was slowly added to the mixture upon vigorous stirring. After the completion of a strongly exothermic reaction, the mixture was heated for another 3 h under reflux, and then diisoamylsulfide was distilled off with water vapor. The organic layer was separated, washed with water, 10% NaOH solution, again with water, dried over $CaCl_2$, and distilled over Na to give 124.9 g (72%) of sulfide, b.p. 80 °C/6 torr, n_D^{20} 1.4518, d_4^{20} 0.8325.

Dialkyl sulfides No. 1–5 (Table 2.5) were obtained analogously.

2.4.2 Reactions of Thiols with Tertiary Alkyl Halides and Alcohols

***tert*-Butylphenylsulfide** (No. 8, Table 2.1) a) A mixture of thiophenol (11.0 g, 0.1 mol) and *tert*-butyl chloride (18.6 g, 0.2 mol) was refluxed for 12 h, and after cooling it was diluted with benzene (100 mL), washed with 5% NaOH solution (4 × 50 mL), dried over $CaCl_2$, the solvent was evaporated and the residue was distilled in vacuum to give 8.9 g (54%) of sulfide, b.p. 55–56 °C/2 torr, n_D^{20} 1.5320, d_4^{20} 0.9658.

tert-Butyl(2,4,6-trimethylphenyl)sulfide (No. 127, Table 2.1) was obtained analogously.

b) To a mixture of thiophenol (11.0 g, 0.1 mol) and *ter*t-butyl alcohol (14.8 g, 0.2 mol) in glacial acetic acid (50 mL), concentrated H2SO$_4$ (9.8 g, 0.1 mol) was added dropwise at 18–20 °C. The reaction mixture was stirred vigorously for 2 h at room temperature and then was allowed to stand for 24 h. Afterwards the mixture was poured into water (200 mL) and extracted with ether (3 × 80 mL). The extract was washed with 5% NaOH solution (3 × 50 mL), with water until neutral pH, dried over $CaCl_2$, the ether was evaporated, and the residue was distilled in vacuum to give 12.6 g (76%) of sulfide.

***tert*-Butyl(4-methylphenyl)sulfide** (No. 41, Table 2.1). A mixture of 4-methylthiophenol (12.4 g, 0.1 mol) and *tert*-butyl bromide (27.4 g, 0.2 mol) was heated at 75–80 °C for 12 h. Then the light fractions were distilled off in a water-jet pump under vacuum, the residue was distilled in vacuum to give 16.1 g (89%) of sulfide, b.p. 84 °C/3.5 torr, n_D^{20} 1.5300, d_4^{20} 0.9507.

***tert*-Butyl(4-fluorophenyl)sulfide** (No. 65, Table 2.1) a) A mixture of 4-fluorothiophenol (12.8 g, 0.1 mol) and *tert*-butyl bromide (13.7 g, 0.1 mol) was heated at 75–80 °C for 6 h. Afterwards additional portion of *tert*-butyl bromide

(13.7 g, 0.1 mol) was added and heating was continued (75–80° C, 6 h). Then the reaction mixture was diluted with benzene (100 mL), washed with 5% NaOH solution (4 × 50 mL), dried over $CaCl_2$, the solvent was removed, and the residue was distilled in vacuum to give 11.9 g (65%) of sulfide, b.p. 66 °C/4 torr, n_D^{20} 1.5122, d_4^0 1.0380.

b) To a mixture of 4-fluorothiophenol (3.2 g, 0.025 mol) and *tert*-butyl alcohol (3.7 g, 0.05 mol) in glacial acetic acid (20 mL), concentrated H_2SO_4 (2.45 g, 0.025 mol) was added dropwise upon stirring at 80 °C. After 2 h, the mixture was diluted with water (100 mL) and extracted with benzene (3 × 50 mL), washed with 5% NaOH solution (3 × 50 mL), then with water until neutral pH and dried over $CaCl_2$, benzene was evaporated, and the residue was distilled in vacuum to give 3.93 g (85%) of sulfide.

***tert*-Butyl(4-chlorophenyl)sulfide** (No. 94, Table 2.1). A mixture of 4-chlorothiophenol (14.5 g, 0.1 mol) and *tert*-butyl bromide (27.4 g, 0.2 mol) was heated at 75–85 °C for 12 h. Then the reaction mixture was cooled, diluted with benzene, and filtered through a layer of anion exchange resin (AN-2F or AB-16). The filtrate was evaporated, and the residue was distilled in vacuum to give 17.4 g (85%) of sulfide, b.p. 88 °C/3 torr, n_D^{20} 1.5475, d_4^{20} 1.0845.

tert-Alkyl aryl sulfides No. 11, 37, 49, 53, 58, 68, 110, 118, 119, 124 (Table 2.1), *tert*-alkyl benzyl sulfides No. 8, 10, 16, 30 (Table 2.3), and amyl *tert*-butyl sulfide No. 9 (Table 2.5) were obtained analogously.

***tert*-Butyl(3-fluorobenzyl)sulfide** (No. 16, Table 2.3). A mixture of 3-fluorobenzylthiol (14.2 g, 0.1 mol) and *tert*-butyl bromide (13.7 g, 0.1 mol) was heated under reflux closed with a calcium chloride tube at 75–80 °C for 6 h. After the addition of *tert*-butyl bromide (13.7 g, 0.1 mol), the solution was boiled until the termination of the HBr release. Then the reaction mixture was diluted with benzene (100 mL), washed with 5% NaOH solution (3 × 50 mL), dried over $CaCl_2$, the solvent was removed, and the residue was distilled in vacuum to give 15.5 g (78%) of sulfide, b.p. 76 °C/2 torr, n_D^{20} 1.5148, d_4^{20} 1.0364.

Compounds No. 10, 11, 30 (Table 2.3) were obtained similarly.

2.4.3 Reactions of Thiols with Alkenes

(2-Cyanoethyl)(4-fluorophenyl)sulfide (No. 80, Table 2.1) To a mixture of 4-fluorothiophenol (12.8 g, 0.1 mol) and triethylamine (0.1 g), freshly distilled acrylonitrile (5.3 g, 0.1 mol) was added dropwise upon vigorous stirring at such a rate that the temperature of the reaction mixture did not exceed 60 °C. After mixing the reactants, the mixture was stirred for 1.5 h at 60 °C, then it was diluted with benzene (20 mL), and washed with water. The benzene solution was dried over $CaCl_2$, the benzene was removed, and the residue was distilled in vacuum to give 17.0 g (94%) of sulfide, b.p. 137 °C/3 torr, n_D^{20} 1.5493, d_4^{20} 1.2014.

(2-Cyanoethyl)phenylsulfide (No. 30, Table 2.1) was obtained similarly.

Phenyl(2-phenylethyl)sulfide (No. 22, Table 2.1) To a mixture of styrene (10.4 g, 0.1 mol) and Et_3N (0.5 g), cooled to 0 °C, thiophenol (13.2 g, 0.12 mol) was added dropwise under vigorous stirring at such a rate that the temperature of the reaction mixture did not exceed 20 °C. After mixing the reactants, the mixture was kept for 0.5 h at room temperature, diluted with benzene (50 mL), washed with 5% NaOH solution (4 × 50 ml) and water until neutral pH, dried over Na_2SO_4, benzene was removed, and the residue was distilled in vacuum to give 16.3 g (76%) of sulfide, b.p. 156 °C/2 torr, n_D^{20} 1.6098, d_4^{20} 1.0826.

2.4.4 Reactions of Thiols with Acetylenes

Phenylvinylsulfide (No. 18, Table 2.1) A mixture, obtained by stirring of thiophenol (30.0 g, 0.27 mol) in a solution of KOH (30.2 g, 0.54 mol) in water (100 mL) at room temperature (1 h), was placed in a 1-L autoclave, acetylene was fed (initial pressure 12 atm) and the mixture was heated at 100 °C for 3 h. After completion of the reaction, the organic layer was separated from the reaction mixture. Distillation in vacuum gave 34.2 g (93%) of vinyl phenyl sulfide, b.p. 49 °C/2 torr, n_D^{20} 1.5891.

(4-Fluorophenyl)vinylsulfide (No. 75, Table 2.1) A mixture of KOH (5.6 g, 0.1 mol) and -chloroethyl-4-fluorophenyl sulfide (9.53 g, 0.05 mol) (No. 78, Table 2.1) in ethanol (100 mL) was stirred for 2 h upon boiling of the solvent, then the ethanol was removed and benzene (100 mL) was added. The mixture was carefully grinded, the residue was filtered off, and benzene was removed. Distillation of the residue in vacuum gave 5.80 g (75%) of sulfide, b.p. 66 °C/6 torr, n_D^{20} 1.5574, d_4^{20} 1.1388.

(4-Fluorophenyl)(styryl)sulfide (No. 82, 83, Table 2.1) a) Phenylacetylene (40.8 g, 0.4 mol) was added to 4-fluorothiophenol (12.8 g, 0.1 mol). After mixing the reactants, the mixture was heated to 70 °C due to the exothermic effect. Then the reaction mixture was stirred at the same temperature for another 2 h, cooled, diluted with benzene (60 mL), washed with 20% aqueous solution of NaOH, dried over $CaCl_2$, the solvent was evaporated, the residue was distilled in vacuum to give 19.4 g (84%) of sulfide (according to ^1H NMR data, a mixture of *Z*- and *E*-isomers, 20:80, was formed), b.p. 160–165 °C/4 torr, m.p. 25–26 °C.

b) 4-Fluorothiophenol (12.8 g, 0.1 mol) was added dropwise to phenylacetylene (40.8 g, 0.4 mol) for 1 h, maintaining the temperature at 10 °C by external cooling. The mixture was stirred for another 1 h at room temperature and treated as shown above to obtain 20.2 g (88%) of sulfide (according to ^1H NMR data, a mixture of *Z*- and *E*-isomers, 70:30, was formed), b.p. 160–164 °C/4 torr, n_D^{20} 1.6471, d_4^{20} 1.1761.

(3-Fluorobenzyl(styryl)sulfide (No. 26, Table 2.3) 3-fluorobenzylthiol (10.6 g, 0.075 mol) was added dropwise to phenylacetylene (51.0 g, 0.5 mol) upon stirring at room temperature for 30 min. Then the mixture was stirred at 20 °C for another 1 h. The mixture was heated for 2 h at 70 °C. After cooling, the mixture was diluted with benzene (100 mL), washed with 5% aqueous solution of NaOH, dried over $CaCl_2$, and the solvent was removed. Chromatography of the residue on an

Al_2O_3 column (eluent: hexane/ether, 9: 1) gave 11.7 g (96%) of sulfide (according to ^{1}H NMR data, a mixture of *Z*- and *E*-isomers ~ 1: 1, was formed), m.p. 22 °C.

2.4.5 Diaryl Sulfides

(4-Fluorophenyl)(phenyl)sulfide (No. 81, Table 2) To a solution of sodium ethylate, prepared from Na (2.3 g, 0.1 mol) and absolute EtOH (7 mL), 4-fluorothiophenol (12.82 g, 0.1 mol) was added. The reaction mixture was stirred for 30 min, then the ethanol was removed, copper bronze (0.2 g) and iodobenzene (20.4 g, 0.1 mol) were added. The mixture was heated at 235–240 °C for 2.5 h. After cooling, the mixture was diluted with ethanol (20 mL), Zn dust (~ 1 g) was added, the mixture was acidified with 20% H_2SO_4 and excess iodobenzene was removed with water vapor. The residue was filtered, extracted with ether (2 × 50 mL), dried over $CaCl_2$, the ether is removed. Vacuum distillation gave 13.5 g (66%) of sulfide, b.p. 107 °C/2 torr, n_D^{20} 1.6058, d_4^{20} 1.1847.

Diphenyl sulfide (No. 20, Table 2.1) was obtained similarly.

2.4.6 Functionally Substituted Alkyl Aryl Sulfides

1-((4-Ffluorophenyl)thio)-N,N-diethylmethanamine (No. 87, Table 2.1) To a mixture of diethylamine (7.3 g, 0.1 mol) and 40% formalin (7.5 g, 0.1 mol), 4-fluorothiophenol (12.8 g, 0.1 mol) was added dropwise at 20 °C for 30 min. Then the temperature was raised to 35 °C and the reaction mixture was continued to stir for another 2.5 h. The reaction mixture was further diluted with ether (75 mL), the ether layer was washed five times with water, the ether was removed, and the residue was distilled in vacuum to give 18.3 g (85%) of product, b.p. 99 °C/2 torr, n_D^{20} 1.5325, d_4^{20} 1.0660.

2-(Phenylthio)ethan-1-amine (No. 23, Table 2.1) Freshly distilled ethyleneimine (4.3 g, 0.1 mol) was added dropwise to thiophenol (11.0 g, 0.1 mol) at –30° C for ~ 0.5 h, and the reaction mixture was stirred for 1 h at the same temperature. Afterwards the external cooling was stopped and the reaction mixture was kept at room temperature for another 1 h. The product obtained was distilled in vacuum over NaOH to give 14.1 g (92%) of product, b.p. 120 °C/6 torr, n_D^{20} 1.5927, d_4^{20} 1.0929.

Reactions of 4-fluorobenzylthiol with epichlorohydrin (No. 32–34, Table 2.3) In a three-necked flask, equipped with a stirrer, dropping funnel, reflux condenser, and thermometer, 4-fluorobenzylthiol (14.2 g, 0.1 mol) and a solution of NaOH (4.0 g, 0.1 mol) in ethanol (50 mL) was placed. Then epichlorohydrin (9.25 g, 0.1 mol) was added dropwise to the reaction mixture upon vigorous stirring at 40 ° C for 0.5 h. The stirring was continued for another 1.5–2 h at the same temperature. Ethanol was removed from the reaction mixture, the residue was diluted with water (50 mL) and extracted with benzene (3 × 50 mL). The benzene was removed and the residue was distilled in vacuum to give 6.1 g (31%) of 2-(((4-fluorophenyl)thio) methyl)oxirane (No. 32), b.p. 122 °C/1 torr, n^{20} 1.5472, d_4^{20} 1.1936; 9.3 g (40%) of 1-chloro-3-((4-fluorobenzyl)thio)propan-2-ol (No. 33), b.p. 205 °C/1 torr, n_D^{20} 1.5793, d_4^{20} 1.2493); 8.8 g (26%) of 1,3-bis((4-fluorobenzyl)thio)propan-2-ol (No. 34), b.p. 232 °C/1 torr, n_D^{20} 1.5813, d_4^{20} 1.2482.

***S*-(3-Fluorobenzyl) ethanethiolate** (No. 25, Table 2.3) Condensation of 3-fluorobenzylthiol with chloroacetic acid was carried out in the presence of NaOH. To a mixture of 3-fluorobenzylthiol (10.6 g, 0.075 mol) and 30% aqueous solution of NaOH (4.2 g, 0.075 mol), 30% aqueous solution of chloroacetic acid (7.1 g, 0.075 mol) was added dropwise at 80 °C. The reaction mixture was stirred for 2 h at the same temperature. To isolate mercaptoacetic acid, the sodium salt obtained was decomposed using hydrochloric acid. The product was extracted with hot benzene, the benzene extract was washed several times with water and dried over Na_2SO_4. After removal of the solvent, the residue was distilled in vacuum to give 12.9 g (86%) of (3-fluorobenzylthio)acetic acid, b.p. 160 °C/3 torr, n_D^{20} 1.5400, d_4^{20} 1.2500.

S-(4-Fluorobenzyl) ethanethiolate (No. 35, Table 2.3) was obtained similarly.

Thiodiglycol divinyl ether a) Thiodiglycol (27.5 g, 0.21 mol), KOH (1.3 g, 0.02 mol), and dioxane (100 mL) were placed in a 1-L autoclave. The reaction mixture was saturated with acetylene (initial pressure 16 atm) and heated for 1 h at 130–140 °C. Distillation of the reaction mixture in vacuum gave 5.6 g (20%) of 1-vinyloxy-2-vinylthioethane, 8.4 g (23%) of thiodiglycol divinyl ether, and 1.0 g (3%) of thiodiglycol monovinyl ether [169].

b) In a reaction flask, equipped with thermometer, stirrer and reflux condenser, sodium sulfide $Na_2S{\cdot}9H_2O$ (36.0 g, 0.2 mol), 2-chloroethyl vinyl ether (21.3 g, 0.15 mol), and 50% aqueous solution of catamine AB (4.2 g) were placed. The reaction mixture was heated at 60 °C upon vigorous stirring for 3 h. To dissolve sodium chloride formed, water (10 mL) was added, the organic layer was separated and distilled in vacuum to give 1.8 g of the starting 2-chloroethyl vinyl ether and 15.7 g (90%) of thiodiglycol divinyl ether: a colorless liquid, b.p. 90 °C/3 torr, n_D^{20} 1.4900. IR spectrum (cm^{-1}): 820, 970, 1200, 1320, 1615, 3050 ($OCH = CH_2$). ^1H NMR spectrum, δ, ppm ($CDCl_3$): 6.38 dd (1H, $J = 14.0$, $J = 7.5$ Hz, = CHO), 4.10 dd (1H, $J = 14.0$, Hz, $J = 3.5$ Hz, $= CH_{trans}$), 3.90 dd (1H, $J = 7.5$, $J = 3.5$ Hz; $= CH_{cis}$), 78 t (2H, $J = 7.0$ Hz, OCH_2), 2.73 t (2H, $J = 7.0$ Hz, SCH_2) [171].

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Aromatic Disulfides, Sulfoxides, Sulfones, and Other Derivatives of Aromatic Thiols

3

3.1 Aromatic Disulfides

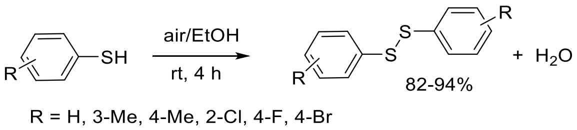
Disulfide structural motif is frequently met in pharmaceuticals, natural products, and biologically active molecules. Disulfides are applied as vulcanizers [1, 2], efficacious agents in the folding and stabilization of proteins [3], in design of rechargeable lithium batteries [4], and as valuable synthetic intermediates in organic synthesis [5–9]. Due to easy interconversion between thiols and disulfides and higher stability of the latter, the disulfides which are often employed are used as sources of thiols.

The approaches to the S–S bond formation are very diverse. Recent advances in this area are summarized in several reviews [10–13]. This section provides examples of the classic and most important modern methods for the synthesis of aryl disulfides.

One of the main strategies in the synthesis of disulfides is the oxidative coupling of thiols. Thiols are relatively readily oxidized by various oxidants to disulfides. A whole series of expedient methods for the synthesis of symmetrical diaryl disulfides have been developed on the basis of this reaction.

Molecular oxygen is most commonly used as the highly atom-economical, non-toxic, and abundant oxidant for the oxidative coupling of thiols [14].

EtOH is an excellent medium for the aerobic S–S coupling reactions of various aryl thiols. A series of useful disulfides ArSSAr have been synthesized in good to excellent yields (82–94%) without using any additional catalyst, oxidant, or additive [15].



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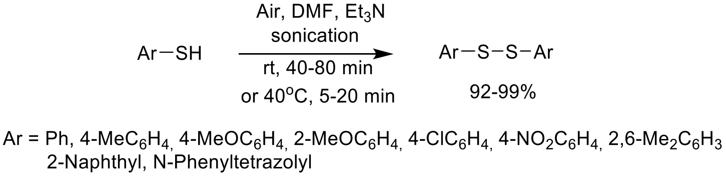
Naphth-2-yl and pyridine-2-yl thiols give slightly lower yields (75–78%). Moreover, the products could be obtained by simply removing the solvent after completion of the reaction. Satisfactory results are achieved for both mg- and g scale reactions.

Molecular oxygen is also efficiently employed in the oxidative coupling of thiols to disulfides in subcritical water [16]. Symmetrical aryl and heteroaryl (2-pyridyl and benzthiazolyl) disulfides have been prepared by oxidation of thiols in subcritical water (100 °C, 5–20 bar) in the absence of metal catalysts. The procedure utilizes water and does not require support materials and metal salts to provide high yields of the products (95%).

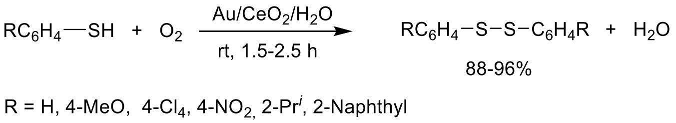
Aerobic oxidation of aryl thiols to diaryl disulfides is accelerated in polar aprotic solvents having high dielectric constants. Moreover, the reaction times can be shortened by the addition of bases, capable of forming thiolates from thiols [17]. Aryl and heteroaryl symmetrical disulfides are easily prepared by heating the corresponding thiols for several hours at 80 °C with Et_3N in DMF under atmospheric oxygen [18]. These reactions are markedly accelerated by ultrasounds (usually less than 1 h at rt). This method tolerates both aromatic (with electron-rich and electron-poor substituents) and heteroaromatic thiols. The yields are almost quantitative, and the process is implemented in multigram scale without losing its efficacy.



Aerobic oxidative coupling of aryl thiols in the K_2CO_3/MeCN system (rt, 20 min–24 h) affords diaryl disulfides in 90–96% yields [19]. Other potassium salts (KF, KBr) also promote this reaction. This method satisfies the requirement of contemporary green chemistry and is suitable for practical purposes. Analogously, aromatic and heteroaromatic thiols are effectively oxidized to their corresponding disulfides in the presence anhydrous K_3PO_4 in acetonitrile at room temperature (1–2 h, 85–92% yield) [20].

The reactions of aerial oxidation of thiols are sensitive to the presence of a catalyst. The processes are successfully catalyzed by metal ions (Fe [21–24], Cu [24–26], Mn [27] and Co [28–30]), Ni- [31] and Au-nanoparticles [32], photoredox catalysts [33]. As a rule, these methods allow the symmetrical disulfides to be synthesized in high yields and under mild conditions.

Thus, aromatic thiols are smoothly and efficiently oxidized to disulfides with air in the presence of gold nanoparticles supported on CeO_2 in water as well as in the absence of solvents, using oxygen as an electron acceptor [32].



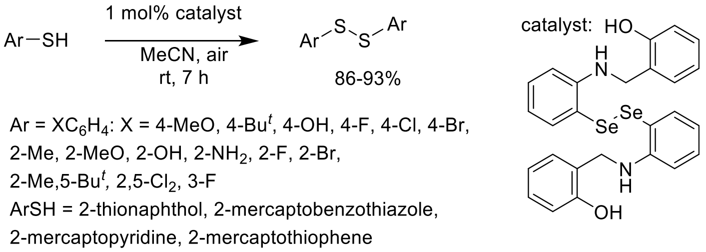
$$RC_6H_4{-}SH + O_2 \xrightarrow[\text{rt, 1.5-2.5 h}]{\text{Au/CeO}_2\text{/H}_2\text{O}} \underset{88\text{-}96\%}{RC_6H_4{-}S{-}S{-}C_6H_4R} + H_2O$$

R = H, 4-MeO, 4-Cl_4, 4-NO_2, 2-Pr^i, 2-Naphthyl

Spin trapping studies by EPR spectroscopy suggest that the reaction follows a radical pathway through the combination of two thiyl radicals, oxygen being the final electron acceptor. The simplicity of the system, excellent yields (up to 100% without solvent), and the reasonable reaction time (1.5–2.5 h) make Au/CeO_2 an attractive environmentally benign catalyst for the synthesis of diaryl disulfides.

An operationally simple procedure for the aerobic oxidation of thiols to disulfides using Eosin Y (1 mol%) as a photoredox catalyst and visible-light irradiation (standard 24 W compact fluorescent light bulb) has been elaborated [33]. Thiophenols bearing a variety of functional groups undergo the complete conversion for 16 h at room temperature to deliver the corresponding disulfides in near quantitative isolated yields. Free hydroxyl (3-OH, 4-OH) and halogen (4-Br, 4-F) groups well tolerate the mild reaction conditions. Sterically hindered thiophenols with *ortho*-methyl or -methoxy substituents are also efficiently transformed into disulfides. The addition of a base (TMEDA, 1 equiv.) substantially accelerates the reaction (from 16 h to 2–4 h reaction time). The plausible mechanism suggests that the tarent disulfides are produced via the electrophilic thiyl radical.

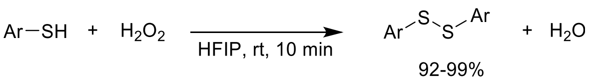
A novel organodiselenide, which mimics sulfhydryl oxidases and glutathione peroxidase (GPx) enzymes, catalyzes the aerobic oxidation of thiols into disulfides using aerial O_2 without any reagents/additives, bases, and light source [34]. A variety of aromatic thiols, namely thiophenols containing OH, OMe, NH_2, CH_2OH, Cl, Br, F, thionaphthols, heteroaryl thiols (2-mercaptobenzothiazole, 2-mercaptopyridine, 2-mercaptothiophene), are oxidized into the respective disulfides.



Ar = XC_6H_4: X = 4-MeO, 4-Bu^t, 4-OH, 4-F, 4-Cl, 4-Br, 2-Me, 2-MeO, 2-OH, 2-NH_2, 2-F, 2-Br, 2-Me,5-Bu^t, 2,5-Cl_2, 3-F

ArSH = 2-thionaphthol, 2-mercaptobenzothiazole, 2-mercaptopyridine, 2-mercaptothiophene

Hydrogen peroxide is also frequently employed for the oxidation of thiols since water is the sole side product [14]. However, further oxidation of the initially formed disulfide may occur rapidly in the presence of excess oxidant. Therefore, the progress of the reaction requires careful monitoring. A mild, efficient, and selective oxidation of thiols in fluorous medium (hexafluoroisopropanol, HFIP) under neutral conditions using 30% aqueous H_2O_2 (r.t., 10 min) furnishes diaryl disulfides in quantitative yields [35].



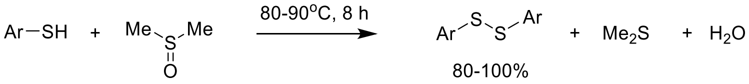
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_6$, 4-ClC_6H_4, 2-$NH_2C_6H_4$
ArSH = furfurylthiol, 2-pyridinethiol, 2-pyrimidinethiol

Benzene-, 4-methylbenzene-, 4-chlorobenzene-, and 4-methoxybenzenethiols quickly give the corresponding disulfides in excellent yields, no noticeable effect of the substituents being observed. Under the same conditions, 2-aminobenzenethiol affords the disulfide in 96% yield. The facile conversion of heteroaromatic thiols has been demonstrated by the oxidation of furfuryl-, 2-pyridine-, and 2-pyrimidinethiol. These thiols are selectively oxidized to the disulfides in excellent yields at ambient temperature with 1.1 equivalents of aqueous 30% hydrogen peroxide in trifluoroethanol. However, the reaction times (0.5–8 h) are longer than in HFIP. The solvent is recovered during the work-up by distillation as an azeotrope and can be recycled.

Also, aromatic thiols are effectively oxidized into disulfides by the reaction with hydrogen peroxide in the presence of a catalytic amount of iodide ion or iodine [36]. This reaction affords the products in high yield (92–99%) under very mild reaction conditions (1 equiv. 30% H_2O_2, 1 mol% NaI, EtOAc, r.t., 30 min).

Recently, in the oxidative coupling of aryl thiols with hydrogen peroxide, heterogeneous catalysts have been employed, for example, indium and thallium on isonicotinamide(INA)-functionalized mesoporous MCM-41 [37], anchoring Gd(III) complex on the surface of Fe_3O_4 with aspartic acid as a green ligand [38], isonicotinamide (INA) complexes of praseodymium(III) and dysprosium(III) onto modified mesoporous MCM-41 [39]. These catalysts ensure good to excellent yields of dithiols for short reaction times (5–60 min, r.t.) and can be recycled up to nine times with almost comparable yields.

DMSO as a mild oxidant is used for the preparation of symmetrical disulfides. The heating of aryl thiols with excess DMSO (80–90 °C, 8 h) leads to the corresponding diaryl disulfide (80–100% yield) [40].

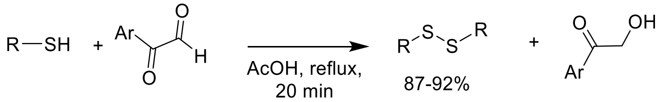


Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 2-$NH_2C_6H_4$

A wide variety of catalytic system has been used to improve the oxidation of thiols to disulfides: I_2 (or HI)/DMSO [41, 42], Re/DMSO [43], or Mo/DMSO [44]. Various aromatic disulfides with electron-withdrawing (Cl, Br, CF_3, NO_2), electron-donating (Me, OMe, NH_2), and bulky groups (*tert*-butyl) have been synthesized in good to excellent yields in short reaction times (5–30 min) at room temperature, employing 1.0 equiv. of DMSO and 20 mol% of iodine [42]. Selective and quantitative conversion of thiols to disulfides (91–96% yield) is effected by DMSO under mild conditions (r.t, 5–30 min) in the presence of dichlorodioxomolybdenum(VI) (1 mol%) [44]. The catalyst is very resistant to degradation.

Addition of new batches of thiol to the resulting reaction mixture shows no significant loss of the activity. The order of reactivity observed for thiols roughly correlates with their acidity. Thiols having electron-withdrawing substituents are oxidized for 10 min, whereas, for instance, the reaction with 4-methoxybenzenethiol takes 30 min. 2-Pyridinethiol is quantitatively transformed to 2,2-dipyridine disulfide under these conditions for 12 h.

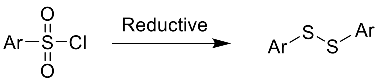
The disulfide bond is formed by the oxidation of thiols with halogens [45–47], chromates [48–51], nitrogen- [52–54], and sulfur-containing oxidants [55–57]. SO_2Cl_2 provides simple access to several symmetrical aromatic and heteroaromatic disulfides in excellent yield [56]. The major drawback of this method is the release of acidic and toxic gaseous SO_2 and HCl. These by-products limit the application scope of thiols having no acid-sensitive groups. Symmetrical diaryl disulfides are efficiently produced using arylglyoxals [58] and ascorbinic acid [59] as oxidants. The advantages of these methods are simple available starting materials, short reaction time, simple work-up, neutral reaction conditions, and high yields. For example, the stoichiometric oxidation of aryl thiols by arylglyoxals (glacial acetic acid, reflux, 20 min) leads to homodisulfides in good yields (87–92%) [58].



R = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 2-MeC_6H_4, 2-naphthyl, 2-pyridyl

Another example of efficient catalytic oxidation of thiols to disulfides (ascorbic acid, 5 mol%) is found to be practical, inexpensive, and reusable and has a simple work-up procedure [59]. This oxidation is suitable for a wide range of substituted aromatic and aliphatic thiols. The reaction is carried out in water under a N_2 atmosphere (room temperature, 5–10 min) to give the target products in high yields (94–100%). It is assumed that ascorbic acid, after deprotonation, forms the ascorbyl radical, which generates a thiyl radical from thiol, and finally gives two thiyl radicals that undergo dimerization to form the S–S bond.

In the last decade, the preparation of diaryl disulfides using arylsulfonyl chlorides is of interest owing to their availability. A number of preparative methods have been devised with different reductive system.

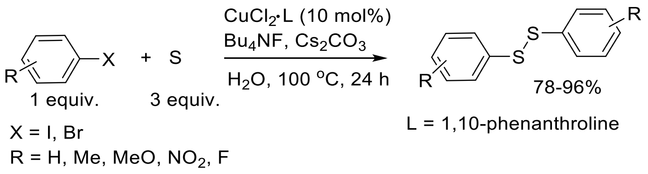


[60]	[61]	[62]	[63]
$TiCl_4$/Sm/THF	Sm/$NiCl_2$/KI/HMPA	$(Bu^n)_4$NI/DMF	Ph_3P/THF
60°C, 2 h	60°C, 3 h	20-25°C, 20 h	20-25°C, 20 h
62-83%	62-74%	72-93%	75-92%
8 examples	8 examples	22 examples	12 examples

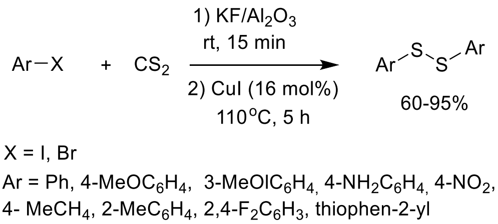
$TiCl_4$/Sm system reduces arylsulfonyl chlorides and sodium arylsulfinates to the corresponding diaryl disulfides in 62–83% yields in THF at 60 °C [60]. Also, arylsulfonyl chlorides can be readily reduced to disulfides with Sm/$NiCl_2$/KI system (HMPA, 60 °C, 3 h) in moderate to good yields [61]. Symmetrical diaryl disulfides are synthesized by the reduction of aryl sulfonic acid derivatives using $(Bu^n)_4NI$ in DMF at rt [62]. Various functional groups including ether, ketone, ester, halide, cyano, and nitro one well tolerate the reaction. A practical method for the synthesis of diaryl disulfides using commercially available and inexpensive triphenylphosphine and arylsulfonyl chlorides in anhydrous tetrahydrofuran under mild reaction conditions (rt, 20 h) has been developed [63]. All these transformations probably proceed through a reducing–coupling pathway.

Nowadays, the direct syntheses of diaryl disulfides via C–S cross-coupling reactions of aryl halides with S-transfer reagents have attracted a lot of attention. Sulfur, carbon disulfide [64, 65] and dithiocarbonates [66, 67] are also involved in the preparation of diaryl disulfides through the coupling with aryl halides.

A simple and efficient protocol for copper-catalyzed reactions between aryl halides and elemental sulfur (H_2O, Cs_2CO_3, 100 °C, 24 h) has been developed [68]. An easily available catalyst is formed in situ by $CuCl_2$ and 1,10-phenanthroline. The reaction can be carried out in air without inert gas. Such functional groups as methyl, chloro, nitro, and methoxyl could be introduced into aryl halides to generate the corresponding disulfides in good to excellent yields (78–95%). In general, aryl iodides give slightly higher yields than their bromo analogs. Heterocyclic halides, e.g. 3-bromopyridine, also afford the desired products in 87% yield.

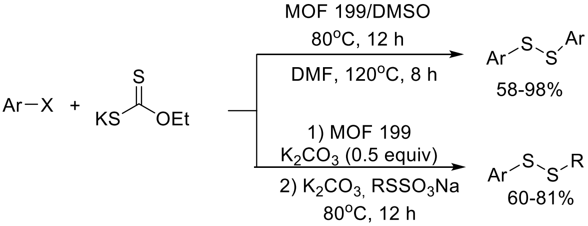


A large number of symmetrical diaryl and heteroaryl disulfides bearing both electron-withdrawing and electron-donating substituents at *ortho*-, *para*-, and *meta*-position have been synthesized by the one-pot reaction of aryl halides (iodides and bromides) with the in situ generated trithiocarbonate ion in the presence of a strong, recycle and heterogeneous base KF/Al_2O_3 and CuI under air atmosphere (110 °C, 5 h) [64].

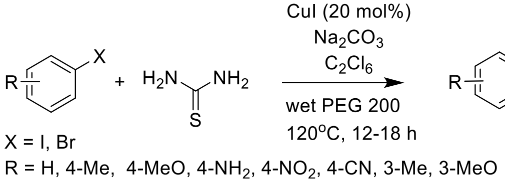


Analogously, a one-pot preparation of diaryl disulfides employing CS_2 as a sulfur surrogate, diethylamine as a base, and CuI as a catalyst in PEG200 is described [65]. This method allows the conversion of aryl iodides (110 °C, 20–22 h) and phenolic tosylates (130 °C, 21–24 h) to produce diaryl disulfides in 81–90% and 70–75% yields. It is reported that CS_2 reacts with diethylamine in NaOH aqueous solution to furnish sodium *N*,*N*-diethyldithiocarbamate, which in the presence of aryl compounds gives aryl *N*,*N*-diethyldithiocarbamate. The latter after hydrolysis with aqueous KOH and neutralization of the reaction mixture with concentrated HCl delivers the corresponding diaryl disulfides. The reaction of aryl halides with morpholin-4-ium morpholine-4-carbodithioate in DMF/H_2O (CuCl (1.5 equiv.), KOH (18 equiv.), 110 °C, 20 h) proceeds in a similar manner [66]. This protocol enables to efficiently synthesize the disulfides with both electron-donating and electron-withdrawing groups in good yields.

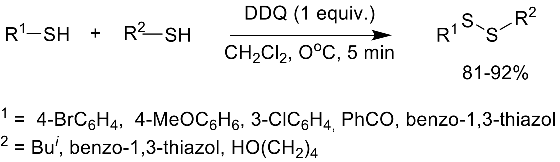
An efficient new method for the synthesis of disulfides via the reaction of aryl halides with ethyl potassium xanthogenate in the presence of metal–organic frameworks (MOF-199) is disclosed [67]. Heterogeneous catalysts of MOFs type feature high internal surface area, good activity, microporosity, ease of product separation, stability, diffusion, and high metal content. *O*-Ethyl-*S*-aryl carbonodithioate has a key role as an intermediate in this procedure. It is converted into the symmetrical diaryl disulfides in DMF (120 °C, 8 h) in good to excellent yields. Additionally, it could be applied to the synthesis of unsymmetrical alkyl aryl and diaryl disulfides by the reaction with *S*-alkyl(aryl) thiosulfates (Bunte salts) in DMSO (80 °C, 24 h).



An improved protocol has been developed for the one-pot CuI-catalyzed preparation of symmetrical diaryl disulfides from their available aryl halides using thiourea as a sulfur transfer agent and hexachloroethane (C_2Cl_6) as an oxidant under ligand-free conditions in wet poly(ethylene glycol) (PEG200) and in the absence of an inert atmosphere [69]. The oxidation of in situ generated thiophenols from the reaction of aryl halides with thiourea in the presence of CuI as catalyst affords diaryl disulfides in 85–95% yields. The oxidant used in this method is strong to obtain disulfides without formation of sulfide by-product and is sufficiently mild that it does not destroy the thiourea and avoids thiol overoxidation.



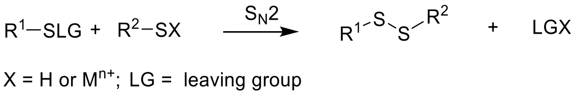
Synthesis of unsymmetrical diaryl disulfides through the oxidation of two different thiols is difficult to implement since the reaction is accompanied by the formation of symmetrical disulfides and other by-products. Nevertheless, the efficient approach to the synthesis of unsymmetrical disulfides directly from two thiols using strong oxidant DDQ has been developed [70]. The mixture of two thiols with DDQ (1:1:1 molar ratio, CH_2Cl_2, 0 °C, 5 min) form of heteroaryl–aryl disulfides and aryl–alky disulfides in high yields (81–92%).



The reaction does not occur in many of the other reagents including $Mn(OAc)_2$, $K_3Fe(CN)_6$, $Mg(NO_3)_2$, and $AgNO_3$. But such reagents as PCC (pyridinium chlorochromate), IBX (2-iodoxybenzoic acid), and DMP (Dess-Martin periodinate) can be employed as the oxidants in these reactions giving the products in slightly lower yields. Unfortunately, the aryl–aryl disulfides have not been tested in this strategy.

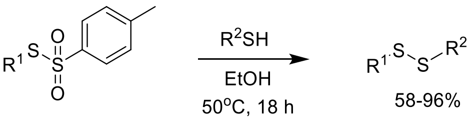
Similarly, oxidative coupling of two different thiols bearing aliphatic, alicyclic, aromatic, and heteroaromatic moieties promoted by mild oxidizing agents, viz., sterically hindered *o*-benzo(imino)-quinones, in *N*-methylpyrrolidone at room temperature leads to the unsymmetrical disulfides [71]. Among the studied oxidizers, the most active is 3,6-di-*tert*-butyl-*o*-benzoquinone, which, in contrast to 3,5-di-*tert*-butyl-*o*-benzoquinone, is not involved in the Michael addition. Under the optimal reaction conditions, the yields of the target unsymmetrical disulfides reach 81%.

The classical methods affording unsymmetrical disulfide include an S_N2 process, in which prefunctionalized thiols with a leaving group are utilized as one of the sulfur sources:



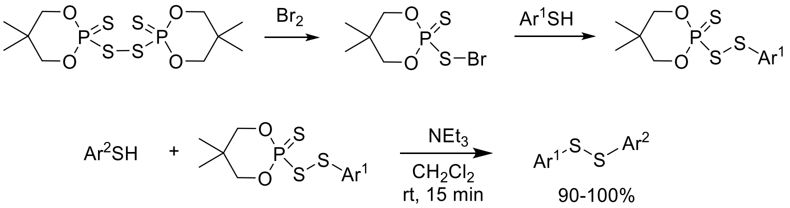
The most notable reagents currently available for constructing the unsymmetrical disulfides are aryl sulfenyl derivatives, such as thiocarbonates [72], thiosulfates (Bunte salts) [73] and thiosulfonates [74], thiophosphates [75], thioimides [76, 77], benzotriazolyl sulfides [78], etc.

Arylthiosulfonates, synthesized by copper-catalyzed coupling of thiols or disulfides with sodium sulfinates [79], easily react with aromatic and aliphatic thiols (EtOH, 50 °C, 18 h) to form the unsymmetrical disulfides in 58–96% yields [74]. The effect of steric hindrance is not observed. Not only arylthiosulfonates but also alkylthiosulfonates can be employed in the reaction.



R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-MeC_6H_4, 2-BrC_6H_4, Me, Bu^n
R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-HOC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2-BrC_6H_4, Pr^i, Bu^n, $Octyl^n$, $HOCH_2CH_2$

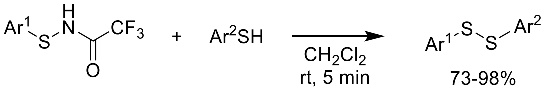
Dithiophosphoric acids anions represent very good leaving groups. A convenient method for the synthesis of unsymmetrical diaryl disulfides under mild conditions involves readily available organophosphorus sulfenyl bromides as activating agents for the formation of unsymmetrical disulfide bond. Bis(5,5-di-methyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) disulfide is treated with bromine at −30 °C to afford the corresponding sulfenyl bromide, which reacts, without isolation, with aryl thiols. The reaction of aryl 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl disulfides with a variety of aryl thiols in dichloromethane at room temperature is generally completed within 15 min to give unsymmetrical diaryl disulfides exclusively in excellent isolated yields. The unsymmetrical diaryl disulfides can be obtained from aromatic thiol derivatives bearing electron-withdrawing or electron-donating groups.



Ar^1 = Ph, 2-$MeO_2CC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-HOC_6H_4, 2-naphthyl
R^2 = Ph, 2-$MeO_2CC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-HOC_6H_4, 4-$NO_2C_6H_4$, 2-naphthyl

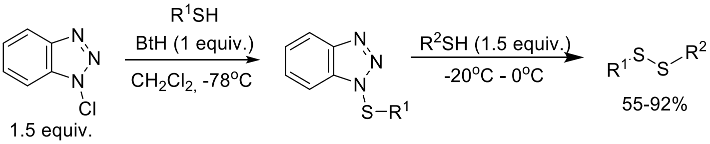
The success of the reaction is ensured by the very fast formation of the target disulfides from aryl 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl disulfides so that further disulfide exchange is avoided and unsymmetrical diaryl disulfides are obtained exclusively.

The reaction of sulfonamides with thiols is a popular method for the preparation of unsymmetrical disulfides. *N*-Trifluoroacetyl arenesulfenamides [80] are effective precursors for the synthesis of unsymmetrical disulfides. Reactions of these sulfonamides with aromatic thiols (CH_2Cl_2, room temperature) are generally completed for 5 min to give unsymmetrical diaryl disulfides in high yields (73–98%) [77]. Thiol–disulfide exchange does not occur during the reaction. Alkyl aryl disulfides have been prepared from the aliphatic thiols and *N*-trifluoroacetyl arenesulfenamides (acetone, reflux, 1 h) in 72–98% yields.



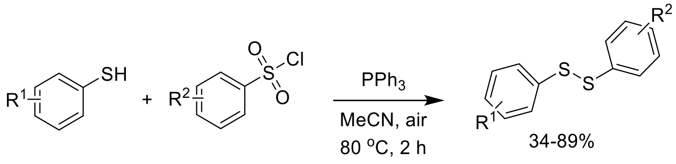
Ar^1 = Ph, 2-$MeO_2CC_6H_4$, 4-MeC_6H_4, 2-BrC_6H_4, 4-$NO_2C_6H_4$
Ar^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4

One of the most promising S_N2 reactions is based on the inexpensive, one-pot procedure using 1-chlorobenzotriazole. This methodology has been applied to the synthesis of various disulfides: aryl/aryl(hetaryl), alkyl/aryl, and alkyl/alkyl [78]. The reaction of thiol R^1SH with 1-chlorobenzotriazole (BtCl) at −78 °C in CH_2Cl_2 affords benzotriazolyl sulfide $BtSR^1$ in high yield without appreciable formation of the symmetrical disulfide R^1SSR^1. $BtSR^1$ then reacts with a second thiol R^2SH to form the unsymmetrical disulfide in a one-pot sequence with green character that avoids the use of toxic and harsh oxidizing agents.



R^1 = 2-$MeO_2CC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-pyridyl
R^2 = 2-$MeO_2CC_6H_4$, 4-MeC_6H_4, 2-pyridyl, Pr^n, Bu^t, allyl, *n*-hexyl

A facile and rapid synthesis of unsymmetrical aryl disulfides using PPh_3-mediated reductive coupling of thiophenols with aryl sulfonyl chlorides is documented [81]. Good functional group tolerance and scalability are achieved in this strategy: the reduction of sulfonyl chloride with PPh_3 produces the intermediate ArS–Cl, which is attacked by thiophenol to generate aryl disulfide. More importantly, the approach enables the introduction of sulfonyl chlorides into the synthesis of asymmetrical organic disulfides under catalyst- and base-free conditions. Using this method, unsymmetrical aromatic disulfides are prepared from inexpensive and readily available starting materials in moderate to excellent isolated yields, through a nucleophilic substitution pathway.

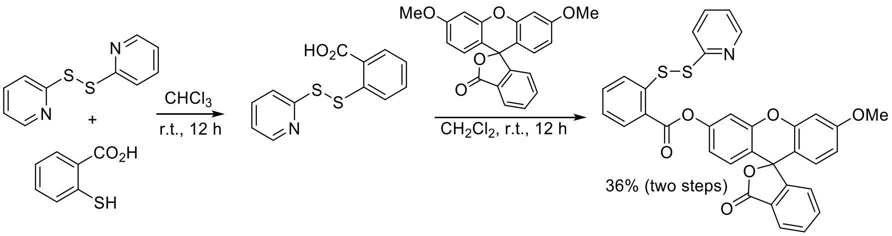


R^1 = Pr^i, Bu^t, F, Cl, Br, CF_3, AcNH, Me
R^2 = CO_2Me, CN, AcNH, OMe

The thiol exchange with symmetrical disulfide represents a convenient and expedient strategy for the synthesis of unsymmetrical disulfides.

$$R^1{-}SH \;+\; R^2SSR^2 \;\rightleftharpoons\; R^1SSR^2 \;+\; R^2{-}SH$$

Thiol–disulfide exchange reactions play an important role in many aspects of cellular function. Sometimes, these reactions are used for design of molecules with desirable structure. In particular, the reactions between di(2-pyridyl)disulfide and thiols are employed for the preparation of releasable luciferin–transporter conjugates [82] and fluorescent probe for visualization of hydrogen sulfide [83]. A pyridyl disulfide readily undergoes an interchange reaction with a thiol to yield a single mixed disulfide product. This is due to the fact that the pyridyl disulfide contains a leaving group that is easily transformed into a non-reactive compound (pyridine-2-thione) not capable of participating in further mixed disulfide formation.

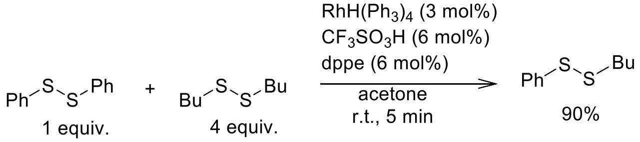


Another variant of the disulfide exchange reaction is electrochemical oxidation at a platinum electrode of organic disulfides affording the transient electrophilic sulfenium cation R^1S^+ [84]. Electrophilic cations react with thiols R^2SH to furnish unsymmetrical disulfides. Since the latter is also oxidized like the symmetrical ones, they are prepared in a two-step process. The reaction also allows one to obtain unsymmetrical disulfides using another disulfide R^2SSR^2 as a nucleophile, but with a lower yield (47–60%).

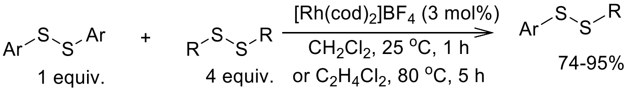
$$R^1SSR^1 \xrightarrow[\substack{0.1\text{M } Bu_4NClO_4\\ CH_2Cl_2,\ 20\text{ h}}]{W_p\ 1.5\text{-}1.8\text{ V}} R^1S^+ \;+\; 2\bar{e} \xrightarrow{R^2SH} \underset{61\text{-}90\%}{R^1SSR^2}$$

R^1 = Ph, CH_2Ph, Me; R^2 = Ph, CH_2Ph, Pr^n, Bu^t

Compared with the conventional and electrochemical exchange reactions, Rh-catalyzed reactions take place rapidly under mild conditions. Diphenyl disulfide reacts with dibutyl disulfide in the presence of $RhH(PPh_3)_4$, 1,2-bis(diphenylphosphino)ethane (ddpe), and trifluoromethanesulfonic acid (acetone, r. t., 5 min) to give butyl phenyl disulfide in 90% yield [85].

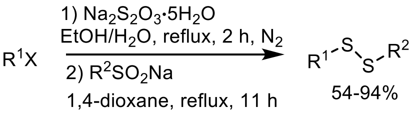


A phosphine-free cationic rhodium(I) complex, $[Rh(cod)_2]BF_4$, is also an effective catalyst for disulfide exchange reaction of symmetrical disulfides to unsymmetrical disulfides under inert atmosphere [86]. The exchange of primary alkyl disulfide and aryl disulfide proceeds at 25 °C for 1 h. The reaction of two different aryl disulfides takes place at 80 °C for 5 h. This reaction is carried out using unpurified commercial-grade solvents under air without decrease of yields and reaction rates.



Ar = 4-MeC_6H_4, 2-benzothiazolyl
R = Bu^n, Cy, Ph

Another approach for the construction of unsymmetrical alkyl aryl disulfides, including derivatives of natural products, by sulfur redox process has been developed [87]. In this strategy, one of the sulfur atoms exhibiting low-valence (−2) in thiosulfate is supposed to be oxidized by an appropriate high-valent sulfide (+6 or +4) to achieve unsymmetric disulfide (+1) via comproportionation.



X = Cl, Br
R^1 = $(CH_2)_3CN$, $(CH_2)_2CO_2H$, Bu^n, $PhCH_2$, 4-$MeC_6H_4CH_2$, 4-$NCC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 4-$FC_6H_4CH_2$, 3-$FC_6H_4CH_2$, 3-$MeOC_6H_4CH_2$, etc.
R^2 = 4-$MeOC_6H_4$, 4-$CF_3OC_6H_4$, 4-$Bu^tC_6H_4$, naphthyl, 2,5-dichlorothienyl

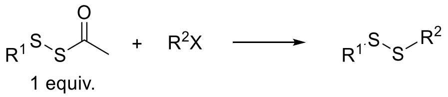
In this two-step, one-pot process, alkyl thiosulfate is formed in situ through the reaction of $Na_2S_2O_3$ and alky halides. Various alky halides and aryl sulfinates give the corresponding disulfides in moderate-to-high yields. Unsymmetrical diaryl disulfides cannot be achieved in this approach. These are obtained by utilizing the preformed aryl thiosulfate.

Over the last years, a novel concept for the construction of unsymmetrical disulfides via the direct one-step introduction of two sulfur atoms by copper-catalyzed oxidative cross-coupling under mild reaction condition has been formulated [88, 89]. On the basis of masked strategy, a new type of nucleophilic disulfurating reagents has been designed and synthesized. Disulfide compounds are smoothly obtained in two steps. The *S*-alkyl 4-methylbenzenesulfonothioate is produced through combination of sodium 4-methylbenzenesulfonothioate and alkyl halides. A replacement of *S*-alkyl 4-methylbenzenesulfonothioate with thioacetate affords the target disulfide [88].

$$\mathrm{TolSO_2Na} \xrightarrow[\text{step 1}]{\text{RX (X = Cl or Br}} \mathrm{TolSO_2SR} \xrightarrow[\text{step 2}]{\text{KSAc}} \underset{\text{up to 89\%}}{\mathrm{RSSAc}}$$

Primary and secondary benzyl derivatives, containing a propargyl group, aliphatic chains and even a bromo-substituted alkyl group have been generated in this manner efficiently.

Acetyl, a readily dissociate electron-withdrawing group, is served as a preeminent mask for disulfide, which is utilized to construct unsymmetrical disulfide with arylboronic acid (Suzuki-type cross-coupling) [88] or silicon-based nucleophiles (Hiyama-type cross-coupling) [89] under mild copper-catalyzed oxidative cross-coupling conditions through a highly selective C–S bond cleavage. The pH value of the system plays a key role in achieving highly selective cleavage of the C–S bond instead of the S–S bond in transformation.



[88]	[89]
$R^2X = ArB(OH)_2$ (1.4 equiv.)	R^2X = (Het)$ArSi(OR')_3$ (3 equiv.)
$CuSO_2 \cdot 5H_2O$ (5 mol%)	$CuSO_2 \cdot 5H_2O$ (10 mol%)
Bipy (20 mol%)	4,4'-diMeO-Bipy (20 mol%)
$FeSO_4$ $7H_2O$ (20 mol%)	PhOH (0.5 equiv.)
LiOTf (40 mol%)	TsOH H_2O (0.3 equiv.)
Na_2CO_3 (1 equiv.)	TBAF (20 mol%)
EtOH, O_2, r.t., 12 h	MeOH, O_2, r.t., 10 h
48-85%	60-85%

Diverse arylboronic acids bearing electron-withdrawing and electron-donating functional groups at the *ortho*-, *meta*-, and *para*-positions and both electron-rich and electron-deficient arylsilanes are found to be compatible with this new transformation. Unfortunately, unsymmetrical diaryl disulfides cannot be synthesized through this approach.

A class of stable and multifaceted polysulfurating reagents with masked strategy has been designed and a general methodology for polysulfuration has been elaborated. The methodology allows directly introducing two sulfur atoms into functional molecules. Electrophilic disulfurating reagents (RSS+) are prepared through hydroperdisulfide anions (RSS−) and methanol via the oxidative cross-coupling [90].

$$\text{RSSAc} \xrightarrow[\text{MeOH, 20 °C, 15 h}]{\substack{\text{CuSO}_4\ 5\text{H}_2\text{O (0.25 mol\%)} \\ \text{4,7-Ph}_2\text{-1,10-phenanthroline (0.5 mol\%)} \\ \text{PhI(OPiv)}_2\text{ (2.2 equiv.), Li}_2\text{C)}_3\text{ (1 equiv.)}}} \underset{\text{up to 88\%}}{\text{RSSOMe}}$$

Electron-rich arenes and heteroarenes are smoothly coupled with methoxyl-substituted disulfides under transition-metal-free, and base-free conditions (5 mol% $B(C_6F_5)_3$, PhMe, 0 °C, 24 h) especially suitable for the late-stage modification of natural products and pharmaceuticals [90].

$$\underset{\text{1.5 equiv.}}{\text{Ar—H}} + \underset{\text{1 equiv.}}{\text{MeOSSR}} \xrightarrow[\text{PhMe, 0 °C, 24 h}]{\text{B(C}_6\text{F}_5\text{)}_3\text{ (5 mol\%)}} \underset{\text{up to 99\%}}{\text{ArSSR}}$$

The designed reagents are compatible with a considerable range of significant biomolecules, such as saccharides, amino acids, peptides, and variety of heterocycles. Following the activation mode, (+)-δ-tocopherol, an important bioactive molecule, could be disulfurated directly despite the presence of free hydroxyl group. Indole and pyrrole, ubiquitous in natural products and pharmaceuticals, are excellent coupling partners as well. Indoles bearing both electron-rich and electron-deficient functional groups are readily disulfurated to afford the corresponding 3-indolyl-disulfides. This protocol showcases the wide utility of carbon nucleophiles in the synthesis of functional disulfides.

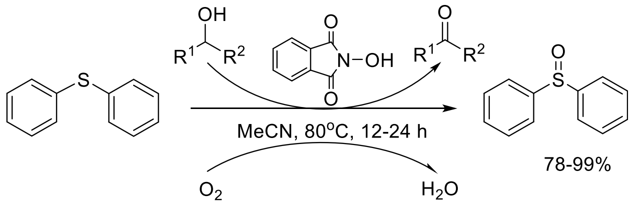
The past several decades have seen much development and wide applications of novel strategies for the syntheses of various disulfides under mild reaction conditions. There is no method for preparing disulfide bonds that is suitable for all types of substrates. The most important methods for the synthesis of disulfides are oxidation of thiols and thioalkylation (thiolysis) of sulfur-containing compounds. The oxidation of thiols is used mainly in the preparation of symmetrical disulfides, whereas thiolysis is favored for the synthesis of unsymmetrical disulfides. Although many effective methods for the synthesis of disulfides have been elaborated, the problems of substrate compatibility, selectivity, and efficiency still remain a great challenge. More efficient and practical strategies for direct construction of disulfides are needed.

3.2 Aromatic Sulfoxides

Organic sulfoxides, including aromatic ones, are extensively used in academic research, medicine and industry as reagents [91–99], components of superbasic media [100–103], selective extractants of metals [104–108], flotation reagents [109], active solvents [110, 111], selective oxidants [112, 113], physiologically active substances [114, 115], and drugs (Omeprazole, Esomeprazole, Rabeprazole, Armodafinil, Sulindac) [116–118]. Therefore, synthesis of sulfoxides has remained a point of attraction for synthetic organic chemists.

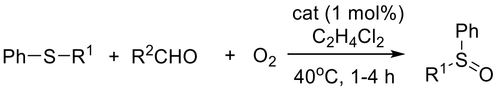
Extensive reviews on the sulfoxides synthesis and applications are available in the literature [92, 119, 120]. Numerous reagents and methods have been developed in an effort to produce sulfoxides as selectively and inexpensively as possible. Among these, the oxidation of sulfides has been proven as one of the most durable and pervasive methods in synthetic organic chemistry. However, the use of the many inorganic oxidants for instance is seen as less than optimal due to their tendency to over-oxidize sulfides and interfere with sensitive functional groups.

The most expedient and environmentally benign synthesis of organic sulfoxides is based on direct oxidation with molecular oxygen under various conditions. Direct introduction of molecular oxygen to sulfide is difficult because the ground state of oxygen is the inert triplet. Therefore, molecular oxygen as an oxidizing agent is used in the presence of some reducing agent such as H or aldehyde. Thus, the selective oxidation of aromatic sulfides, for example, diphenyl sulfide, to sulfoxides with oxygen, catalyzed by hydroxyphthalimide in acetonitrile in the presence of alcohols, has been described [121].



$R^1 = H$, $R^2 = i$-Pr, n-C_8H_{17}, $PhCH_2$; R^1-R^2 cyclo-C_6H_{11}

Aromatic sulfides are oxidized by molecular oxygen to sulfoxides in moderate and high yields and good selectivity in the presence of transition metal compounds (MnO_2, $Cu(OH)_2$, $Cu(OAc)_2$, Fe_2O_3) and aldehydes [122].

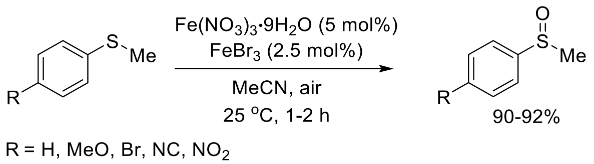


$$Ph{-}S{-}R^1 + R^2CHO + O_2 \xrightarrow[40^\circ C,\ 1\text{-}4\ h]{\text{cat (1 mol\%)}\ C_2H_4Cl_2} R^1S(O)Ph$$

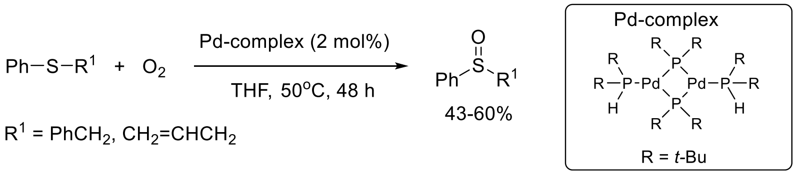
41-81%

$R^1 = Ph, Me, Et$
$R^2 = i$-Pr, i-Bu, n-C_6H_{13} Ph
cat: MnO_2, $Cu(OH)_2$, $Cu(OAc)_2$, Fe_2O_3

The binary catalytic system $Fe(NO_3)_3$–$FeBr_3$ is very effective for the selective air-oxidation of alkyl aryl sulfides to sulfoxides [123]. The reaction proceeded under very mild condition (MeCN, 25 °C, 1–2 h) and in a simple procedure to the oxidation and isolation, giving a high yield (90–92%) in the presence of different functional groups on the sulfide. Other binary systems such as $Fe(NO_3)_3$–$FeBr_2$ and $Cu(NO_3)_2$–$CuBr_2$ are also effective catalysts for sulfoxidation.

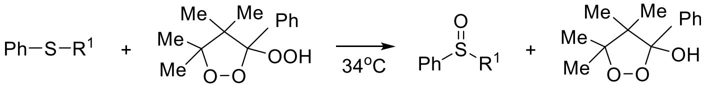


It is reported on aerobic oxidation of aromatic sulfides to sulfoxides in THF in the presence of 2 mol% palladium precatalyst {Pd[P(*t*-Bu)$_2$H][μ-P(*t*-Bu)$_2$]} [124].



Upon contact with oxygen, the initial palladium complex is transformed into an active catalytic system, which provides for the selective formation of aryl sulfoxides.

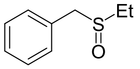
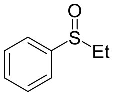
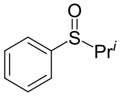
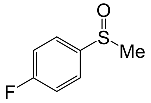
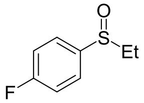
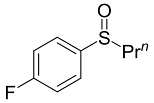
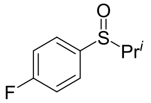
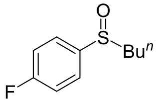
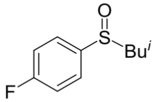
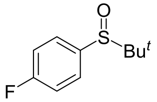
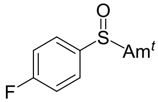
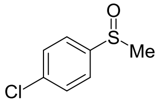
Often, various peroxide compounds are used to oxidize sulfides to sulfoxides. For instance, the reaction of aromatic sulfides with 3-hydroperoxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane delivers the corresponding sulfoxides and 3-hydroxy-1,2-dioxolane in quantitative yield [125].



However, it is most efficient to employ an available peroxide compound, hydrogen peroxide, for the oxidation of sulfides to sulfoxides [126]. In this line, a method for the selective oxidation of sulfides to sulfoxides with H_2O_2 in the presence of acetic anhydride has been elaborated [127]. Up to 30 °C, the oxidation proceeds selectively to give sulfoxide in a high yield. The method is applicable to the synthesis of dialkyl-, diaryl-, and alkyl aryl sulfoxides, as well as sulfoxides containing electron-withdrawing groups.

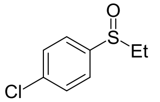
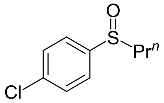
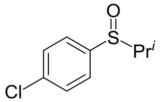
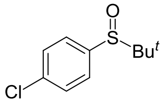
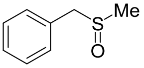
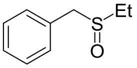
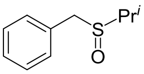
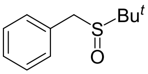
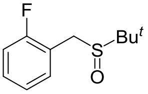
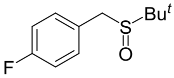
A methodology for the selective oxidation of sulfides with a 30% (in the case of *n*-and *i*-alkyl) or 40% (in the case of *t*-alkyl) solution of hydrogen peroxide [$(AcO)_2O$, equimolar ratio of the reactants, room temperature, 5–6 h] is applied to obtain a model series of alkyl aryl sulfoxides for theoretical and physical-chemical studies [128–130] (Chap. 6). The yields of alkyl aryl sulfoxides range 49–85% (Table 3.1, entries 1–16).

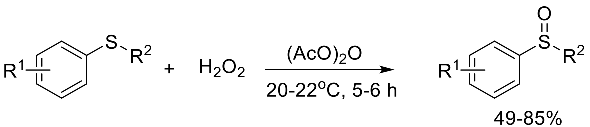
Table 3.1 Alkyl aryl and alkyl benzyl sulfoxides

No.	Structure	Yield, %	B.p., °C /torr (m.p., °C)	n_D^{20}	d_4^{20}
1	2	3	4	5	6
1		82	108/1	1.5555	1.1523
2		85	125/2	1.5520	1.1176
3		82	115/1	1.5540	1.1030
4		51	101/1	1.5262	1.2175
5		49	110/1	1.5473	1.1750
6		50	120/1	1.5328	1.1617
7		53	115/1	1.5440	1.1804
8		50	131/1	1.5240	1.1271
9		66	130/1	1.5250	1.1296
10		53	140/1	1.6040	1.1675
11		72	148/2	1.6006	1.2203
12		51	116/1	1.5900	1.3042

(continued)

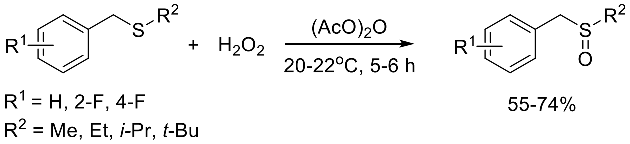
Table 3.1 (continued)

13		60	125/1	1.5793	1.2604
14		50	131/1	1.5708	1.2520
15		68	(69)		
16		74	(70)		
17		73	120/3	1.5310	1.0893
18		74	128/3	1.5330	1.0785
19		73	134/3	1.5585	1.0843
20		70	(72)		
21		55	130/5	1.5131	1.0709
22		63	(58)		



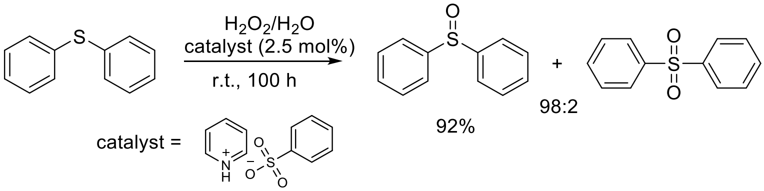
R^1 = H, 4-F, 4-Cl
R^2 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, *t*-Am

Under similar conditions, alkyl benzyl sulfoxides are synthesized in 55–74% isolated yields (Table 3.1, entries 17–22).



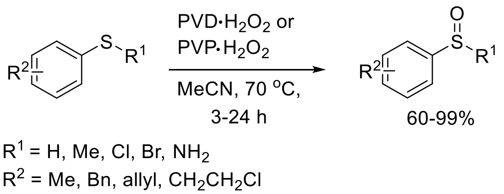
Several catalyst and reaction conditions have been reported to accelerate the sulfoxidation using H_2O_2. Synthesis of sulfoxides from sulfides and hydrogen peroxide with very high conversion and selectivity for sulfoxides (sulfone formation being only 0.4%) has been developed using ultrasonic irradiation in the presence of catalyst $(NH_4)_2MoO_4$ [131].

Free metal ammonium and pyridinium salts can be used efficiently as chemoselective catalysts in the oxidation of aromatic and aliphatic organosulfides [132]. The reactions were carried out in 30% aqueous H_2O_2 (r.t., 60–100 h), using 2.5–5 mol % catalyst loading to give sulfoxides in high yields (75–93%) and excellent selectivity (97–99%) [133]. Catalysts can be easily recycled by simple filtration and extraction with dichloromethane and/or used several times without any detrimental effects on the catalytic activity.



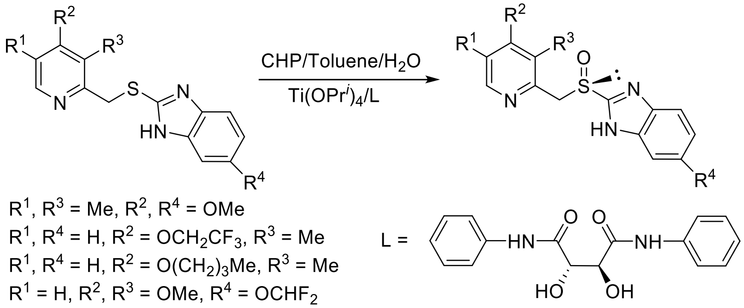
Important improvements have been recently achieved by using Brønsted acids [133]. In the acid-catalyzed oxidation of sulfides to the corresponding sulfoxides, pH-dependence is a common feature, and no matter which Brønsted acids are used, they can all achieve their optimal catalytic performance in their aqueous solution of pH 1.30.

Complexes of urea, poly(*N*-vinylpyrrolidone) (PVD), and poly(4-vinylpyridine) (PVP) with hydrogen peroxide have been documented as solid H_2O_2 equivalents for the selective oxidation of sulfides to sulfoxides. Urea-hydrogen peroxide adduct (1:1) has been used in oxidative synthesis of sulfoxides under solvent-free conditions (85 °C, 7–15 min) [134]. The reaction rate is faster for alkyl sulfides as compared to aromatic sulfides. No reaction occurs at room temperature. Unlike many other oxidants, complexes PVD-H_2O_2 and PVP-H_2O_2 prove highly amenable to control and optimization making the reaction highly tunable. It is found that various alkyl aryl sulfides undergo oxidation under mild conditions (MeCN, 70 °C, 3–24 h) to provide the respective sulfoxides in high yields [135].



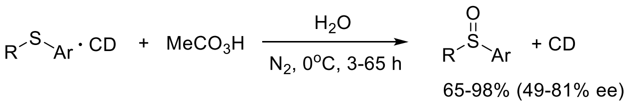
R^1 = H, Me, Cl, Br, NH_2
R^2 = Me, Bn, allyl, CH_2CH_2Cl

Catalytic asymmetric oxidation of sulfides is still considered the most general and convenient approach for the synthesis of chiral sulfoxides with high enantiomeric excess (*ee*) [120]. The asymmetric oxidations of 1*H*-benzimidazolyl pyridinylmethyl sulfides with cumene hydroperoxide (CHP) catalyzed by titanium complexes, formed in situ from $Ti(OPr^i)_4$, (*S*,*S*)-tartramides, and water, afforded the pharmacologically important proton pump inhibitors omeprazole, lansoprazole, rabeprazole, and pantoprazole in high yields (up to 92%) and with excellent enantioselectivities (up to 96% *ee*) [136].



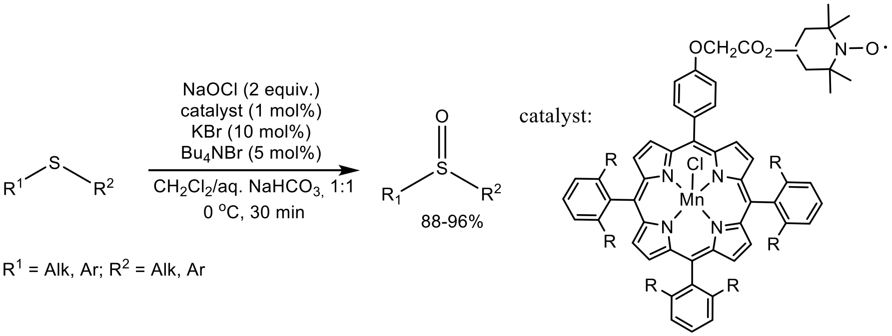
R^1, R^3 = Me, R^2, R^4 = OMe
R^1, R^4 = H, R^2 = OCH_2CF_3, R^3 = Me
R^1, R^4 = H, R^2 = $O(CH_2)_3Me$, R^3 = Me
R^1 = H, R^2, R^3 = OMe, R^4 = $OCHF_2$

An efficient and simple method for the oxidation of alkyl aryl sulfides to chiral sulfoxides in a high isolated yield (up to 98%) and good enantioselectivity (49–81% *ee*) has been proposed [137]. The reaction of *α*-, *β*-, and *γ*-cyclodextrins (CD) with alkyl aryl sulfides affords crystalline 1:1 or 2:1 complexes, depending on the cavity size and the nature of sulfide substituents. The high level of enantioselective oxidation of solid complexes suspended in water is due to the rigid fixation of sulfides in the chiral cavity. Sodium hypochlorite, hydrogen peroxide, *tert*-butylperoxide, or peracetic acid can act as oxidizing agents.

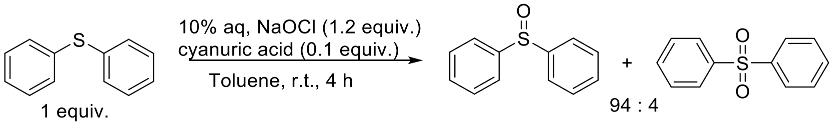


R = Me, Et, *n*-Pr, *n*-Bu, *i*-Bu, *t*-Bu
Ar = Ph, 1-naphthyl, 2-naphthyl, 9-phenanthryl

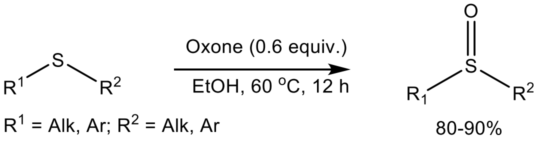
A number of procedures for the oxidation of sulfides to sulfoxides include treatment with halogens and its derivatives [138–140] and commercially available Oxone [141, 142]. Mn complexes of TEMPO-linked porphyrins efficiently catalyze the selective oxidation of sulfides using NaOCl as oxidant [139]. Various sulfides including diaryl sulfides were oxidized to the corresponding sulfoxides (metalloporphyrin, KBr/Bu_4NBr, CH_2Cl_2/saturated aq. $NaHCO_3$, 0 °C, 30 min) and no overoxidation to sulfone was observed on the basis of TLC analysis. The yields are excellent (88–96%) and the protective groups and hydroxyl groups remained intact during the reaction.



The oxidation of sulfides using aqueous NaOCl in the presence of a catalytic amount of imide under two-phase conditions has been developed [140]. The combination effectively converts various sulfides, including diaryl sulfides to the corresponding sulfoxides and sulfones. It was deduced that the imide could react with NaOCl to produce N-chloroimide, which would play roles of both the active oxidizing reagent and phase transfer catalyst.



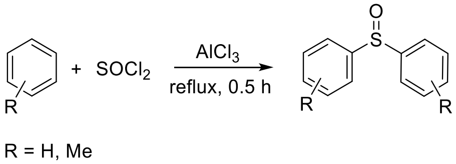
Oxone is a stable 2:1:1 ternary composite of $KHSO_5$, K_2SO_4 and $KHSO_4$, and its use in various organic transformations. Selective oxidation of sulfides was successfully performed by employing oxone as oxidant without using any catalyst/additive under mild reaction conditions (EtOH, 60 °C, 12 h) [141]. Notably, the reaction can be controlled by the chosen solvent. When water was used as the solvent, sulfones were obtained. This protocol worked well for various sulfides to the corresponding sulfoxides in ethanol or sulfones in water.



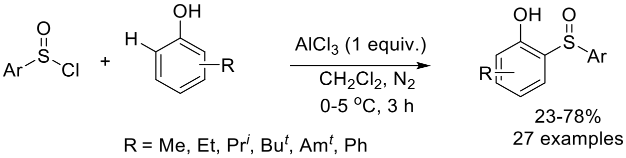
Recently, an ecobenign, catalyst-free, and scalable protocol for the chemoselective oxidation of sulfides to sulfoxides using Oxone as an oxidant has been developed [142]. Treatment of alkyl and aryl sulfides with oxone (0.7 equiv.) in MeCN/H_2O (1:3 v/v, r.t., 10–20 min) gives chemoselective corresponding sulfoxides in 88–95%. Various substituted alkyl aryl sulfides bearing methyl, nitro, bromo, iso-propyl and cyclopropyl as well as aldehyde and primary or secondary alcoholic groups were subjected to oxidation. During oxidation of diaryl and dibenzyl sulfides, chemoselective oxidation of sulfides to corresponding sulfoxides was also observed. In all the cases, the corresponding sulfoxides were obtained in excellent yield.

2,6-Dicarboxypyridinium chlorochromate was found to be an efficient and reasonable oxidizing agent for the very fast conversion of sulfides to sulfoxides under neutral and anhydrous conditions [49]. Both aliphatic and aromatic sulfides are oxidized with their reagent (MeCN, r.t., 8–50 min) to the corresponding sulfoxides in 80–96% yield. The oxidants/substrates ratios of 2:1 are employed. This reaction system can be applied to the oxidation of alkyl aryl and diaryl sulfides. Even an aryl sulfide with two strong electron-withdrawing NO_2-groups reacted smoothly to give the corresponding sulfoxide in 80% yield.

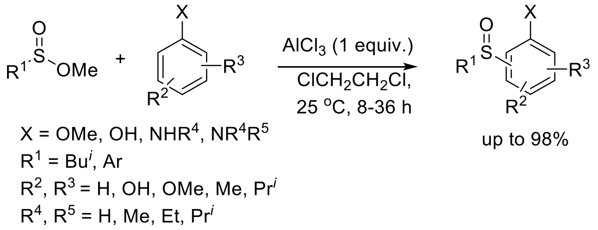
Classical method for incorporation of sulfenyl group into arenes is based on the reaction of aromatic compounds with thionyl chloride in the presence of $AlCl_3$ (Friedel–Crafts reaction) [143].



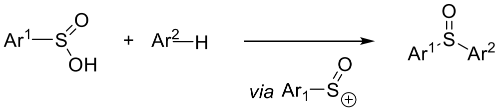
In the past years, the novel strategies for the sulfinylation of arenes were developed. It was shown that aryl sulfinyl chlorides [144] methyl sulfinates [145] and arylsulfinic acids can be used as electrophiles in [146, 147] reactions with aromatic systems. A number of 2- and 4-hydroxydiaryl sulfoxides by the direct arenesulfinylation of substituted phenols in the presence of anhydrous aluminum chloride was obtained. The reaction of equivalent amounts of unsubstituted or *para*-substituted benzenesulfinyl chlorides, substituted phenols, and anhydrous aluminum chloride in methylene chloride near 0 ° for several hours, followed by a simple work-up and purification, led to fair to good yields of hydroxydiaryl sulfoxides [144].



Methyl sulfinates were reacted with aromatic systems activated by OH, OR, NHR, and NR_2 groups under $AlCl_3$ catalysis ($ClCH_2CH_2Cl$, 25 °C, 8–36 h), to give aryl sulfoxides in up to 98% yield [145]. The very high regioselectivity usually observed in these sulfinylation reactions is rationalized on the basis of a Wheland intermediate having a trigonal bipyramidal structure in which steric and electronic interactions are significant factors strongly destabilizing the attack to the *ortho* positions.



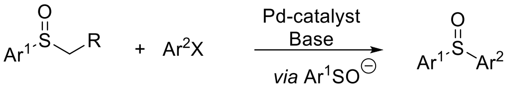
A novel and efficient electrophilic sulfenylation of indoles and arenes with arylsulfinic acids via an unusual sulfinyl cation was realized.



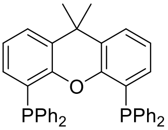
The substituted arylsulfinic acids bearing methyl, *tert*-butyl, methoxy, trifluoromethyl, and halogen on the aromatic rings reacted with various *N*-substituted indoles in water under catalyst- and additive-free conditions (r.t., 24 h) to afford the corresponding 3-arylsulfinylindoles with high yield (40 examples, up to 98% yield) [146]. More bulky 1,1′-biphenyl-, 1-naphthyl-, and 2-naphthylsulfinic acids also reacted with indoles smoothly to offer the desired sulfoxides in 70–81% yield. Analogously, diaryl sulfoxides from arylsulfinic acids and arenes have been prepared [147]. The reaction proceeds in air (CH_2Cl_2, 30 °C, 50 min) at the presence of $BF_3{\cdot}Et_2O$ (1.2 equiv.). At these conditions, substituted arylsulfinic acids underwent the reactions with electron-rich arenes (metoxy- and dimethoxybenzene derivatives), providing the corresponding sulfoxides in 50–91% yield. However, no product was obtained when toluene and benzene were used as arene sources.

Apart from the aforementioned methods, Pd-catalyzed synthesis of diaryl sulfoxides via arylation of in situ generated sulfenate anions with aryl halides has been developed. Sulfinyl esters [148], allyl [149], methyl [150], and benzyl sulfoxides [151] could be utilized as substrate to generate diaryl sulfoxides. For example, base mediated deprotonation of the *β*-sulfinyl esters under biphasic conditions (aqueous KOH/toluene, 1:1) first gives the corresponding ester enolate. The following retro-Michael reaction generates the sulfenate anion, which undergoes palladium-catalyzed cross-coupling with aryl iodide and produces the diaryl sulfoxide [148]. Allylic sulfoxides, via [2, 3]-sigmatropic rearrangement and oxidative addition of the resulting allylic sulfenate esters to Pd(0), are found to be excellent precursors of sulfenate anions. This hitherto unknown reactivity is applied in a new Pd(0)-catalyzed domino sequence involving sulfenate anion generation followed by arylation to afford aryl sulfoxides [149]. The direct *S*-arylation of unactivated aryl sulfoxides catalyzed by [Pd(IPr*)(cin)Cl] is described. Several aryl methyl sulfoxides were coupled to various aryl bromides and chlorides in moderate to good yields

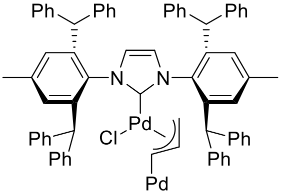
(17 examples, 34–85%) [150]. The [Pd(dba)$_2$]/NiXantPhos catalyst system successfully promotes a triple relay process involving sulfoxide α-arylation, C–S bond cleavage, and C–S bond formation [151]. A wide range of aryl benzyl sulfoxides, as well as alkyl benzyl sulfoxides with various (hetero)aryl bromides were employed in the triple relay process in good to excellent yields (85–99%). Moreover, aryl methyl sulfoxides, dibenzyl sulfoxides, and dimethyl sulfoxide could be utilized to generate diaryl sulfoxides involving multiple catalytic cycles by a single catalyst.



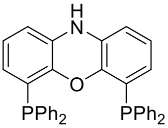
[148]	[149]	[150]	[151]
R = $CH_2CO_2Bu^t$	R = CH=CH$_2$	R = H	R = Ph
X = I	X = I	X = Br, Cl	X = Br
Pd(dba)$_2$ (5 mol%)	Pd(dba)$_2$ (2 mol%)	[Pd(IPr*)(cin)Cl] (5 mol%)	Pd(dba)$_2$ (5 mol%)
Xantphos (10 mol%)	Xantphos (5 mol%)	KOAm^t (3 equiv.)	NiXantphos (7.5 mol%)
KOH (20 equiv.)/H$_2$O	KOBu^t (2 equiv.)	CPME, 110 °C, 20 h	NaOBu^t (3 equiv.)
Toluene, 70 °C, 4 h	Toluene, reflux, 2 h	34-85%	CPME, 80 °C, 12 h
35-96%	28-60%		85-94%



Xantphos



[Pd(IPr*)(cin)Cl]



NiXantphos

3.3 Aromatic Sulfones

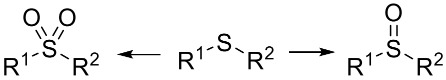
Sulfones are applied in laboratory and industry as solvents (sulfolane and sulfolene) and dyes (Active Blue 2KT, Active Orange ZhT). They are used in the directed synthesis of new drugs [152] and high-tech materials [153–155]. Aryl sulfones serve as a platform for design of such chemo-therapeutic agents as dapsone, solusulfone, diutsifon, and sulfamethin.

Aromatic sulfones are also intriguing models for studying the nature of electronic interaction of the aromatic core with the RSO$_2$ fragment [156]. Theoretically, the conformational structure of such compounds can be determined by the conjugation and induction effect as well as steric factors, which, in the case of alkyl aryl sulfones, depend mainly on the volume of the alkyl radical.

Alike sulfoxides, synthesis of sulfones can be achieved following oxidative as well non-oxidative routes [119, 157]. Aromatic sulfones are most often obtained by the action of various oxidizing agents on the corresponding sulfides and sulfoxides.

Concentrated or fuming nitric acid, $KMnO_4$, hypochloric acid or sodium hypochlorite, chromic acid, and hydrogen peroxide are common oxidizing agents. However, when nitric acid is used, the reaction usually stops at the sulfoxide formation stage.

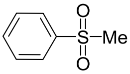
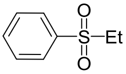
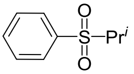
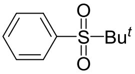
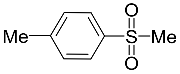
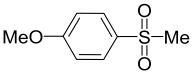
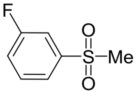
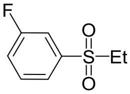
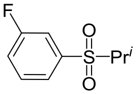
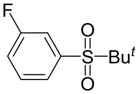
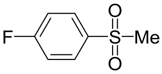
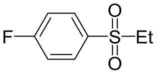
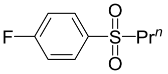
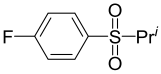
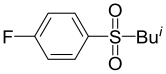
The direct oxidation of sulfides is undoubtedly the most straightforward, atom-economical, and reliable way to form sulfones and sulfoxides. A few procedures are suitable for switchable synthesis of sulfoxides or sulfones via the oxidation reaction of sulfides with the same oxidant by adjusting a reaction parameter such as temperature [147, 158, 159], time [134, 160], pH value [161], additive [140, 142, 160], or solvent [141, 158].



An efficient and switchable methodology for the chemoselective synthesis of sulfones and sulfoxides via oxidation of sulfides was developed [159]. The chemoselectivities of products were simply controlled by reaction temperature using O_2/air as the terminal oxidant and oxygen source. A wide variety of diaryl sulfides and aryl(heteroaryl) alkyl sulfides with both electron-donating and electron-withdrawing groups were compatible to assemble the desired sulfones (O_2/air, 100 °C, 20 h) in 72–98% yield (20 examples). Dipropyleneglycol dimethyl ether (DPDME) had a dual role of solvent and promoter and could be reused at least three times in 74 − 86% yield due to its good reusability performance. Oxidation of sulfides at 80 °C for 20 h produced sulfoxides in 13–87% yield. Oxidation of sulfides by employing Oxone as oxidant (1.5 equiv., 60 °C, 12 h) in water almost exclusively gave the sulfone (88–97% yield) [141]. When ethanol was used as the solvent, only sulfoxides were obtained in excellent yield. Reaction of sulfides with oxidative system Oxone/wet Al_2O_3 (1 equiv.) in refluxing CH_2Cl_2 gave only sulfoxides, while reaction with excess oxidant in refluxing $CHCl_3$ gave only sulfones (via the corresponding sulfoxide) [158]. The selective oxidation of sulfides to sulfones was achieved (MeOH, r.t., 2.5–24 h) in 75–97% yields with borax as a recyclable catalyst and H_2O_2 as the terminal oxidant under the pH 10–11 of the reaction medium [161]. The borax/H_2O_2 system can chemoselectively oxidize alkyl and aryl sulfides in the presence of oxidation-prone functional groups such as C=C, CN, and OH.

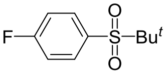
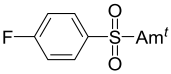
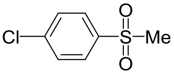
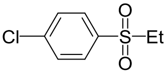
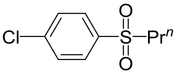
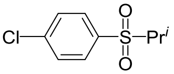
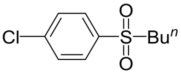
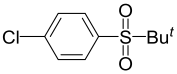
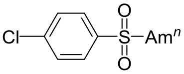
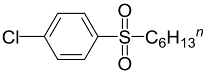
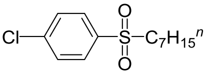
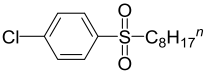
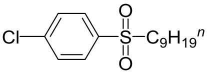
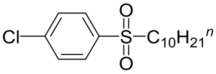
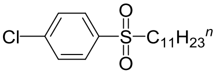
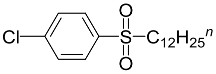
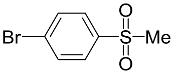
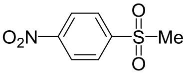
In many cases, hydrogen peroxide in acetic acid is employed for the synthesis of sulfones. The yields of sulfones are good and the target products are easily separated. Using this approach, a series of alkyl aryl sulfones bearing functional substituents in the benzene ring has been synthesized (Table 3.2). The oxidation of alkyl aryl sulfides is carried out with a 30% solution of H_2O_2 in acetic acid (60–70 ° C, 2.5–3 h). The reaction selectively proceeds without oxidation of functional groups in the aromatic ring to furnish sulfones in high isolated yields (89–100%) [128–130].

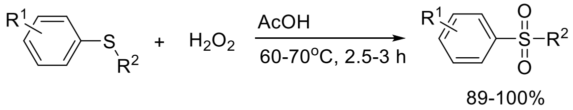
Table 3.2 Alkyl aryl sulfones

No.	Structure	Yield, %	B.p., °C /torr (m.p., °C)	n_D^{20}	d_4^{20}
1		96	(87)		
2		96	140/1 (42)		
3		95	140-142/1	1.5300	1.1598
4		92	(99)		
5		94	(89)		
6		95	(115)		
7		94	123/2 (40)		
8		95	127/2	1.5156	1.2966
9		94	127/1.5	1.5100	1.2667
10		96	(117)		
11		95	(73)		
12		92	129/2 (29)		
13		96	129/1.5 (42)		
14		97	(84)		
15		95	(40)		

(continued)

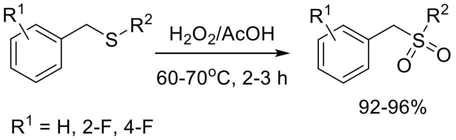
Table 3.2 (continued)

16		90	(91)		
17		92	(102)		
18		95	(98)		
19		94	(35)		
20		98	(39)		
21		97	(83)		
22		98	(36)		
23		97	(92)		
24		99	(29)		
25		97	(34)		
26		98	(15)	1.5305	1.1530
27		95	(28)		
28		98	(30)		
29		100	(34)		
30		99	(50)		
31		99	(48)		
32		93	(103)		
33		89	(143)		



R^1 = H, 4-Me, 4-MeO, 3-F, 4-F, 4-Cl, 4-Br, 4-NO_2
R^2 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, *t*-Am, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17},
n-C_9H_{19}, *n*-$C_{10}H_{21}$, *n*-$C_{11}H_{23}$, *n*-$C_{12}H_{25}$

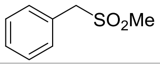
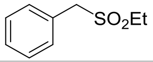
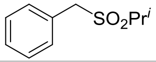
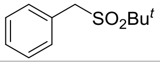
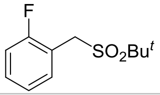
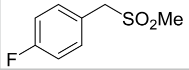
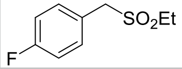
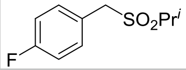
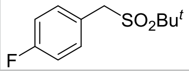
Under the action of a 30% solution H_2O_2 on alkyl benzyl sulfides (AcOH, 60–70 °C, 2–3 h), alkyl benzyl sulfones have been synthesized in 92–96% yields (Table 3.3) [130].



R^1 = H, 2-F, 4-F
R^2 = Me, Et, *i*-Pr, *t*-Bu

The obtained sulfones are white crystalline substances. The structure of alkyl radicals and substituents in the benzene ring does not affect the yield of sulfones.

Table 3.3 Alkyl benzyl sulfones

No.	Structure	Yield (%)	M.p., °C
1		95	127
2		93	81
3		94	57
4		93	121
5		92	59
6		94	105
7		96	82
8		93	110
9		92	131

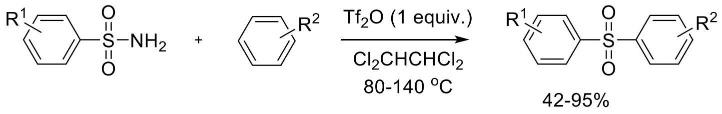
Other procedures for aryl sulfones preparation are based on the electrophilic aromatic substitution of arenes with arenesulfonic acids [162, 163] or with sulfonic halides [163–166] (Friedel–Crafts reaction). Alkyl aryl sulfones are usually synthesized from alkyl sulfonyl chlorides and aromatic hydrocarbons [167, 168].

$$\mathrm{RSO_2X} \quad + \quad \mathrm{Ar{-}H} \xrightarrow{\text{Lewis or Bronsted acid}} \mathrm{RSO_2Ar}$$

R = Alk, Ar; X = OH, Cl

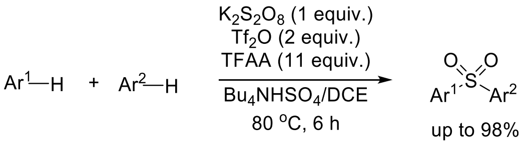
In the classic version, these reactions are performed in the presence of stoichiometric amounts of conventional Lewis ($AlCl_3$, $FeCl_3$) or Brønsted acid (H_3PO_4). A variety of more efficient catalysts have been developed throughout the last decades. 1-Butyl-3-methylimidazolium chloroaluminate ionic liquids have been employed as an unconventional reaction media and as Lewis acid catalyst for Friedel–Crafts sulfonylation reaction of substituted benzenes with 4-methylbenzenesulfonylchloride. The substrates exhibited enhanced reactivity, furnishing almost quantitative yields of diaryl sulfones, under ambient conditions [166]. The simple methodology for sulfonylation of arenes with sulfonyl chloride, sulfonic anhydride or sulfonic acid as sulfonylating agent, catalyzed by a small amount of reusable solid acid catalyst has been developed [163, 164]. The high activity of Fe^{3+}-montmorillonite is due to a compatible mixture of Lewis and Brønsted acid sites in large number per unit volume. Fe^{3+}-montmorillonite is capable of catalyzing the sulfonylation of activated and deactivated arenes such as chlorobenzene and bromobenzene.

An alternative access to aryl sulfones via Friedel–Crafts reaction is sulfonylation of arenes with stable primary sulfonamides in the presence of triflic anhydride as activating agent. The reaction of arenes with sulfonamides proceeded smoothly in $Cl_2CHCHCl_2$ at 80–140 °C to give the desired products in good to excellent yields [169].

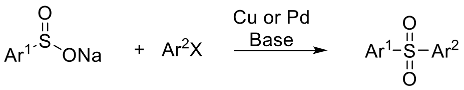


R^1 = H, 4-Me, 4-Cl, 4-NO_2
R^2 = H, Me, OMe, Cl, I, Br, Ph, 1,4-Me_2, 1,3-Me_2, 1,3,5-Me_3

An unprecedented double C–S bond formation method has been developed to prepare both symmetrical and unsymmetrialc diarylsulfones with simple arenes and $K_2S_2O_8$ as a highly effective sulfonating agent in a single step [170]. The reaction demonstrates excellent reactivity (46 examples), good functional group tolerance and high yields (up to 98%). In most cases of using mono-substituted arenes, one *para* regioisomer was obtained as the major product and only trace amounts of other regioisomers could be observed.

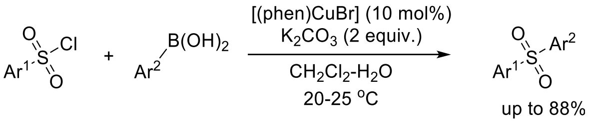


In recent years, transition-metal-catalyzed coupling reactions of either sulfinates as nucleophilic or sulfonyl halides as electrophilic coupling partners have emerged as attractive alternatives to the traditional procedures. They allow the synthesis of sulfones in a regiospecific manner, often under milder reaction conditions compared to those used in sulfide oxidation or electrophilic sulfonylation reactions. Therefore, metal-catalyzed coupling reactions can expand the functional group compatibility considerably.

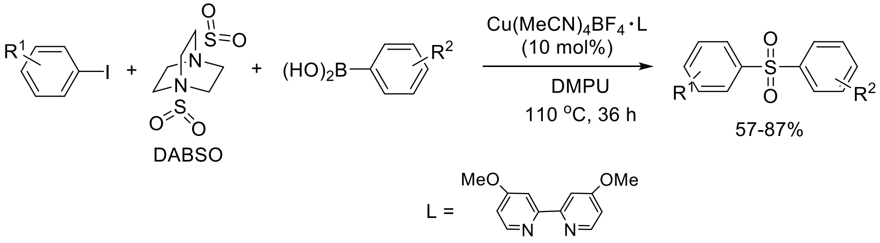


Various efficient catalyst systems for the sulfonylation were developed. The progress in the synthesis of diaryl sulfones via the cross-coupling reactions is mainly associated with the use of copper salts. Since the first report by Suzuki [171] on the copper-assisted coupling of sodium sulfinates with non-activated iodoarenes (CuI, DMF, 110 °C, 6 h), several catalytic versions of this type of coupling were reported [172, 173]. Arenediazonium salts [174] and boronic acids [175–178] as alternative to aryl halides can be used for the synthesis of diaryl sulfones.

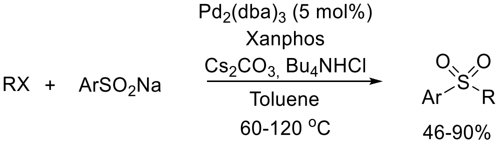
An efficient and convenient method for the synthesis of diaryl sulfones was developed through the Cu-catalyzed cross-couplings of arylsulfonyl chlorides and arylboronic acids at room temperature in open air [176]. This method is characterized by the use of inexpensive and readily available catalyst (CuBr, 1,10-phenanthroline) and substrates, mild reaction conditions, wide functionality tolerance, short reaction times for most substrates (<10 min), and moderate to good yields.



Using a simple copper(I) catalyst has allowed a high-yielding sulfonylative Suzuki–Miyaura cross-coupling reaction to be developed [177]. The process provides a single-step route to diaryl sulfones from the direct combination of aryl boronic acids, sulfur dioxide and aryl iodides, and represents the first sulfonylative variant of a classic cross-coupling reaction. Sulfur dioxide is delivered from the surrogate reagent, DABSO. Variation of the reaction conditions allowed interruption of the sulfonylative-Suzuki coupling, resulting in the formation of a presumed Cu–sulfinate intermediate. These sulfinates could be trapped as their sodium salts and treated with electrophiles to allow access to arylalkyl sulfones, *β*-hydroxyl sulfones, sulfonamides, and sulfonyl fluorides.



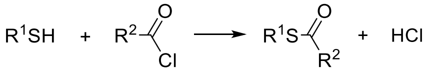
The palladium-catalyzed reaction of sulfinic acid salts with a wide variety of aryl and vinyl halides or triflates provides unsymmetrical diaryl sulfones and aryl vinyl sulfones in good to excellent yields [179, 180]. The reaction is strongly influenced by the presence of *n*-Bu_4NCl, and the use of Xantphos, a rigid bidentate ligand with a wide natural bite angle, was found to be crucial for the success of the reaction. With neutral, electron-rich, and electron-poor aryl iodides best results were obtained by using $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, and *n*-Bu_4NCl, in toluene at 80 °C [179]. Two general procedures were employed with aryl bromides and triflates: sodium *p*-toluenesulfinate, $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, 120 °C, in toluene with *n*-Bu_4NCl (for neutral, electron-rich, and slightly electron-poor aryl bromides or triflates) and without *n*-Bu_4NCl (for electron-poor aryl bromides or triflates). Under these conditions, the reaction gives unsymmetrical diaryl sulfones in good to high yields with many neutral, electron-rich and electron-poor aryl and heteroaryl bromides or triflates and tolerates a variety of functional groups, including ether, cyano, aldehyde, and nitro groups. With vinyl triflates, best results were obtained at 60 °C omitting *n*-Bu_4NCl [180].



3.4 *S*-Alkyl, *S*-Aryl, *S*-Benzylthioacylates, and Organylthiobenzoates

Thiocarboxylic acid S-esters play an important role in design of pharmaceutical and biologically active compounds, as well as natural congeners [181–184]. To date, numerous methods for the preparation of thiocarboxylic acid esters have been developed. Generally, these methods comprise esterification of thiols or their derivatives with various acylating agents. Recent advances in this area are summarized in the review [185].

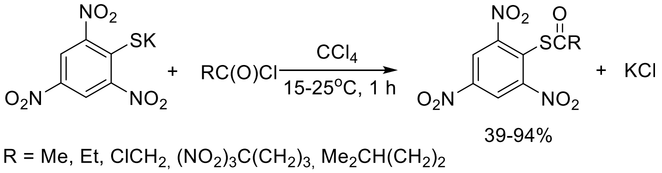
Among the classical and most popular acylating agents are carboxylic acid chloroanhydrides. Aromatic esters of thiocarboxylic acids ArSC(O)R are obtained by the reaction of carboxylic acid chloroanhydrides with aryl thiols. These reactions should be executed in the presence of bases capable of binding the released HCl (for example, pyridine, triethylamine, etc.).



2-Mercaptobenzoxazole and -benzothiazole interact with benzoyl chlorides (THF, pyridine as a base, reflux, 24 h) to give the corresponding *S*-benzoates in a yield of 60–89% [186]. At the same time, a similar reaction under the action of ultrasonic activation occurs at room temperature for 5 min and leads to the formation of thioesters in almost quantitative yields (81–100%).

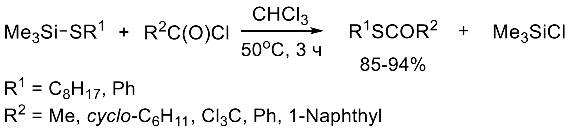
The two-phase system, aqueous alkali/CH_2Cl_2, in combination with tetrabutylammonium chloride as a phase transfer catalyst turns out to be an efficient medium for the acylation of alkyl- and aryl thiols by various acyl chlorides [187]. The reaction takes place at 0 °C for 5 min affording the target products in 87–100% yields.

When potassium 2,4,6-trinitrothiophenolate is allowed to contact with alkyl- and nitroalkylcarboxylic chlorides at room temperature, the corresponding *S*-arylthioacylates are easily formed in 39–94% yields [188].



Using acryloyl chloride as an example, it has been shown that unsaturated acid chloroanhidrides undergo this reaction upon heating (CCl_4, reflux, 3 h).

Acyl chlorides react with trimethylsilyl thioesters without catalysts and bases ($CHCl_3$, 50 °C, 3 h) delivering thiocarboxylic acid esters in 85–94% yields [189].



$$Me_3Si\text{-}SR^1 + R^2C(O)Cl \xrightarrow[50^\circ C,\ 3\ ч]{CHCl_3} \underset{85\text{-}94\%}{R^1SCOR^2} + Me_3SiCl$$

$R^1 = C_8H_{17}$, Ph

R^2 = Me, *cyclo*-C_6H_{11}, Cl_3C, Ph, 1-Naphthyl

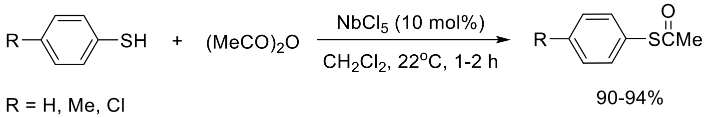
Carboxylic acids and their anhydrides act as alternative acylating agents. As a rule, the reactions of thiols with anhydrides proceed at room temperature in the presence of basic or acid catalysts.

The interaction of alkyl-, benzyl-, and aryl thiols with carboxylic acid anhydrides in polar solvents (MeCN, EtOAc) in the presence of K_2CO_3 (22–24 °C, 8–24 h) gives rise to thiocarboxylic acid esters with a yield of 85–97% [190].

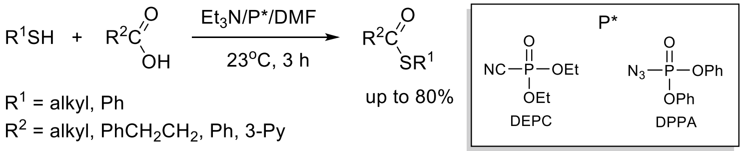
$$\mathrm{R^1SH} + \mathrm{(R^2CO)_2O} \xrightarrow[22\text{-}24^{\circ}\mathrm{C},\ 8\text{-}24\ \mathrm{h}]{\mathrm{K_2CO_3\ (2\ equiv.)}\ \ \mathrm{MeCN}} \underset{85\text{-}97\%}{\mathrm{R^2C(O)SR^1}} + \mathrm{R^2CO_2H}$$

R^1 = Ph, 4-MeC_6H_4, 4-BrC_6H_4, $PhCH_2$, *n*-$C_{12}H_{25}$, cyclo-C_6H_{11}, $OH(CH_2)_2$, $OH(CH_2)_4$
R^2 = Me, *t*-Bu, *t*-BuO, Ph

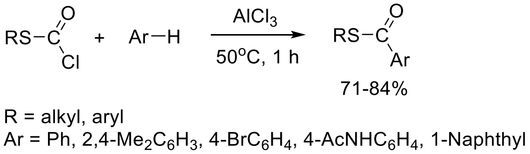
With catalytic amounts of $NbCl_5$ (CH_2Cl_2, room temperature, 1–2 h), this reaction proceeds much faster to produce *S*-arylacetates in 90–94% yields [191].



The heating or activating agents and catalysts are employed to activate carboxylic acids in condensation reactions with thiols. For instance, auxiliary reagents, diethyl phosphorocyanidate (DEPC), and diphenyl phosphoroazidate (DPPA) promote the condensation of carboxylic acids with aliphatic and aromatic thiols. The reaction proceeds in DMF in the presence of triethylamine (room temperature, 3 h), the yield of organthioacylates being up to 80% [192].



An alternative approach to the synthesis of *S*-arylacylates is the interaction of alkyl- and arylthiocarboxylic acid chloroanhidrides $R^1SC(O)Cl$ with aromatic compounds under the Friedel–Crafts reaction conditions [193].



Also, thiocarboxylic acid *S*-esters can be obtained in moderate yields (24–58%) via carbonylation of aromatic and aliphatic thiols and their derivatives (sulfides, disulfides) with carbon monoxide [194]. The reaction is carried out in the presence of carbonyls of cobalt, chromium or aluminum oxides ($Co_2(CO)_3$, CoO/Al_2O_3, Cr_2O_3/Al_2O_3) at 250–300 °C under high pressure (100–1000 atm) [194].

$$2\,RSH + CO \xrightarrow[\substack{250\text{-}300^{\circ}C,\\ 100\text{-}1000\ atm}]{Co_2(CO)_3/toluene} RCOSR + H_2S$$

To study the conjugation effects, a series of *S*-alkyl, *S*-aryl, and *S*-benzylthioacylates has been synthesized by the reaction of alkyl-, aryl-, and benzyl thiols with acyl halides (60–100 °C, 4–6 h) in the absence of catalysts and condensing agents (Table 3.4) [128, 195–199].

$$R^1SH + R^2C(O)Cl \xrightarrow[60\text{-}100^{\circ}C,\ 4\text{-}6\ h]{} \underset{44\text{-}98\%}{R^1SC(O)R^2} + HCl$$

R^1 = Et, *n*-Pr, Ph, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-AcC_6H_4, 4-$NO_2C_6H_4$, 2,4,6-$Me_3C_6H_2$, $PhCH_2$, 2-$FC_6H_4CH_2$, 3-$FC_6H_4CH_2$, 4-$FC_6H_4CH_2$

R^2 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, CH_2Cl, CCl_3, Ph

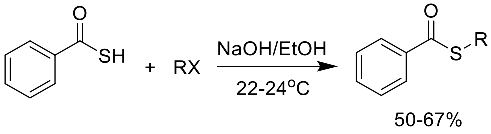
Acylation of the same thiol with different acylating agents proceeds faster for acyl halides bearing a stronger electronegative substituent R^2 in acylhalide. The reaction is facilitated in the series $MeC(O)Cl < ClCH_2C(O)Cl < Cl_3CC(O)Cl$ due to an increase in the positive charge on the carbonyl carbon atom, i.e. owing to polarization of the Cl–C bond. When going from acetic acid chloroanhidride to chloroacetic acid and trichloroacetic acid chloroanhidride, the yield of thioacetate augments (Table 3.4).

Naturally, the acylation rate also depends on the structure of the starting aromatic thiol R^1SH: the higher electron density on the sulfur atom, the higher is the reaction rate.

The constants of the synthesized *S*-alkyl-, *S*-aryl-, and *S*-benzylthioacylates are presented in Table 3.4.

The effect of substituents in the benzene ring on stretching vibrations of the carbonyl group in thioacylates is discussed in detail in Sect. 6.4.

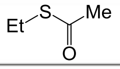
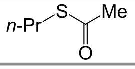
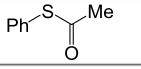
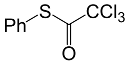
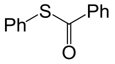
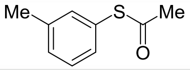
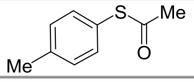
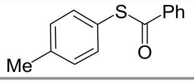
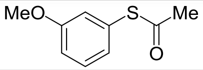
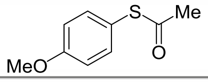
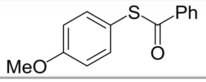
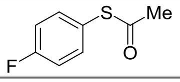
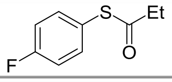
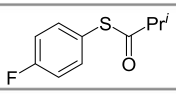
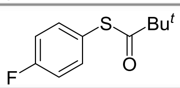
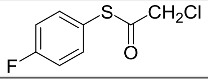
An alternative approach, based on the interaction of thiobenzoic acid with alkyl halides, has been employed to synthesize alkylthiobenzoates. In the case of primary and secondary alkyl halides, the reaction proceeds at room temperature in an alcohol solution of NaOH and results in the formation of thiobenzoic acid *S*-esters in a yield of 50–67% (Table 3.5).



R = Me, Et, *i*-Pr, CH_2CH_2Cl, CH_2CH_2OH
X = I, Br, Cl

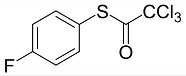
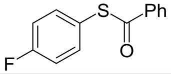
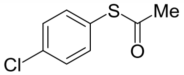
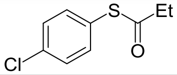
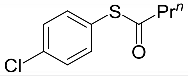
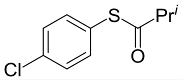
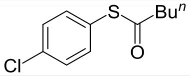
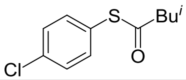
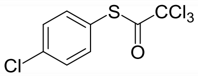
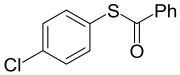
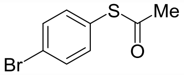
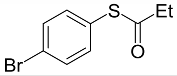
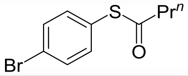
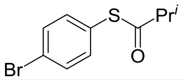
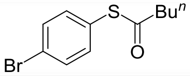
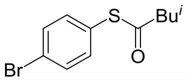
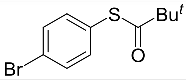
The reaction with thiobenzoic acid and dichloromethane and -ethane is accomplished under similar conditions, the corresponding alkylenedithiobenzoates being obtained in 60 and 25% yields, respectively [130].

Table 3.4 *S*-Alkyl-, *S*-aryl- and *S*-benzylthioacylates

No.	Formula	Yield, %	B.p., °C /torr (m.p., °C)	n_D^{20}	d_4^{20}
1	2	3	4	5	6
1		82	116	1.4518	0.9775
2		82	136	1.4556	0.9793
3		79	85/3.5	1.5706	1.1218
4		94	118/2 (55)		
5		85	152/2 (55)		
6		90	96/3	1.5572	1.0886
7		90	76/0.5	1,5635	1,0871
8		77	174/2 (63)		
9		66	105/1	1.5706	1.1596
10		77	98/0.5	1.5721	1.1586
11		75	(95)		
12		65	84-85/4	1.5452	1.2100
13		89	93/3	1.5369	1.1563
14		88	92/2	1.5300	1.1246
15		68	89/1	1.5176	1.0851
16		72	108/2	1.5660	1.3626

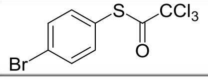
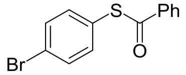
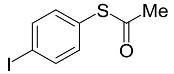
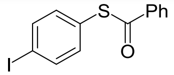
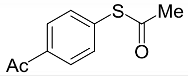
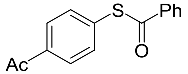
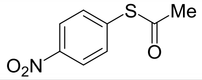
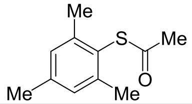
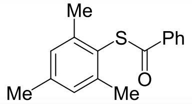
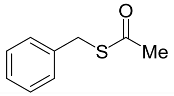
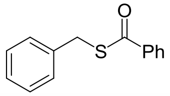
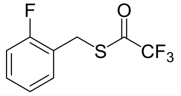
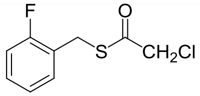
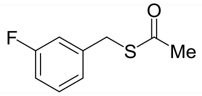
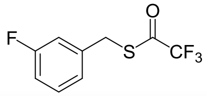
(continued)

Table 3.4 (continued)

17		86	117/2	1.5670	1.4995
18		93	162/3 (51)		
19		66	108/3 (36)	1.5785^{30}	1.176^{30}
20		90	138/9	1.5731	1.2245
21		88	150/9	1.5621	1.1725
22		86	159/10	1.5587	1.1676
23		87	154/6	1.5550	1.1465
24		86	126/1.5	1.5501	1.1386
25		92	135/4 (42)		
26		85	186/3 (68-69)		
27		78	96/1 (53)		
28		89	120/1.5	1.5933	1.4420
29		88	138/2.5	1.5802	1.3881
30		87	120/1.5	1.5790	1.3833
31		87	154/1	1.5728	1.3441
32		86	141/2	1.5690	1.3413
33		66	135/2	1.5742	1.2787

(continued)

Table 3.4 (continued)

34		91	165/7 (45.5)		
35		84	196/3 (82)		
36		78	(56)		
37		85	200/3 (89-90)		
38		76	(55-56)		
39		73	(132)		
40		75	(82-83)		
41		44	115/2 (53-54)		
42		69	170/2 (85)		
43		93	84/2	1.5409	1.1843
44		90	(37)		
45		77	72/1	1.4850	1.3681
46		85	120/1	1.5651	1.3459
47		95	85/2	1.5405	1.1850
48		96	160/13	1.4145	1.2653

(continued)

Table 3.4 (continued)

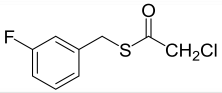
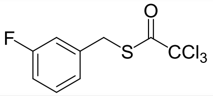
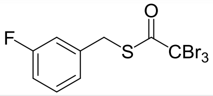
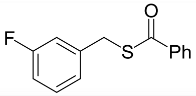
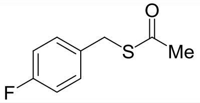
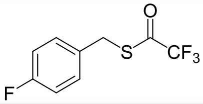
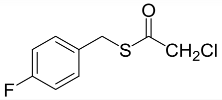
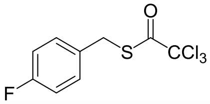
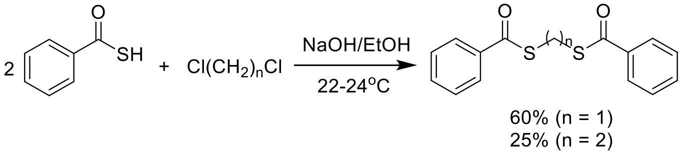
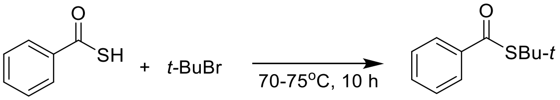
49		98	130/2	1.5548	1.3284
50		96	140/6	1.5649	1.4426
51		97	140/1	1.6180	2.0452
52		97	155/17 (105)		
53		95	87/2	1.5436	1.1882
54		84	72/1	1.4875	1.4465
55		95	124/1	1.5587	1.3182
56		88	135/1 (37)		

Table 3.5 Organyl thiobenzoates

No.	Structure	Yield (%)	B.p., °C/torr (m.p., °C)	n_D^{20}	d_4^{20}
1	PhC(O)SMe	60	82/2	1.5933	1.1533
2	PhC(O)SEt	65	86/2	1.5640	1.0967
3	PhC(O)SPr^i	62	84/2	1.5615	1.0685
4	PhC(O)SBu^t	20	80/2	1.6006	1.0362
5	PhC(O)SCH$_2$CH$_2$Cl	50	125/2	1.5940	1.3235
6	PhC(O)SCH$_2$CH$_2$OH	67	140/2	1.5960	1.2362
7	PhC(O)SCH$_2$SC(O)Ph	60	(107)		
8	PhC(O)SCH$_2$CH$_2$SC(O)Ph	25	(101)		



The heating of thiobenzoic acid with *tert*-butyl bromide (70–75 °C, 10 h) gives *tert*-butylthiobenzoate in 20% yield [130].

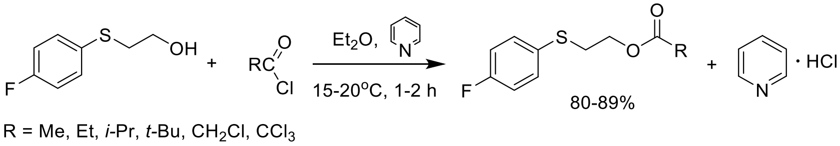


The analysis of ^{13}C NMR spectra of aromatic thioesters and the effect of various substituents R on chemical shifts of the benzene ring and the carbonyl group carbons (effects of *p*–π conjugation) are discussed in Sect. 6.1.2 of this monograph.

3.5 2-(Arylthio)ethyl acylates

2-(4-Halophenylthio)ethanols are employed as the starting reagents for the synthesis of 2-(arylthio)ethyl acylates, model compounds for the study of the mutual influence of aryl and acyl radicals and conjugation effects through a sulfur atom and two methylene groups.

The reaction of 2-(4-fluorophenylthio)ethanol with organic acid chloroanhidrides in the presence of pyridine as a base (Et_2O, room temperature, 1.5–2 h) affords a series of 2-(arylthio)ethyl acylates in up to 89% yields (Table 3.6) [200].

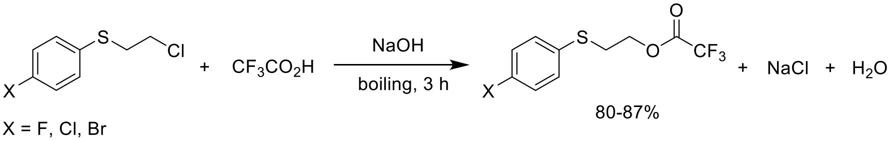


The reaction proceeds exothermically and in some cases requires external cooling to remove the exothermic effect.

CF_3CO_2H is a less reactive acylating agent. The esterification of trifluoroacetic acid with 2-(4-fluorophenylthio)ethanol in the presence of H_2SO_4 results in the corresponding trifluoroacetate in a moderate yield (36%). The trifluoroacylation of 2-(4-halophenylthio)ethyl chloride gives 2-(arylthioethyl) trifluoroacylates in the yield of 80–87% (Table 3.6) [200].

Table 3.6 2-(Arylthio)ethyl acylates

No.	Structure	Yield (%)	B.p., °C/torr	n_D^{20}	d_4^{20}
1	$4\text{-}FC_6H_4SCH_2CH_2OC(O)Me$	89	114/2	1.5295	1.2105
2	$4\text{-}FC_6H_4SCH_2CH_2OC(O)Et$	82	124/1	1.5356	1.1750
3	$4\text{-}FC_6H_4SCH_2CH_2OC(O)Pr^i$	81	122/1	1.5340	1.1592
4	$4\text{-}FC_6H_4SCH_2CH_2OC(O)Bu^t$	86	114/1	1.5200	1.1400
5	$4\text{-}FC_6H_4SCH_2CH_2OC(O)CH_2Cl$	86	150/2	1.5470	1.3238
6	$4\text{-}FC_6H_4SCH_2CH_2OC(O)CCl_3$	87	168/2	1.5478	1.4259
7	$4\text{-}FC_6H_4SCH_2CH_2OC(O)CF_3$	83	96/2	1.4917	1.3448
8	$4\text{-}ClC_6H_4SCH_2CH_2OC(O)CF_3$	87	153/13	1.5052	1.3845
9	$4\text{-}BrC_6H_4SCH_2CH_2OC(O)CF_3$	80	138/5	1.5232	1.5695



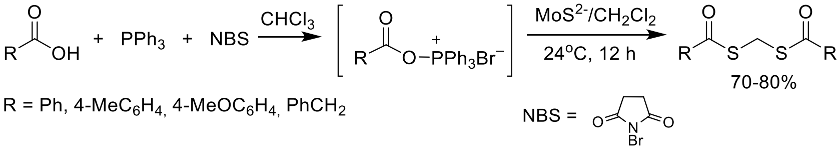
3.6 Dithiocarboxylic Acid Dibenzyl Esters

Dithiodicarboxylic acid diesters $RSC(O)R^1C(O)SR$ are of interest as physiologically active substances, stabilizers of polymeric materials, additives to oils and fuels, as well as intermediates for organic synthesis [183, 201–206].

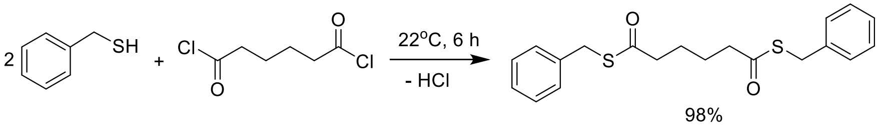
The closest analogs of these compounds are monothiocarboxylic acid esters $R^1C(O)SR$. The latter are commonly synthesized by the reaction of preliminarily prepared alkali or alkali-earth metal thiolates with carboxylic acid chloroanhidrides. The reaction is implemented in an alcohol, aqueous-alcohol or aqueous solution usually using a stoichiometric amount of alkali or alkali-earth metal hydroxides [207, 208].

Examples of $RSC(O)R^1C(O)SR$ synthesis are described in [209], where it is shown that dicarboxylic acid chloroanhydrides readily react with thiols in the presence of pyridine. Under similar conditions (pyridine, room temperature), benzoyl chloride interacts with dithiols to form dithioesters in moderate yields [202].

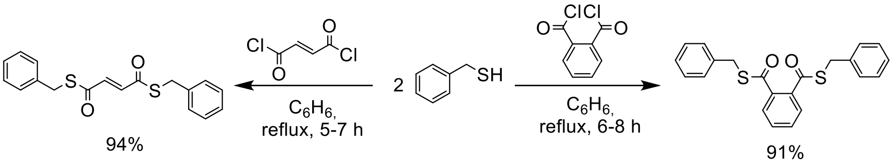
A fundamentally new method for the synthesis of thioesters from carboxylic acids via acyloxyphosphonium intermediates using benzyltriethylammonium tetrathiomolybdate as the synthetic equivalent of sulfide-ion has been developed [210].



At the same time, it has been demonstrated [211] that the reaction of adipinic acid dichloroanhydride with benzyl thiol is successfully realized upon simple mixing the reactants at room temperature to furnish the corresponding dithioester in almost quantitative yield (98%).



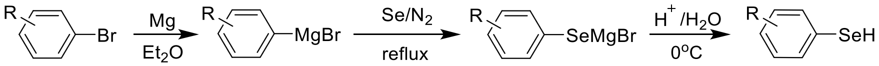
The benzyl dithioesters of fumaric and phthalic acids are obtained from benzyl thiol and the corresponding dichloroahnydrides by boiling in benzene (5–8 h), the yields ranging 91–94% [211].



Dithiocarboxylic acid dibenzyl esters are colorless crystalline substances, readily soluble in common organic solvents, and are stable upon storage. In the IR spectra of the obtained thioesters, the stretching vibration bands of the carbonyl group are observed at 1690–1720 cm^{-1}.

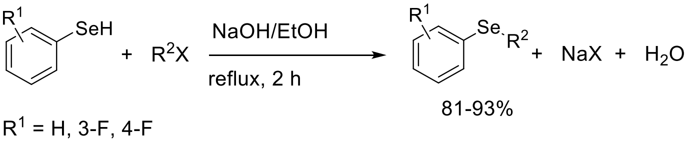
3.7 Derivatives of Aromatic Selenols

Selenols are selenium analogs of thiols. The most reliable and general method for their synthesis is based on the interaction of Grignard reagents with dry powdered selenium in boiling ether with subsequent hydrolysis (according to the Foster method [212]).



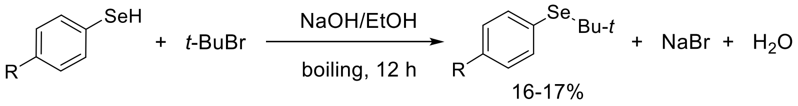
A series of aromatic selenols (45–61% yields) has been obtained by the reaction of substituted aryl magnesium bromides RC_6H_4MgBr (R=H, 4-MeO, 4-EtO, 4-F) and 3-fluorophenyl magnesium chloride $3\text{-}FC_6H_4MgCl$ with elemental selenium under helium atmosphere (to prevent the formation of diselenides). The selenols obtained are used as the starting compounds for the preparation of aryl organyl selenides, analogs of the corresponding sulfides [130].

Under the conditions of aryl thiols alkylation (NaOH/EtOH, 80 °C), aryl selenols interact with primary and secondary alkyl halides to form alkyl aryl selenides in a yield of 81–93% (Table 3.7) [130].



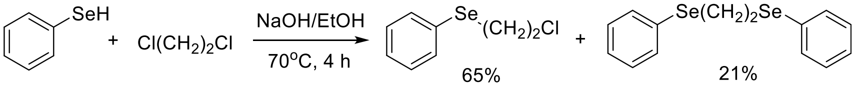
R^1 = H, 3-F, 4-F
R^2 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *s*-Bu, *n*-Am, Allyl, *cyclo*-C_6H_{11}, $PhCH_2$
X = Cl, Br, I

In contrast to aryl thiols, aryl selenols react with tertiary alkyl halides not so readily. Despite a two-fold molar excess of *t*-BuBr and an increase in the reaction time up to 12 h, the isolated yield of aryl *tert*-butyl selenides does not exceed 17%.

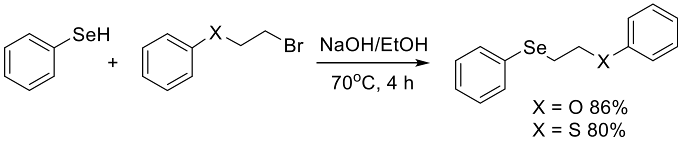


R = H, 4-F

The interaction of selenophenol with an excess of dichloroethane (NaOH/EtOH, 70 °C, 4 h) produces 2-chloroethylphenyl selenide (yield 65%) and bis(phenylseleno)ethane (yield 21%).



Under similar conditions (NaOH/EtOH, 70 °C, 4 h), selenophenol readily reacts with 2-bromoethylphenyl ether and 2-bromoethylphenyl sulfide affording the corresponding selenides in 86 and 80% yield, respectively.



Alkylation of aryl selenols with alkyl iodides proceeds more easily than with alkyl bromides and chlorides. Thus, bis(phenylseleno)methane has been synthesized in a yield of 87% by the reaction of selenophenol with CH_2I_2 in the system NaOH/EtOH (60 °C, 2 h).

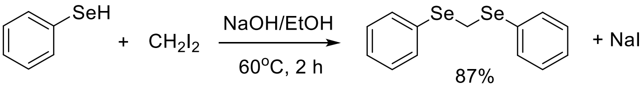
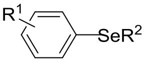
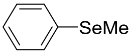
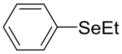
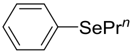
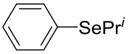
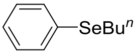
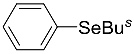
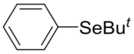
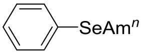
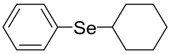
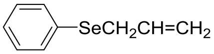
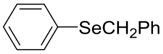
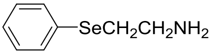
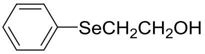
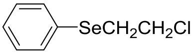
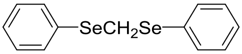
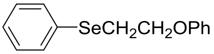
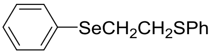
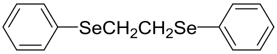
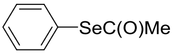
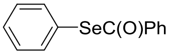
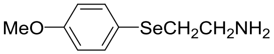


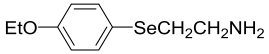
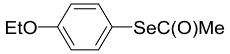
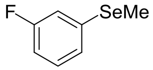
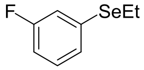
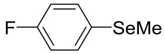
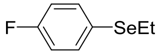
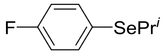
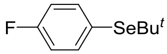
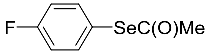
Table 3.7 Aryl organyl selenides



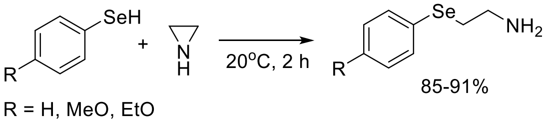
No.	Structure	Yield, %	B.p., °C /torr (m.p., °C)	n_D^{20}	d_4^{20}
1		91	76/6	1.6083	1.3930
2		93	70/3	1.5846	1.3266
3		90	89/4	1.5739	1.2730
4		92	73/3	1.5658	1.2552
5		90	94/3	1.5641	1.2161
6		89	79/1	1.5603	1.1819
7		16	80/6	1.5569	1.2143
8		89	109/3	1.5556	1.1836
9		82	135/4	1.5871	1.2314
10		87	82/3	1.5953	1.3004
11		91	144/2	1.6352	1.2988
12		91	115/3	1.6052	1.3736
13		81	124/2	1.6069	1.4457
14		65	106/3	1.6014	1,4428
15		87	192/3	1.6736	1,5464
16		86	128/3 (53-54)		
17		79	194/3 (49-50)		
18		21	175/3 (61)		
19		91	95/4	1.5924	1.4276
20		88	160/2 (63)		
21		85	144/1	1.5550	1.2732

(continued)

Table 3.7 (continued)

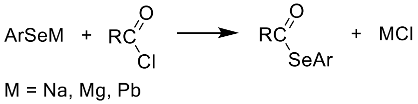
22		86	152/1	1.5888	1.3323
23		94	I3I/1 (44-45)		
24		89	75/5	1.5608	1.4748
25		87	75/2.5	1.5587	1.3964
26		90	63/5	1.5669	1.5032
27		89	72/4	1.5522	1.4025
28		87	78/6	1.5389	1.3542
29		17	67/5	1.5324	1.2995
30		91	90/3	1.5542	1.4744

Aromatic selenols react smoothly with aziridine at room temperature to form β-amino selenides (85–91% yields).



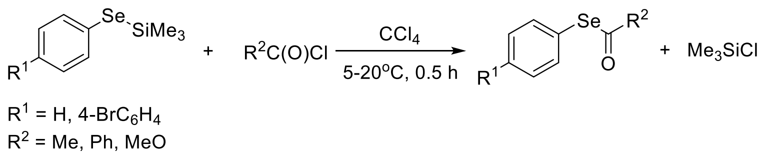
Selenoesters, RC(O)SeR, are applied in organic synthesis and are of interest as potential physiologically active substances, additives to lubricating oils and fuels, and stabilizers for polymeric materials [213].

Usually, the synthesis of Se-aryl esters of monoselenic carboxylic acids is carried out under the action of carboxylic acid chloroahnydries on sodium, magnesium, or lead selenates in an inert atmosphere [214].



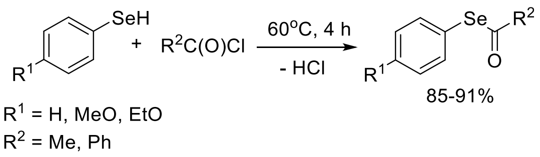
However, among the shortcomings of this method are sophisticated isolation procedure and relatively low yields of the target products.

The synthesis of mono-selenocarboxylic acid *Se*-aryl esters via the reaction of trimethyl(arylseleno)silanes with carboxylic acid chloroanhydrides has been reported [215].



The reaction proceeds easily at room temperature in methylene chloride or CCl_4 and allows *Se*-esters in analytically pure form and with almost quantitative yield to be synthesized. However, this method involves a separate stage of preparation of the starting materials, trimethyl(arylseleno)silanes.

It has been established [216] that aryl esters of monoselenic carboxylic acids are formed via the interaction of aryl selenols with carboxylic acid chloroanhydrides in the absence of catalysts or condensing agents in neutral organic solvents (hexane, heptane, isooctane, benzene, etc.) at 50–80 °C.



The reaction of aryl selenols with carboxylic acid chloroanhydrides is triggered even at room temperature, but its completion requires a short heating. The reaction is accompanied by the release of HCl that be used to control the conversion of aryl selenols. The structure of *Se*-esters is confirmed by spectral methods (^{1}H NMR), thin-layer chromatography, and elemental analysis. The results of physical-chemical studies are in agreement with the previously published data for selenoesters of this type [213–215, 217]. This one-step preparative method for the synthesis of aryl esters of monoselenic carboxylic acids is characterized by exceptional simplicity and availability of the starting materials, high yields and purity of the target products.

The relative basicity, conformational structure of the synthesized compounds as well as the conjugation effects of aromatic selenides are discussed in Sects. 6.1.6 and 6.3.3 of this monograph.

3.8 Examples of Syntheses

3.8.1 Aromatic Sulfoxides

***tert*-Butyl 4-fluorophenyl sulfoxide** (entry 10, Table 3.1) To *tert*-butyl 4-fluorophenyl sulfide (9.2 g, 0.05 mol) and acetic anhydride (30 mL), 40% hydrogen peroxide (4.2 g, 0.05 mol) was added dropwise at room temperature upon stirring. After addition of the total amount of the peroxide, the reaction mixture was stirred for another 5–6 h and allowed to stand overnight (until complete conversion of H_2O_2). Acetic anhydride was removed and distillation in vacuum gave 6.5 g (65%) of *tert*-butyl 4-fluorophenyl sulfoxide, b.p. 140 °C/1 Torr, n_D^{20} 1.6040, d_4^{20} 1.1675. The absence of sulfone was controlled by TLC on a Al_2O_3 layer (hexane/ether, 1:6).

Sulfoxides No. 1–9, 11–22 were obtained similarly (Table 3.1).

3.8.2 Alkyl Aryl Sulfones

Methyl 4-fluorophenyl sulfone (entry 11, Table 3.2) In a flask, equipped with stirrer, thermometer, and dropping funnel, methyl 4-fluorophenyl sulfide (3.2 g, 0.023 mol) was placed and glacial acetic acid (50 mL) was added. The temperature in the flask was raised to 65–70 °C. 30% H_2O_2 ($\sim$7 g of, molar excess) was added dropwise upon continuous stirring for 2 h and then the mixture was stirred for additional 1.5 h. After cooling, the reaction mixture was poured into cold water. The obtained white crystals were filtered off, washed with water until no acid reaction was observed. The yield of methyl 4-fluorophenyl sulfone was 3.7 g (94%), m.p. 73 °C.

Alkylaryl (No. 1–10, 12–33, Table 3.2) and alkyl benzyl sulfones (No. 1-9, Table 3.3) were obtained similarly.

3.8.3 Alkyl-, Aryl- and Benzylthioacylates

S-F4-fluorophenyl thioacetate (entry 12, Table 3.4) A mixture of 4-fluorothiophenol (12.4 g, 0.1 mol) and acetyl chloride (15.7 g, 0.2 mol) was heated for 4 h at 60 °C, then cooled, diluted with benzene (100 mL), and passed through a column with B-16 anion-exchange resin. The solvent was removed, the residue was distilled in vacuum to give 15.3 g (90%) of 4-fluorophenyl thioacetate, b.p. 84–85 °C/4 Torr, n_D^{20} 1.5452, d_4^{20} 1.2100.

S4-Chlorophenyl thioacetate (entry 19, Table 3.4) A mixture of 4-chlorothiophenol (14.5 g, 0.1 mol) and acetyl chloride (15.7 g, 0.2 mol) was heated for 4 h at 60 °C, then diluted with benzene (60 mL), washed several times with saturated solution of $NaHCO_3$ and dried over $MgSO_4$. After removing the solvent, the residue was fractionated in vacuum to give 16.8 g (90%) of 4-chlorophenyl thioacetate , b.p. 108 °C/3 Torr, m.p. 36 °C.

Compounds No. 1–11, 13–18, 20–56 (Table 3.4) were obtained similarly.

2-(4-Fluorophenylthio)ethyl acetate (No. 1, Table 3.6). To a mixture of 2-(4-fluorophenylthio)ethanol (8.6 g, 0.05 mol) and pyridine (6.0 g) of ether (50 mL), acetyl chloride (5.5 g, 0.07 mol) in ether (20 mL) was added dropwise upon stirring and cooling in a water bath. The mixture was stirred for 1.5–2 h, then diluted with water (100 mL), extracted with ether (3 × 50 mL), and dried over Na_2SO_4. The solvent was removed and fractionation of the residue in vacuum gave 9.5 g (89%) of 2-(4-fluorophenylthio)ethyl acetate, b.p. 114 °C/2 Torr, n_D^{20} 1.5295, d_4^{20} 1.2105.

2-Arylthioethylacetates (entries 2–6, Table 3.6) were obtained similarly.

2-(4-Fluorophenylthio)ethyl trifluoroacetate (No. 7, Table 3.6) a) To a mixture of 2-(4-fluorophenylthio)ethanol (12.9 g, 0.075 mol) and CF_3CO_2H (11.4 g, 0.1 mol) in isooctane (50 mL), a few drops of conc. H_2SO_4 were added and the mixture was stirred at 50 °C for 3 h. After the reaction completion, the mixture was cooled, diluted with water (200 mL), extracted with ether (3 × 50 ml), washed with water until neutral pH, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was distilled in vacuum to give 6.05 g (36%) of 2-(4-fluorophenylthio)ethyl trifluoroacetate, b.p. 96 °C/2 Torr, n_D^{20} 1.4917, d_4^{20} 1.3448.

b) To a mixture of CF_3CO_2H (4.6 g, 0.04 mol) and NaOH (1.6 g, 0.04 mol), 2-(4-fluorophenylthio)ethyl chloride (6.0 g, 0.03 mol) was added dropwise upon continuous stirring, and the mixture was refluxed for 3 h. Then the mixture was cooled, diluted with water and extracted with ether (3 × 50 ml). The extract was washed with water, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was distilled in vacuum to give 7.1 g (83%) of 2-(4-fluorophenylthio)ethyl trifluoroacetate.

2-Arylthioethyl trifluoroacetates (entries 8, 9, Table 3.6) were obtained similarly.

3.8.4 Dithiocarboxylic Acid Dibenzyl Esters

Dithioadipinic acid *S,S*'-dibenzyl ester To benzyl thiol (24.8 g, 0.2 mol), adipinic acid dichloroanhydride (12.0 g, 0.1 mol) was gradually added. The mixture was kept for 6 h at room temperature, then diluted with benzene (100 mL), washed with 5% Na_2CO_3 solution (3 × 50 mL), and dried over $CaCl_2$. The solvent was removed and the reaction product was recrystallized from ethanol to give 35.2 g (98%) of dithioadipinic acid dibenzyl ester, m.p. 83–84 °C.

Dithioumaric acid S,S'-dibenzyl ester To a solution of benzyl thiol (24.8 g, 0.2 mol) in benzene (50 mL), fumaric acid dichloroahnydride (15.3 g, 0.1 mol) was added. The mixture was boiled for 7 h until the evolution of HCl was stopped, the benzene was removed, and the residue was recrystallized from hexane to give 31.2 g (95%) of the target product, m.p. 86–87 °C.

Dithiophthalic acid S,S'-dibenzyl ester was obtained similarly, yield 92%, m.p. 58–59 °C.

3.8.5 Derivatives of Aromatic Selenols

Methyl phenyl selenide (No. 1, Table 3.7) To a selenophenol solution of (15.7 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in EtOH (25 mL), methyl iodide (14.2 g, 0.1 mol) was added dropwise for 30 min in an atmosphere of helium at 80 °C, and the mixture was stirred for another 1.5 h. Afterwards, ethanol was removed, and the residue was diluted with water (25 mL) and extracted with benzene (3 × 25 mL).

The extract was washed with a saturated solution of $NaHCO_3$, dried over $CaCl_2$, and the solvent was removed. Distillation in vacuum over metallic sodium gave 15.5 g (91%) of methyl phenyl selenide, b.p. 76 °C/6 Torr, n_D^{20} 1.6083, d_4^{20} 1.3930.

Selenides (No. 2–6, 8–11, 13, 25–28, Table 3.7) were obtained similarly.

2-Chloroethyl phenyl selenide (No. 14, Table 3.7) To a solution of selenophenol (15.7 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in ethanol (25 mL), 1,2-dichloroethane (19.8 g, 0.2 mol) was added under inert atmosphere. Afterwards, the reaction mixture was heated upon stirring (70 °C, 4 h), ethanol and excess dichloroethane were removed, and the residue was treated with benzene (3 × 25 mL). The extract was washed with a saturated solution of $NaHCO_3$, dried over $CaCl_2$, the solvent was removed, and the residue was distilled in vacuum to give 14.3 g (65%) of 2-chloroethyl phenyl selenide, b.p. 106 °C/3 Torr, n_D^{20} 1.6014, d_4^{20} 1.4418 and 3.5 g (21%) of bis-1,2-(phenylseleno)ethane (No. 18, Table 3.7), b.p. 175 °C/3 Torr.

Similarly, [2-(phenoxy)ethyl]phenyl selenide (yield 86%, m.p. 53–54 °C, No. 16, Table 3.7) and [2-(phenylthio)ethyl]phenyl selenide (yield 79%, m.p. 49–50 °C, No. 17, Table 3.7) were obtained from selenophenol and 2-bromoethylphenyl ether or 2-bromoethylphenyl sulfide.

Diphenylselenomethane (No. 15, Table 3.7) To a solution of selenophenol (15.7 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in EtOH (30 mL), CH_2I_2 (13.4 g, 0.05 mol) was added dropwise at 60 °C for 30 min under inert atmosphere, and the mixture was stirred for another 1.5 h. The mixture was treated as described above to give 14.1 g (87%) diphenylselenomethane, b.p. 192 °C/3 Torr, n_D^{20} 1.6736, d_4^{20} 1.5464.

***tert*-Butylphenyl selenide** (No. 7, Table 3.7) A mixture of selenophenol (15.7 g, 0.1 mol) and *tert*-butyl bromide (13.7 g, 0.1 mol) was refluxed for 6 h. Then the mixture was cooled and another 1 equivalent of *tert*-butyl bromide (13.7 g, 0.1 mol) was added and the mixture was refluxed for another 6 h. After cooling, the reaction mixture was diluted with benzene (50 mL), washed with 10% NaOH solution (3 × 50 mL), dried over $CaCl_2$, the solvent was removed, and the residue was distilled in vacuum to give 3.5 g (16%) *tert*-butylphenyl selenide, b.p. 80 °C/6 Torr, n_D^{20} 1.5569, d_4^{20} 1.1836.

tert-Butyl-(4-fluorophenyl) selenide (No. 29, Table 3.7) was obtained similarly.

2-Aminoethyl phenyl selenide (No. 12, Table 3.7) To selenophenol (15.7 g, 0.1 mol), cooled to -30 °C, freshly distilled ethyleneimine (4.3 g, 0.1 mol) was added dropwise for ~0.5 h. The mixture was kept under cooling for 1 h, after which the cooling was stopped and the reaction mixture was stirred at room temperature for 1 h and distilled over NaOH in vacuum to give 18.1 g (90%) of 2-aminoethyl phenyl selenide, b.p. 115 °C/3 Torr Hg, n_D^{20} 1.6052, d_4^{20} 1.3736.

Selenides (No. 21, 22, Table 3.7) were obtained similarly.

***Se*-phenyl selenoacetate** (No. 19, Table 3.7) A mixture of selenophenol (15.7 g, 0.1 mol) and acetyl chloride (15.7 g, 0.2 mol) was heated for 4 h at 60 °C in an inert atmosphere. Then the mixture was cooled, diluted with benzene (60 mL), washed with saturated $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was removed and fractionation of the residue in vacuum gave 16.8 g (84%) of acetyl phenyl selenide, b.p. 95 °C/4 Torr, n_{D}^{20} 1.5924, d_4^{20} 1.4276.

Selenides (No. 20, 23, 30, Table 3.7) were obtained similarly.

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Reactivity of Aromatic Thiols and Their Derivatives

4

This chapter deals with peculiarities of the reactivity of aromatic thiols and their derivatives (sulfides and aryl thioacylates) mainly in terms of assessing the structural effects on the course of chemical processes. Selected typical reactions such as oxidation, halogenation, hydrolysis, and further functionalization are discussed.

4.1 Electrochemical Oxidation of Aryl Thiols and Their Derivatives

4.1.1 Aryl Thiols

Organic compounds of bivalent sulfur exhibit electrochemical activity in the anode potential region and are oxidized on different electrodes [1]. The literature contains only few data on the electrochemical oxidation of organic thiols. Moreover, these data have not been comprehensively analyzed in terms of the structural effects on main characteristics of the process.

The electrochemical encyclopedia of elements [2] reports on the electrochemical oxidation of some alkyl thiols, thiophenol, and cysteine. The electrochemical oxidation of 6-mercaptopurine [3, 4], xanthates thiolate anions [5], 2,6-dimercapto-1,4-thiopyroncarboxylic acid [6] was also studied. In scanty works devoted to the electrochemical oxidation of aryl thiols, thiophenol [6, 7], thiosalicylic (2-mercaptobenzoic) acid [8, 9], and 2-aminothiophenol [10] were considered. Some results of systematic investigations into structural peculiarities and reactivity of aryl thiols in electrochemical oxidation reactions are presented for the first time in this chapter.

Voltamperometric measurements of thiophenol electrochemical oxidation carried out an OH-102 electronic polarograph (Radelkis, Hungary) using a stationary disk graphite anode at 25 °C ± 0.5 °C and a polarization rate of 500 mV/min. 1 N $HClO_4$ (50% isopropyl alcohol-water) and 1 N $LiClO_4$ (absolute MeOH) were the

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background. A cadmium half-cell, consisting of a cadmium disk with a diameter of 10 cm immersed in a 0.5 M aqueous solution of $CdSO_4$, was used as a reference electrode. The potential of the latter was 0.68 V relative to the saturated calomel electrode.

The concentration of the depolarizer in the background electrolyte was 10^{-3} mol/L. Current-potential curves were recorded in integral and differential modes. The deviation of $E_{p/2}$ value from the average value at 5–7 measurements did not exceed ±0.01 V.

Electrochemical oxidation of a series of thiophenols with various electron-donating and electron-withdrawing substituents has been studied [11–15].

The measurements were performed in aqueous media in a wide range of pH (~0–13). For all compounds, well-resolved current-potential curves were obtained only in strongly acidic media. In alkaline media, the curves of electrochemical oxidation were observed not for all compounds due to the easy oxidation of the thiol functions in their anionic forms.

In strongly acidic media ($pH \leq 4$), the current-potential curves (recorded on a stationary graphite microelectrode) of all aryl thiols show two waves of electrochemical oxidation. The values of the half-peak potential ($E_{p/2}$) of the electrochemical oxidation of both waves depend on the pH of the background electrolyte. It should be noted that character of the dependence indicates that the electrochemical oxidation of all the samples studied proceeds according to the same mechanism.

4.1.1.1 Structural Effects in Electrochemical Oxidation of Substituted Thiophenols

It is known that aromatic thiols are oxidized much more easily (by ~ 0.6–0.8 V) than their oxygen analogs, phenols [16, 17]. In fact, all the investigated thiols RC_6H_4SH (R = H, 3-Me, 4-Me, 4-Et, 4-Pr^i, 3-MeO, 4-MeO, 3-F, 4-F, 4-Cl, 3-Br, 4-Br, 4-I, 4-Ac, 4-NO_2) are oxidized so readily that for some compounds even in media with pH > 8, electrooxidation curves are not observed.

The dependence of electrooxidation $E_{p/2}$ on the background electrolyte pH for the studied thiophenol derivatives is more complex as compared to that of structurally similar phenols. However, the current-potential curves show the regions corresponding to oxidation of both non-ionized thiol functions and thiolate anions.

The values of $E_{p/2}$ measured under identical conditions for representatives of the studied thiophenols expectedly depend on the substituent and its position relative to the thiol group. The comparison was carried out in strongly acidic media (pH 2), in which pronounced current-potential curves can be observed for all the compounds. Predictably, the introduction of electron-donating substituents facilitates electrochemical oxidation of aryl thiols as compared to unsubstituted thiophenol, while the electron-withdrawing groups hinder this process (Table 4.1). As follows from Table 4.1, $E_{p/2}$ values of *meta*- and *para*-substituted thiophenols are not very sensitive to the substituents effect.

Table 4.1 Half-peak potentials ($E_{p/2}$) of electrochemical oxidation of 3- and 4-substituted thiophenols, measured in aqueous media with different pH values [14]

No.	Thiophenol	$E_{p/2}$, V					
		pH 0[a]		pH 1.0[b]		pH 2.0[c]	
		I wave	II wave	I wave	II wave	I wave	II wave
1	PhSH	0.25	0.61	0.27	0.58	0.28	0.49
2	3-MeC$_6$H$_4$SH	0.24	0.53	0.21	0.52	0.16	0.46
3	4-MeC$_6$H$_4$SH	0.23	0.50	0.19	0.47	0.13	0.44
4	4-EtC$_6$H$_4$SH	0.23	0.50	0.20	0.50	0.16	0.45
5	4-Pr^{i}C$_6$H$_4$SH	0.24	0.50	0.20	0.48	0.16	0.46
6	3-MeOC$_6$H$_4$SH	0.25	0.55	0.22	0.52	0.18	0.50
7	4-MeOC$_6$H$_4$SH	0.18	0.44	0.12	0.44	0.09	0.36
8	3-FC$_6$H$_4$SH	0.27	0.60	0.25	0.56	0.21	0.54
9	4-FC$_6$H$_4$SH	0.25	0.54	0.21	0.51	0.16	0.46
10	4-ClC$_6$H$_4$SH	0.26	0.55	0.22	0.51	0.17	0.47
11	3-BrC$_6$H$_4$SH	0.27	0.59	0.26	0.57	0.22	0.53
12	4-BrC$_6$H$_4$SH	0.26	0.55	0.23	0.54	0.19	0.47
13	4-IC$_6$H$_4$SH	0.26	0.55	0.22	0.53	0.20	0.47
14	4-AcC$_6$H$_4$SH	0.30	0.59	0.27	0.57	0.24	0.55
15	4-NO$_2$C$_6$H$_4$SH	0.33	0.65	0.30	0.60	0.27	0.59

[a]1 M $HClO_4$. [b] 0.1 M $HClO_4$. [c] Britton-Robinson buffer solution ($\mu = 0.25$)

The correlation processing of the experimental data was performed by the least squares method using reliable values of substituent σ-constants. Parameters of the correlation processing are as follows: n is the number of experimental dots used to derive correlation equations, a is the free term, ρ is the slope factor, r and R are the linear and multiple correlation coefficients, respectively, s and s_o are the standard deviation of the linear and multiple regression.

Quantitative assessment of the substituents effects on $E_{p/2}$ values of thiophenols electrooxidation was performed using a set of different types of substituent constants (σ^o, σ, σ^+). The corresponding correlation equations ($E_{p/2}$ as a function of substituent constants) show that a more reliable dependence is observed in the case of electrophilic σ^+ constants, although the point for thiophenol strongly deviates on the correlation line. For this reason, data for unsubstituted thiophenol were excluded from further calculations. In correlation-statistical calculations, the data on 14 *meta*-and *para*-substituted thiophenols were used (Table 4.1, entries 2–15).

In strongly acidic media (pH $\leq$ 2), two waves of electrochemical oxidation were detected. Correlation-statistical calculations for both waves gave the following results:

pH = 0	I wave	II wave
	$E^R_{p/2} = 0.25 + 0.08\sigma^+$ (V) $r = 0.977$; $s = 0.008$	$E^R_{p/2} = 0.54 + 0.12\sigma^+$ (V) $r = 0.991$; $s = 0.007$
pH = 1	I wave	II wave
	$E^R_{p/2} = 0.22 + 0.10\sigma^+$ (V) $r = 0.980$; $s = 0.009$	$E^R_{p/2} = 0.52 + 0.10\sigma^+$ (V) $r = 0.957$; $s = 0.013$
pH = 2	I wave	II wave
	$E^R_{p/2} = 0.18 + 0.11\sigma^+$ (V) $r = 0.974$; $s = 0.011$	$E^R_{p/2} = 0.48 + 0.13\sigma^+$ (V) $r = 0.960$; $s = 0.016$

The best linear correlation in the case of σ^+ constants confirms the electrophilic character of thiophenols electrooxidation and indicates the direct polar conjugation of electron-donating +C-substituents with electron-deficient reaction center (in this case, with a radical cation localized on sulfur atom). A similar regularity was observed for the electrochemical oxidation of various oxygen- and nitrogen-containing aromatic compounds [16–18].

The results of correlation-statistical calculations evidence that $E_{p/2}$ values of the thiophenols studied are less sensitive to substituents effect. For comparison, in Table 4.2, the values of voltamperometric constants (ρ_π) for thiophenols [14] and phenols [18] measured under the same conditions are given.

From the sensitivity constants ρ_π of substituted phenols and thiophenols (Table 4.2), it follows that $E_{p/2}$values of thiophenols are almost by 3 times less sensitive to the electronic effects of the substituents than $E_{p/2}$ of the corresponding phenols.

It is a common knowledge [19] that σ^+ constants, apart from the effect of direct polar conjugation, also account for inductive and mesomeric effects. To separately evaluate the contributions of purely polar and hyperconjugation effects of substituents for series of thiophenols series, a two-parameter correlation of $E_{p/2}$ values with purely polar σ^0 and hyperconjugation $\Delta\sigma$ substituents constants was calculated using the modified Yukawa–Tsuno–Palm equation [20]:

$$E^R_{p/2} = E^H_{p/2} + \rho E^o_\pi \sigma^o + \rho^+_\pi \Delta\sigma^+_c$$

where $\Delta\sigma^+_c = \sigma^+_n - \sigma^o$.

Table 4.2 Electrooxidation constants ρ_π (V) of substituted thiophenols and phenols, measured by voltammetric method

pH	Thiophenols [14]		Phenols [18]
	I wave	II wave	
0	0.08	0.12	0.33
1.0	0.10	0.10	0.31
2.0	0.11	0.13	0.29

The following correlation equations are obtained:

pH 0	I wave	II wave
	$E^{\mathrm{R}}_{p/2} = 0.25 + 0.08\sigma^{\mathrm{o}} + 0.08\Delta\sigma^{+}_{\mathrm{c}}$ (V) $R = 0.980$; $s = 0.007$	$E^{\mathrm{R}}_{p/2} = 0.54 + 0.12\sigma^{\mathrm{o}} + 0.13\Delta\sigma^{+}_{\mathrm{c}}$ (V) $R = 0.990$; $s = 0.008$
pH 1	I wave	II wave
	$E^{\mathrm{R}}_{p/2} = 0.22 + 0.10\sigma^{\mathrm{o}} + 0.13\Delta\sigma^{+}_{\mathrm{c}}$ (V) $R = 0.989$; $s = 0.007$	$E^{\mathrm{R}}_{p/2} = 0.52 + 0.10\sigma^{\mathrm{o}} + 0.11\Delta\sigma^{+}_{\mathrm{c}}$ (V) $R = 0.973$; $s = 0.011$
pH 2	I wave	II wave
	$E^{\mathrm{R}}_{p/2}\ 0.18 + 0.10\sigma^{\mathrm{o}} + 0.11\Delta\sigma^{+}_{\mathrm{c}}$ (V) $R = 0.975$; $s = 0.011$	$E^{\mathrm{R}}_{p/2} = 0.49 + 0.11\sigma^{\mathrm{o}} + 0.18\Delta\sigma^{+}_{\mathrm{c}}$ (V) $R = 0.973$; $s = 0.014$

In the correlation-statistical calculations, the potentials of the same thiophenols were used as in the case of a single correlation with σ^+, except for the thiophenol with R = H, n = 14 (Table 4.1, entries 2–15).

Comparison of the reaction constants values, expressing sensitivity of the oxidation potentials ($E_{p/2}$) of the investigated thiophenols toward purely polar (ρ^{o}_{π}) and hyperconjugation ($\Delta\sigma^{+}_{\mathrm{c}}$) substituent effects shows that, within the experimental error, the ρ^{o}_{π} and ρ^{+}_{π} values are close to each other and much less than the total effect of substituents for the electrochemical oxidation of substituted phenols [18].

Since it is established that $\rho^{\mathrm{o}}_{\pi} \approx \rho^{+}_{\pi} = \rho_{\pi}$,

$$\begin{aligned} E^{R}_{p/2} &= E^{H}_{p/2} + \rho^{o}_{\pi}\sigma^{o} + \rho^{+}_{\pi}\,\Delta\sigma^{+}_{c} \\ &= E^{H}_{p/2} + \rho_{\pi(}\sigma^{o} + \Delta\sigma^{+}_{c})\sigma^{o} + \Delta\sigma^{+}_{c} \\ &= \sigma^{+}\ \text{then}\ E^{R}_{p/2} = E^{H}_{p/2} + \rho_{\pi}\sigma^{+}. \end{aligned}$$

Thus, influence of the substituents on $E_{p/2}$ in the studied series of compounds is adequately described by a set of electrophilic σ^+-constants, the sensitivity of oxidation potential $E_{p/2}$ toward purely polar and hyperconjugation effects being almost the same. This is also evidenced by the values of the pair *r* and multiple *R* correlation coefficients, which in the case of both waves are close to each other.

The study of electrochemical oxidation of the substituted phenols has shown [18] that in the media with pH 0 and 1.0, ρ^{+}_{π} significantly exceeds ρ^{o}_{π}, i.e. $E_{p/2}$ sensitivity toward the effects of direct polar conjugation of electron-donating substituents and, accordingly, its contribution to the oxidation potential is much higher than in the case of σ^+ constants. For the substituted thiophenols, this is not observed.

Thus, the investigations of electrochemical oxidation of substituted thiophenols and the analysis of the quantitative data obtained indicate that this process differs significantly from the corresponding reaction for a number of substituted phenols (in terms of the effect of structural variations in the molecule on this process). As was shown above, these differences consist in the appearance of two waves during the electrochemical oxidation of thiophenols in strongly acidic media, in lower sensitivity of the corresponding $E_{p/2}$ to the substituent effects and in a smaller (in comparison with the substituted phenols) contribution of the direct polar conjugation effect to the $E_{p/2}$ values of both waves in media with pH 0 and pH 1.

These differences in the electrooxidation of substituted thiophenols and phenols are obviously due to specificity of the sulfur atom having a vacant 3*d*-orbital, a larger volume (compared to the oxygen atom) and ability of deeper oxidation. In addition, the sulfur atom, unlike the oxygen atom, can undergo more diverse chemical interactions and, thus, electrochemical oxidation as a whole can involve both purely electrode (E) and various chemical (C) stages.

In general, the electrochemical oxidation of thiophenols has an electrophilic nature. This reaction features the effects of direct polar conjugation of electron-donating substituents with an electron-deficient reaction center, the latter apparently being a radical cation located on the sulfur atom.

4.1.1.2 Protolytic and Electrochemical Stages in Oxidation of Thiophenols

The study of electrochemical oxidation of thiophenol and its C-derivatives on a stationary graphite microanode in aqueous media (pH 0–13) [15] has revealed an unusual dependence of the current-potential curves on pH value. Figure 4.1 shows $E_{p/2} = f(\text{pH})$ dependence for unsubstituted thiophenol. For other derivatives RC_6H_4SH (R = 3-Me, 3-MeO, 4-MeO, 4-C1, 4-NO_2), similar curves are observed. In these curves, the regions are slightly shifted in one or another direction depending on the nature of R substituent in the benzene ring.

In strongly acidic media (pH $\leq$ 4), the current-potential curves which display two electrooxidation waves are observed, the potentials of half-peak $E_{p/2}$ of both

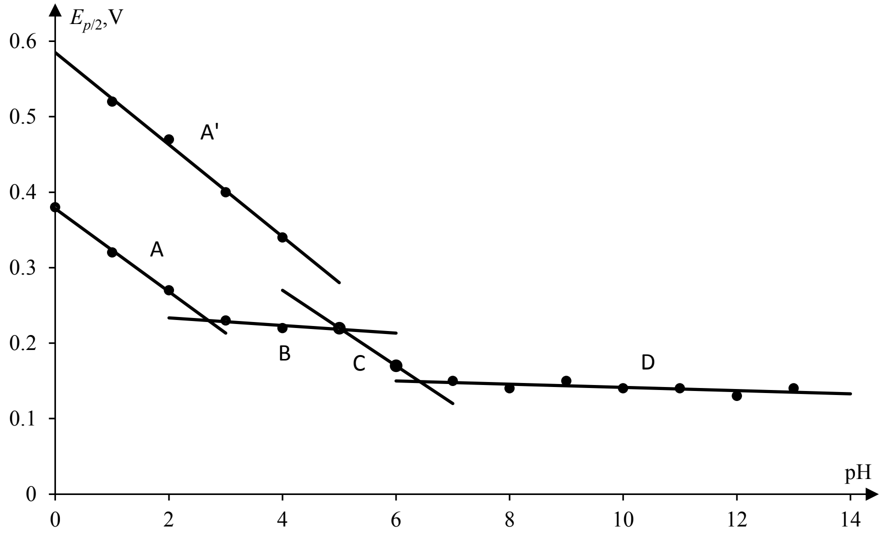


Fig. 4.1 Dependence of thiophenol electrooxidation $E_{p/2}$ on pH of the background electrolyte

Table 4.3 pK_a Values of acidic dissociation of thiophenols RC_6H_4SH

Method of determination	H	3-Me	3-MeO	4-MeO	4-Cl	4-NO_2
Anode voltamperometry [15]	6.60	6.70	6.50	6.90	6.20	4.60
Spectrophotometry [21]	6.615	6.660	6.385	6.775	6.135	4.715

waves being dependent on pH of the background electrolyte. In media with pH > 4, the second wave, observed at more positive potentials, disappears, and the current-potential curves show one wave of electrooxidation at less positive potentials. When pH of the background electrolyte increases from 0 to 4, the value of $E_{p/2}$ of the second wave (A') decreases linearly, the slope $\Delta E_{p/2}/\Delta pH$ being approximately equal to –60 mV/unit pH. The dependence of first wave $E_{p/2}$ on pH of the background electrolyte has a more complex form: $E_{p/2} = f(pH)$ of the first wave demonstrates the breaks, formed by separate straight sections A, B, C, D.

Analysis of $E_{p/2}$ dependence on pH allows us to conclude that the breaks on $E_{p/2} = f(pH)$ plot of the first wave are due to the presence of various forms of thiophenols, namely, protonated, neutral, and dissociated (deprotonated), in media with different pH values. Protolytic processes involving different depolarizers change the potentials of half-peak thus altering pH and inducing the breaks on $E_{p/2} = f(pH)$ plot.

The values of $\Delta E_{p/2}/\Delta pH$ slopes for sections A and C of the first wave, as well as for section A' of the second wave (Fig. 4.1) are –59 ± 2 mV, which indicates that the electrode reaction proceeds with transfer of the same number of protons and electrons.

To clarify a mechanism of the electrode process, or rather its potential-determining stages, a semi-log analysis of the observed current-potential electrooxidation curves was performed. The compliance of the wave shape with the Heyrovsky–Ilkovich equations for the reversible process and with Koutecki–Ganush for the reversible process with subsequent rapid dimerization of the electrode reaction product was checked.

In acidic media, the observed current-potential curves correspond to the Heyrovsky-Ilkovich equation, the values of $\Delta E/\Delta \lg I(I_d - I)$ slopes being close to 59 mV. This suggests that the reaction of thiophenols electrooxidation in acidic media proceeds with a reversible transfer of one electron. In weakly acidic and alkaline media, the current-potential curves are described by the Koutecki–Ganush equation, and the slopes $\Delta E/\Delta \lg I^{2/3}(I_d - I)$ of curves are also close to 59 mV. Therefore, it can be concluded that under these conditions the electrode process proceeds with reversible transfer of one electron, and the primary reaction products quickly dimerize.

Consequently, both the analysis of the dependence of $E_{p/2}$ on pH of the background electrolyte and the semi-log analysis of the wave shape of thiophenols electrooxidation in media of various protogenicities show that, depending on pH of the medium, the potential-determining stage of the electrode process proceeds differently.

In strongly acidic media (pH $\leq$ 2), protonated thiophenols undergo electrooxidation. The first of two waves characterizes a stage that proceeds with the reversible transfer of one proton and one electron:

$$ArSH_2^+ \xrightleftharpoons[+H^+,\ +e^-]{-H^+,\ -e^-} ArSH^{+\bullet}$$

Apparently, the radical cation formed is subjected to further oxidation. Consequently, a second wave appears on the electrooxidation curves, which also occurs with reversible transfer of one electron and one proton:

$$ArSH^{+\bullet} \xrightleftharpoons[+H^+,\ +e^-]{-H^+,\ -e^-} ArS^+$$

These stages correspond to segments A and A' Fig. 4.1.

The sulfenium cation ArS^+, formed in the second stage, being unstable and extremely reactive, can react with different nucleophilic particles, which are contained in the solution. Since the process takes place in an aqueous medium generating nucleophilic particles OH^-, the interaction of ArS^+ cation with OH^- anions can afford sulfenic acid.

$$ArS^+ + OH^- \longrightarrow ArSOH$$

Further, transformations of the reaction product under the conditions of classical volt-amperometry are not detected: the corresponding model compounds do not show an electrooxidation wave.

In media with 4 > pH > 2, the electrode reaction occurs with participation of neutral ArSH molecules. Under these conditions, the potential-determining stage of the electrode process involves proton transfer (Fig. 4.1, segment B). The first wave characterizes a reversible process with the transfer of one electron without consumption of a proton:

$$ArSH \xrightleftharpoons[+e^-]{-e^-} ArSH^{+\bullet}$$

Further, the electrode reaction proceeds with a reversible transfer of one electron and one proton (formation of a sulfenium cation) to furnish sulfenic acid ArSOH.

In media with 4 < pH < pK_a, the electrode reaction occurs with a proton transfer that is evidenced from dependence of $E_{p/2}$ on pH (Fig. 4.1, segment C). The analysis of $E_n/_2$/pH dependence and semi-log plots show that the observed electrooxidation curve describes the process involving a reversible transfer of one proton and one electron:

$$ArSH \xrightleftharpoons[+H^+,\ +e^-]{-H^+,\ -e^-} ArS^{\bullet}$$

The formed thienyl radical $ArS^{\bullet}$ quickly dimerizes (as indicated by the correspondence of the electrooxidation waves to the Koutecki–Ganush equation)

$$2ArS^{\bullet} \longrightarrow ArSSAr$$

Finally, in the media with pH > pK_a, the thiophenolate anions ArS^- undergo electrooxidation. Since the process proceeds without the participation of protons, $E_{p/2}$ does not depend on pH of the background electrolyte (Fig. 4.1, segment D):

$$ArS^- \underset{+e^-}{\overset{-e^-}{\rightleftharpoons}} ArS^{\bullet}$$

In this case, dimerization of thiyl radicals also follows the electron abstraction.

It is assumed that the subsequent stages of the electrode process include oxidation of the reaction products (ArSOH, ArSSAr) to the corresponding sulfinic and sulfonic acids, sulfoxides and sulfones. However, these further transformations cannot be detected using a stationary graphite electrode.

The pH value corresponding to the intersection point of the straight segment C and D on the $E_{p/2} = f(\mathrm{pH})$ plot characterizes the pK_a value of acidic dissociation of the studied thiophenol. The good agreement of pK_a values found for 6 monosubstituted thiophenols using a photometric method [21] (Table 4.3) allows the proposed technique to be employed for a quick approximate evaluation of pK_a values of structurally diverse thiophenols.

4.1.2 Aromatic Sulfides

Aromatic sulfides also exhibit electrochemical activity in the anode region of potentials and undergo oxidation on various electrodes. The electrochemical oxidation of organic sulfides is poorly studied [22]. It is known that those organosulfur compounds, which are usually resistant to the action of oxygen, are easily oxidized electrochemically [23]. Research papers in this field [1, 2, 24–28] are mainly devoted to the synthetic issues and mechanistic aspects of electrochemical oxidation of organic sulfides. At the same time, little attention is paid to regularities of the substituents effect on reactivity of organic sulfides in electrochemical oxidation. In particular, the influence of substituents on the electrochemical oxidation potentials of thioanisoles RC_6H_4SMe containing Me, MeO, Cl, Br substituents in the aromatic ring has been studied [29].

This section deals with electrochemical oxidation of three series of aromatic sulfides containing alkyl and electron-withdrawing substituents both at the sulfur atom and in the aromatic ring: alkyl phenyl sulfides RSPh, substituted thioanisoles RC_6H_4SMe and alkyl aryl sulfides $R^1SC_6H_4R^2$ [30–36] as well as dialkyl sulfides (for comparison). To elucidate the relationship between substituent nature and ability of the studied molecules to oxidation, correlation analysis in combination with the principle of free energy linearity (FEL) was used. Previously, this approach was considered in detail and justified by Zuman [37].

4.1.2.1 Alkyl Phenyl Sulfides

The $\boldsymbol{E_{p/2}}$ values of a series of alkyl phenyl sulfides, measured by one of the authors of this monograph [38], are presented in Table 4.4.

Graphic processing of the data from Table 4.4 in $E_{p/2} - \sigma^*$ and $E_{p/2} - E_s$ coordinates clearly shows the absence of a general linear dependence between the values of oxidative potential and parameters of induction and steric effects of substituents in the studied series of sulfides (Figs. 4.2, 4.3). Analysis of the dependence of $E_{p/2}$ values on the substituent effects using a two-parameter equation

$$E_{p/2} = E^{\mathrm{o}}_{p/2} + \rho * \sigma * + \delta E_{\mathrm{s}}$$

also did not give positive results.

Table 4.4 Half-peak potentials ($E_{p/2}$) of electrochemical oxidation of alkyl phenyl sulfides PhSR and constants of substituent

No.	Structure	$E^{\mathrm{a}}_{p/2}$, V	σ^*	E_{s}	$\overset{\mathrm{o}}{E}_{\mathrm{s}}$	$\overset{\mathrm{o}}{E}_{\mathrm{sCH_2R}}$
1	PhSMe	1.00	0	0	0	–0.27
2	PhSeT	1.02	–0.10	–0.07	–0.27	–0.56
3	$PhSPr^{n}$	1.04	–0.115	–0.36	–0.56	–0.59
4	$PhSPr^{i}$	1.07	–0.19	–0.47	–0.85	–1.13
5	$PhSBu^{n}$	1.01	–0.13	–0.39	–0.59	–0.60
6	$PhSBu^{i}$	1.02	–0.125	–0.93	–1.13	–0.55
7	$PhSBu^{s}$	1.05	–0.21	–1.13	–1.53	–1.13
8	$PhSBu^{t}$	1.20	–0.30	–1.54	–2.14	–1.94
9	$PhSAm^{n}$	1.08	–0.162	–0.40		
10	$PhSAm^{i}$	1.02	–0.162	–0.35		
11	$PhSC_6H^{n}_{13}$	1.04		–0.30		
12	$PhSC_6H^{n}_{15}$	1.01		–0.33		–0.53
13	$PhSC_6H^{n}_{17}$	1.00		–0.33		
14	$PhSC_6H^{n}_{19}$	1.04				
15	$PhSC_6H^{n}_{21}$	1.03				
16	$PhSCH_2CH{=}CH_2$	1.07	0.18	–0.40		
17	$PhSC_6H_{11}$-*cyclo*	1.07	–0.20	–0.79	–1.19	–1.18
18	PhSPh	1.13	0.60			
19	$PhSCH_2Ph$	1.11	0.215	–0.38	–0.71	
20	$PhSCH_2CH_2Ph$	1.01	0.08	–0.38	–0.58	
21	$PhSCH_2CH_2OH$	1.06	0.198	–0.77		
22	$PhSCH_2CH_2Cl$	1.11	0.385	–0.90	–1.10	
23	$PhSCH_2CH_2Br$	0.92	0.26	–1.27		
24	$PhS(CH_2)_3Br$	1.06	0.093	–0.48		
25	$PhS(CH_2)_4Br$	0.89	0.37			
26	$PhS(CH_2)_5Br$	1.02	0.215			
27	$PhSCH_2CH_2CN$	1.20	0.80	–0.99		
28	PhSAc	1.26	1.65			

[a] Relative to saturated calomel electrode

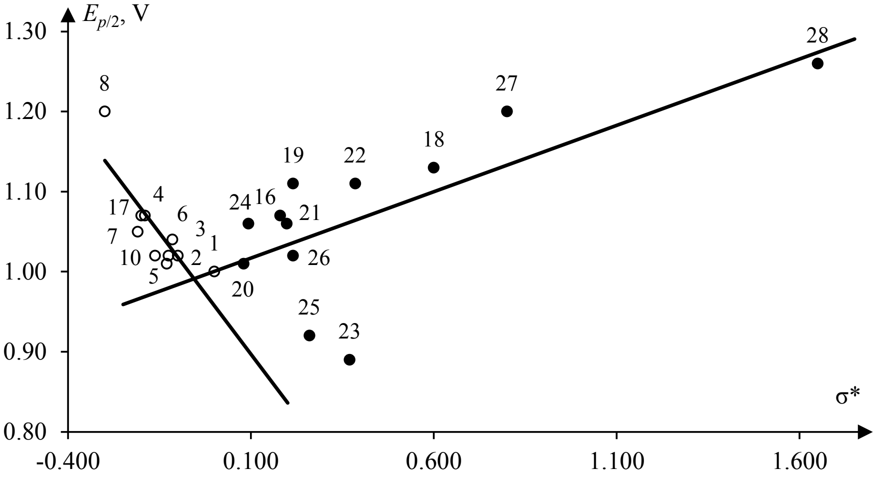


Fig. 4.2 Parameters of $E_{p/2} - \sigma^*$ correlation for electrooxidation of alkyl phenyl sulfides PhSR (the numbering of the compounds corresponds to Table 4.4)

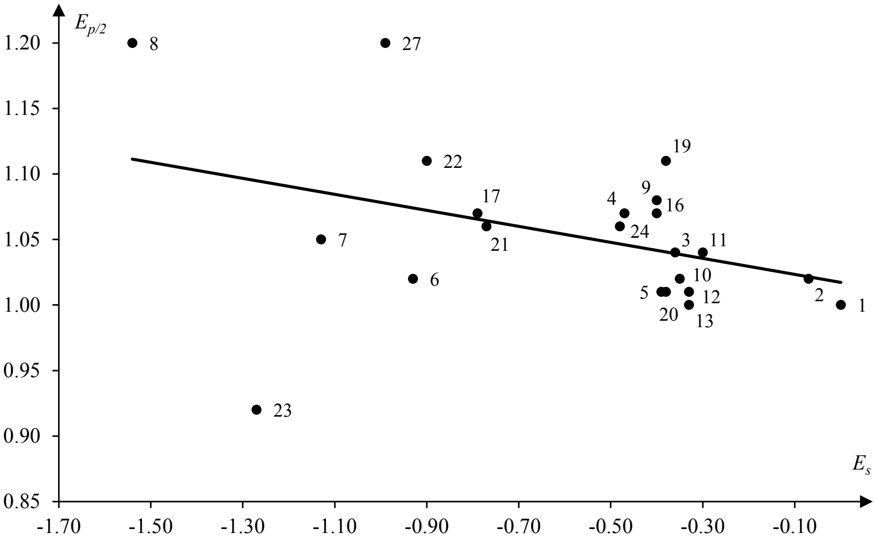


Fig. 4.3 Parameters of $E_{p/2} - E_s^o$ correlation for electrooxidation of alkyl phenyl sulfides PhSR (the numbering of the compounds corresponds to Table 4.4)

For the quantitative evaluation of the steric effect, the principle of isosterity is used [39], according to which this effect of RS substituent is equal to the steric effect of the RCH_2 group with a steric constant E_s^o.

In a series of alkyl phenyl sulfides (Table 4.4, compounds 1–8, 12, 17), a very clear linear dependence of $E_{p/2}$ values on $E_\mathrm{s}^\mathrm{o}(\mathrm{CH_2R})$ is observed:

$$E_{P/2} = 0.953 - 0.113E_s^o(CH_2R); r = 0.951, s = 0.02, n = 10.$$

The situation is different in the case of alkyl phenyl sulfides with electron-withdrawing substituents (Table 4.4, compounds 16, 18–28). The analysis of the dependence of $E_{p/2}$ values on E_s^o constants for such sulfides reveals only a very mediocre linear correlation $E_{p/2}$–σ^*:

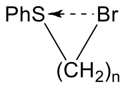
$$E_{P/2} = 1.04 + 0.156\mathbf{s}*, r = \mathbf{0.920}, s = \mathbf{0.03}, n = \mathbf{12}.$$

From the obtained dependence, it follows that $E_{p/2}$ values are mainly determined by induction effect of the substituents, even if the latter has an ability of conjugating with sulfur atom (such as Ph and Ac).

This result confirms the conclusion [40] that the effects of alkyl and electron-withdrawing substituents on the reaction center are essentially different. This difference is observed not only for the induction effect, but also, apparently, for the steric effect (*cf.* [41]).

A possible reason for this (in this particular case) is the progressive violation of coplanarity of the molecule (partial elimination of sulfur lone electron pair from conjugation with the benzene ring) with increasing the alkyl substituent branching.

Noteworthy is the alternation of $E_{p/2}$ values in a series of compounds PhS $(\mathrm{CH_2})_n\mathrm{Br}$ (n = 2–5, Table 4.4, entries 23–26). Sulfides with an even number of carbon atoms in the alkyl chain are oxidized more easily than those with odd number. It is obvious that regularity in the variation of $E_{p/2}$ values in $\mathrm{PhS(CH_2)_nBr}$ is due to different delocalization of the positive charge in the corresponding radical cation, although the nature of this effect remains unclear:



It is known [42] that electrochemical oxidation starts with abstraction of one or two electrons at the anode to generate single- or double-charged positive ions, presumably radical cations. Here, the electron is removed from the highest occupied molecular orbital, as in the case of measuring ionization potentials. The possibility of charge distribution over the whole molecule is very important for stabilization of radical cations. Therefore, violation of the PhSR coplanarity decreases a degree of conjugation of lone electron pair of the sulfur atom with the benzene ring. That is, the degree of charge delocalization reduces and, consequently, the oxidative potential increases.

Thus, the dependence of $E_{p/2}$ values on steric changes in a molecule should be considered as a result of two effects: the influence of these changes, on the one hand, on energy of the original molecule and, on the other hand, on energy of the corresponding radical cation (*cf.* [43]).

4.1.2.2 Substituted Thioanisoles

Electrochemical oxidation (1 M $HClO_4$, EtOH/H_2O = 1:1 by volume) of substituted thioanisoles RC_6H_4SMe [35] gives clearly expressed current-potential curves with one wave of electrooxidation (Table 4.5). The semi-log analysis of the current-potential electrooxidation curves in the coordinates E–lg$I/(I_p - I)$ shows that the potential-determining stage for all compounds proceeds according to the same mechanism with the participation of one electron ($\Delta E/\Delta \lg I/(I_p\text{-}I)$ values are close to the theoretical ones, 59 mV).

The half-peak potentials of substituted thioanisoles electrooxidation vary greatly (from 0.85 to 1.22 V), being dependent on nature of the substituents and their position in the benzene ring relative to electroactive SMe group (Table 4.5). The introduction of electron-donating substituents in the 3- and 4-position of the benzene ring relative to the MeS-group facilitates electrochemical oxidation and, consequently, decreases $E_{p/2}$ values. Electron-withdrawing substituents, in turn, hinder electrochemical oxidation and increase $E_{p/2}$ values.

A comparison of $E_{p/2}$ values of *ortho*-substituted derivatives with those of the starting thioanisol shows that the *ortho*-substitution occurs specifically. If typical electron-donating substituents Me and MeO in the *para*-position relative to the MeS-group exhibit a pronounced effect, in the *ortho*-position they display very weak electron-donating properties. At the same time, Cl and Br substituents in the *ortho*-position demonstrate stronger electron-withdrawing properties than in the *meta*-position.

The $E_{p/2}$ of *meta*-substituted thioanisoles electrooxidation perfectly correlates with the purely polar σ^o-constants of substituents. Correlation-statistical calculations for a series of 5 compounds (R = H, 3-Me, 3-MeO, 3-F, 3-Br) give the following results:

$$E^R_{p/2} = (1.00 \pm 0.05) + (0.25 \pm 0.01)\sigma^o_m(\mathrm{V}); r = 0.997; s = 0.004.$$

For the studied series of compounds (Table 4.5, n = 17, *meta*- and *para*-substituted thioanisoles), a single linear dependence of $E_{p/2}$ values on reactivity constants of substituents has been found. Noteworthy, upon transition from σ^o to σ and then to σ^+-constants, the quality of correlation is noticeably improved as evidenced by the data of correlation-statistical calculations:

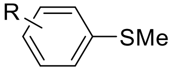
$$E^{\mathrm{R}}_{p/2} = 0.97 + 0.28\sigma^o(\mathrm{V}); r = 0.900; S = 0.042;$$

$$E^R_{p/2} = 0.98 + 0.28\sigma\,(\mathrm{V}); r = 0.977; S = 0.020;$$

$$E^{\mathrm{R}}_{p/2} = (1.01 \pm 0.02) + (0.22 \pm 0.01)\sigma^+(\mathrm{V}); r = 0.995; S = 0.01.$$

This indicates that, apart from purely polar effects, the direct polar conjugation of electron-donating +C-substituents is also observed in the reactions of thioanisoles electrodioxidation [19].

Table 4.5 Half-peak potentials ($E_{p/2}$) of electrochemical oxidation of thioanisoles RC_6H_4SMe and constants of the substituent



No.	R	$E_{p/2}$[a], V	σ^o	σ	σ^+
1	H	1.00	0	0	0
2	2-Me	0.99			
3	3-Me	0.98	–0.072	–0.069	–0.066
4	4-Me	0.93	–0.15	–0.170	–0.311
5	4-Et	0.95		–0.151	–0.295
6	4-Pr^i	0.94		–0.151	–0.280
7	4-Bu^t	0.95	–0.18	–0.197	–0.256
8	2-MeO	0.99			
9	3-MeO	1.02	0.06	0.115	0.047
10	4-MeO	0.85	–0.12	–0.268	–0.778
11	4-PhO	0.90		–0.028	–0.50
12	3-F	1.08		0.337	0.352
13	4-F	1.00	0.17	0.062	–0.073
14	2-Cl	1.14			
15	4-Cl	1.03	0.27	0.227	0.114
16	2-Br	1.14			
17	3-Br	1.10	0.38	0.391	0.405
18	4-Br	1.03	0.26	0.232	0.150
19	4-I	1.02	0.27	0.276	0.135
20	4-Ac	1.12	0.43	0.516	0.491
21	4-NO_2	1.22		0.778	0.790

[a] Relative to saturated calomel electrode

The difference in ρ_π-constant of *meta*- and *para*-substituted thioansoles (0.22 V) from that of only *meta*-substituted thioanisoles (0.25 V) points to the fact that contribution of the direct polar conjugation for these compounds is distinct from contribution defined by standard electrophilic σ^+-constants.

For a separate estimation of the contributions from purely polar effects and direct polar conjugation effect of the substituents on $E_{p/2}$ values of 3- and 4-substituted thioanisoles electrooxidation, $E_{p/2}$ values are correlated with purely polar σ^o-constants and $\Delta\sigma_c^+$-constants of the substituents (where $\Delta\sigma_c^+ = \sigma_p^+ - \sigma_p^o$), which account for the contribution of the direct polar conjugation effect, using the modified two-parameter Yukawa–Tsuno–Palm equation [20].

Correlation-statistical calculations (for a series of 17 compounds) give the following results:

$$E^{R}_{p/2} = (1.00 \pm 0.01) + (0.23 \pm 0.01)\sigma^{o} + (0.20 \pm 0.03)\Delta\sigma_{c}^{+}\,(\mathrm{V}); R = 0.996; S = 0.009.$$

The $\varepsilon = \rho_\pi^+/\rho_\pi^o$ value, which expresses a relative contribution of the direct polar conjugation effect to effective $\sigma_{\mathrm{ef.}}^+$-constants is 0.85, i.e. in this series of compounds, the above effect is less pronounced than in the solvolysis of *tert*-cumyl chloride, on the basis of which the standard σ_p^+- constants have been calculated.

$$\sigma_{ef}^{+} = \sigma_{p}^{o} + 0.85\Delta\sigma_{c}^{+}$$

For comparison, $E_{p/2}$ values of thioanisoles electrooxidation, obtained in [29] on a rotating platinum microanode against 0.1 mol/L NEt_4ClO_4 in acetonitrile, are processed similarly. Correlation-statistical calculations in the 99% confidential interval give the following results:

$$\begin{aligned} E^{R}_{p/2} &= (1.12 \pm 0.07) + (0.36 \pm 0.16)\sigma^{o} + (0.35 \pm 0.15)\Delta\sigma_{c}^{+}\,(\mathrm{V}); \\ &R = 0.993; S = 0.22; \varepsilon = \rho_{\pi}^{+}/\rho_{\pi}^{o} = 0.95 \\ n &= 7(\mathrm{R} = \mathrm{H}, 4-\mathrm{Me}, 4-\mathrm{MeO}, 3-\mathrm{Cl}, 4-\mathrm{Cl}, 3-\mathrm{Br}, 4-\mathrm{Br}). \end{aligned}$$

In this case, an excellent linear correlation is also observed.

Comparison of ρ_π^o and ρ_π^+ constants obtained upon electrochemical oxidation of thioanisoles on a stationary graphite (0.1 mol/L $HClO_4$ in aqueous ethanol) [35] and a rotating platinum microanods (0.1 mol/L NEt_4ClO_4 in acetonitrile) [29] shows that in 99% confidential interval they are not essentially different (ρ_π^o 0.23 ± 0.01 and 0.36 ± 0.16; ρ_π^+ = (0.20 ± 0.02) and (0.35 ± 0.15), respectively). However, a relative contribution of the direct polar conjugation effect to the oxidation potentials in the latter case is somewhat higher, which may be to some extent due to the use of various media.

It should be noted that in the considered series of electrooxidation, the direct polar conjugation effects of only electron-donating substituents, capable of enhanced conjugation with electron-deficient reaction center, are observed. Due to abstraction of an electron, the reaction center becomes positively charged, causing an additional attraction of the electron cloud from *para*-substituents. Only electron-donating substituents are capable of increased loss of electron, which in fact takes place.

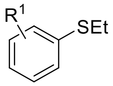
Strong electron-withdrawing substituents (Ac, NO_2), which are not capable of increased conjugation with loss of electrons, exhibit purely polar effects and their contributions to $E_{p/2}$ are described by σ^o-constants. This is evidenced by the correlation of $E_{p/2}$ values with σ^o-constants of 4-acetyl- and 4-nitroanisoles (like for *meta*-substituted thioanisoles). At the same time, correlation-statistical calculations give an excellent linear correlation, the level of significance of which is at least 99%:

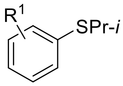
$$\begin{aligned} E^R_{p/2} &= (1.00 \pm 0.01) + (0.25 \pm 0.01)\sigma^o(\mathrm{V}), \\ R &= 0.999; S = 0.003; n = 7 \\ (\mathrm{R} &= \mathrm{H}, 3-\mathrm{Me}, 3-\mathrm{MeO}, 3-\mathrm{F}, 3-\mathrm{Br}, 4-\mathrm{Ac}, 4-\mathrm{NO_2}). \end{aligned}$$

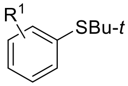
The obtained experimental data and the results of their correlation-statistical processing with different constants of the substituents indicate that electrochemical oxidation of thioanisoles is electrophilic and leads to the effects of direct polar conjugation of electron-donating +C-substituents.

4.1.2.3 Alkyl Aryl Sulfides

The study of direct polar conjugation effects depending on substituents at the sulfur atom has been extended over a series of ethyl-, isopropyl-, and *tert*-butyl aryl sulfides with the same set of substituents in the aromatic ring [36]:







All studied compounds give clearly defined integral and differential electrooxidation current-potential curves with a single peak. The $E_{p/2}$ values of the studied compounds measured in 1 mol/L aqueous-ethanol (1:1 v/v) $HClO_4$ solution vary significantly (from 0.90 to 1.44 V relative to the saturated calomel electrode), thus showing dependence on the nature of substituent in the aromatic ring and the character of the alkyl group at sulfur atom (Table 4.6).

Within the same reaction series, the introduction of electron-donating substituents R^1 into the aromatic ring facilitates electrochemical oxidation of substituted sulfides as compared to unsubstituted alkyl phenyl sulfide, while electron-withdrawing substituents hinder this process.

The effects of R^1 substituents on $E_{p/2}$ of electrooxidation in the studied alkyl aryl sulfides are qualitatively evaluated using the correlation equations for the free energy linearity (FEL) with different sets of substituent constants (σ^o, σ, σ^+). Moreover, for each reaction series, two correlations ratios are proposed:

Table 4.6 Electrooxidation half-peak potentials ($E_{p/2}$) of alkyl aryl sulfides $R^1C_6H_4SR^2$ [36]

Strucrure	$E^{a}_{p/2}$, V			
	R^2 = Me	R^2 = Et	R^2 = Pr^i	R^2 = Bu^t
$PhSR^2$	1.00	1.02	1.07	1.20
$4\text{-}MeC_6H_4SR^2$	0.93	0.97	1.02	1.15
$3\text{-}MeOC_6H_4SR^2$	1.02	1.03	1.09	1.22
$4\text{-}MeOC_6H_4SR^2$	0.85	0.93	0.98	1.15
$3\text{-}FC_6H_4SR^2$	1.08	1.12	1.17	1.30
$4\text{-}FC_6H_4SR^2$	1.00	1.03	1.09	1.25
$4\text{-}ClC_6H_4SR^2$	1.03	1.06	1.13	1.27
$4\text{-}AcC_6H_4SR^2$	1.12	1.16	1.21	1.33
$4\text{-}NO_2C_6H_4SR^2$	1.22	1.26	1.32	1.44

[a] Relative to saturated calomel electrode

- separately for the potentials of *meta*-derivatives (R = H, MeO, F) and representatives of *para*-derivatives with electron-withdrawing (Ac, NO_2) substituents (given that these substitutes exhibit purely polar effects in electro-oxidation reactions [18]);
- for the potentials of all representatives of the reactionary series.

Since the substituent constants of all three considered series do not differ significantly from each other in their values for *meta*-substituents as well as for electron-withdrawing –C-type substituents, in this case only $E_{p/2} - \sigma^{o}$ correlations are deduced.

Correlation-statistical calculations of the first type ($n = 5$) give the following results:

For reaction series $R^1C_6H_4SEt$ – $E^{R}_{p/2} = 1.02 + 0.27\sigma^{o}$ (V); $r = 0.998$; $s = 0.007$;

For reaction series $R^1C_6H_4SPr^i$ – $E^{R}_{p/2} = 1.07 + 0.28\sigma^{o}$ (V); $r = 0.999$; $s = 0.003$;

For reaction series $R^1C_6H_4SBu^t$ – $E^{R}_{p/2} = 1.20 + 0.27\sigma^{o}$ (V); $r = 0.998$; $s = 0.005$.

In all the considered series, excellent linear correlations $E_{p/2} - \sigma^{o}$ ($r \geq 0.99$) are observed, i.e. the substituents here show only purely polar effects.

In the case of all representatives of the series, including electron-donating +C-substituents in the *para*-position relative to the reaction site, capable of direct polar conjugation with the electron-deficient polar center [18, 19], the correlation ratios within each reaction series ($n = 9$) are built with all sets of the substituent constants (σ^{o}, σ, σ^{+}) (Table 4.6).

The linear correlation coefficients of the second type (r) for each reaction series vary depending on a set of the substituent constants. So, when using σ^{o}-constants in the series of sulfides $RC_6H_4SMe \rightarrow RC_6H_4SEt \rightarrow RC_6H_4SPr^i \rightarrow RC_6H_4SBu^t$, the correlation gradually improves and becomes excellent in the case of aryl *tert*-butyl

Table 4.7 Correlation-statistical processing of alkyl aryl sulfides electrooxidation [36]

Reaction series	$E^R_{p/2} = E^H_{p/2} + \rho^0_\pi \sigma^o$	$E^R_{p/2} = E^H_{p/2} + \rho^0_\pi \sigma^o$	$E^R_{p/2} = E^H_{p/2} + \rho^+_\pi \sigma^+$
$R^1C_6H_4SMe$	$0.99 + 0.32\sigma^o$ $r = 0.959$; $s = 0.032$	$0.99 + 0.32\sigma^o$ $r = 0.959$; $s = 0.032$	$1.01 + 0.22\sigma^+$ $r = 0.995$; $s = 0.010$
$R^1C_6H_4SEt$	$0.99 + 0.32\sigma^o$ $r = 0.959$; $s = 0.032$	$1.01 + 0.30\sigma$ $r = 0.990$; $s = 0.016$	$1.04 + 0.22\sigma^+$ $r = 0.985$; $s = 0.020$
$R^1C_6H_4SPr^i$	$1.05 + 0.31\sigma^o$ $r = 0.979$; $s = 0.023$	$1.07 + 0.29\sigma$ $r = 0.999$; $s = 0.006$	$1.10 + 0.21\sigma^+$ $r = 0.972$; $s = 0.026$
$R^1C_6H_4SBu^t$	$1.19 + 0.28\sigma^o$ $r = 0.996$; $s = 0.009$	$1.21 + 0.26\sigma$ $r = 0.992$; $s = 0.013$	$1.24 + 0.18\sigma^+$ $r = 0.936$; $s = 0.035$

sulfides ($r = 0.996$). A similar regularity in improving the correlation (except for aryl *tert*-butyl sulfides) is observed if the Hammett σ-constants are employed.

With electrophilic σ^+-constants, which have an excellent linear correlation for substituted thioanisoles, the correlation in the series of ethyl-, isopropyl-, *tert*-butyl sulfides gradually worsens (Table 4.7).

Thus, none of the substituent constants provides a universal linear correlation for the *meta*- and *para*-substituted representatives of the reaction series studied.

The improved correlation with different sets of the substituent constants in the series of aryl methyl-, ethyl-, isopropyl-, and *tert*-butyl sulfides as well as the differences in the reaction correlation constants of the first and second types within each reaction series indicate that in the electrooxidation of compounds studied, the effects of direct polar conjugation of electron-donating +C-type substituents manifest themselves in various manner.

For a separate evaluation of the contributions of purely polar effects as well as the effect of direct polar conjugation of the R substituents to $E_{p/2}$ of electrooxidation, the Yukawa–Tsuno–Palm equation is used [20]:

$$E^{\mathrm{R}}_{p/2} = E^{\mathrm{H}}_{p/2} + \rho^{\mathrm{o}}_\pi \sigma^{\mathrm{o}} + \rho^+_\pi \Delta\sigma^+_{\mathrm{c}},$$
$$\text{where } \sigma^+_{\mathrm{c}} = \sigma^+_p - \sigma^{\mathrm{o}}_p;\ \varepsilon = \rho^+_\pi / \rho^{\mathrm{o}}_\pi.$$

Excellent linear correlations are observed in all the reaction series ($R > 0.99$). In 99% confidence interval, the reaction constant ρ^{o}_π, which characterizes the contribution of purely polar effects of the R substituents, is the same and does not depend on the reaction series (Table 4.8). This evidences that for all compounds studied, the substituents R contribute equally to $E_{p/2}$, due to the purely polar effects of the substituents. At the same time, the reaction constant ρ^+_π, which expresses sensitivity of $E_{p/2}$ toward direct polar conjugation of electron-donating substituents R and characterizes the contribution of these effects to $E_{p/2}$, decreases sharply in the series of alkyl aryl sulfides from Me to *t*-Bu. This indicates a strong dependence of the contribution of the direct polar conjugation effect on the alkyl group at the sulfur atom.

Table 4.8 The correlation-statistical processing of electrooxidation $E_{p/2}$ of alkyl aryl sulfides according to Yukawa-Tsuno-Palm equation

Reaction series	$E_{p/2}$, v	$\overset{o}{\rho}_{\pi}$, V	ρ^{+}_{π}, V	ε	*s*	*R*
$R^1C_6H_4SMe$	1.00 ± 0.02	0.25 ± 0.02	0.18 ± 0.02	0.75	0.004	0.999
$R^1C_6H_4SEt$	1.02 ± 0.02	0.27 ± 0.03	0.14 ± 0.04	0.54	0.008	0.997
$R^1C_6H_4SPr^i$	1.07 ± 0.02	0.28 ± 0.02	0.10 ± 0.03	0.37	0.006	0.999
$R^1C_6H_4SBu^t$	1.20 ± 0.01	0.27 ± 0.02	0.04 ± 0.01	0.13	0.006	0.999

The ε value, which characterizes the relative contribution of the direct polar conjugation effect to $E_{p/2}$, also sharply decreases (from 0.75 to 0.13) in the above series. If in the standard series, solvolysis of *tert*-cumyl chlorides, on the basis of which the electrophilic σ^+-constants are calculated [19], $\varepsilon = 1$ and $\sigma^+ = \sigma^o + \Delta\sigma^+_c$, then for electrooxidation of alkyl aryl sulfides $\varepsilon < 1$, and $\sigma^+_{ef.} = \sigma^o + \varepsilon\Delta\sigma^+_c$.

The excellent linear correlation for σ^o-constants in the case of aryl *tert*-butyl sulfide suggests that in this series pure polar effects of the substituents in the benzene ring are predominant, while the effects of direct polar conjugation play a minor role.

The decrease in contribution of the direct polar conjugation effect in the series of methyl-, ethyl-, isopropyl-, and *tert*-butyl aryl sulfides, apparently, may be due to the steric effects of the alkyl groups at the sulfur atom, resulting in "inhibition" of the conjugation between sulfur atom, π-system of the aromatic rings and substituents R in the *para*-position owing to the increased volume of the alkyl substituent and violation of coplanarity of the molecules.

4.1.2.4 Dialkyl Sulfides

For comparison, the electrochemical oxidation of dialkyl sulfides has been studied on a stationary graphite microanode (Table 4.9).

All investigated dialkyl sulfides, except for di(*tert*-butyl) sulfide, give clear current-potential curves with one maximum. The $E_{p/2}$ values, measured in 1 mol/L water-ethanol (1:1, v/v) $HClO_4$ solution, vary in a narrow range (from 1.04 to 1.12 V relative to the saturated calomel electrode), depending mainly on steric nature of the substituent.

For di(*ter*t-butyl) sulfide, despite the strong electron-donating nature of the *tert*-butyl group, a wave of electrochemical oxidation is not observed under the same conditions, while *tert*-butyl phenyl sulfide gives a distinct wave of electrochemical oxidation. This fact confirms the conclusion that the decisive contribution of substituents to electrochemical oxidation of sulfides depends not only on electron density of the sulfur atom, but also on steric effect of its surrounding.

Table 4.9 Half-peak potentials ($E_{p/2}$, V) of electrochemical oxidation of dialkyl sulfides

Structure	Me_2S	Et_2S	*n*-Pr_2S	*i*-Pr_2S	*n*-Bu_2S	*n*-BuSEt	*t*-$BuSCH_2Ph$
$E^a_{p/2}$	1.04	1.07	1.04	1.12	1.04	1.05	1.12

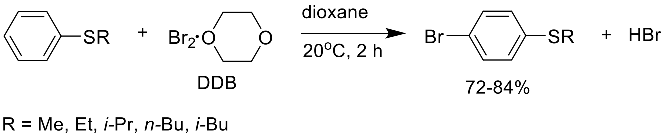
[a] Relative to saturated calomel electrode

4.2 Bromination of Alkyl Aryl and Alkyl Benzyl Sulfides

Aromatic and heteroaromatic bromides represent a key building block in organic synthesis, especially with the emergence of cross-coupling reactions. Therefore, they are important intermediates in the synthesis of natural products, physiologically active compounds, and novel materials [44]. The methodology for producing bromoarenes via C–H functionalization has been extensively developed. A large number of convenient preparative methods for various bromoarenes, including heterocyclic derivatives, have been designed [45]. Ligand directed transition-metal-catalyzed bromination is becoming a more universal tool for introducing a bromine atom.

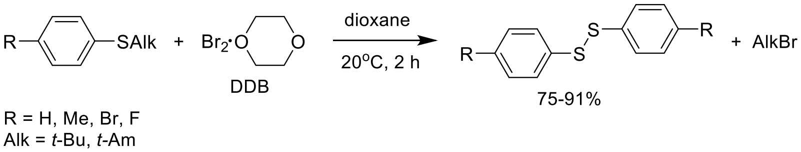
At the same time, direct halogenation of reactive aromatic and heteroaromatic compounds (with halogen-dioxane complexes, which have been obtained by Favorsky [46] as far back as 1906) is the widely accepted technique [47–53].

Primary and secondary alkyl phenyl sulfides (R = Me, Et, *i*-Pr, *n*-Bu, *i*-Bu) are found to react smoothly with dioxane dibromide (DDB) at room temperature (dioxane, 2 h) to form 4-bromosubstituted alkyl phenyl sulfides in 72–84% yields [54, 55].

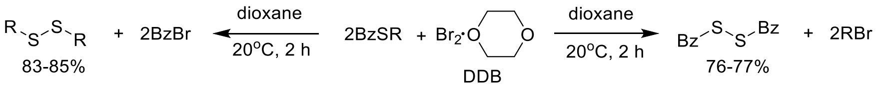


The reaction proceeds regioselectively; no bromination products at the *ortho*-position of the benzene ring are detected in the reaction mixture. Thus, DDB turns out to be a convenient reagent for the 4-bromination of alkyl aryl sulfides.

The reaction of *tert*-alkyl aryl sulfides with DDB under similar conditions proceeds in a different fashion: instead of alkyl 4-bromaryl sulfides only diaryl disulfides and *tert*-alkyl bromides are formed (yield 75–91%) [55].



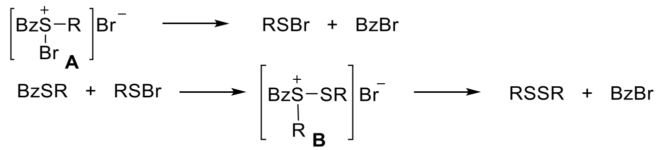
Alkyl benzyl sulfides also behave “abnormally” in the reaction with the DDB complex: instead of electrophilic substitution into the aromatic ring, the C–S bond cleavage occurs to afford either dialkyl disulfides and benzyl bromide (in the case of primary and secondary alkyl benzyl sulfides) or dibenzyl disulfide and *tert*-butyl bromide (in the case of benzyl *tert*-butyl sulfides). The reaction is highly chemoselective.



R = Me, Et, *i*-Pr, $PhCH_2$
Bz = $PhCH_2$, $4\text{-}FC_6H_4CH_2$

R = *t*-Bu
Bz = $PhCH_2$, $3\text{-}FC_6H_4CH_2$, $4\text{-}FC_6H_4CH_2$

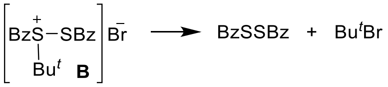
The results obtained indicate that the sulfur atom in alkyl benzyl sulfides is a stronger nucleophilic center than the benzene ring relative to the bromine cation. In this case, the reaction, apparently, proceeds through the intermediate formation of sulfonium salts **A** and **B**:



R = Me, Et, *i*-Pr, $PhCH_2$; Bz = $PhCH_2$, $4\text{-}FC_6H_4CH_2$

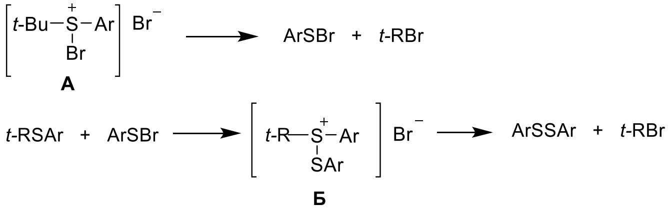
The direction of sulfonium complex **B** decomposition is defined, obviously, by stability of the carbocation (or the corresponding radical, if one-electron transfer occurs), which is formed during the C–S bond cleavage. When Bz^+ competes with primary and secondary alkyl carbocations (Me^+, $Et^{+,}$ and *i*-Pr^+), the Bz–S bond is cleaved to furnish dialkyl disulfides and benzyl bromide.

In the case of benzyl *tert*-butyl sulfides bromination, decomposition of sulfonium complex **B** proceeds in opposite direction, which confirms a higher stability of the *tert*-butyl cation (or the corresponding radical) as compared to benzyl. As a result, *tert*-butyl bromide and dibenzyl disulfide are formed (in up to 77% yield).

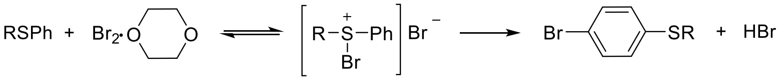


Bz = $PhCH_2$, $3\text{-}FC_6H_4$, $4\text{-}FC_6H_4$

tert-Alkyl aryl sulfides interact with DDB in a similar way via the formation of sulfonium salts **A** and **B**:



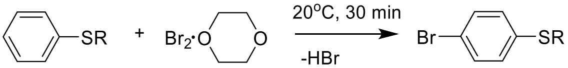
Obviously, in the case of primary and secondary alkyl aryl sulfides, sulfonium salts are also produced, but they should be more stable due to a lower stability of the carbocations, which they can generate. Therefore, normal bromination can proceed through the equilibrium:



A

Owing to a lower basicity of the sulfur atom in primary and secondary alkyl aryl sulfides (as compared with *tert*-alkyl analogs) [56, 57], the equilibrium concentration of free sulfide is higher in them. The latter fact contributes to direct bromination of the ring. In addition, the benzene ring in this series of alkyl aryl sulfides is activated by a stronger *p*–π-conjugation of lone electron pair of the sulfur atom with the aromatic π-system, unlike *tert*-alkyl aryl sulfides, where such conjugation is weakened due to a violation of coplanarity due to steric reasons [58].

Such conclusions are confirmed by the yields of alkyl 4-bromophenyl sulfides obtained by bromination of *tert*-alkyl phenyl sulfides with dioxane dibromide under comparable (but not optimum) conditions (equimolar ratio of the reagents, 20 °C, 30 min).



R	Me	Et	*i*-Pr	*n*-Bu	*i*-Bu
Yield, %	75	62	55	53	54

The yields of the bromination products in this series decrease with an increase in basicity of the sulfur atom and steric hindrances around this atom and with a decrease in the expected stability of the carbocations, which can be formed by sulfonium salt **A**. These results are in agreement with an order of alkyl phenyl sulfides activity in bromination with elemental bromine in 90% acetic acid (Me > Et > *i*-Pr), observed in [59], in which formation of the sulfonium salt is also suggested. Upon bromination of alkyl aryl ethers, where formation of such an intermediate is impossible, a normal effect of the substituent (opposite to that in the alkyl aryl sulfides) is observed [59].

Earlier, the study of electrophilic aromatic substitution has revealed [60] a special effect of 4-methylthio group on bromination (Br_2, $AcOH_{dry}$, 25 °C) and acetylation (AcCl, $AlCl_3$, dichloroethane, 25 °C) of thioanisole. However, no explanation of such effect has been given. To evaluate the constancy of electronic contribution of the 4-MeS-group, Brown’s extended selectivity treatment was applied. On dependency diagram of selectivity factor logarithm ($lg\ p_f$) against the electrophilic substituent constants (σ^+) for bromination and acylation, the point, corresponding to the 4-SMe substituent, does not lie near the least square line, but somewhat lower [60]. At the same time, excellent selectivity of aromatic substitution in the *para*-position relative to the methylthio group is shown using the Yukawa–Tsuno equation. It is assumed [55] that this may be a result of complexation between bromine cation and sulfur atom of the methylthio group.

Table 4.10 Products of alkyl aryl and alkyl benzyl sulfides bromination [55]

No.	Structure	Yield, %	M.p., °C	^{1}H NMR chemical shifts, δ, ppm
1	4-BrC_6H_4SMe	84	35	2.43 (Me), 7.14, 7.42 (Ar)
2	4-BrC_6H_4SEt	78	Oil	1.33 (Me), 2.97 (CH_2), 7.26, 7.48 (Ar)
3	4-$BrC_6H_4SPr^i$	74	Oil	1.26 (Me), 3.29 (CH), 7.22, 7.38 (Ar)
4	4-$BrC_6H_4SBu^i$	72	Oil	1.02 (Me), 1.95 (CH), 2.78 (CH_2), 7.25, 7.47 (Ar)
5	PhSSPh	78	60	7.35 (Ph)
6	$(4\text{-}MeC_6H_4S)_2$	77	44–45	2.28 (Me), 7.07, 7.36 (Ar)
8	$(4\text{-}BrC_6H_4S)_2$	91	94	7.05, 7.48 (Ar)
9	$(4\text{-}FC_6H_4S)_2$	75	148–150/4	7.40 (Ar)

The physical-chemical and spectral (^{1}H NMR) characteristics of the products of alkyl aryl- and alkyl benzyl sulfides bromination are given in Table 4.10.

In the IR spectra of disulfides obtained, vibrations of the S–S bond correspond to bands at 460 and 469 cm^{-1}. The aromatic ring is represented by bands at 830, 1460, 1490–1500, 1575, 1590 cm^{-1}. The intense bands of alkyl substituents, characteristic of the starting *tert*-alkyl aryl sulfides at 2850–3050 cm^{-1}, disappear.

4.3 Acylation of Alkyl Aryl Sulfides

Acyl alkylthiobenzenes [(alkylthio)acetophenones] are known to be valuable intermediates in organic synthesis. For example, they are employed in manufacturing antiviral drugs [61] and other pharmacologically important substances [62, 63] as well as in the synthesis of alkyl thiophenyl pyrroles [64, 65], etc. Among the approaches to the preparation of alkyl thioacyl benzenes is acylation of alkyl aryl sulfides under the Friedel–Crafts conditions [61, 66, 67]. However, prior to publications [38, 68, 69], the effects of the starting compounds structure on yield of the acylation products were not systematically studied.

It has been shown [69] that primary and secondary alkyl phenyl sulfides react regiospecifically with acyl chlorides in the presence of Lewis acids ($AlCl_3$ or $SnCl_4$) in carbon tetrachloride or dichloroethane at 0–25 °C to deliver 1-acyl-4-alkylthiobenzenes exclusively in 35–80% yields (Table 4.11).

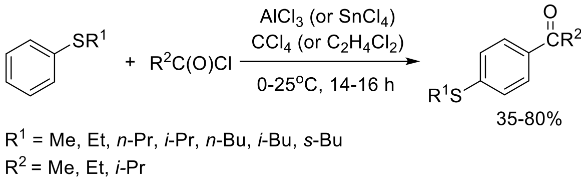


Table 4.11 Products of alkyl aryl sulfides acylation [64, 67]

No.	Structure	Yield, %	B.p., °C/torr (m.p., °C)	n_D^{20}	d_4^{20}
1	4-$MeSC_6H_4C(O)Me$	80	140/4 (79)		
2	4-$EtSC_6H_4C(O)Me$	76	124/1 (41)		
3	4-$Pr^nSC_6H_4C(O)Me$	74	130/1 (38)		
4	4-$Pr^iSC_6H_4C(O)Me$	70	142/3 (29)	1.5850^{30}	1.0140^{30}
5	4-$Bu^nSC_6H_4C(O)Me$	61	134/1 (24-25)	1.5846	1.0886
6	4-$Bu^iSC_6H_4C(O)Me$	64	142/1	1.5816	1.0441
7	4-$Bu^sSC_6H_4C(O)Me$	66	134/1	1.5808	1.0422
8	4-$Pr^nSC_6H_4C(O)Et$	74	139/2 (58)		
9	4-$Me^nSC_6H_4C(O)P^r$	35	140/2 (31)		
10	4-$EtSC_6H_4C(O)Et$	75	137/2 (43)		
11	2-EtS-5-$FC_6H_3C(O)Me$	42	118/2 (60)		
12	2-Bu^t-5-$FC_6H_3C(O)Me$	40	125/1 (43)		

Yields of the acylation products depend on nature of the alkyl radicals (R^1 and R^2) and decrease in the following order: Me > Et > *n*-Pr > *i*-Pr > *s*-Bu > *i*-Bu > *n*-Bu (for R^1); Me > Et > *i*-Pr (for R^2). Pivalyl chloride (R^2 = *t*-Bu) turns out to be completely inactive in this reaction.

The acylation of *para*-substituted alkyl aryl sulfides occurs regiospecifically at the *ortho*-position relative to the alkylthio group. Acylation of alkyl 4-fluorophenyl sulfides with acetyl chloride gives 1-acetyl-2-alkylthio-5-fluorobenzenes in 40–42% yields (Table 4.11) [69].

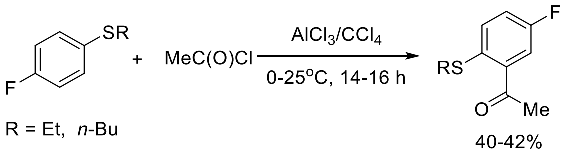
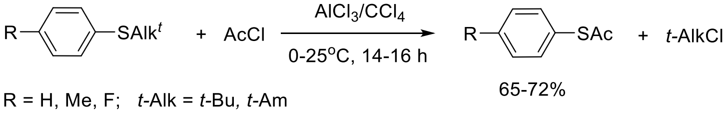


Table 4.12 Dependence of *S*-aryl thioacetate yields on *tert*-alkyl aryl sulfides structure

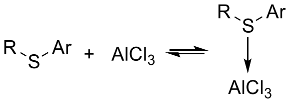
t-Alkyl	R	Structure	Yield, %
t-Bu	H	PhSC(O)Me	68 (69)[a]
t-Am	H	PhSC(O)Me	67
t-Bu	Me	4-MeC$_6$H$_4$SC(O)Me	72
t-Bu^t	F	4-FC$_6$H$_4$SC(O)Me	65

[a] SnCl$_4$ was employed instead of AlCl$_3$

Under similar conditions, *tert*-alkyl aryl sulfides react with acyl chlorides in other manner: instead of acylation of the benzene ring, the cleavage of the S-C bond$_{(t\text{-Alk})}$ and formation of aryl thioacetates are observed [68, 69]. The yield of the latter (65–72%) does not almost depend on nature of the substituent in the benzene ring (R) and branching of the *tert*-alkyl group (Table 4.12).

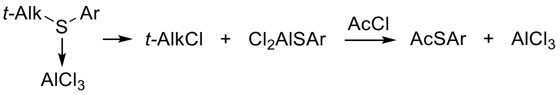


For acylation of primary and secondary alkyl aryl sulfides, the observed dependence of yields on the sulfide structure is opposite to that expected for direct aromatic electrophilic substitution, which is facilitated by electron-donating substituents in the ring. The decrease in the acylation products yield with an increase in electron-donating ability of substituent R is similar to that observed for bromination of alkyl aryl sulfides by both elemental bromine [59] and DDB [55]. As discussed above (Sect. 4.2), intermediate sulfonium salts are formed in these reactions. Thus, the change in 1-acyl-4-alkylthiobenzenes yield in the series Me > Et > *n*-Pr > *i*-Pr > *s*-Bu > *i*-Bu > *n*-Bu can be explained from the same positions, i.e. by the formation of complexes between sulfides and catalyst, a Lewis acid (AlCl$_3$ or SnCl$_4$).



$$\mathrm{R{-}S{-}Ar} + \mathrm{AlCl_3} \rightleftharpoons \mathrm{R{-}\underset{\downarrow\,AlCl_3}{S}{-}Ar}$$

In this case, it is abundantly clear that the higher basicity of the sulfur atom, the lower should be reactivity of the benzene ring with respect to electrophilic attack. In addition, this mechanism explains and predicts cleavage of the S–C bond upon the acylation of *tert*-alkyl aryl sulfides:



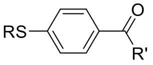
$$t\text{-Alk}{-}\underset{\downarrow\,\mathrm{AlCl_3}}{\mathrm{S}}{-}\mathrm{Ar} \longrightarrow t\text{-AlkCl} + \mathrm{Cl_2AlSAr} \xrightarrow{\mathrm{AcCl}} \mathrm{AcSAr} + \mathrm{AlCl_3}$$

It is known [70] that the ease of the C–S bond cleavage in RSAr under the action of $AlBr_3$ or HBr, leading to the formation of thiophenols ArSH, decreases, depending on the structure of R, in the following order: $Ph_3C > Ph_2CH > PhCH_2 > Ph(CH_2)_2$, i.e. the more stable the cation formed, the easier the reaction. This is consistent with regularities of substituents effect observed during formation of thioacetates from *tert*-alkyl sulfides upon their acylation, as well as with weak dependence of thioacetates yield on structure of the alkylthio group (Table 4.12).

Due to violation of coplanarity in *tert*-alkyl aryl sulfides, *p*–π-conjugation drastically decreases in their molecules, which is confirmed by NMR data [71] and measurements of relative basicity [56, 57]. This infringes the donor effect transfer from the *tert*-alkyl part moiety of the sulfur atom to the benzene ring and, thus reorienting electrophilic attack on the sulfur atom.

The values of ^{13}C chemical shifts of 1-acyl-4-alkylthiobenzenes are presented in Table 4.13. As seen, a decrease in the *p*–π-conjugation upon branching of the alkyl substituent takes place in this series of compounds. This is also evidenced from deshielding of carbon atoms in the *para*-position of the benzene ring (augmentation of ^{13}C chemical shifts depending on an increase in branching of the alkyl radical) in the following order: Me > Et > *i*-Pr > *t*-Bu. Small changes are observed for compounds with R = *i*-Pr and *t*-Bu, which indicates the predominance of non-planar form in the latter case. A change in the *p*–π-conjugation between sulfur atom and the benzene ring does not affect the screening of the carbonyl group.

Table 4.13 The ^{13}C NMR chemical shifts of 4-acylphenyl alkyl sulfides



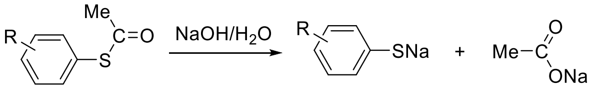
No.	Structure	Chemical shifts, δ, ppm				
		C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	C=O
1	$4\text{-MeSC}_6H_4C(O)Me$	133.30	128.64	124.79	145.83	197.03
2	$4\text{-EtSC}_6H_4C(O)Me$	133.82	128.82	126.30	144.70	197.21
3	$4\text{-Pr}^nSC_6H_4C(O)Me$	133.77	128.80	126.38	144.98	197.28
4	$4\text{-Pr}^iSC_6H_4C(O)Me$	134.28	128.77	128.42	143.88	197.28
5	$4\text{-Bu}^nSC_6H_4C(O)Me$	133.74	128.77	126.26	145.04	197.22
6	$4\text{-Bu}^iSC_6H_4C(O)Me$	134.39	129.21	126.72	145.37	196.39
7	$4\text{-Bu}^tSC_6H_4C(O)Me$	137.60	128.83	137.32	139.50	197.06
8	$4\text{-MeSC}_6H_4C(O)Et$	134.30	129.13	125.81	146.23	199.47
9	$4\text{-MeSC}_6H_4C(O)Pr^i$	133.26	129.41	125.81	146.17	202.94
10	$4\text{-EtSC}_6H_4C(O)Et$	134.49	129.09	126.99	144.80	199.34

4.4 Hydrolysis of *S*-Aryl Thioacylates

4.4.1 The Effect of Leaving Group (Arylthioanion) on Kinetics of Alkaline Hydrolysis of *S*-Aryl Thioacylates

The available literature data on alkaline hydrolysis of thiocarboxylic *S*-esters are contradictory. For example, the alkaline hydrolysis constants of *S*-(4-nitrophenyl) thioacetate, measured in water at 298 K, differ almost 4 times in the works [72, 73].

The systematic studies of hydrolytic decomposition of aryl thioacetates have allowed the bimolecular rate constants *k* of the alkaline hydrolysis of thioacetic *S*-acid aryl esters ($AcSC_6H_4R$) to be measured in water at 298 K [74].



R = H, 4-Me, 3-MeO, 4-MeO, 4-F, 4-Cl, 4-Br, 4-NO_2

For kinetic measurements of alkaline hydrolysis of aryl thioacetates, a spectrophotometric technique with continuous recording of the change in transmittance at a given wavelength was used [73]. The device was based on a Spectromom-201 spectrophotometer; deuterium lamp was employed as a light source. The recording system was “FEU-39A” with a recorder “EZ-9” at the output.

The rate of hydrolysis was measured under pseudomonomolecular conditions at 25 ± 0.05 °C. The concentration range of NaOH was chosen basing on requirements of pseudomonomolecularity and proportionality of k_1 constant to concentration of the alkali. To select the working wavelength, the spectrum of thioester was recorded on a Specord-UV Vis instrument before and after hydrolysis. The wavelength for kinetic measurements was chosen according to the maximum difference ε for thioester and products of its hydrolysis. For each compound, the validity of Beer’s law at the selected wavelength in the used concentration range of thioester was checked.

To study the kinetics, rectangular cuvettes with ground plugs, placed in a massive thermostated cuvette holder, were used. A pre-thermostated solution of thioester (0.01–0.03 mL of a solution, concentration 0.002–0.004 mol/L) was added directly from a micropipette to a cuvette with alkali. Then, the changes in transmission T (%) during the reaction were continuously recorded.

When the reaction was carried out under pseudo-first-order conditions (an excess of NaOH), the following rate constants were obtained [74]:

R	*k*	R	*k*
H	0.92 ± 0.01	4-F	1.04 ± 0.01
4-Me	0.73 ± 0.01	4-Cl	1.35 ± 0.03
3-MeO	0.95 ± 0.01	4-Br	1.33 ± 0.02
4-MeO	0.73 ± 0.01	4-NO_2	4.78 ± 0.02

In this experiment [74], the ionic strength of the solution was not kept constant, since it is known [75, 76] that this factor has a little effect on the kinetics of alkaline cleavage of esters having uncharged substituents.

The obtained rate constant k for 4-nitrophenyl thioacetate is slightly different from the reported [72] and is significantly lower than such constant recorded using a constant ionic strength of the solution (μ 1.0) [77]. Apparently, the rate constants given in [75] are much overestimated, since k value for S-(4-nitrophenyl) thioacetate in water at 298 K and an ionic strength of 1.0 (KCl additive) coincide within the limits of experimental error [74].

The kinetics of hydrolysis of S-thioesters $AcSC_6H_4R$ and their oxygen analogs $AcOC_6H_4R$ obeys the laws of second-order reactions (first order in ester and alkali). The effect of R substituent on the hydrolysis of thioesters is adequately described by the Hammett–Taft equation using constants $\overline{\sigma}^o$.

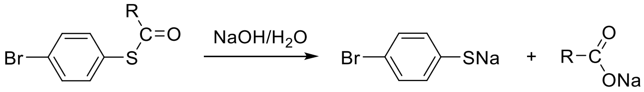
$$\lg k = (-0.062 \pm 0.016) + (0.787 \pm 0.046)\overline{\sigma}^o; r = 0.99, s = 0.04, n = 8.$$

The alkaline hydrolysis constants of aryl thioacetate obtained in [72] give the best correlation with the σ^--constants. The authors suggest that hydrolysis proceeds according to a mechanism involving cleavage-addition processes ($E1cB$). However, relatively low statistical indicators of this correlation (r = 0.979, s = 0.087) testify rather against this mechanism than in its favor.

It has been established [73] that aryl esters ($AcOC_6H_4R$) are hydrolyzed via the addition-cleavage mechanism ($B_{Ac}2$). There is no reason to believe that the sulfur analogs, aryl thioacylates should be hydrolyzed by another mechanism. In this case, the ratio of sensitivity constants ρ_S (0.787 ± 0.046) and ρ_O (0.947 ± 0.037) [73] in the Hammett–Taft equation can be taken as a ratio of conductivities of the substituents electronic effect through the –S– and –O– bridges. Indeed, the ratio $\rho_S/\rho_O = 0.831 \pm 0.081$ agrees with that of the corresponding bridges conductivity calculated from the spin-spin coupling constants in the methyl group of substituted toluene, anisole, and thioanisole: $Z_S/Z_O = 0.72/0.80 = 0.90$ [78].

4.4.2 The Effect of Acyl Group on Alkaline Hydrolysis of *S*-Aryl Thioacylates

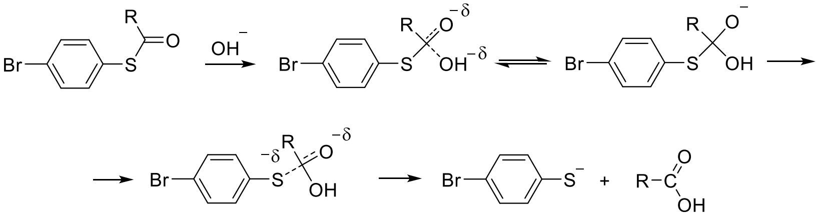
To make a reasonable choice between two mechanisms of addition-elimination ($B_{Ac}2$) [79] and elimination-addition ($E1cB$) [72] of alkaline hydrolysis of S-aryl thiocarboxylic acid esters, kinetics of the reaction was studied spectrophotometrically under pseudo-first-order conditions (excess NaOH) at 15, 25, and 55 °C on the example of S-(4-bromophenyl) thioacylates, $4\text{-}BrC_6H_4SC(O)R$ [80].



The following bimolecular rate constants of alkaline hydrolysis *k* (L•mol^{-1}•s^{-1}) were found:

R	15 °C	25 °C	55 °C
Me	0.67 ± 0.03	1.33 ± 0.02	12.08 ± 0.21
Et	0.56 ± 0.01	1.14 ± 0.03	6.39 ± 0.24
n-Pr	0.22 ± 0.02	0.52 ± 0.01	3.80 ± 0.17
i-Pr	0.21 ± 0.01	0.36 ± 0.01	2.98 ± 0.20
n-Bu	0.31 ± 0.02	0.47 ± 0.01	3.98 ± 0.11
i-Bu	0.05 ± 0.003	0.11 ± 0.002	1.10 ± 0.09

If the assumption [81, 82] on the approximate similarity of induction effects of the alkyl groups is valid, and the rate-determining stage of alkaline hydrolysis of *S*-aryl esters of thiocarboxylic acid is a nucleophilic attack of the hydroxide anion on the carbonyl group carbon, then hydrolysis rate constants of thioesters, 4-$BrC_6H_4SC(O)R$, at a fixed temperature should be linearly related to the steric constants of the E_s substituents.

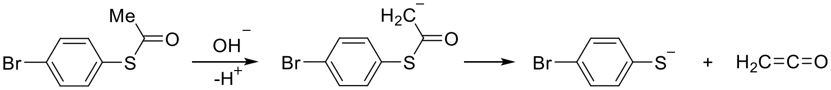


Such correlations do exist, and the coefficient of sensitivity to the steric effects of substituents within the limits of error does not depend on temperature and coincides with the value obtained for the RC(O)OPh esters [83].

$$\lg k_{(15°C)} = (-0.18 \pm 0.04) + (1.18 \pm 0.08)E_s; r = 0.991; s = 0.06;$$
$$\lg k_{(25°C)} = (0.11 \pm 0.03) + (1.17 \pm 0.06)E_s; r = 0.994; s = 0.05;$$
$$\lg k(_{55°C}) = (0.98 \pm 0.04) + (1.05 \pm 0.10)E_s; \mathrm{r} = 0.983; s = 0.07.$$

The value of activation energy calculated from the Arrhenius equation does not depend on the substituent and equals (54.9 ± 3.6) kJ/mol, which corresponds to the $B_{Ac}2$ mechanism [79]. Hydrolysis of phenylacetates in water and aqueous-ethanol mixtures represents also an isoenthalpic process [84].

The alternative *E*1*cB* mechanism implies the formation of a ketene intermediate, the rate-determining stage being generation of a carbanion (proton abstraction from the substituent α-carbon atom in the acyl counterpart) [72].



If this mechanism is valid, a correlation between the constants of 4-$BrC_6H_4SC(O)R$ thioesters hydrolysis and the constants of base-catalyzed enolization of alkyl phenyl ketones RC(O)Ph [85], the rate-determining stage of which also involves the formation of carbanion [86], should be observed. For comparison, statistically corrected rate constants of the alkaline hydrolysis of esters 4-$BrC_6H_4SC(O)CHR^1R^2$ and enolization of ketones $R^1R^2CHC(O)Ph$ [87] are used, since with this approach the formal reaction center is the hydrogen of α-methine group. However, such a correlation is absent (55 °C, $r = 0.617$, $s_o = 0.281$) [82].

Thus, the regularities of structural effects of the acyl moiety and the leaving group as well as temperature [74] on the rate of alkaline hydrolysis of aryl thioacylates are similar to those observed for their oxygen analogs. They completely agree with $B_{Ac}2$ mechanism and are not consistent with $E1cB$ mechanism.

4.4.3 The Combined Effects of Structure, Medium and Temperature on Alkaline Hydrolysis of *S*-aryl Thioacylates in Aqueous-Ethanol Mixtures

Usually, the interpretation of factor-property type dependencies is significantly complicated by the fact that intensity and often sign of the effecting factor are defined by the values of other factors of the multilinear equation. Comparing the equation obtained for the studied process with that for the model reaction, the mechanism of which has been established, one can draw conclusions about the nature of the investigated mechanism. In order to avoid accidental coincidence of regularities of the factors effect, such comparative method should imply the variation of the largest possible number of these factors within the widest possible range.

To check the above conclusions on mechanistic similarity of hydrolysis of aryl thioacetates $AcSC_6H_4R$ and acetates $AcOC_6H_4R$, apart from structural effects (substituent R), the influence of aqueous-ethanol medium and temperature have been studied [88].

As follows from Sect. 4.4.2, esters $AcSC_6H_4R$ are most likely hydrolyzed via addition-elimination mechanism $B_{Ac}2$, the rate-determining first stage being the attack of hydroxide anion on the carbonyl group carbon. Some authors also consider the possibility of alternative mechanism for thioesters hydrolysis through the elimination-addition ($E1cB$) [72]. These mechanisms as well as the synchronous $E2$ mechanism are kinetically indistinguishable; the reaction has the first orders in terms of the reagent and substrate and general second order.

The bimolecular rate constants k of thioesters $AcSC_6H_4R$ hydrolysis and their root-mean-square errors, measured spectrophotometrically under pseudo-first-order conditions (excess NaOH), are given in Table 4.14. Similar data for esters $AcOC_6H_4R$ were obtained in [84].

Table 4.14 Rate constants *k* of esters $AcSC_6H_4R$ alkaline hydrolysis in water and aqueous ethanol [88]

T, °C	Content of EtOH, vol.%	k, $L \cdot mol^{-1} \cdot s^{-1}$			
		R = 4-Me	R = H	R = 4-Br	R = 4-NO_2
15	0	0.30 ± 0.003	0.41 ± 0.005	0.67 ± 0.030	2.20 ± 0.035
15	10	0.63 ± 0.02	0.69 ± 0.03	1.30 ± 0.02	5.00 ± 0.044
15	20	0.86 ± 0.01	1.11 ± 0.01	1.92 ± 0.02	8.11 ± 0.069
15	30	0.88 ± 0.01	1.24 ± 0.01	2.28 ± 0.02	11.05 ± 0.16
15	50	0.70 ± 0.02	1.05 ± 0.07	2.35 ± 0.01	11.61 ± 0.12
15	70	0.78 ± 0.01	1.10 ± 0.03	2.90 ± 0.03	27.31 ± 0.27
15	90	0.92 ± 0.01	1.23 ± 0.02	3.86 ± 0.04	40.08 ± 0.80
25	0	0.73 ± 0.01	0.92 ± 0.01	1.33 ± 0.02	4.78 ± 0.02
25	50	1.36 ± 0.04	1.64 ± 0.03	3.60 ± 0.21	19.32 ± 1.13
25	70	1.67 ± 0.04	2.00 ± 0.04	5.64 ± 0.08	39.89 ± 0.61
25	90	1.85 ± 0.06	2.27 ± 0.08	9.27 ± 0.15	80.68 ± 2.25
55	0	5.44 ± 0.16	6.99 ± 0.11	12.08 ± 0.21	37.00 ± 1.20
55	50	7.12 ± 0.13	10.79 ± 0.46	17.54 ± 1.23	107.9 ± 5.1
55	70	8.14 ± 0.42	9.83 ± 0.26	31.96 ± 0.60	245.7 ± 2.6
55	90	10.22 ± 0.13	13.92 ± 0.27	44.42 ± 0.89	non determined

The rate of thioesters $AcSC_6H_4R$ hydrolysis depends on all three factors: structure, medium, and temperature. As in the case of $AcOC_6H_4R$ esters [85], the effect of temperature and structure on the studied process obeys the principle of linear free energy (LFE), that is, it can be described by equations of Arrhenius (Table 4.15):

$$\lg k = \lg A - E_a/2.3RT$$

and Hammett–Taft (Table 4.16, Figs. 4.4 and 4.5):

$$\lg k = \lg k_o + \rho\overline{\sigma}^o$$

As seen from Table 4.17, constant of sensitivity ρ toward a substituent influence depends rather strongly on the reaction medium and, within the limits of experimental errors, does not depend on temperature. The same regularity is observed for esters $AcOC_6H_4R$ [85]. However, the ρ values for aryl thioacetates are somewhat lower than the corresponding values for esters $AcOC_6H_4R$, which can be due to a lower transmittance of the substituent electronic effect through the sulfur atom as compared to the oxygen atom [74]. Figure 4.4 shows that the straight lines for solutions containing 50, 70, and 90% EtOH tend to intersect at one point. This situation is typical for the case of non-additive influence of two factors (in this case, the structure of $AcSC_6H_4R$ and composition of the medium), and is described by a single multilinear equation [20]. Straight lines for water and for solutions

Table 4.15 Parameters of Arrhenius equation [88]

R	Content of EtOH, vol.%	*lg A*	E_a, kJ·mol^{-1}	*r*	s_o
4-Me	0	0.71 ± 0.30	56.35 ± 1.76	0.999	0.028
	50	8.11 ± 0.12	45.59 ± 0.67	0.999	0.011
	70	8.17 ± 0.45	45.53 ± 2.58	0.998	0.042
	90	8.52 ± 0.16	47.20 ± 0.92	0.999	0.015
H	0	9.70 ± 0.11	55.60 ± 0.65	0.999	0.010
	50	8.49 ± 0.71	44.93 ± 4.10	0.996	0.066
	70	7.84 ± 0.01	43.06 ± 0.04	0.999	0.001
	90	8.73 ± 0.20	47.96 ± 1.17	0.999	0.019
4-Br	0	10.22 ± 0.39	57.48 ± 2.24	0.999	0.036
	50	7.63 ± 0.45	40.21 ± 2.66	0.998	0.045
	70	9.01 ± 0.02	47.14 ± 0.11	0.999	0.002
	90	9.13 ± 0.76	46.93 ± 4.38	0.996	0.071
4-NO_2	0	10.40 ± 0.01	55.49 ± 0.04	0.999	0.001
	50	9.09 ± 0.37	44.38 ± 2.18	0.998	0.035
	70	9.44 ± 0.81	44.42 ± 4.73	0.994	0.076
	90	10.70	50.18	a	a

[a] Calculated by two values

Table 4.16 Parameters of Hammett-Taft equation [88]

T, °C	Content of EtOH, vol.%	*lg* k_o	ρ	*r*	*s*
15	0	–0.395 ± 0.006	0.827 ± 0.012	0.999	0.010
15	10	–0.117 ± 0.024	0.905 ± 0.051	0.996	0.041
15	20	0.051 ± 0.009	0.950 ± 0.020	0.999	0.015
15	30	0.090 ± 0.004	1.062 ± 0.007	0.999	0.005
15	50	0.024 ± 0.019	1.178 ± 0.041	0.998	0.033
15	70	0.071 ± 0,018	1.519 ± 0.037	0.999	0.030
15	90	0.147 ± 0.029	1.626 ± 0.062	0,998	0,049
25	0	–0.045 ± 0.018	0.794 ± 0.039	0.998	0.031
25	50	0.256 ± 0.023	1.145 ± 0.049	0.998	0.039
25	70	0.369 ± 0.035	1.377 ± 0.075	0.997	0.060
25	90	0.457 ± 0.058	1.641 ± 0.122	0.995	0.097
55	0	0.853 ± 0.010	0.807 ± 0.020	0.999	0.016
55	50	1.003 ± 0.027	1.133 ± 0.057	0.998	0.045
55	70	1.073 ± 0 043	1.479 ± 0.092	0.996	0.073
55	90	1.200 ± 0.041	1.649 ± 0.244	0.989	0.070

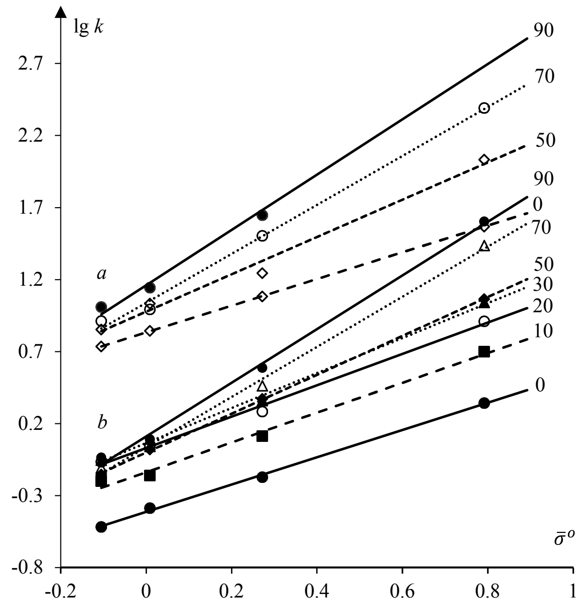


Fig. 4.4 Dependencies of lg k of $AcSC_6H_4R$ alkaline hydrolysis on substituent R constant $\overline{\sigma}^o$ at 55 (**a**) and 15 °C (**b**). The numbers correspond to the content of ethanol, vol.%

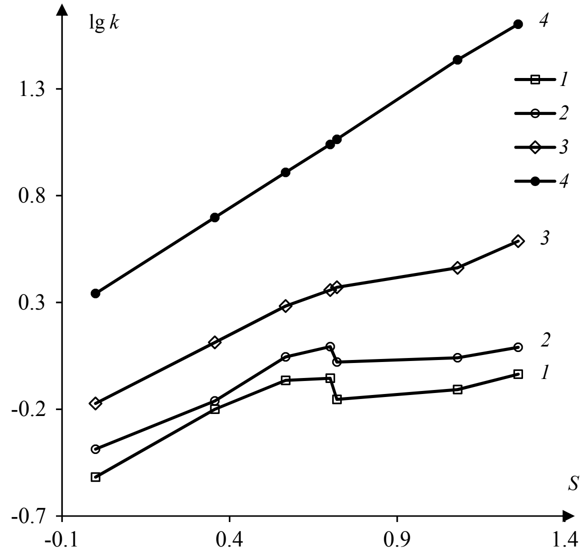


Fig. 4.5 Dependencies of lg k of $AcSC_6H_4R$ alkaline hydrolysis on medium factor parameter S for R = 4-Me (1), H (2), 4-Br (3) and 4-NO_2 (4) at 15 ° C

containing 10, 20 and 30% ethanol do not intersect at the above point and, therefore, represent another set of straight lines.

The effect of medium has been studied in detail for a temperature of 15 °C. A quantitative characteristic of this factor (S) is introduced operatively [89, 90]

Table 4.17 Coefficients and statistical parameters of polylinear equation for alkaline hydrolysis of aryl thioacylates $AcSC_6H_4R$ (R = 4-Me, H, 4-Br, 4-NO_2) in aqueous ethanol[a] [88]

Coefficients and statistical parameters	Regression 1 (standard medium: 50% EtOH)			Regression 2 (standard medium: water)		
	a	b	Expected values	a	b	Expected values
b_0	0.277 ± 0.018	0.273 ± 0.017	0.214[b]	–0.027 ± 0.019	–0.006 ± 0.022	–0.036[b]
b_1	1.176 ± 0.037	1.173 ± 0.035	1.145[c]	0.794 ± 0.041	0.785 ± 0.047	0.794[c]
b_2	0.265 ± 0.044	0.279 ± 0.041		0.402 ± 0.024	0.377 ± 0.028	
b_3	–2.319 ± 0.093	–2.380 ± 0.051	–2.451[d]	–2.840 ± 0.101	–2.585 ± 0.068	–2.904[d]
b_4	0.785 ± 0.097	0.773 ± 0.093		0.656 ± 0.054	0.684 ± 0.063	
b_5	0.114 ± 0.201			0.016 ± 0.219		
b_6	–0.220 ± 0.230			0.378 ± 0.128		
b_7	–0.462 ± 0.637			0.168 ± 0.356		
n	35	35		34[e]	35	
R	0.998	0.997		0.997	0.995	
s_o	0.053	0.052		0.058	0.070	

[a] Parameter was calculated from the value lg *k* for 4-$NO_2C_6H_4SAc$ at 25 °C: *S* =lg *k* (j medium) – lg *k* (standard medium); [b] lg *k* for R = H in standard medium at 25 °C; [c] ρ in standard medium at 25 °C; [d] $-E_A/2.3$ R for AcSPh in standard medium; [e] lg *k* was excluded for R = 4-Br at 15 °C in 50% ethanol

similarly to the Grünwald–Winstein parameter [20] as a difference between rate constant logarithms in aqueous-alcohol solution and in water:

$$S = \lg k(\mathrm{R} = 4-\mathrm{NO_2},\ \mathrm{j}^{n}\mathrm{medium}, 15^{\circ}\mathrm{C}) - \lg k(\mathrm{R} = 4-\mathrm{NO_2},\ \mathrm{H_2O}, 15^{\circ}\mathrm{C}).$$

If the LFE principle is applicable to the effects of medium on the rate of alkaline hydrolysis of $AcSC_6H_4Br$ thioesters with a fixed substituent and temperature, the following equation should be fulfilled:

$$\lg k = a_0 + a_1 S.$$

In the diagrams (Fig. 4.5) corresponding to this equation, two regions (0–20 vol.% and 50–90 %vol. EtOH) of linear dependences and an inflection region (30–50 vol.% EtOH) are observed. At 25 and 55 °C, the picture is similar to that observed at 15 °C. Thus, for all range of changes in composition of the aqueous–organic solvent in the case of $AcSC_6H_4Br$ thioesters, as opposed to $AcOC_6H_4Br$ esters, the LFE principle is not applicable to the effect of medium.

The activation energy (Table 4.15) of thioesters $AcSC_6H_4R$ alkaline cleavage in 50–90% ethanol is constant and equal to (45.80 ± 2.57) kJ/mol, which coincides with E_a value for $AcOC_6H_4R$ esters and is in good agreement with $B_{Ac}2$ mechanism [79]. The E_a values for all studied $AcSC_6H_4R$ thioesters (R = 4-Me, H, 4-Br, 4-NO_2) in water also do not depend on the structure of the ester, though they are somewhat higher (56.24 ± 0.92 kJ/mol). This confirms the conclusion that the lg *k* values in water do not coincide with the values obtained in mixtures containing more than 50% of ethanol.

Thus, the experimental data (Table 4.14) allow the dependences of lg *k* on the medium factor *S* to be calculated only in solutions of 50–90% ethanol.

The influence of all three factors on the reactivity of aryl thioacylates in the reaction of their alkaline hydrolysis in aqueous-ethanol mixtures can theoretically be described by a single multilinear equation:

$$\sigma_0$$

where σ_0, *S*, τ are influence factors of substituent R, medium, and temperature; τ is a centered temperature scale, introduced to avoid the correlation of matrix columns of the initial data, $\tau = 10^3(1/T - 1/T_0)$, $T_0 = 298$ K.

All possible equations, which take into account the combined influence of two factors, are special cases of the above multilinear equation. A good description of the experimental data obtained using this equation is confirmed by its statistical indicators as well as by coincidence of b_0-b_3 coefficients with their expected values (Table 4.17, regression 1). The coefficients, responsible for non-additive effect of structural factors and temperature (b_5), medium and temperature (b_6), and all three factors (b_7), are statistically insignificant (regression 1a) and their exclusion does not worsen the quality of the description (regression 1b).

Thus, the regression model, which adequately describes the influence of substrate structure, composition of aqueous-ethanol mixture and temperature on alkaline hydrolysis of aryl thioacylates, has exactly the same form as a model describing the effect of the same factors on the alkaline cleavage of $AcOC_6H_4R$ esters [84]. It should be noted, however, that in the latter case, the regression model covers the range of ethanol media from 0 to 90%.

The use of lg *k* for constructing a multilinear model of values for thioesters, measured in water, 50 and 90% ethanol (Table 4.17), leads to the appearance of a significant contribution of medium and temperature factors ($S\tau$) (regression 2a), the exclusion of which does not essentially worsen the description (regression 2b). A similar picture (a noticeable deviation of the values measured in water from the dependences observed for 50–90% ethanol) is observed for alkaline hydrolysis of $AcOC_6H_4R$ [84]. For example, energy activation value (E_a) for $AcOC_6H_4R$ esters hydrolysis in 50 and 90% ethanol is almost constant and equals to (42.26 ± 3.91) kJ/mol; the corresponding value measured in water is (47.49 ± 0.85) kJ/mol [for thioesters are (45.80 ± 2.57) and (56.24 ± 0.92) kJ/mol, respectively]. Apparently, the deviation of values for water from the total data for aryl acetates is expressed much weaker than in the case of aryl thioacetates, and therefore for the former it is statistically insignificant.

4.4.4 Alkaline Hydrolysis of Aryl Thioacylates in Aqueous–Organic Solvents

The violations of LFE principle for alkaline hydrolysis of aryl thioacylates in water and 50-90% ethanol (lack of a single linear correlation), noted in Sect. 4.4.3, can be caused by simultaneous hydrolysis and alcoholysis [91, 92]. The observed rate constant in this case is the total for two parallel processes.

In order to exclude alcoholysis from consideration as well as to better understand the effect of the medium, the combined influence of substitution and medium composition on alkaline hydrolysis of aryl thioacylates has been studied for mixtures of water with dioxane and acetonitrile [93]. The bimolecular rate constants *k* for $AcSC_6H_4R$, measured using spectrophotometric approach under pseudo-first-order conditions (excess NaOH) at 25 °C, are given in Table 4.18.

A non-monotonic dependence of *k* values on composition of the medium is especially pronounced in aqueous acetonitrile. A similar dependence is observed also for aryl acylates [73, 94], extreme values of the constants in both cases correspond approximately to the same content of acetonitrile in the mixture. Such a U-shaped view of the rate constant *k* dependence on composition of the medium has been reported earlier [95, 96]. However, in all media, the influence of substituent R on the kinetics of hydrolysis of aryl thioacylates and their oxygen analogs [94–96] is described by the Hammett–Taft equation (Table 4.19, Fig. 4.6).

$$\lg k = \lg k_0 + \rho\overline{\sigma}^o$$

Table 4.18 Rate constants *k* ($L \cdot mol^{-1} \cdot s^{-1}$) of $AcSC_6H_4R$ alkaline hydrolysis in water and its mixtures with dioxane and acetonitrile at 25 °C

Content of solvent, vol.%	R = 4-Me	R = H	R = 4-Br	R = 4-NO_2
0	0.726 ± 0.008	0.921 ± 0.010	1.332 ± 0.023	4.779 ± 0.024
Water–dioxane				
20	0.548± 0.010	0.738± 0.012	1.267± 0.036	5.901± 0.050
50	0.369± 0.003	0.529± 0.007	1.466± 0.017	10.14 ± 0.09
70	0.363± 0.006	0.558± 0.008	1.948± 0.026	15.34± 0.24
Water–acetonitrile				
30	0.300± 0.005	0.382± 0.013	0.807± 0.022	4.309± 0.048
50	0.174± 0.005	0.256± 0.006	0.568± 0.010	2.807± 0.053
60	0.153 ± 0.012	0.195± 0.003	0.511± 0.023	3.053± 0.081
70	0.096± 0.007	0.212± 0.024	0.549± 0.012	3.853± 0.095
80	0.300± 0.027	0.317± 0.010	1.053± 0.030	7.321± 0.166

Table 4.19 Correlation parameters of the Hammett-Taft equation for alkaline hydrolysis of $AcSC_6H_4R$ in water and its mixtures with dioxane and acetonitrile at 25 °C

Content of solvent, vol.%	lg k_0	ρ	*r*	s_o
0	–0.045 ± 0.018	0.794 ± 0.038	0.998	0.030
Water – dioxane				
20	–0.135 ± 0.012	1.002 ± 0.024	0.999	0.019
50	–0.243 ± 0.024	1.408 ± 0.050	0.999	0.040
70	–0.208 ± 0.042	1.587 ± 0.090	0.997	0.071
Water – acetonitrile				
30	–0.390 ± 0.016	1.140 ± 0.033	0.999	0.026
50	–0.584 ± 0.017	1.167 ± 0.036	0.999	0.028
60	–0.660 ± 0.027	1.286 ± 0.057	0.998	0.046
70	–0.723 ± 0.054	1.502 ± 0.115	0.994	0.091
80	–0.392 ± 0.056	1.409 ± 0.119	0.993	0.094

The sensitivity coefficient ρ for both series of esters increases with growth of the organic component content in the mixture. In the case of aqueous dioxane, this growth is observed for all range of the component ratios except for hydrolysis of aryl acylate esters in 85% dioxane.

In aqueous-acetonitrile mixtures, the ρ value increases with augmentation of acetonitrile content in the mixtures only up to 60% of acetonitrile concentration. Further increase in concentration of the organic component enhances reactivity of all compounds. The ρ value remains constant within the experimental error both for aryl thioacylates and their oxygen analogs [94].

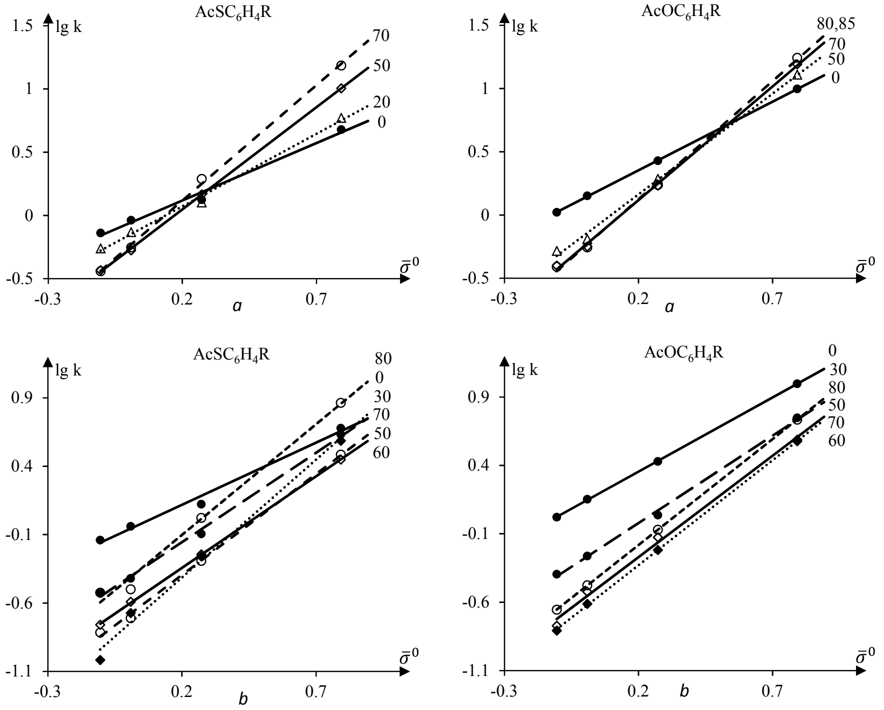


Fig. 4.6 Correlation between lg k of alkaline hydrolysis of AcSC$_6$H$_4$R thioesters and AcOC$_6$H$_4$R esters (R = H, 4-Me, 4-Br, 4-NO$_2$) and $\bar{\sigma}^{\text{o}}$ of substituent R in the leaving group at 25 °C in mixtures of water with dioxane (**a**) and acetonitrile (**b**). Numbering of straight lines corresponds to the content of the organic component (vol.%)

The effect of the medium composition on alkaline hydrolysis of the studied esters is more complicated: the FEL principle in this case is not applicable in the entire range of changes in the organic component content (Fig. 4.7). The deviation from linearity in the case of aryl acylates AcOC$_6$H$_4$R is observed for 80–85% dioxane. For thioesters, noncompliance with the LFE principle begins already with mixtures containing 70% dioxane, and the deviation from linearity is much greater. For aqueous acetonitrile, the effect of medium composition is studied in more detail. In both series of esters there are two regions, in which the LFE principle is fulfilled: the region of 0–60% acetonitrile, where sensitivity to the influence of medium composition depends on substituent R and the region of 60–80% acetonitrile, where such dependence is absent. Non-observance of the LFE principle in the entire range of changes in the medium composition is expressed in the fact that the straight lines in coordinates lg $k - \bar{\sigma}^{\text{o}}$ (Fig. 4.6), corresponding to two regions, form two families: a beam of straight lines intersecting outside the experimental region (0–60%) and a series of parallel lines (60–80%). For aryl thioacylates, this effect is more pronounced than for their oxygen analogs.

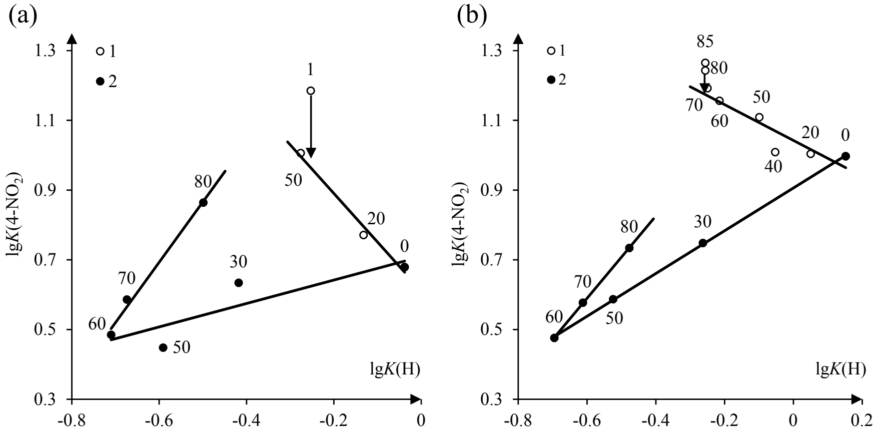


Fig. 4.7 Non-observance of the LFE principle for the effect of medium on hydrolysis of thioesters $AcSC_6H_4R$ (**a**) and esters $AcOC_6H_4R$ (**b**) in mixtures of water with dioxane (1) and acetonitrile (2); The numbering of the points corresponds to content of organic component (vol.%)

The combined effect of two factors (substituent and medium) can be described, within the limits of LFE principle applicability, by the following multilinear equations:

$$\lg k = a_0 + a_1\overline{\sigma}^0 + a_2 S + a_3\overline{\sigma}^0 S$$

where S is a parameter of the medium introduced operationally [89, 90] from the difference of lg k of hydrolysis of the corresponding unsubstituted ester in the j–n and standard media. The results of statistical analysis of the experimental data according to the equation, which takes into account the effect of substituent and medium (Table 4.20), show that the equation describes them adequately. The equations corresponding to hydrolysis of aryl thioacylates and their oxygen analogs in aqueous dioxane have similar form, and even isoparametric value of the substituent constant $\overline{\sigma}^o$ [20] for both types of esters is approximately the same (Fig. 4.6a). For aqueous acetonitrile, the regularities of combined effect of two factors on hydrolysis of two types of esters are also similar, although the equations for these two regions differ significantly for both aryl thioacylates and aryl acylates. So, the equations for 0–60% region have a significant non-additive contribution, which determines the dependence of ρ in the Hammett–Taft equation on medium composition as well as sensitivity to the medium effect on the nature of substituent R. In the equations corresponding to 60–80% content of acetonitrile, this contribution turned out to be insignificant, and its exclusion does not worsen the quality of the description.

Table 4.20 Coefficients and statistical parameters of a multilinear equation

Medium	a_0	a_1	a_2	a_3	n	R	S_o
$AcSC_6H_4R$ (R = H, 4-Me, 4-Br, 4-NO_2)							
0–50% dioxane[a]	–0.049 ±0.016	0.780 ± 0.034	0.814 ±0.105	–2.568 ±0.224	12	0.998	0.030
0–60% acetonitrile[a]	–0.045 ±0,021	0.819 ±0,044	0.889 ±0,041	–0.659 ±0.088	16	0.998	0.037
60–80% acetonitrile[b]	–0.713 ±0.040	1.380 ±0.085	1.469 ±0.324	0.228 ±0.688	12	0,992	0,087
60–80% acetonitrile[b]	–0.717 ±0.035	1.399 ±0.060	1.527 ±0.259		12	0.992	0.083
$AcOC_6H_4R$							
0–70% dioxane[a,c]	0.153 ±0.015	0.949 ±0.032	0.914 ±0.056	–1.555 ±0.119	12	0.999	0.027
0-60% acetonitrile[a]	0.171 ±0.019	0.939 ±0.039	1.076 ±0.033	–0.478 ±0.069	15[d]	0.999	0.034
60–80% acetonitrile[b]	–0.693 ±0.021	1.322 ±0.045	1.314 ±0.194	0.164 ±0.411	12	0.998	0.044
60–80% acetonitrile[b]	–0.696 ±0.018	1.335 ±0.030	1.355 ±0,155		12	0.998	0.041

[a]Standard medium: water; [b]Standard medium: 60% acetonitrile [c]Regression taken from [73]. [d] The value k for R = 4-Br in 50% acetonitrile was excluded

Thus, an analogy of structural effects and medium influence on the rate of alkaline hydrolysis of aryl thioacylates and their oxygen analogs is confirmed once again. This can be explained by the similarity of both reactions mechanism.

The curve on LFE dependences related to medium factor is not likely associated with a change in the reaction mechanism. Otherwise, it should be assumed that the reaction mechanism for both series of the studied compounds is changed, which is not consistent with the concepts of nucleophilic substitution reactions involving esters [79, 97–99]. Such a non-monotonic dependence of the rate constant on composition of the medium is obviously of a purely solvation nature. The non-additive influence of structure and medium factors on k value is due to the different degree of the substituent R effect on free solvation energies of the initial and transition states of the reaction. With increasing content of the organic component in the mixture, the effect of substituent R on solvation of the transition state becomes closer to this effect on solvation of the initial state of ester molecule, and from a certain moment, both effects become almost the same. This compensates the corresponding contributions to the total change in free energy.

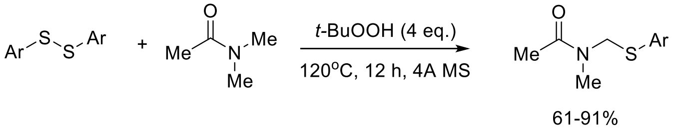
4.5 Other Reactions Involving Aromatic Thiols and Their Derivatives

Over the last decade, interest in the reactivity of aromatic thiols and their derivatives is not faded away. Three basic types of reactions continue to be studied, namely free radical, ionic, and transition-metal-catalyzed ones. In this line, ever-increasing attention is paid to mechanistic aspects of the studied transformations. Below, typical recent publications, covering the main research trends in this area, are discussed.

4.5.1 Free Radical Reactions

4.5.1.1 Oxidation Reactions

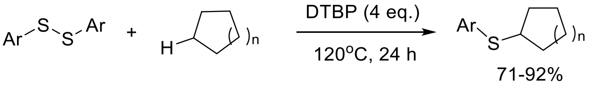
One of the hot topics in organosulfur chemistry is the direct oxidative thiylation of the $C_{(sp)^3}$-H bond. The first example of direct oxidative thiylation of activated alkanes at the $C^3_{(sp)}$–H-bond conjugated with amide group has been published in 2011 [100]. Under the action of diaryl disulfides, dimethyl acetamide in the presence of *tert*-butyl hydroperoxide (120 °C, 4Å MS) forms *N*-methyl-*N*-(arylthiomethyl)acetamides in 61–91% yields. It is assumed that molecular sieves 4Å perform the role of a weak base, maintaining pH of the medium.



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 2-$MeCO_2C_6H_4$, 2-Me-3-Furyl

The reaction is of a general character and tolerates diaryl disulfides, which contain different substituents in the aromatic ring. Aliphatic disulfides form the products in a moderate yield (up to 50%).

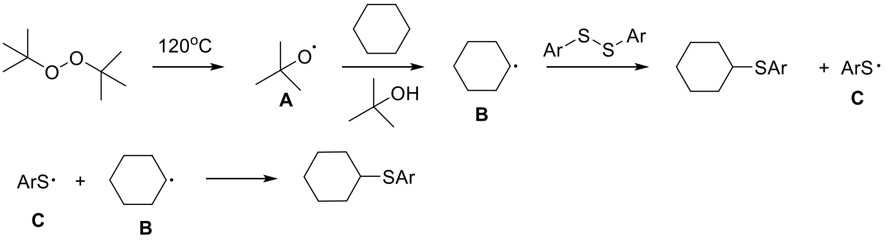
Shortly after, a series of works devoted to the synthesis of alkyl aryl sulfides via direct oxidative thiylation of non-activated alkanes in the presence of various oxidizing agents has been published. Thus, cycloalkanes C_nH_{2n} (n = 5-8) interact with *ortho*-, *meta*-, and *para*-substituted diaryl disulfides in the presence of 4 equivalents of di(*tert*-butyl) peroxide (DTBP, 120 °C, 24 h) to afford cycloalkyl aryl sulfides in 71–92% yields [101].



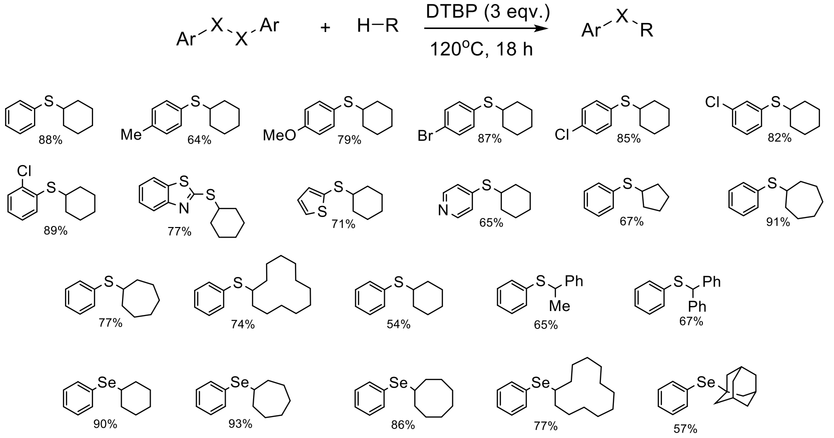
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-Py, 2-thienyl, 2-benzothiazolyl, 1-(5-phenyl)tetrazolyl

Hetaryl disulfides successfully participate in this reaction, while with dibenzyl disulfide, the target product is formed only in trace amounts.

A tentative mechanism of this reaction involves the thermal homolysis of Bu^{t}OOBu^t generating a *tert*-butoxy radical **A**, which attacks the cycloalkane at the C–H bond to deliver C-centered radical **B**. The latter interacts with the disulfide molecule giving rise to the target product and thiyl radical **C**, which reacts with cycloalkyl radical **B** to furnish another molecule of the product.



Such a methodology allows synthesizing alkyl aryl sulfides and selenides by direct metal-free functionalization of the $C_{(sp)^3}$–H bond in alkanes. Under the action of three equivalents of DTBP as an oxidizing agent, the reaction of aromatic disulfides and diselenides with alkanes (such as cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclododecane, and adamantane) leads to sulfides and selenides in 93% yield [102].

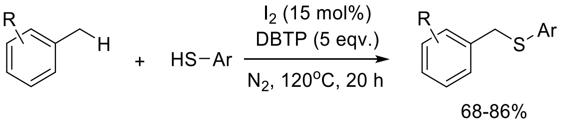


Under optimal conditions (argon, 120 °C, 18 h), the open-chain alkanes also undergo the direct oxidative thiylation. The order of reactivity and regioselectivity decreases in the series R_3C–H > R_2C–H > RH_2C–H that agrees with stability of the formed radical intermediates [102].

A wide range of diaryl(hetaryl) disulfides has also been employed in the reaction. The nature and position of substituents in the benzene ring of diaryl disulfides do not significantly affect the yield of the target products. Other oxidizing agents

($[PhC(Me)_2O]_2$, t-BuOOH, $[BzO]_2$) turn out to be less effective or completely inactive (1,4-benzoquinone, $K_2S_2O_8$, H_2O_2, O_2) in this reaction.

Elemental iodine-catalyzed oxidative cross-coupling of alkanes with aromatic thiols in the presence of peroxide DTBP has been described [103].

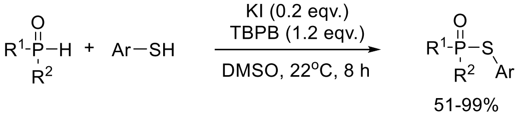


R = 4-Me, 4-Cl, 2-Br, 4-Br, 3,5-Me_2
Ar = 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 4-$AcNHC_6H_4$, 2-thiophenyl

The reaction proceeds upon heating the reagents (120 °C, 20 h) in excess of alkane. Along with the substituted toluenes, cycloalkanes, acetone, and acetylacetone participate in the process. It is assumed that the reaction starts with oxidation of thiols to disulfides, and the rate-determining stage is cleavage of the $C_{(sp)^3}$–H bond. Application of new methodology for $C_{(sp)^3}$–S bond formation permits to obtain alkyl aryl sulfides in a yield of up to 90% directly from alkanes without preliminary functionalization and metal complex catalysts.

Practically feasible methods for the S–P bond formation have been developed. The methods are based on oxidative cross-coupling of aromatic thiols and disulfides with P(O)H compounds (H-phosphine oxides, H-phosphinates, and H-phosphonates) under the action of organic peroxides, *tert*-butylperoxybenzoate or di(*tert*-butyl) peroxide [104, 105].

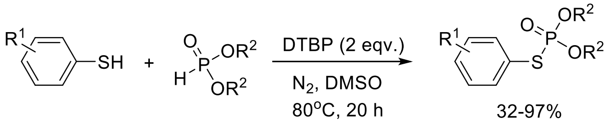
Substituted thiophenols easily interact with secondary phosphine oxides and *H*-phosphinates (DMSO, room temperature, 8 h) in the presence of 1.2 equivalents of *tert*-butylperoxybenzoate (TBPB) and catalytic amounts of KI to deliver aryl thiophosphinates and thiophosphonates in 51-99% yields [104].



$R^1 = R^2$ = Ph, 2-MeC_6H_4, 4-ClC_6H_4, 2-naphthyl; R^1 = Ph, R^2 = $PhCH_2$, 2-naphthyl, 4-ClC_6H_4, OEt
Ar = Ph, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2,-ClC_6H_4, 4ClC_6H_4, 3-BrC_6H_4, 4-$AcNHC_6H_4$

The reaction easily occurs with *ortho*-, *meta*-, and *para*-methoxy-, fluoro-, chloro-, bromo-, and amidothiophenols. The exception is trifluoromethyl- and nitroderivative of thiophenols, which are inactive in this reaction due to high dissociation energy of the S–H bond [106]. The reaction proceeds through the formation of thiyl and phosphorus-centered radicals, therefore the choice of oxidant [PhC(O)OOBu-*t*] and catalyst (KI) are crucial factors for effective implementation of the process.

Functionalized aryl thiophosphates, promising biologically active compounds, have been synthesized by the reaction of thiophenols with *H*-phosphonates in the presence of an oxidizing agent in an inert atmosphere (DMSO, 80 °C, 20 h) [105]. The reaction is carried out with twofold excess of *H*-phosphonate and an oxidizing agent, the best of which is di-*tert*-butyl peroxide DTBP.

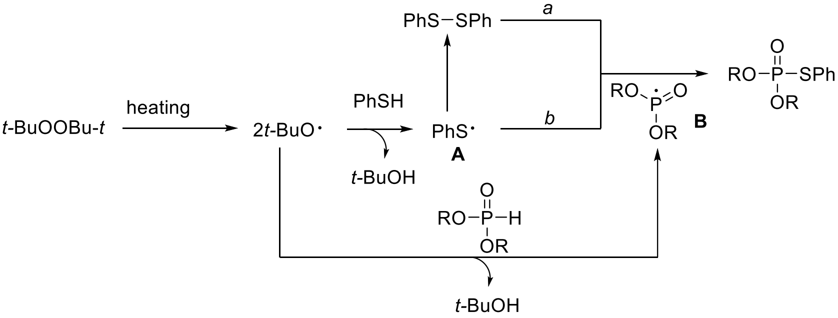


R^1 = H, 3-Me, 2,6-Me_2, 2-MeO, 3-MeO, 4-MeO, 4-Et, 2-NH_2, 3-NH_2, 3-OH, 3-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 3,4-Cl_2, 3-Br, 4-Br;

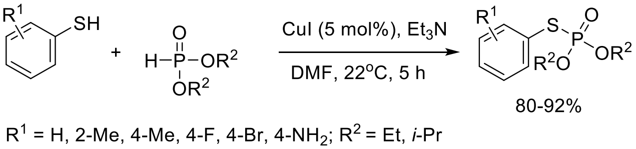
R^2 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *s*-Bu, *n*-Am, *n*-C_6H_{13}, *n*-C_8H_{17}, $CH_2CH_2OCH_2CH_2Cl$

Using diethylphosphite as an example, it has been shown that under similar conditions diaryl disulfides interact with *H*-phosphonates to form thiophosphates in 61–92% yield. The effect of substituents in the *para*- and *meta*-positions of thiophenols (except for the strong electron-withdrawing nitro group) on the yield of aryl thiophosphates is insignificant, while substituents in the *ortho*-position sterically shield the thiol group, slowing down the reaction.

Special studies have revealed that the reaction proceeds in the dark with the same efficiency as in the light, but it slows down significantly (in the case of aryl thiols) or is not implemented at all (in the case of diaryl disulfides) in the presence of radical process inhibitors (TEMPO). Based on these facts, a mechanism has been proposed that involves the homolysis of di-*tert*-butyl peroxide. Butoxyl radicals further react with thiophenol and phosphite to give thiyl **A** and phosphoryl **B** radicals. Radicals **A** quickly recombine to form a disulfide, which reacts with radical **B** through substitution (path *a*), or directly adds to radical **B** (path *b*) affording thiophosphates [105].

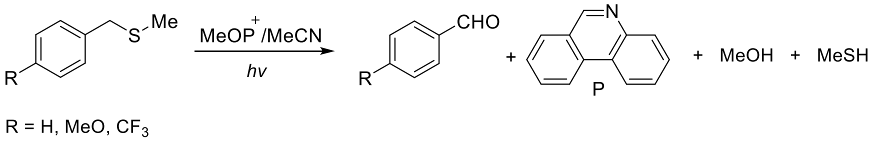


The CuI-catalyzed oxidative cross-coupling of thiophenols with *H*-phosphonates occurs in DMF at room temperature under aerobic conditions to produce thiophosphates in a yield of up to 92% [107].

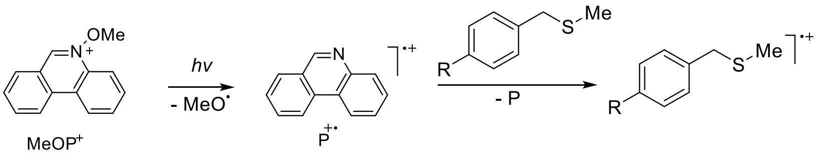


The synthesis of aryl thiophosphonates (up to 91% yield) by the oxidative coupling of aryl thiols with *H*-phosphine oxides and H-phosphonates under the action of atmospheric oxygen has been described [108]. The reaction proceeds upon activation with visible light (10 W blue LEDs) in the presence of 5 mol% of organic dye Bengal rose as a photocatalyst (DMF, room temperature, 12 h).

The photoinduced oxidation of 4-methoxybenzyl methyl sulfide, benzyl methyl sulfide, and 4-cyanobenzyl methyl sulfide has been studied in the presence of *N*-methoxyphenanthridinium hexafluorophosphate ($MeOP^+PF_6^-$) in acetonitrile under nitrogen atmosphere [109]. Under conditions of stationary photolysis, the corresponding aldehydes are formed exclusively.

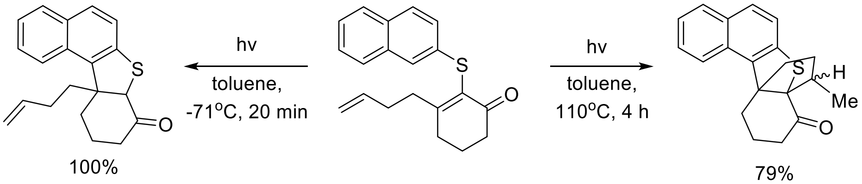


It has been shown that the photooxidation of sulfides proceeds as a one-electron transfer. The measurements of laser flash photolysis indicate that radical cations of sulfides are formed in the reaction, which are detected in their dimeric form.

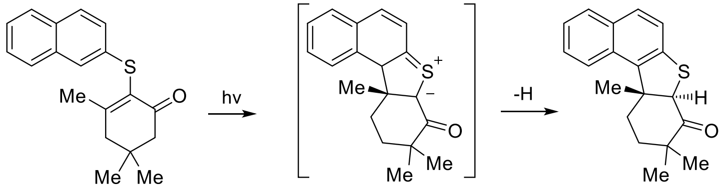


4.5.1.2 Photorearrangement and Addition Reactions

Photolysis of aryl vinyl sulfides (Hg lamp, 450 W) demonstrates a temperature dependence of the reactions of 6π-electron photoinduced cyclization and intramolecular addition [110].

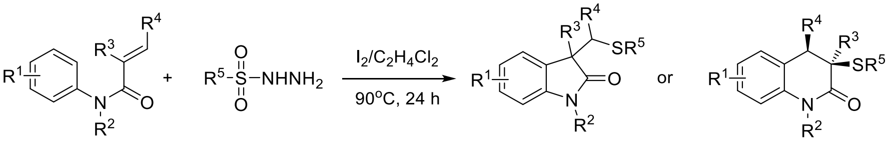


Further, photochemical investigations of aryl vinyl sulfides and aryl vinyl ethers have confirmed the formation of thiocarbonyl and carbonyl ylides [111].

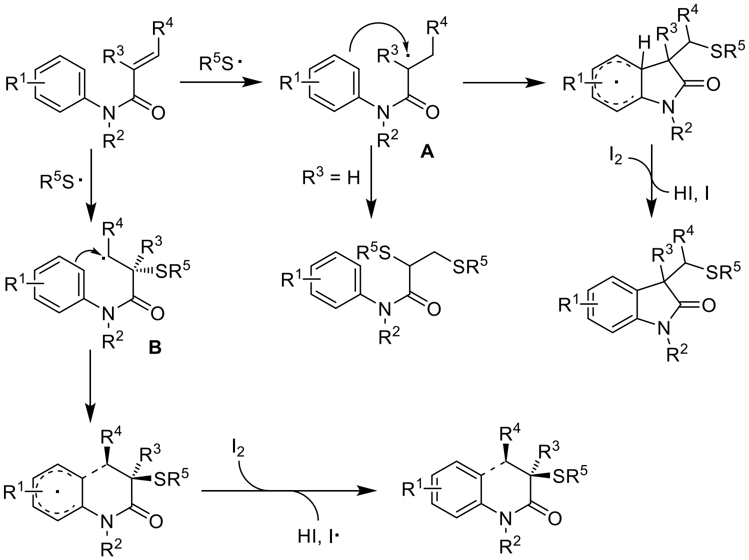


These intermediates are formed from these compounds upon their laser irradiation with a wavelength of 308 nm. In benzene, ylides show long-lived absorption bands in the region of 600–800 nm and a second weaker band at 460 nm. In methanol, which is known to quench zwitterionic particles, lifetime of the intermediates is significantly shortened.

Tandem radical cyclization/sulfenylation of *N*-arylacrylamide under the action of sulfonyl hydrazides in the presence of iodine, leading to the selective formation of 3- (sulfenylmethyl)oxindoles and 3-sulfenyl-3,4-dihydroquinolin-2(1*H*)-ones [112], has been studied.

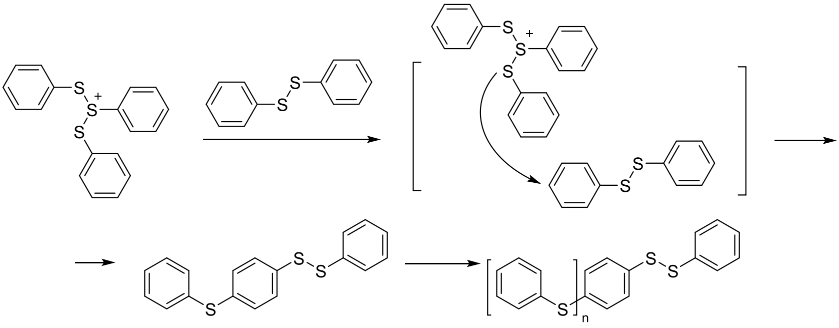


In this reaction, I_2 acts as an oxidant, reducing agent, and radical initiator. The mechanistic study shows that in the first stage, sulfonyl hydrazide reacts with iodine to form the sulfinic acid R^5SO_2H and sulfenyl iodide R^5SI, further transformations of which furnish thiyl radical $R^5S\bullet$. The latter regioselectively adds to *N*-aryl acrylamides to give radicals **A** or **B** (depending on the substituents R^3 and R^4). For *β*-unsubstituted and *β*-alkylsubstituted *N*-aryl acrylamides, the radicals **A** are more stable. These radicals undergo 5-exo-trig cyclization to deliver 3- (sulfenylmethyl) oxindoles. At the same time, *β*-aryl acrylamides generate radicals **B** via sulfenation, which are subjected to 6-exo-trig cyclization to form 3-sulfenyl-3,4-dihydroquinolin-2(1*H*)-ones. In the case of α-unsubstituted *N*-aryl acrylamides (R^3 = H), the conformation is unfavorable for cyclization, and the radical **A** is coupled with the thiyl radical, producing bis-thioester.

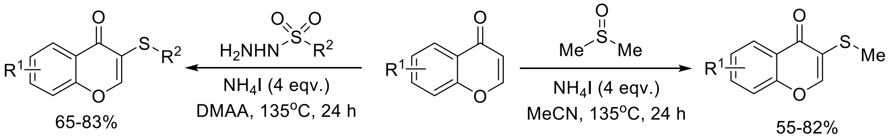


4.5.2 Ionic Reactions

It is concluded [113] that phenyl bis(phenylthio)sulfonium cation is an intermediate of the electrophilic reaction during the oxidative polymerization of diphenyl disulfide. In the model reaction of methyl bis(methylthio)sulfonium cation Me $(MeS)_2S^+$ with anisole, 4-phenyl thioanisole and diphenyl disulfide (by-product) are formed. Computer simulation has shown that the phenyl bis(phenylthio)sulfonium cation can react as an effective electrophile in the course of the C–S bond formation. Thus, during the oxidative polymerization of diphenyl disulfide, affording poly-(*para*-phenylene sulfide), an elementary reaction between the phenylthio group of the phenylbis(phenylthio)sulfonium cation and carbon in the *para*-position of the phenyl ring takes place.



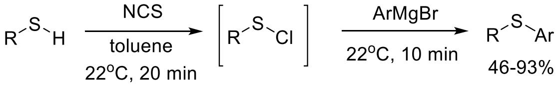
The direct regioselective functionalization of flavones at the C–H bond by sulfur-containing electrophiles, generated via reductive dehydration of dimethyl sulfoxide (MeCN, 135 ° C), and alkyl(aryl)sulfonyl hydrazide [dimethyl acetamide (DMAA), 135 °C] under the action of ammonium iodide has been implemented [114].



R^1 = 7-Me, 7-Cl, 7-NO_2, 8-OH, 8-Me, 7-Me, 8-Br, 7-Cl, 8-Me
R^2 = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$Bu^tC_6H_4$

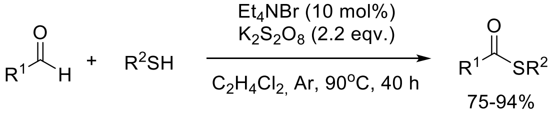
In the presence of radical traps, the reaction proceeds in the usual manner to give the target products in comparable yields, thus excluding a radical mechanism. Other heterocyclic compounds with electron-saturated double bonds in their structure (indole, 2-phenylimidazo[1,2-*a*]pyridine) react with (4-methylphenyl)sulfonyl hydrazine under similar conditions (DMAA, 135 °C, 24 h) to deliver the corresponding sulfides in 83–85% yields.

The cross-coupling of aliphatic and aromatic thiols with Grignard reagents under the action of N-chlorosuccinimide is considered as a convenient method for the preparation of aryl sulfides [115]. The reaction of thiols with chlorosuccinimide furnishes sulfenyl chloride, which further under mild conditions (room temperature, 10 min) interacts with the Grignard reagent, forming aryl sulfides in a yield of up to 93%.

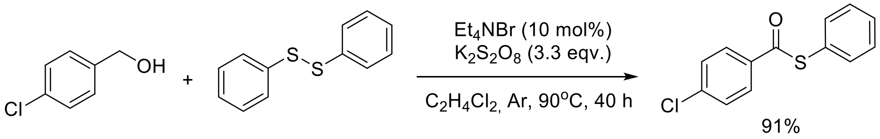


R = 2-MeC_4H_8, n-$C_{12}H_{25}$, $PhCH_2$, $EtOC(O)CH_2$, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-Naphth, 2-benzothiazolyl
Ar = Ph, 4-MeC_6H_4, 4-FC_6H_4

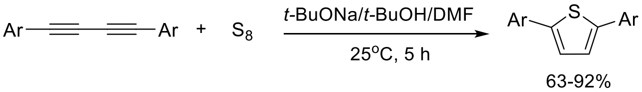
Tetraethylammonium bromide catalyzes the oxidative formation of thioesters from aldehydes (or alcohols) upon their contact with thiophenols or disulfides in the absence of metal compounds [116]. The reaction takes place in dichloroethane (90 ° C, 40 h) in the presence of an oxidant, potassium persulfate. This approach provides an efficient and economical synthesis of the target products in high yield.



R^1 = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-CNC_6H_4, 2-Naphthyl, 2-furyl, 2-thienyl, *n*-Bu, $PhCH_2CH_2$
R^2 = Ph, 4-ClC_6H_4, $PhCH_2$



The reaction of 1,3-diynes with elemental sulfur in the presence of *t*-BuONa, leading to the substituted thiophenes in high yield, has been described [117].



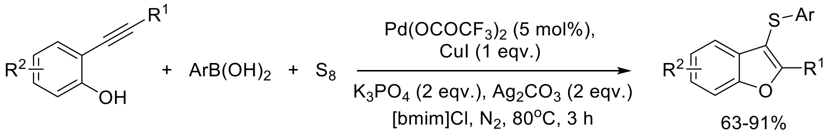
Ar = Ph, 4-MeC_6H_4, 4-AmC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-Py, 2-thienyl

EPR experiments have confirmed that the key intermediate in the synthesis of thiophenes is trisulfide anion-radical $S_3^{\bullet-}$, generated from S_8 by the action of a strong base in polar non-hydroxylic solvents:

$$S_8 \xrightarrow{t\text{-BuONa}} S_8^{2-} \longrightarrow S_6^{2-} + 1/4\ \text{cyclo-}S_8$$
$$S_6^{2-} \rightleftharpoons S_3^{\bullet-}$$

4.5.3 Transition Metal-Catalyzed Reactions

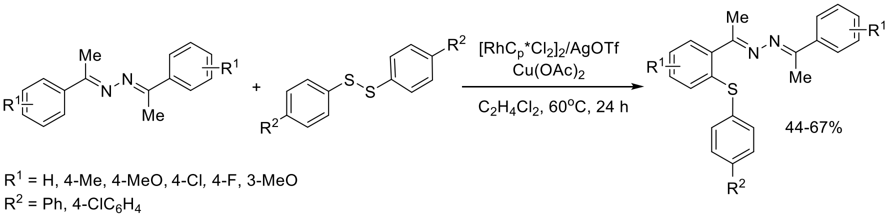
Cascade assembly of 3-sulfenylbenzofurans is accomplished by palladium-catalyzed reactions of 2-alkynylphenols with arylboronic acids and elemental sulfur, which proceed in the imidazolium ionic liquid [bmim]Cl (K_3PO_4, Ag_2CO_3 as an oxidant, 80 °C, 3 h) [118].



R^1 = Ph, 4-EtC_6H_4, 4-Pr^n, 4-$Bu^tC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2,4-$Me_2C_6H_3$, 3,4-$Cl_2C_6H_3$
R^2 = H, 4-Me; Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 2-furyl

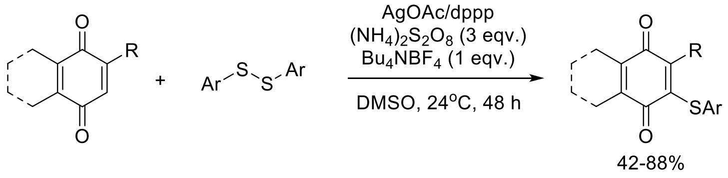
The ionic liquid acts not only as an activating medium, but also participates in the formation of a palladium complex, which attacks the triple bond to generate an annulated vinyl palladium intermediate. Transmetalation of the Pd-intermediate with a copper-organic thiolate complex obtained from elemental sulfur and aryl boronic acid in the presence of CuI and the subsequent reductive elimination of palladium gives the target 3-sulfenylbenzofurans. The reaction mechanism has general character, and a large number of 2-alkynylamines react with arylboronic acids and elemental sulfur to afford 3-sulfenylindoles (yield 63–89%).

The direct *ortho*-functionalization of aromatic ketazines with diaryl disulfides has a rich synthetic potential. The proposed catalytic system $[\mathrm{RdC_p}{}^*\mathrm{Cl_2}]_2$/AgOTf and $\mathrm{Cu(OAc)_2}$ as an oxidant allows employing a wide range of substrates and ensures formation of the C–S bonds under relatively mild conditions (60 °C, 24 h) [119].



R^1 = H, 4-Me, 4-MeO, 4-Cl, 4-F, 3-MeO
R^2 = Ph, 4-$\mathrm{ClC_6H_4}$

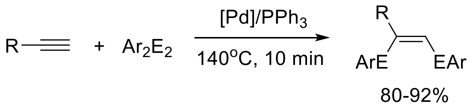
It is reported on successful synthesis of aryl quinonyl sulfides by the cross-coupling of substituted quinones with diaryl disulfides in the presence of a silver catalyst under mild conditions (room temperature, 48 h) [120]. High yields of the target products are reached owing to the combination of silver acetate with diphenylphosphinepropane ligand (dppp) (20 and 24 mol%, respectively) and application of ammonium persulphate $\mathrm{(NH_4)_2S_2O_8}$ as an oxidant with additive of $\mathrm{Bu_4NBF_4}$. It has been demonstrated that DMSO plays an important role in this reaction.



R = H, Me, Ph, 2-$\mathrm{ClC_6H_4}$, 3-$\mathrm{ClC_6H_4}$, 4-$\mathrm{ClC_6H_4}$, 4-$\mathrm{MeOC_6H_4}$, PhCONH, $\mathrm{PhOCH_2}$
Ar = Ph, 4-$\mathrm{MeC_6H_4}$, 4-$\mathrm{MeOC_6H_4}$, 4-$\mathrm{ClC_6H_4}$, 3-$\mathrm{FC_6H_4}$, 3-$\mathrm{NO_2C_6H_4}$

The presence of electron-donating and electron-withdrawing groups in the aromatic ring of disulfides does not hinder C–S-cross-coupling. However, in the case of donor substituents, the yields are higher. The method also tolerates a wide variety of substrates. One of the key stages is the interaction of diaryl disulfide with the silver complex, [Ag(I)dppp]OAc, leading to the formation of silver thiolate ArSAg (dppp) and sulfonyl acetate ArSOAc.

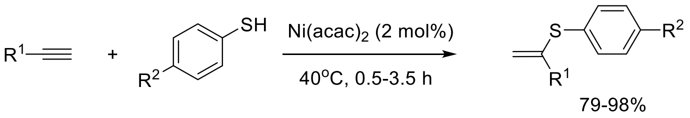
The unusual structural effect of transition metal complexes during formation of the C–S and C–Se bonds has been noted in the review [121]. The homogeneous catalytic system based on the palladium phosphine complex (which can be used as $Pd(PPh_3)_4$ as well as the available salts $Pd(OAc)_2$ and $PdCl_2$ in the presence of excess triphenylphosphine provides stereoselective addition of aromatic disulfides and diselenides to acetylenes. The reaction can be carried out in benzene or toluene [80 °C, 2–3 mol% $Pd(PPh_3)_4$] [122–124], or in the absence of a solvent (140 °C, ~10 min, 0.1 mol% $[Pd]/PPh_3$) [125].



E = S, Se; R = $(CH_2)_2OH$, *n*-Bu, CH_2NMe_2, cyclo-$C_6H_{10}OH$;
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4

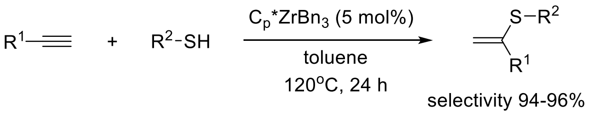
Under the action of microwave radiation, this catalytic system activates not only the chalcogen-chalcogen bonds, but also carbon-chalcogen bonds to trigger a side reaction leading to formation of triarylphosphine sulfide/ or selenide $Ar_3P{=}E$ from Ar_2E_2 and PPh_3 [126].

In the case of addition of thiols and selenols to terminal acetylenes, the phosphine complexes of Pd, Pt, and Rh do not ensure selective formation of adducts according to Markovnikov's rule in a high yield [121], while heterogeneous nickel catalysts allow regioselectively obtaining adducts of aromatic thiols with acetylenes [127].



R^1 = Me_2COH, MeEtCOH, $(CH_2)_2OH$, *n*-Bu, cyclo-$C_6H_{10}OMe$, $Me_2COC(O)Me$
R^2 = H, Me, Cl

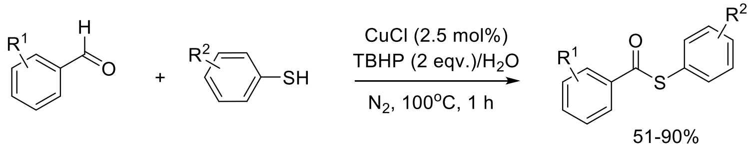
In the presence of organozirconium complexes formed from zirconium pre-catalysts $C_p{}^*ZrBn_3$, $C_p{}^*ZrCl_2NMe_2$ and $Zr(NMe_2)_4$, terminal alkynes interact regioselectively not only with aromatic, but also with less reactive benzyl and aliphatic thiols (120 °C, 24 h) to furnish vinyl sulfides according to Markovnikov's rule [128].



R^1 = Ph, 3-Py, $PhCH_2$, *cyclo*-$C_6H_{11}CH_2$, *t*-Bu, *cyclo*-C_6H_{11}
R^2 = Et, CF_3CH_2, *n*-C_5H_{11}, *cyclo*-C_6H_{11}, t-Bu, $PhCH_2$, Ph

A novel approach to the synthesis of thioesters is based on copper(I)-catalyzed reaction of aldehydes with thiols in an aqueous medium in the presence of *tert*-butyl hydroperoxide (TBHP) as an oxidant (100 °C, 1 h) [129]. Catalytic amounts of

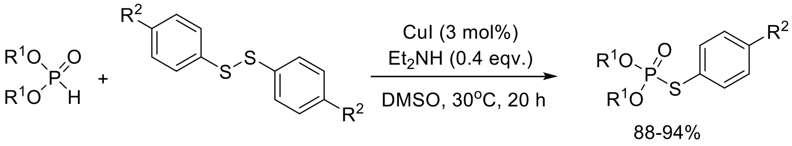
CuCl (2.5 mol%) contribute to formation of the target products in moderate to good yields.



R^1 = H, 2-Me, 3-Me, 3-I, 3-CN, 4-MeO, 4-F, 4-CF_3, 4-Cl, 4-Br
R^2 = 2-Me, 2-Br, 3-Me, 3-CF_3, 4-Me, 4-F, 4-Cl, 4-Br, 4-MeO

Both aromatic and aliphatic aldehydes and alkane thiols can also participate in a similar reaction.

The reactions of dialkyl phosphites with diaryl disulfides are considered as promising for the formation of the S–P(O) bond [130–132]. In the presence of catalytic amounts of CuI and Et_2NH as a base, dialkyl diphosphites undergo cross-coupling with *para*-substituted diphenyl disulfides (DMSO, 30 °C, 20 h) to deliver *S*-aryl thiophosphonates in a high yield [130].



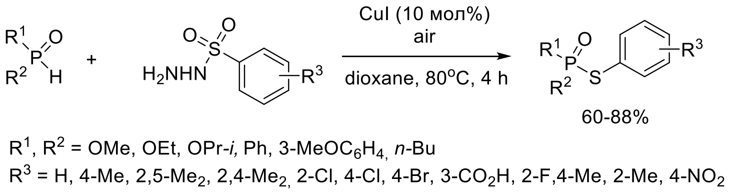
R^1 = Me, Et, *i*-Pr, *n*-Bu, *n*-C_6H_{13}; R^2 = H, Me, Cl

This method is of general character and allows synthesizing, under similar conditions, *Se*-aryl seleno- and *Te*-aryl tellurophosphonates in 82–92 and 72–87% yields, respectively [130].

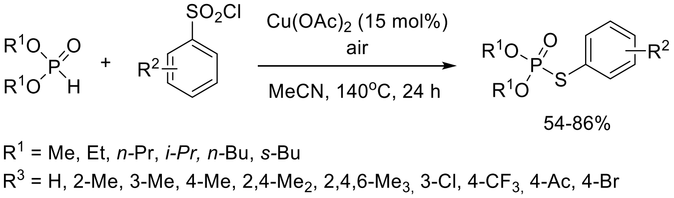
A similar reaction, leading to S-aryl thiophosphonates in up to 95% yield, is carried out on air in the presence of catalytic amounts of CsOH (DMSO, room temperature, 20 h) [131]. Other hydroxides (NaOH, KOH, and RbOH) are less active in this reaction; with LiOH, the reaction does not take place. A prerequisite is the employment of DMSO, which acts in this reaction not only as a solvent, but also as an oxidant.

Aryl chalcogenophosphonates can also be prepared by the reaction of dialkyl phosphites with diaryl dichalcogenides in the presence of zinc in EtOH. The reaction proceeds easily (room temperature, 30 min) and gives the target products up to 84% yield.

The high yield CuI-catalyzed synthesis of *S*-alkyl thiophosphates and *S*-aryl thiophosphonates via the cross-coupling of alkyl(aryl)-*H*-phosphonates and phosphine oxides with sulfonyl hydrazides has been documented [133].



The cross-coupling of *H*-phosphonates with sulfochlorides, catalyzed by Cu $(OAc)_2$, is another alternative route to formation of the S–P(O) bond [132]. This method enables to widely vary the substituents in phosphonates and sulfochlorides and obtain *S*-aryl thiophosphonates in up to 86% yield.



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Acylated Aromatic Sulfides in Organic Synthesis

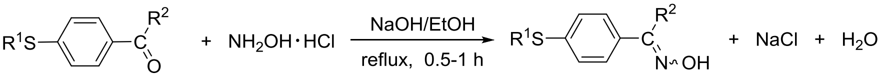
5

Acylated aromatic sulfides (alkylthio acetophenones) are promising intermediates for organic synthesis, which provide ample opportunities for obtaining various derivatives of aromatic thiols. They can be involved in all reactions, in which ketones usually participate. This is, first of all, the addition of various nucleophilic reagents (amines, alcohols, thiols, C–H acids, hydroxylamines, hydroxides, etc.) at the carbonyl group. Thus, these compounds are highly reactive universal carriers of an aromatic sulfide fragment, capable of reacting with different functional groups that allow them to be introduced into a variety of organic molecules. In this chapter, this possibility is illustrated by the example of introducing an alkyl thioaryl substituent into the pyrroles and *N*-vinylpyrroles scaffold via the reaction of ketoximes with acetylene or its synthetic equivalents (vinyl halides or dihaloalkanes) in superbasic media (Trofimov reaction) [1–9].

5.1 Synthesis of Oximes of Acylated Aromatic Sulfides

The extension of the Trofimov reaction [1–7] over 4-(alkylthio)phenyl- and 4-(phenylthio) phenyl alkyl ketoximes permits to synthesize [10–12] hitherto unknown (alkyl thio)arylpyrroles and their *N*-vinyl derivatives.

First of all, a series of 4-(alkylthio)aryl alkyl ketoximes has been synthesized. The reaction of 4-(alkylthio)aryl alkyl ketones with hydroxylamine hydrochloride proceeds smoothly in an aqueous–alcoholic solution to afford the corresponding oximes in quantitative yields (Table 5.1).



R^1 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, Ph; R^2 = Me, Et

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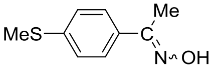
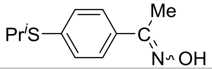
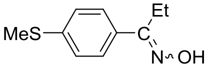
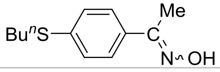
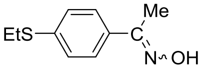
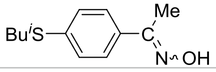
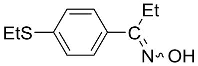
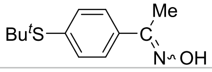
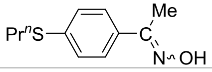
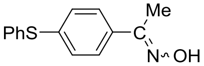
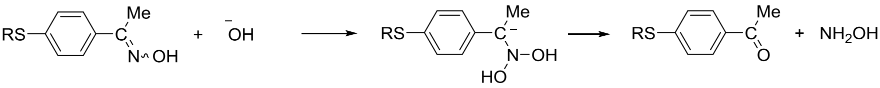
https://doi.org/10.1007/978-3-030-69621-4_5

Table 5.1 4-(Alkylthio)aryl alkyl ketoximes

No.	Structure	M.p., °C	No	Structure	M.p., °C
1		119	6		64
2		88	7		78
3		87	8		76
4		71	9		80
5		72	10		97

Commonly, the oximes obtained represent an equilibrium mixture of *syn*- and *anti*-isomers, the ratio of which can be reliably determined from ^{13}C NMR spectra (C^{13}–C^{13} spin–spin coupling constants) [13–15]. The target oximes are quite stable compounds, although upon prolonged (5–6 months) contact with air at room temperature they are deoximized apparently due to hydrolysis by atmospheric moisture.



The synthesized ketoximes, intended in this case for the assembly of (alkylthio) aryl pyrroles, are of great independent interest as building blocks for the synthesis of diverse heterocyclic structures and amino acids, as well as potential biologically active substances [16–19].

5.2 Alkylthioaryl Pyrroles

A number of natural aryl pyrrole antibiotics are known [20]. Therefore sulfur-containing aryl pyrroles are of particular pharmacological interest. However, for a long time, no general approaches to their synthesis were developed.

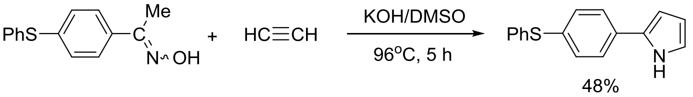
A new general synthesis of pyrroles and *N*-vinylpyrroles from ketoximes and acetylene in the superbasic system alkali metal hydroxide/dimethyl sulfoxide (the Trofimov reaction) has been elaborated about 40 years ago. Now it is a commonly recognized strategy in the chemistry of heterocyclic compounds due to its high efficacy [1, 6, 7, 21–23]. The reaction allows not only the most diverse 2- and 2,3-substituted pyrroles, but also their *N*-vinyl derivatives to be obtained. Along with alkyl- and aryl-substituted pyrroles, other representatives of these compounds that were previously difficult to obtain or were not known at all became available.

5.2.1 Synthesis from (Alkylthio)aryl Alkyl Ketoximes and Acetylene

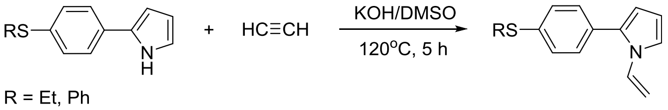
In the superbasic catalytic system KOH/DMSO, 4-(ethylthio)phenyl ketoxime interacts with acetylene (ketoxime: KOH molar ratio = 1:1, atmospheric pressure, 96 °C, 5 h) to afford 2-(4-(ethylthio)phenyl)pyrrole (47% yield) [24].

Along with the major product, the intermediate *O*-vinyloxime is identified (yield 3%) in the reaction mixture.

The reaction of 4-(phenylthio)phenyl ketoxime with acetylene, catalyzed by the KOH/DMSO system, under similar conditions leads to the formation of 2-(4-(phenylthio)phenyl)pyrrole (yield 48%).



Vinyl derivatives of 2-(4-(ethylthio)phenyl)- and 2-(4-(phenylthio)phenyl)pyrroles under the conditions studied are practically not formed (yield ~1%), but they are synthesized by direct vinylation of the corresponding pyrroles with acetylene under atmospheric pressure in the system KOH/DMSO at a higher temperature (120 °C, 5 h, molar ratio of pyrrole: KOH = 1:6) in 48% yield (pyrrole conversion ~70%) [24].



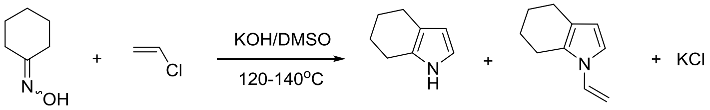
The results obtained indicate that the nature of the substituent in aryl radical of the initial ketoxime does not have a noticeable effect on the composition and yields of the reaction products.

5.2.2 Synthesis from (Alkylthio)aryl Alkyl Ketoximes and Vinyl Chloride

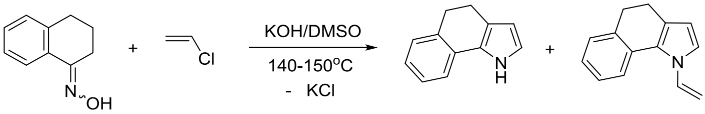
A version of the Trofimov reaction implies the use of vinyl halides as synthetic equivalents of acetylene [1, 6, 7, 25]. Given the industrial availability of vinyl chloride, this version of pyrrole synthesis may be more convenient for the implementation of low-tonnage production of chemicals.

It has been shown that ketoximes react with vinyl halides in the superbasic system NaOH/DMSO at 80–130 °C in an autoclave [25] or under atmospheric pressure (KOH/DMSO, 120–150 °C) [26–28] to furnish the corresponding pyrroles and *N*-vinylpyrroles. By varying the ratio of reagents and conditions, it is possible to carry out the reaction selectively, obtaining mainly NH-pyrroles or their *N*-vinyl derivatives.

The condensation of cyclohexanone oxime with vinyl halides under atmospheric pressure in the presence of alkali metal hydroxides in polar non-hydroxylic solvents is studied [29].



4,5-Dihydrobenzo[*g*]indole and its *N*-vinyl derivative (in a total yield of 50%) are synthesized from α-tetralone oxime and vinyl chloride (KOH/DMSO, 140–150 °C, 3–4 h) [26].



However, prior to the works [10, 12, 30], this reaction was not used for the synthesis of sulfur-containing pyrroles (the only exception was the synthesis of thienylpyrroles [31]).

In the system KOH/DMSO, alkyl aryl ketoximes, obtained from acylated aromatic sulfides, interact with vinyl chloride (120–140 °C, atmospheric pressure) to deliver 2-(4-(alkylthio)phenyl)pyrroles and their *N*-vinyl derivatives in a total yield up to 55% (Table 5.2) [10, 12, 27, 32, 33]. The yields of the corresponding *N*-vinylpyrroles are 6–18%.

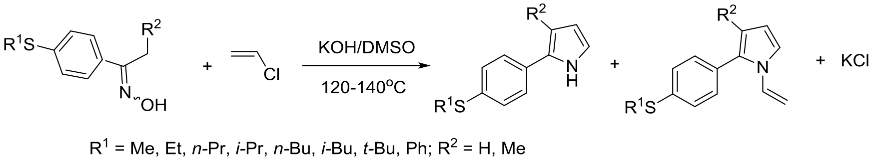
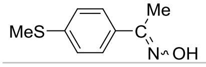
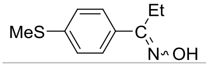
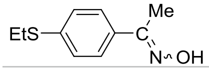
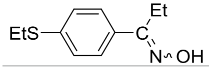
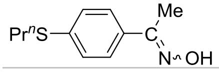
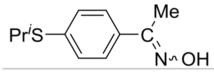
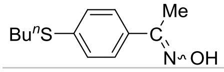
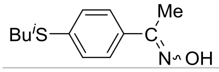
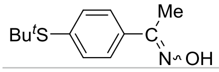
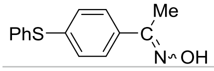


Table 5.2 The reaction of 4-(alkylthio)aryl ketoximes with vinyl chlorides: conditions and outcomes

Reactants, mol			DMSO, mL	T, °C	t, h	Yield, %	
Ketoxime	Vinyl chloride	KOH				Pyrrole	*N*-vinylpyrrole
0.05 	0.27	0.30	150	140	3	29	9
0.026 	0.156	0.26	100	130	3.5	36	19
0.1 	0.50	0.60	150	130	3	45	7
0.03 	0.20	0.30	100	130	3.5	45	10
0.005 0.028 	0.05 0.14[a]	0.55 0.168	100 100	130 130	1.5 3	38 40	8
0.05 	0.25	0.30	100	130	3	42	6
0.02 	0.10	0.12	100	130	3	43	6
0.025 0.02 	0.25 0.30[a]	0.275 0.32	150 150	120 120	3 5	43 24	traces 22
0.015 	0.15	0.165	100	130	3	36	8
0.005 	0.025	0.03	100	130	3	19	traces

[a] Vinyl bromide was used as a vinylating agent

The reaction is carried out upon continuous bubbling of vinyl chloride through a heated KOH/DMSO suspension containing the initial ketoxime. The preferred molar ratio of ketoxime: vinyl chloride: NaOH is 1:5–6:6–10.

The reaction of 4-(methylthio)acetophenone oxime with a five–six-fold excess of vinyl chloride in the KOH/DMSO medium at 140 °C gives rise to 2-(4-(methylthio)phenyl)pyrrole (yield 29%) and 1-vinyl-2-(4-(methylthio)phenyl)pyrrole (yield 9%) [10]. The lower yields of the target products compared with those of sulfur-free aryl pyrroles [27] are probably owing to the deoximation of the initial ketoximes. Indeed, when the reaction temperature decreases to 130 °C (all other conditions being the same), the total yield of 4-(ethylthio)acetophenone oxime vinylation products increases to 52%. The presence of methyl substituent in the position 3 of the pyrrole ring facilitates the vinylation: 1-vinyl-2-aryl-3-methylpyrroles, under these conditions, are formed in 10–18% isolated yields (6–8% in the case of 1-vinyl-2-arylpyrroles).

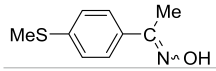
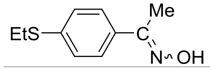
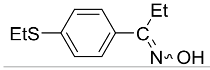
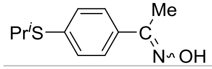
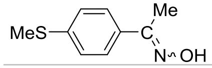
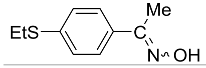
When the molar excess of vinyl halide and KOH in the reaction mixture increases, the yield of the *N*-vinyl derivative augments. The interaction of 4-propylthioacetophenone oxime with vinyl bromide (130 °C, 3 h, the molar ratio of ketoxime: vinyl bromide: KOH = 1:5:6) gives 2-(4-(propylthio)phenyl)pyrrole (40% yield) and 1-vinyl-2-(4-(propylthio)phenyl)pyrrole (yield 8%). The reaction of 4-(isobutylthio)acetophenone oxime with vinyl bromide (120 °C, 5 h, the molar ratio of ketoxime: vinyl bromide: KOH = 1:15:16) affords 2-((4-isobutylthio)phenyl)pyrrole and 1-vinyl-2-((4-isobutylthio)phenyl)pyrrole in 24 and 22% yields, respectively.

5.2.3 Synthesis from (Alkylthio)aryl Alkyl Ketoximes and Dihaloalkanes

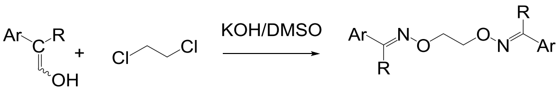
Along with vinyl halides, 1,2-dihaloalkanes can also be employed as synthetic equivalents of acetylene for the preparation of pyrroles and *N*-vinylpyrroles from ketoximes [1, 6, 7, 34–36]. As with vinyl halides, depending on the ratio of reagents and conditions, the reaction can be directed toward the predominant formation of NH-pyrroles or *N*-vinylpyrroles. Recently, an effective one-pot synthesis of pyrroles directly from ketones and dichloroethane in the KOH/DMSO system has been developed. According to the protocol, ketoximes are formed in situ upon the addition of hydroxylamine to the reaction mixture [37].

The reaction of 4-alkylthiophenyl alkyl ketoximes with 1,2-dichloro(dibromo)ethane and 1,2-dibromopropane as acetylenic equivalents proceeds in the KOH/DMSO system at 120–140 °C under atmospheric pressure to give 2-(4-alkylthiophenyl)-3- and 5-methylpyrroles and their N-vinyl derivatives (Table 5.3).

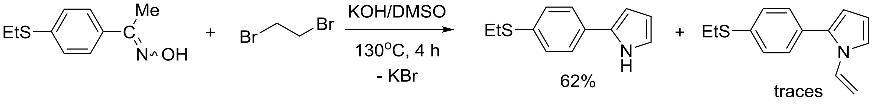
Table 5.3 The reaction of 4-(alkylthio)aryl ketoximes with 1,2-dihaloalkanes: conditions and outcomes [33]

Reactants, mol			DMSO, mL	T, °C	t, h	Yield, %	
Ketoxime	Vinylating agent	KOH				Pyrrole	*N*-vinylpyrrole
0.058 	$ClCH_2CH_2Cl$ 0.232	0.812	150	130	4	48	10
0.05 	$BrCH_2CH_2Br$ 0.15	0.51	100	130	4	62	Traces
0.03 	$BrCH_2CH_2Br$ 0.15	0.63	100	140	5	54	11
0.025 	$ClCH_2CH_2Cl$ 0.075	0.25	60	120	4	61	0
0.033 	$BrCH_2CHBrMe$ 0.099	0.495	120	130	5	48	0
0.03 	$BrCH_2CHBrMe$ 0.15	0.63	100	140	4.5	45	0

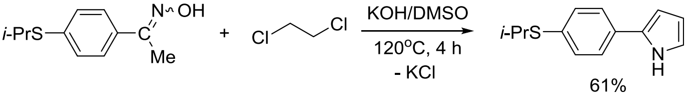
To selectively synthesize NH-pyrroles, it is preferable to use a three-fold excess of the vinylating agent with respect to ketoxime. Also, 1,2-dihaloalkanes should be slowly added to the suspension consisting of an excess of KOH, ketoxime, and DMSO. Otherwise, the reaction of nucleophilic substitution of a halogen by oximate anions can occur to form ketoxime glycol diethers.



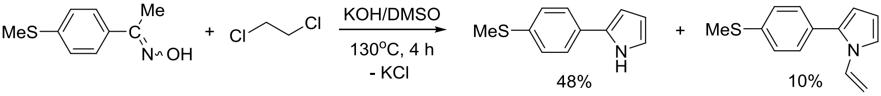
2-(4-(Ethylthio)phenyl)pyrrole is obtained in a yield of 62% by the reaction of 4-(ethylthio)acetophenone oxime with a three-fold excess of 1,2-dibromoethane. In this case, only traces of the *N*-vinyl derivative are detected in the reaction mixture by TLC [33].



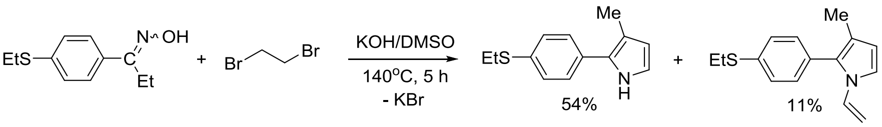
The interaction of 4-(isopropylthio)acetophenone oxime with a three-fold excess of 1,2-dichloroethane (120 °C, 4 h) affords only 2-(4-(isopropylthio)phenyl)pyrrole in 61% yield [33].



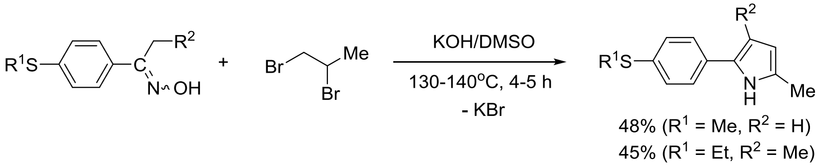
An increase in the relative content of dihaloethane and KOH in the reaction mixture facilitates the formation of *N*-vinylpyrrole. When the reaction of 4-(methylthio)acetophenone oxime with a four-fold excess of 1,2-dichloroethane is carried out in the KOH/DMSO at 130 °C, 2-(4-(methylthio)phenyl)pyrrole and 1-vinyl-2-(4-(methylthio)phenyl)pyrrole are formed in 48 and 10% yields, respectively [33].



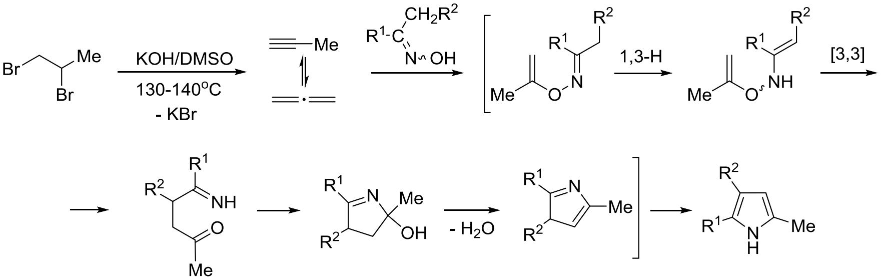
When the reaction temperature increases to 140 °C and molar ratio of oxime: 1,2-dibromoethane: KOH is equal to 1: 5: 21, the total yield of 3-methyl-2-(4-(ethylthio)phenyl)pyrrole and 1-vinyl-3-methyl-2-(4-(ethylthio)phenyl)pyrrole is 65%.



For the synthesis of 2,5-disubstituted pyrroles by the Trofimov reaction, 1,2-dibromopropane, a homolog of haloethanes, can be employed (Table 5.3). The reaction of 4-(methylthio)- and 4-(ethylthio)acetophenone oximes with 1,2-dibromopropane in the system KOH/DMSO system leads to corresponding pyrroles in 48 and 45% yields [33].



Synthesis of 2-(4-(alkylthio)phenyl)pyrroles using 1,2-dibromopropane involves a number of consecutive stages: conversion of 1,2-dibromopropane under the action of potassium hydroxide to an equilibrium mixture of methylacetylene and allene, which further add the initial ketoxime (in the form of an oximate anion) to furnish the same adduct, O-isopropenyloxime. The latter through a cascade of transformations (1,3-prototropic shift and 3,3-sigmatropic shifts) gives the corresponding pyrrole [36].



Before the works [33, 36], pyrroles bearing substituents in the positions 2 and 5 were obtained by the Trofimov reaction with phenylacetylene only [38], which is not capable of prototropic isomerization. Later [7, 39–41], it has been reported that this reaction leads to pyrroles having phenyl substituents in the positions 5 or 4. The interaction between methylacetylene (or its mixture with allene) and ketoximes in the systems MOH/DMSO (M = K, Cs) or *t*-BuOK/DMSO delivers 5-methyl- and 3 (4)-methylpyrroles [7, 42].

To attain synthetically acceptable yields of the pyrroles in this or similar reaction, an excess of alkali relative to 1,2-dibromopropane should be used. At the same time, with equimolar amounts of alkali and 1,2-dibromopropane, the synthesis is expected to be ineffective, since all amount of alkali is consumed for dehydrobromination and the medium ceases to be superbasic (pyrroles are formed in trace amounts).

Similar to the protocol based on vinyl chloride, this method is simple, safe, and expedient and may be more acceptable for laboratories that do not have free acetylene and no experience with handling this chemical.

5.2.4 Structure and Physical–chemical Characteristics of 2-(4-(Alkylthio)phenyl)pyrroles

Some of the physical–chemical characteristics of 2-(4-(alkylthio)phenyl)pyrroles and *N*-vinyl-2-(4-(alkylthio)phenyl)pyrroles are given in Tables 5.4 and 5.5.

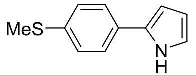
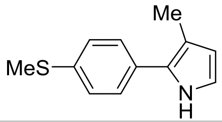
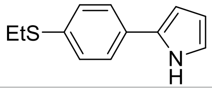
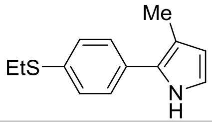
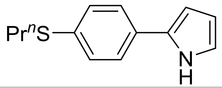
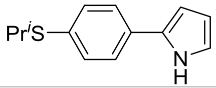
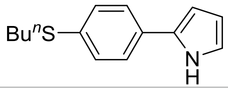
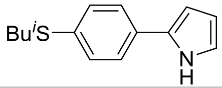
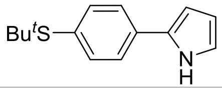
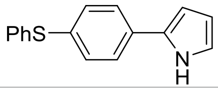
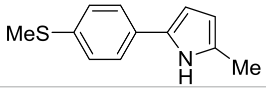
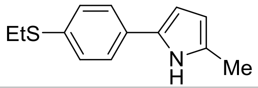
The values of ^{1}H and ^{13}C chemical shifts of 2-(4-(alkylthio)phenyl)pyrroles and *N*-vinyl-2-(4-(alkylthio)phenyl)pyrroles (Tables 5.4 and 5.5) are in good agreement with those of other known aryl pyrroles and their N-vinyl derivatives [1, 6, 7].

In the ^{1}H NMR spectra of sulfur-containing pyrroles (Table 5.6), signals of the NH group protons resonate in the weakest field (8.02–8.47 ppm), and those of the pyrrole ring H^3, H^4, and H^5 are observed in the regions 6.14–6.34, 5.80–6.49, and 6.63–6.84 ppm, respectively.

Analysis of the ^{13}C chemical shifts in the spectrum of *N*-vinyl-2-(4-(methylthio)phenyl)pyrrole (Table 5.7) in comparison with the spectra of phenyl pyrrole and methoxyphenyl-substituted analog [43] indicates a weaker donating effect of the MeS group compared to the methoxy group upon transfer via the benzene ring (shielding of the position 5 in the pyrrole ring by −0.1 ppm and by −0.9 ppm in *N*-vinyl-2-(4-methoxyphenyl)pyrrole is detected). Chemical shifts of the vinyl group β-carbon atom are most sensitive to the effect of substituents in the positions 2 and 3 of the pyrrole ring of *N*-vinylpyrroles: in 2-methylpyrroles, C_β signal is shifted to a strong field by 1.9–2.2 ppm (Table 5.7, *cf.* entries 1 and 2, 3 and 4).

The IR spectra of 2-(4-(alkylthio)phenyl)pyrroles show common frequencies of the skeletal vibrations of the pyrrole ring at 1550, 1420, 1380, and 1110 cm^{-1}. An intense band at 710 cm^{-1} corresponds to bending vibrations of the C–H bond, and the benzene ring is identified by the bands at 830 (non-planar C–H bending vibration), 1460, 1490–1500, 1575, and 1590 cm^{-1} (skeletal vibrations of the ring). Unlike alkyl phenyl pyrroles [27], in these compounds, frequencies and intensities of low-field bands of skeletal ring vibrations are reduced. A band of stretching vibrations of the C = CN group has a maximum at $\sim$1640 cm^{-1}, the NH group (in vaseline oil) corresponds to a band with a maximum at 3380 cm^{-1}, and a weak band in the region 530–550 cm^{-1} is assigned to stretching vibrations of the C−S bond.

Table 5.4 Pyrroles obtained by the Trofimov reaction from 4-(alkylthio)phenyl ketoximes

No	Structure	Yield, %	M.p., °C	References
1		29 48	163	[10] [33]
2		36 54	132	[12] [33]
3		45 47 62	133–134 129–130	[12] [24] [33]
4		45	50	[12]
5		38 40[a]	118–119	[12] [12]
6		42 61	77–78	[12] [33]
7		43	93–94	[12]
8		43 24[a]	104–105	[12] [12]
9		36	112	[12]
10		19 48	175–176 (with decomp.) 180 (with decomp.)	[12] [24]
11		48	143	[33]
12		45	115	[33]

[a] With vinyl bromide

Table 5.5 *N*-Vinylpyrroles obtained by the Trofimov reaction from 4-(alkylthio)phenyl ketoximes

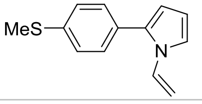
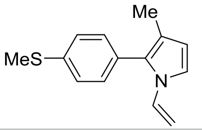
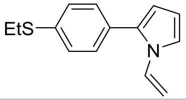
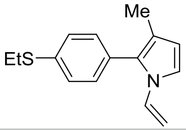
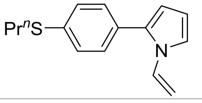
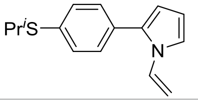
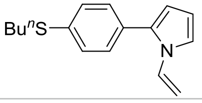
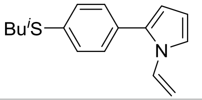
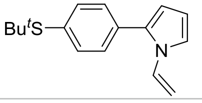
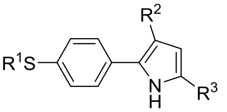
No	Structure	Yield, %	B.p., °C/torr	n_D^{20}	d_4^{20}	References
1		9 10	160/2	1.6505	1.1136	[12] [33]
2		19	142/1	1.6305	1.1020	[33]
3		7 48	165–167/3 160–162/3	1.6340 1.6338	1.0688 1.0685	[12] [24]
4		10 11	155/1	1.6118	1.1243	[12] [33]
5		8	172–174/1	1.6080	1.0520	[12]
6		6	150/1	1.6096	1.0609	[12]
7		6	166–168/1	1.5884	1.0910	[12]
8		22	168–170	1.5788	0.9972	[12]
9		8	167–168	1.5895	0.9960	[12]

Table 5.6 The ^{1}H and ^{13}C NMR chemical shifts of 2-(4-(alkylthio)phenyl)pyrroles



No	R^1	R^2	R^3	^{1}H NMR chemical shifts, CDCl$_3$, δ, ppm	^{13}C NMR chemical shifts, CDCl$_3$, δ, ppm
1	Me	H	H	2.40 (s, 3H, MeS), 6.28 (d, *J* 3 Hz, 1H, H^3), 6.43 (d, *J* 3 Hz, 1H, H^4), 6.84 (d, *J* 3 Hz, 1H, H^5), 6.97 (m, 4H, C$_6$H$_4$), 8.20 (bs, 1H, NH)	16.2 (MeS), 105.9 (C^3), 110.2 (C^4), 118.4 (C^5), 124.1 (C^{2,6}-Ph), 127.5 (C^{3,5}-Ph), 130.0 (C^1-Ph), 131.5(C^2), 137.0 (C^4-Ph)
2	Me	Me	H	2.23 (s, 3H, Me), 2.47 (s, 3H, MeS), 6.03 (d, *J* 3 Hz, 1H, H^4), 6.63 (d, *J* 3 Hz, 1H, H^5), 7.03 (m, 4H, C$_6$H$_4$), 8.02 (bs, 1H, NH)	
3	Et	H	H	1.24 (t, *J* 6 Hz, 3H, Me), 2.83 (d, *J* 6 Hz, 2H, CH$_2$S), 6.14 (d, 1H, H^3), 6.34 (d, 1H, H^4), 6.63 (d, 1H, H^5), 7.23 (m, 4H, C$_6$H$_4$), 8.21 (bs, 1H, NH)	
4	Et	Me	H	1.35 (t, *J* 6 Hz, 3H, Me), 2.23 (s, 3H, Me), 2.87 (d, *J* 6 Hz, 2H, CH$_2$S), 6.08 (d, *J* 3 Hz, 1H, H^4), 6.65 (d, *J* 3 Hz, 1H, H^5), 7.31 (m, 4H, C$_6$H$_4$), 8.02 (bs, 1H, NH)	13.1 (Me), 14.6 (Me), 27.5 (CH$_2$S), 112.6 (C^4), 116.5 (C^3), 118.4 (C^5), 127.2 (C^{2,6}-Ph), 128.0 (C^2), 130.3 (C^{3,5}-Ph), 134.0 (C^1-Ph), 133.0 (C^4-Ph)
5	Pr^n	H	H	1.09 (t, *J* 6 Hz, 3H, Me), 1.65 (m, 2H, CH$_2$), 2.90 (t, *J* 6 Hz, 2H, CH$_2$S), 6.17 (d, *J* 3 Hz, 1H, H^3), 6.42 (d, *J* 3 Hz, 1H, H^4), 6.72 (d, *J* 3 Hz, 1H, H^5), 7.36 (m, 4H, C$_6$H$_4$), 8.21 (bs, 1H, NH)	13.5 (Me), 23.3 (CH$_2$), 36.4 (CH$_2$S), 106.6 (C^3), 110.2 (C^4), 120.0 (C^5), 124.9 (C^{2,6}-Ph), 130.7 (C^{3,5}-Ph), 132.0 (C^2), 132.2 (C^1-Ph), 134.5 (C^4-Ph)
6	Pr^i	H	H	1.27 (d, *J* 6.5 Hz, 6H, Me), 3.27 (q, *J* 6.5 Hz, 1H, CHS), 6.21 (d, *J* 3 Hz, 1H, H^3), 6.42 (d, *J* 3 Hz, 1H, H^4), 6.70 (d, *J* 3 Hz, 1H, H^5), 7.31 (m, 4H, C$_6$H$_4$), 8.39 (bs, 1H, NH)	23.4 (2Me), 38.8 (CHS), 106.8 (C^3), 110.3 (C^4), 120.1 (C^5), 124.7 (C^{2,6}-Ph), 131.9 (C^4-Ph), 133.0 (C^2, C^1-Ph), 133.4 (C^{3,5}-Ph)
7	Bu^n	H	H	0.95 (t, *J* 6.5 Hz, 3H, Me), 1.56 (m, 4H, CH$_2$), 2.88 (t, *J* 6.5 Hz, 2H, CH$_2$S), 6.21 (d, *J* 3 Hz, 1H, H^3), 6.42 (d, *J* 3 Hz, 1H, H^4), 6.72 (d, *J* 3 Hz, 1H, H^5), 7.30 (m, 4H, C$_6$H$_4$), 8.28 (bs, 1H, NH)	

(continued)

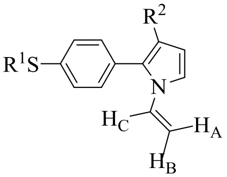
Table 5.6 (continued)

No	R^1	R^2	R^3	^1H NMR chemical shifts, $CDCl_3$, δ, ppm	^{13}C NMR chemical shifts, $CDCl_3$, δ, ppm
8	Bu^i	H	H	1.09 (d, *J* 6 Hz, 6H, Me), 1.81 (m, 1H, CH), 2.80 (d, *J* 6 Hz, 2H, CH_2S), 6.24 (d, *J* 3 Hz, 1H, H^3), 6.45 (d, *J* 3 Hz, 1H, H^4), 6.70 (d, *J* 3 Hz, 1H, H^5), 7.31 (m, 4H, C_6H_4), 8.28 (bs, 1H, NH)	22.2 (2Me), 28.4 (CH), 43.1 (CH_2S), 106.0 (C^3), 110.3 (C^4), 118.9 (C^5), 124.3 ($C^{2,6}$-Ph), 129.8 ($C^{3,5}$-Ph), 132.0 (C^2), 132.6 (C^1-Ph), 134.9 (C^4-Ph)
9	Bu^t	H	H	1.26 (s, 9H, Me), 6.19 (d, *J* 3 Hz, 1H, H^3), 6.41 (d, *J* 3 Hz, 1H, H^4), 6.72 (d, *J* 3 Hz, 1H, H^5), 7.38 (m, 4H, C_6H_4), 8.47 (bs, 1H, NH)	
10	Ph	H	H	6.18 (d, *J* 3 Hz, 1H, H^3), 6.49 (d, *J* 3 Hz, 1H, H^4), 6.79 (d, *J* 3 Hz, 1H, H^5), 7.51 (bm, 9H, C_6H_4, Ph), 8.10 (bs, 1H, NH)	
11	Me	H	Me	2.25 (s, 3H, Me), 2.41 (s, 3H, MeS), 5.80 (d, *J* 3 Hz, 1H, H^4), 6.24 (d, *J* 3 Hz, 1H, H^3), 7.22 (m, 4H, C_6H_4), 7.96 (bs, 1H, NH)	13.0 (Me), 14.8 (Me), 29.8 (CH_2S), 106.6 (C^3), 108.4 (C^4), 124.4 ($C^{2,6}$-Ph), 128.3 ($C^{3,5}$-Ph), 129.9 (C^2), 130.8 (C^5), 131.9 (C^1-Ph), 135.4 (C^4-Ph)
12	Et	H	Me	1.27 (t, 3H, Me), 2.30 (s, 3H, Me), 2.89 (d, 2H, CH_2S), 5.91 (d, *J* 3 Hz, 1H, H^4), 6.34 (d, *J* 3 Hz, 1H, H^3), 7.30 (m, 4H, C_6H_4), 7.95 (bs, 1H, NH)	13.0 (Me), 16.2 (MeS), 106.8 (C^3), 108.4 (C^4), 124.4 ($C^{2,6}$-Ph), 130.0 (C^2), 130.7 (C^5), 130.9 ($C^{3,5}$-Ph),132.6 (C^1-Ph), 133.2 (C^4-Ph)

In the UV spectra of 2-(4-(alkylthio)phenyl)pyrroles, the long-wavelength absorption band at λ_{max} ~300 nm corresponds to π–π*-transition of A_{1g}–B_{2u} type and is bathochromically shifted relative to a similar band in the spectrum of 2-phenylpyrrole by 15–19 nm [44], its intensity being increased by more than 1.5 times (Table 5.8). This effect is due to the inclusion of *p*-electrons of the sulfur atom in the conjugation system.

In (2-(4-(methylthio)phenyl)- and (2-(4-(ethylthio)phenyl)-5-methylpyrroles, bearing an alkyl substituent in the position 5 of the pyrrole ring, a further bathochromic shift of the long-wavelength absorption band is observed. Decrease of the band extinction in 2-(4-ethylthiophenyl)-3-methylpyrrole is caused by the weakening of the conjugation of the benzene and pyrrole rings owing to violation of their coplanarity due to steric effect of the methyl group in the position 3 [45].

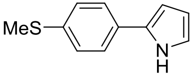
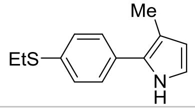
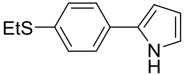
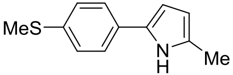
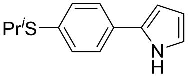
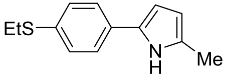
Table 5.7 The ^{1}H and ^{13}C NMR chemical shifts of 1-vinyl-2-(4-(alkylthio)phenyl)pyrroles



No	R^1	R^2	^{1}H NMR chemical shifts^a, $CDCl_3$, δ, ppm	^{13}C NMR chemical shifts, $CDCl_3$, δ, ppm
1	Me	H	2.47 (s, 3H, MeS), 4.77 (dd, 1H, H$_B$), 5.14 (dd, 1H, H$_A$), 6.22 (d, J 3 Hz, 1H, H^4), 6.26 (d, J 3 Hz, 1H, H^3), 6.86 (dd, 1H, H$_C$), 7.09 (d, J 3 Hz, 1H, H^5), 7.26 (m, 4H, C_6H_4)	15.6 (MeS), 98.2 (=CH$_2$), 110.0 (C^3), 110.1 (C^4), 117.9 (C^5), 126.4 (C^{3,5}-Ph), 129.3 (C^1-Ph), 129.4 (C^{2,6}-Ph), 131.9 (NC=), 133.4 (C^2), 137.5 (C^4-Ph)
2	Me	Me	1.97 (s, 3H, Me), 2.43 (s, 3H, MeS), 4.42 (dd, 1H, H$_B$), 4.94 (dd, 1H, H$_A$), 5.98 (d, J 3 Hz, 1H, H^4), 6.59 (dd, 1H, H$_C$), 7.09 (d, J 3 Hz, 1H, H^5), 7.23 (m, 4H, C_6H_4)	11.8 (Me), 15.6 (MeS), 96.0 (=CH$_2$), 112.0 (C^4), 116.4 (C^5), 118.4 (C^3), 126.2 (C^{2,6}-Ph), 128.4 (C^2), 130.0 (C^1-Ph), 131.5 (C^{3,5}-Ph), 131.9 (NC=), 137.7 (C^4-Ph)
3	Et	H	1.34 (t, 3H, Me), 2.94 (q, 2H, CH$_2$S), 4.67 (dd, 1H, H$_B$), 5.13 (dd, 1H, H$_A$), 6.24 (m, 2H, H^{3,4}), 6.86 (dd, 1H, H$_C$), 7.08 (d, J 3 Hz, 1H, H^5), 7.29 (m, 4H, C_6H_4)	14.7 (Me), 27.6 (CH$_2$S), 99.2 (=CH$_2$), 110.8 (C^3), 110.9 (C^4), 119.4 (C^5), 129.2 (C^{2,6}-Ph), 130.1 (C^{3,5}–Ph), 130.5 (C^2), 132.6 (NC=), 134.2 (C^1-Ph), 136.8 (C^4-Ph)
4	Et	Me	1.98 (s, 3H, Me), 1.31 (t, J 6 Hz, 3H, Me), 2.88 (q, J 6 Hz, 2H, CH$_2$S), 4.49 (dd, 1H, H$_B$), 4.92 (dd, 1H, H$_A$), 6.05 (d, J 3 Hz, 1H, H^4), 6.65 (dd, 1H, H$_C$), 6.94 (d, J 3 Hz, 1H, H^5), 7.27 (m, 4H, C_6H_4)	11.8 (Me), 14.4 (Me), 27.4 (CH$_2$S), 97.1 (=CH$_2$), 112.0 (C^4), 116.4 (C^5), 118.5 (C^3), 126.7 (C^2), 128.3 (C^{2,6}-Ph), 131.9 (C^{3,5}–Ph), 132.0 (NC= , C^1-Ph), 136.0 (C^4-Ph)
5	Bu^i	H	1.12 (d, J 6 Hz, 6H, Me), 1.81 (m, 1H, CH), 2.68 (d, J 6 Hz, 2H, CH$_2$S), 4.44 (dd, 1H, H$_B$), 4.88 (dd, 1H, H$_A$), 5.90 (m, 2H, H^{3,4}), 6.40 (dd, 1H, H$_C$), 6.75 (d, J 3 Hz, 1H, H^5), 6.95 (m, 4H, C_6H_4)	

[a] $^2J_{AB}$ 0.8 Hz, $^3J_{AC}$ 15.0 Hz, $^3J_{BC}$ 9.0 Hz

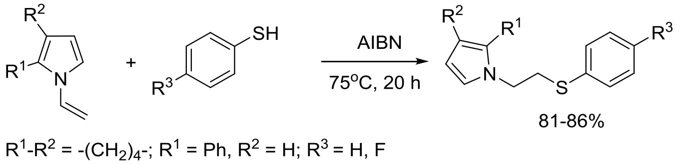
Table 5.8 Characteristics of long-wavelength absorption bands in the UV spectra of pyrroles [44]

Structure	λ, nm	$\varepsilon \cdot 10^{-3}$, $L \cdot mol^{-1} \cdot cm^{-1}$	Structure	λ, nm	$\varepsilon \cdot 10^{-3}$, $L \cdot mol^{-1} \cdot cm^{-1}$
	306	32.2		20.2	304
	306	33.0		314	31.6
	303	31.5		317	31.7

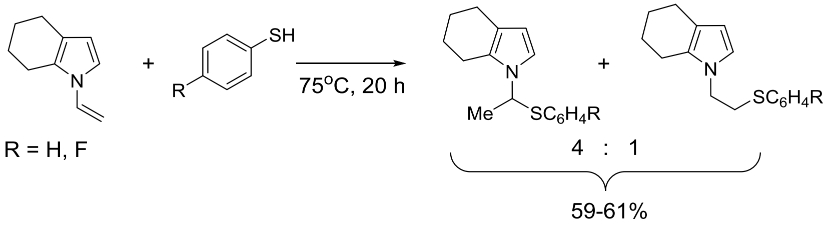
5.2.5 Addition of Aryl Thiols to *N*-vinylpyrroles

N-Vinylpyrroles, which are now available due to the development of a new effective method for their preparation by the Trofimov reaction [1–7] from ketoximes and acetylene in the superbasic system KOH/DMSO, easily add such traditional addends as hydrosilanes [46, 47], alcohols [48, 49], phenols [50], and thiols [51]. Thus, *N*-vinylpyrroles become the ancestors of large families of previously unknown *N*-ethyl-substituted pyrroles with various heteroatoms in the ethyl radical, which can be considered as promising biologically active substances.

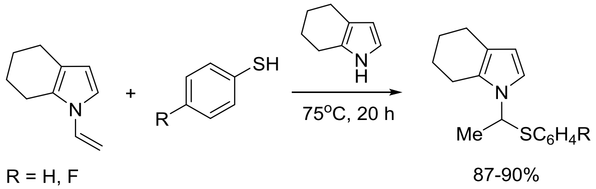
Alkane thiols are selectively joined to *N*-vinylpyrroles in the presence of azobisisobutyronitrile (AIBN) and without initiator (70–80 °C, 18–25 h) to give 1-(2-(alkylthio)ethyl)pyrroles in 70–99% yields [51]. The addition of aromatic thiols to *N*-vinylpyrroles has its own peculiarities. It has been shown [52] that under the conditions of free-radical initiation (AIBN, 75 °C, 20 h), this reaction proceeds selectively to afford α-adducts, 1-(2-(arylthio)ethyl)pyrroles (yield 81–86%).



Under similar conditions without a chemical initiator (75 °C, 20 h), thiophenols are added to *N*-vinyl-4,5,6,7-tetrahydroindole to form a mixture of products according to and against the Markovnikov rule, the content of 1-(1-arylthioethyl) pyrrole reaching 80%. The reaction proceeds via an electrophilic mechanism, which is likely due to the increased acidity of aromatic thiols in comparison with aliphatic analogs.



Thiylation of a mixture of N-vinyl- (28.5%), NH-4,5,6,7-tetrahydroindole (61%), and cyclohexanone oxime (10.5%) obtained by the reaction of cyclohexanone oxime with vinyl chloride in the system KOH/DMSO system [29] upon heating both with AIBN and without an initiator selectively affords α-adducts, since the presence of NH-pyrrole inhibits radical processes and prevents the formation of *β*-adducts.



4-Nitrothiophenol is not added to *N*-vinyl-4,5,6,7-tetrahydroindole: upon stirring the reaction mixture at room temperature, there is a strong self-heating with the formation of polymer products, probably of the same structure as the oligomers obtained in the presence of acids [53, 54].

Thus, unlike alkane thiols, which are added to *N*-vinylpyrroles almost exclusively via a radical mechanism to deliver ***β***-adducts [51], aryl thiols, due to their increased acidity, show a noticeable tendency toward electrophilic addition leading to α-adducts.

In the ^{1}H NMR spectra of adducts, synthesized under the conditions of radical initiation, the nature and integral intensities of signals fully correspond to the structure of 1-(2-(arylthio)ethyl)pyrroles (Table 5.9). The ^{1}H NMR spectra of 1-(1-(arylthio)ethyl)pyrrole, instead of two triplet signals of the SCH_2CH_2 group (2.9 and 3.7–4.0 ppm), show doublet-quartet pairs in the region of 5.2 and 1.7 ppm with an integral intensity of 1:3, indicating the presence of protons of methine and methyl groups.

5.3 Examples of Syntheses

5.3.1 (Alkylthio)aryl Ketoximes

4-(Methylthio)acetophenone oxime. To a solution of 4-(methylthio)acetophenone (4.98 g, 0.03 mol) and hydroxylamine hydrochloride (6.0 g, 0.086 mol) in EtOH (75 mL), a solution of NaOH (10.0 g, 0.25 mol) in water (50 mL) was added and the mixture was carefully boiled for 30–60 min. After cooling, the mixture was poured into a solution of conc. HCl (30 mL) in water (500 mL). The precipitate was filtered off, washed thoroughly with water, and dried to give 5.4 g (~100%) of the product, m.p. 119 °C.

4-(Alkylthio)aceto- and 4-(alkylthio)propiophenone oximes (Table 5.1) were prepared in the same way.

5.3.2 Pyrroles and *N*-vinyl Pyrroles

2-(4-(Methylthio)phenyl)pyrrole and *N*-vinyl-2-(4-(methylthio)phenyl)pyrrole [10, 33]. A mixture of 4-(methylthio)acetophenone oxime (10.4 g, 0.058 mol), powdered KOH (45.5 g, 0.812 mol), and DMSO (120 mL) was heated to 130 °C and upon vigorous stirring, 1,2-dichloroethane (23.0 g, 0.232 mol) in DMSO (30 mL) was added dropwise for 3 h. The reaction mixture was stirred for another 1 h at the same temperature, cooled to room temperature, poured into ice water (800 mL), and extracted with benzene (5 × 80 ml). The extract was washed three times with 30% KOH solution, dried over K_2CO_3, and benzene was distilled off to give a mixture of NH- and *N*-vinylpyrrole, from which NH-pyrrole was isolated by crystallization from isooctane. The products remaining in the mother solution were separated by chromatography (Al_2O_3, ether/hexane, 2:1) to obtain 5.3 g of 2-(4-(methylthio)phenyl)pyrrole (yield 48%, m.p. 163 °C) and 1.2 g (10%) of 1-vinyl-2-(4-(methylthio)phenyl)pyrrole (b.p. 160 °C/2 torr, n_D^{20} 1.6505, d_4^{20} 1.1136). Spectral characteristics are given in Table 5.6.

5-Methyl-2-(4-(methylthio)phenyl)pyrrole [33]. A mixture of 4-(methylthio) acetophenone oxime (6.03 g, 0.33 mol), powdered KOH (27.72 g, 0.495 mol), and DMSO (100 mL) was heated to 130 °C. To the reaction mixture, 1,2-dibromopropane (20.2 g, 0.1 mol) in DMSO (20 mL) was added upon vigorous stirring for 4 h. The reaction mixture was continued to be heated for another 1 h. Upon completion of the reaction, the cooled reaction mixture was poured into ice-cold water (500 mL) and extracted with benzene (5 × 80 mL). The extract was washed with 30% NaOH solution and dried over K_2CO_3. The solvent was distilled off by recrystallization from isooctane to give 3.2 g (48%) of 5-methyl-2-(4-(methylthio)phenyl)pyrrole, m.p. 143 °C. Spectral characteristics are given in Table 5.6.

5-Methyl-2-(4-(ethylthio)phenyl)pyrrole [33]. Similarly, from 4-(ethylthio) acetophenone oxime (5.85 g, 0.068 mol) and 1,2-dibromopropane (30.3 g, 0.15 mol) in the presence of KOH (35.3 g, 0.63 mol) and DMSO (100 mL) at 140 °C for 4.5 h, 2.96 g (45%) of 5-methyl-2-(4-(ethylthio)phenyl)pyrrole was prepared, m.p. 115 °C. Spectral characteristics are given in Table 5.6.

2-(4-(Isopropylthio)phenyl)pyrrole [12, 33]. Similarly, from 4-(isopropylthio) acetophenone oxime (5.22 g, 0.025 mol) and 1,2-dichloroethane (7.5 g, 0.076 mol) in the presence of powdered KOH (14.0 g, 0.25 mol) and DMSO (60 mL) at 120 ° C for 4 h, 3.3 g (61%) of NH-pyrrole was prepared, m.p. 77–78 °C. Spectral data are given in Table 5.6.

2-(4-(Ethylthio)phenyl)pyrrole. a) A suspension of KOH (0.7 g. 12.5 mmol) in DMSO (75 mL) heated to 96 °C was saturated with acetylene for 10 min. Then 4-ethylthioacetophenone oxime (2.43 g, 12.4 mmol) was added to the mixture and acetylene was bubbled upon vigorous stirring for 5 h. The cooled mixture was poured into cold water (300 mL) and extracted with ether (6 × 50 mL). The ether extracts were washed with water and dried over K_2CO_3. The residue, obtained after removal of the solvent, was fractionated on Al_2O_3 column of (hexane/ether, 3:1) to obtain 1.98 g of crude product. Repeated fractionation on plates with a non-fixed layer of Al_2O_3 (ether) gave 1.21 g (47%) of 2-(4-(ethylthio)phenyl)pyrrole (gray plate crystals with pearlescent gloss, m.p. 129–130 °C) and 0.08 g (3%) of *O*-vinyl-4-(ethylthio)acetophenone oxime [24].

(b) A mixture of 4-(ethylthio)acetophenone oxime (9.75 g, 0.05 mol), powdered KOH (28.2 g, 0.51 mol), and DMSO (70 mL) was heated to 130 °C and a solution of 1.2-dibroethane (28.2 g, 0.15 mol) in DMSO (30 mL) was added dropwise upon vigorous stirring for 3 h. The reaction mixture was stirred for another 1 h at the same temperature. After the treatment described above, 6.3 g (62%) of 2-(4-(ethylthio)phenyl)pyrrole was obtained, m.p. 133–134 °C [33].

N-Vinyl-2-(4-(ethylthio)phenyl)pyrrole [24]. A suspension of KOH (0.7 g, 12.5 mmol) and DMSO (30 mL) heated to 120 °C was saturated with acetylene and 2-(4-(ethylthio)phenyl)pyrrole (0.5 g, 2 mmol) was added to the mixture. Then acetylene was added (~ 1 L/h) to the heated reaction mixture for 5 h. The cooled reaction mixture was poured into water (100 mL) and extracted with ether (6 × 30 mL). 1-Vinyl-2-(4-(ethylthio)phenyl)pyrrole (0.27 g, 48%) was isolated from the crude product (0.5 g) by chromatography on Al_2O_3 (eluent ether/hexane, 3:1) (b.p. 160–162 °C / 3 torr, n_D^{20} 1.6338, d_4^{20} 1.068).

2-(4-(Ethylthio)phenyl)pyrrole and 1-vinyl-2-(4-(ethylthio)phenyl)pyrrole [24]. A mixture of 4-(ethylthio)acetophenone oxime (19.5 g, 0.1 mol) and KOH (33.6 g, 0.6 mol) was added portion-wise (every 30 min) to DMSO (150 mL) for 2.5 h at 130 °C gradually passing vinyl chloride (31.2.g, 0.5 mol) through the bubbler. Stirring and heating were continued for another 30 min, then the mixture was cooled to 20 °C, diluted with cold water, and the reaction product was extracted with benzene (5 × 100 mL). The extract was washed with water and dried over K_2CO_3. The benzene was distilled off, and the residue was distilled in a vacuum to obtain a mixture of NH- and *N*-vinylpyrrole, from which a major part of NH-pyrrole was isolated by recrystallization from isooctane. The residue, after evaporation of the mother liquor, was separated by TLC on a thin layer of Al_2O_3 (ether/hexane, 1:2) to give 9.2 g (45%) of 2-(4-(ethylthio)phenyl)pyrrole and 1.5 g (7%) of 1-vinyl-2-(4-(ethylthio)phenyl)pyrrole. Constants are given in Tables 5.4 and 5.5, and spectral characteristics are presented in Tables 5.6 and 5.7.

3-Methyl-2-(4-(methylthio)phenyl)pyrrole and N-vinyl-3-methyl-2-(4-(methylthio)phenyl)pyrrole [12]. Similarly, from 4-methylthiopropiophenone oxime (5.0 g, 0.026 mol) and vinyl chloride (9.81 g, 0.156 mol) in the presence of KOH (14.6 g, 0.26 mol) and DMSO (100 mL) at 130 °C, for 3.5 h, 3-methyl-2-(4-(methylthio)phenyl)pyrrole (1.91 g, 36%, m.p. 132 °C) and 1-vinyl-3-methyl-2-(4-(methylthio)phenyl)pyrrole (1.09 g, 19%, b.p. 142 °C/1 torr, n_D^{20} 1.6305, d_4^{20} 1.1020) were prepared (Table 5.5).

2-(4-(Phenylthio)phenyl)pyrrole [24]. Through a reaction mixture containing 4-phenylthioacetophenone oxime (3.0 g, 12.3 mmol), KOH (0.70 g, 12.5 mmol), and DMSO (75 mL) heated to 96 °C, acetylene was bubbled upon vigorous stirring for 5 h. The reaction mixture was cooled and poured into cold water (300 mL), and the residue formed was separated to obtain 2.5 g of crude product. The aqueous solution was extracted with ether to give another 0.5 g of crude product. The total crude product (3.0 g), dissolved in acetone, was chromatographed on plates with a thin non-fixed layer of Al_2O_3 (ether/EtOH, 50:1) to give 1.51 g (48%) of 2-(4-(phenylthio)phenyl)pyrrole, m.p. 180 °C (with decomp.).

3-Methyl-2-(4-(ethylthio)phenyl)pyrrole and N-vinyl-3-methyl(4-(ethylthio)phenyl)pyrrole [12, 33]. (a) In a suspension containing DMSO (100 mL), powdered KOH (16.8 g, 0.3 mol), and 4-(ethylthio)propiophenone oxime (6.27 g, 0.03 mol) heated to 130 °C, vinyl chloride (12.5 g, 0.2 mol) was added upon vigorous stirring for 3 h and heating was continued for another 30 min. Standard treatment gave 2.91 g (45%) of 3-methyl-2-(4-(ethylthio)phenyl)pyrrole, m.p. 50 °C and 0.70 g (10%) of 1-vinyl-3-methyl-2-(4-(ethylthio)phenyl)pyrrole, b.p. 155 °C/1 torr, n_D^{20} 1.6118, d_4^{20} 1.1243 (Table 5.5).

(b) From 4-(ethylthio)propiophenone oxime (6.27 g, 0.03 mol) and 1,2-dibromoethane (28.2 g, 0.15 mol) in the presence of KOH (35.3 g, 0.63 mol) and DMSO (120 mL) at 140 °C for 5 h, 3.5 g of 3-methyl-2-(4-(ethylthio)phenyl) pyrrole (54%, m.p. 50 °C) and 0.8 g of 1-vinyl-3-methyl-2-(4-(ethylthio)phenyl) pyrrole (11%, b.p. 155 °C/1 torr, n_D^{20} 1.6118, d_4^{20} 1.1243) were prepared (Table 5.5).

1-Vinyl-4,5,6,7-tetrahydroindole [55]. Into a 1-L rotating autoclave, a mixture of cyclohexanone oxime (5.0 g, 0.044 mol), KOH (1.5 g, 0.027 mol), and DMSO (120 mL) was placed. The mixture was saturated with acetylene under a pressure of 1.5 MPa (~ 40 L of acetylene were fed), heated to 120 °C, and stirred for 1 h. The cooled reaction mixture was diluted with water, extracted with ether (3 × 50 mL), the extract was washed with water, the solvent was removed, and distillation in vacuum gave 5.5 g (93%) of 1-vinyl-4,5,6,7-tetrahydroindole, b.p. 85–86 °C/3 torr, n_D^{20} 1.5562, d_4^{20} 1.0010.

4,5,6,7-Tetrahydroindole and 1-vinyl-4,5,6,7-tetrahydroindole [29]. A mixture of cyclohexanone oxime (5.7 g, 0.05 mol), KOH (8.40 g, 0.15 mol), and DMSO (100 mL) was heated at 110 °C for 2 h upon stirring, passing vinyl chloride (6.25 g, 0.1 mol) through the mixture. After cooling, the reaction mixture was poured into ice water and extracted with benzene (5 × 100 mL). The extract was washed with water and dried over K_2CO_3. The solvent was removed and the residue was distilled in a vacuum to give distillate (2.2 g, b.p. 60–150 °C/1 torr) consisting of the starting oxime, tetrahydroindole, and 1-vinyltetrahydroindole.

The experiments at a ratio of oxime: KOH: vinyl chloride equal to 1:6:5 (120–140 °C, 3 h) were carried out similarly. The combined distillates, containing 1-vinyltetrahydroindole (28.5%), NH-tetrahydroindole (61%), and cyclohexanone oxime (10.5%), were used in the synthesis of 1-(1-(arylthio)ethyl)-4,5,6,7-tetrahydroindoles.

N-Vinyl-2-phenylpyrrole [24]. Into a suspension (140 °C) containing DMSO (150 mL), KOH (33.6 g, 0.6 mol), and acetophenone oxime (13.5 g, 0.1 mol), vinyl chloride (31.2 g, 0,5 mol) was added upon vigorous stirring. Afterward, the stirring and heating were continued for another 30 min. The reaction mixture was cooled to room temperature, diluted with cold water, and extracted with benzene (5 × 50 mL). The extract was washed three times with 30% KOH solution, dried over K_2CO_3, benzene was removed, and the residue was distilled in a vacuum to obtain a crude product, from which the major part of pyrrole was isolated by crystallization from isooctane. The remaining 2-phenylpyrrole and 1-vinyl-2-phenylpyrrole were separated by TLC (silica gel 5/40 µm, ether/hexane, 1:2) to give 6.4 g of 2-phenylpyrrole (45%, m.p. 129 °C) and 1.2 g of 1-vinyl-2-phenylpyrrole (7%, b.p. 94 °C/1 torr, n_D^{20} 1.6190, d_4^{20} 1.0443).

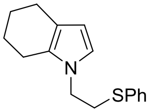
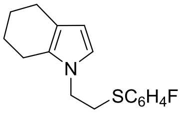
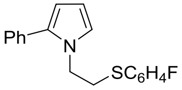
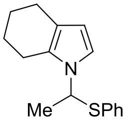
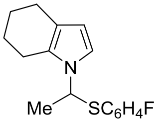
5.3.3 Addition of Thiophenols to *N*-vinylpyrroles [52]

1-(2-(Phenylthio)ethyl)-4,5,6,7-tetrahydroindole. A mixture of 1-vinyltetrahydroindole (2.94 g, 0.02 mol) and thiophenol (2.8 g, 0.025 mol) was heated at 75 ° C in a sealed ampoule for 20 h in the presence of AIBN (0.03 g, 2 wt.%). Distillation in vacuum over finely ground KOH gave 4.3 g (84%) of the product, b. p. 174–176 °C/1 torr.

1-[2-(4-Fluorophenylthio)ethyl]-4,5,6,7-tetrahydroindole and 1-[2-(4-fluorophenylthio)ethyl]-2-phenylpyrrole were obtained similarly (Table 5.9).

1-(2-(Phenylthio)ethyl)- and 1-(1-(phenylthio)ethyl)-4,5,6,7-tetrahydroindoles. A mixture of 1-vinyltetrahydroindole (1.47 g, 0.01 mol) and thiophenol (1.1 g, 0.01 mol) was heated at 75 °C in a sealed ampoule for 20 h. Distillation in vacuum over finely ground KOH gave 1.52 g (59%) of a product containing 1-(2-(phenylthio)ethyl)-4,5,6,7-tetrahydroindole and 1-(1-(phenylthio)ethyl)-4,5,6,7-tetrahydroindole in a ratio of 1: 4 (according to ^{1}H NMR spectroscopy).

Table 5.9 1-(2-(Arylthio)- and 1-(1-(arylthio)ethyl)pyrroles [52]

Structure	Yield, %	B.p., °C/torr	n_D^{20}	d_4^{20}	^{1}H NMR chemical shifts, δ, ppm
	84	174–176/1	1.5970	1.0961	1.63 (m, 4H, $H^{5,6}$), 2.35 (m, 4H, $H^{4,7}$), 2.91 (t, 2H, CH_2S), 3.72 (t, 2H, CH_2N), 5.81 (d, 1H, H^3), 6.30 (d, 1H, H^2), 7.00–7.50 (m, 5H, Ph)
	86	198–202/2	1.5840	1.1571	1.63 (m, 4H, $H^{5,6}$), 2.34 (m, 4H, $H^{4,7}$), 2.90 (t, 2H, CH_2S), 3.74 (t, 2H, CH_2N), 5.85 (d, 1H, H^3), 6.31 (d, 1H, H^2), 6.50–7.30 (m, 4H, C_6H_4)
	81	175–177/1	1.6108	1.1533	2.91 (t, 2H, CH_2S), 4.06 (t, 2H, CH_2N), 6.70 (m, 1H, H^3), 6.95 (t, 1H, H^2), 6.28–7.11 (m, 9H, C_6H_4, Ph)
	88	143–145/1.5	1.5868	1.0752	1.60 (m, 4H, $H^{5,6}$), 1.75 (d, 3H, Me), 2.41 (m, 4H, $H^{4,7}$), 5.20 (q, 1H, NCHS), 5.83 (d, 1H, H^3), 6.64 (d, 1H, H^2), 7.00–7.30 (m, 5 H, Ph)
	90	160–162/2	1.5750	1.1069	1.57 (m, 4H, $H^{5,6}$), 1.72 (d, 3H, Me), 2.39 (m, 4H, $H^{4,7}$), 5.17 (q, 1H, NCHS), 5.85 (d, 1H, H^3), 6.64 (d, 1H, H^2), 6.85–7.20 (m, 4 H, C_6H_4)

Similarly, from 1-vinyltetrahydroindole (1.47 g, 0.01 mol) and 4-fluorothio phenol (1.28 g, 0.01 mol) at 75 °C for 20 h without a chemical initiator, 1.68 g (61%) of a mixture containing 1-[2-(4-fluorophenylthio)ethyl]-4,5,6,7-tetrahydro indole (20%) and 1-[1-(4-fluorophenylthio)ethyl]-4,5,6,7-tetrahydroindole (80%) was obtained (according to ^{1}H NMR spectroscopy).

1-(1-(Phenylthio)ethyl)-4,5,6,7-tetrahydroindole. A mixture of 1-vinyltetrahydroindole (1.95 g, 28.5%), NH-4,5,6,7-tetrahydroindole (61%), and cyclohexanone oxime (10.5%), obtained from cyclohexanone oxime and vinyl chloride according to the procedure [29], and thiophenol (0.6 g, 0.005 mol) without an initiator were kept in a sealed ampoule upon heating (75 °C, 20 h). Distillation in vacuum gave 0.86 g (88%) of 1-[1-(4-fluorophenylthio)ethyl]-4,5,6,7-tetrahydroindole, b.p. 143–145 °C/1.5 torr (Table 5.9).

Under the same conditions and from the same amounts of reagents, but in the presence of AIBN (0.03 g), 0.85 g (87%) of α-adduct was obtained.

1-[1-(4-Fluorophenylthio)ethyl]-4,5,6,7-tetrahydroindole. From a mixture (1.47 g) containing 1-vinyltetrahydroindole (28.5%), NH-4,5,6,7-tetrahydroindole (61%), cyclohexanone oxime (10.5%), and 4-fluorothiophenol (1.28 g, 0.01 mol) at 75 °C for 20 h (no initiator), 0.70 g (90%) of 1-[1-(4-fluorophenylthio)ethyl]-4,5,6,7-tetrahydroindole was obtained, b.p. 160–162 °C/2 torr (Table 5.7).

Under the same conditions and from the same amounts of reagents, but in the presence of AIBN (0.03 g), 0.68 g (87%) of 1-[1-(4-fluorophenylthi)oethyl]-4,5,6,7-tetrahydroindole was prepared.

The reaction of 1-vinyl-4,5,6,7-tetrahydroindole with 4-nitrothiophenol. The mixing of *N*-vinyl-4,5,6,7-tetrahydroindole (1.47 g, 0.01 mol), 4-nitrothiophenol (1.55 g, 0.01 mol), and AIBN (0.03 g) led to a strong self-heating with the formation of a polymer, which was not studied. A similar result was obtained when the reaction was carried out without an initiator.

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Electronic and Conformational Structure of Aromatic Thiols and Their Derivatives

6

6.1 ^{1}H, ^{13}C, ^{17}O, ^{19}F, ^{33}S NMR Spectra

6.1.1 ^{1}H and ^{33}S NMR Spectra of Aromatic Thiols

A large series of synthesized aryl thiols with various electron-donating and electron-withdrawing substituents (see Chap. 1) has been used to comprehensively study their ^{1}H NMR spectra (Table 6.1). As one might expect, the electron-donating substituents shield and the electron-withdrawing substituents deshield a proton of the SH group compared with the parent compound, unsubstituted thiophenol. Table 6.1 shows that, commonly, the values of chemical shifts δ_{HS} in aryl thiols are slightly sensitive toward the effect of substituents and vary within 3.05–3.73 ppm.

A quantitative evaluation of structural effects in the studied series of aromatic thiols on δ_{HS} values has been performed by a correlation analysis using a set of different types of substituent constants $\sigma^{\mathrm{o}}(\sigma^{-})$ and acidity values (pK_{a}) of the thiol function.

Statistical processing of δ_{HS} dependence on $\sigma^{\mathrm{o}}(\sigma^{-})$ indicate a satisfactory linear relationship between the correlated values:

$$\boldsymbol{\delta}_{\mathbf{HS}} = (3.13 \pm 0.03) + (0.37 \pm 0.02)\sigma^{\mathrm{o}}(\sigma^{-}), r = 0.986, s = 0.03, n = 14.$$

Satisfactory linear correlations are obtained earlier between pK_{a} and δ_{HS}:

$$\mathrm{p}K_a = 24.65 - 5.43\delta_{\mathrm{HS}}, r = 0.969; s = 0.23, n = 9[1];$$

$$\mathrm{p}K_a = 32.75 - 7.49\delta_{\mathrm{HS}}, r = 0.946, s = 0.22, n = 9[2];$$

$$\mathrm{p}K_a = 18.79 - 3.90\delta_{\mathrm{HS}}, r = 0.987, s = 0.13, n = 7[3].$$

If δ_{HS} values of aryl thiols are known, their acidity constants can be determined.

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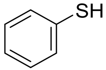
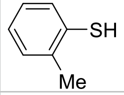
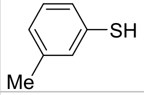
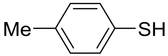
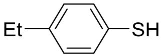
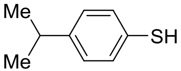
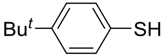
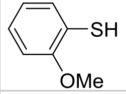
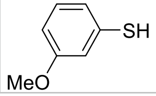
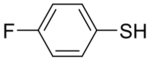
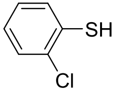
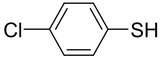
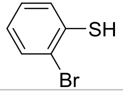
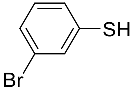
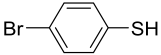
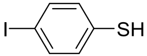
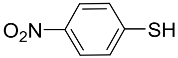
Table 6.1 The ^{1}H NMR chemical shifts δ_{HS}, pK_a values, and substituent constants of aryl thiols [1–3]

No.	Structure	δ_{SH}, ppm	$\sigma^o(\sigma^-)$	pK_a		
				[4]	[5]	[6]
1	2	3	4	5	6	7
1		3.12 [1] 3.16 [2]	0	7.76	9.28	6.615
2		3.05 [1] 3.06 [3]			9.87	
3		3.13 [1]	–0.069	7.96	9.56	6.66
4		3.10 [1] 3.17 [2]	–0.124	8.03	9.60	6.82
5		3.08 [1]	–0.131			
6		3.07 [1]	–0.156			
7		3.12 [1]	–0.174			
8		3.57 [1] 3.66 [3]				
9		3.18 [1]	0.152	7.45	9.14	6.385

(continued)

Table 6.1 (continued)

No.	Structure	δ_{SH}, ppm	$\sigma^o(\sigma^-)$	pK_a		
				[4]	[5]	[6]
1	2	3	4	5	6	7
10		3.20 [1]	0.212		8.88	
11		3.71 [1] 3.82 [2]				
12		3.20 [1] 3.19 [2]	0.281	6.96	8.45	6.135
13		3.73 [1]				
14		3.30 [1]	0.391	6.77	8.20	
15		3.23 [1]	0.296	6.99	8.37	6.02
16		3.20 [1]	0.298	6.94		
17		3.45 [1]	$0.84\sigma^-$			
18		3.62 [1]	$1.23\sigma^-$	5.11		4.715

^{33}S NMR spectroscopy received a certain amount of attention in the 1980s, with the availability of FT spectrometers at a high magnetic field. Thiols (w½ 2000–6500 Hz) give much broader lines making them close to the limit of observation with conventional instruments. Spectral parameters of few thiols have been reported in the literature [7, 8]. Chemical shifts δS are −459 ppm for MeSH [9] and −415 (w½ 2100 Hz) ppm for Bu^{n}SH [10]. The signals observed for PhCH$_2$SH (δS −379 ppm) and PhSH (δS −332 ppm) [11] evidence that the introduction of an aryl group significantly increases the chemical shifts.

6.1.2 ^{13}C NMR Spectra of Aromatic Sulfides

The investigations of alkyl substituents effect on the interaction of 6th group heteroatoms with aromatic scaffolds can contribute to addressing a general challenge related to the elucidation of the nature of the heteroatoms interaction with the neighboring π-electron system of PhXR compounds, where X = O, S, Se [12–17].

The chemical shifts of ^{13}C nuclei, especially those significantly distant from a variable substituent, in the first approximation give information about the changes in charge on the corresponding carbon atoms. In particular, they are quite sensitive to redistribution of π-electron density in the PhX system that allows studying the details of the electronic and spatial structure of molecules incorporating such structures.

Table 6.2 shows the values of ^{13}C chemical shifts of the aromatic ring of alkyl phenyl sulfides as well as some alkyl phenyl ethers and alkylbenzenes [18]. The latter are used as isostructural analogs, which do not contain lone electron pairs (LEP) and vacant orbitals in the “bridge”. The assignment of all signals is based on the data relating to alkylbenzenes [19] and anisoles [20], with different intensities of C^1 and C^4 signals, on the one hand, and C$^{2(6)}$ and C$^{3(5)}$, on the other hand. For sulfides, in which the δ values of C$^{2(6)}$ and C$^{3(5)}$ atoms, as a rule, differ insignificantly, the results obtained for a similar series of alkyl 4-fluorophenyl sulfides are employed.

The δ values of the benzene ring C^1 carbons, coupled directly with the substituent, are in accordance with the group electronegativity of the latter. When the branching of the alkyl substituent changes from Me to *t*-Bu, chemical shifts of C^1 carbon atoms decrease by 6.00 (C^1–S), 4.30 (C^1–O), and 4.85 (C^1–C) ppm. The complexity of accounting for all factors affecting δC^1 (various anisotropic and steric effects of the short-range action) hinders the interpretation of these values.

For δC$^{3(5)}$, it should be noted a slight regular shift of the signals to a strong field with an increase in the branching of the alkyl substituent in all three series of compounds: $\Delta\delta$C$^{3(5)}$ = 0.85 (for ethers), 0.58 (for sulfides), and 0.91 ppm (for alkylbenzenes).

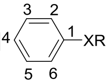
Analysis of the values and changes of (C$^{2(6)}$) and (C^4) chemical shifts of the benzene ring enables us to draw fundamental conclusions about the electronic structure of the compounds under study. Despite the fact that the OMe and SMe groups are acceptors in terms of their induction effect [$\sigma^*_{\text{OMe}} = 1.73$; $\sigma^*_{\text{SMe}} = 1.47$], the C^4 atoms in anisole and thioanisole (120.61 and 124.52 ppm) are more shielded than in unsubstituted benzene and in ethylbenzene (128.50 and 125.67 ppm) containing a typical electron donor [$\sigma^*_{Et} = -0.10$]. Since the shielding of C^4 is mainly determined by a charge density on the considered atom, the inference should be drawn that the increased shielding of C^4 atoms in ethers and sulfides is due to conjugation of free electron pairs of heteroatoms with the π-system of the benzene fragment. A similar picture is observed for $C^{2(6)}$ (see Table 6.2, $\delta C^{2(6)}$). A higher shielding of $C^{2(6)}$ and especially C^4 in the series of alkyl phenyl ethers indicates the greater role of the 2*p*–*π*-interaction of an oxygen atom with the benzene ring compared to the 3*p*–*π*-interaction of the sulfur atom. In the case of sulfides, this may also be owing to competitive 3*d*–π-interaction.

In close-to-planar conformations, *p*–π-conjugation should be maximal. However, molecules of alkyl phenyl sulfides and alkyl phenyl ethers with branched substituents cannot be completely coplanar due to steric hindrances, which inevitably should lead to a violation of the *p*–π-conjugation. Consequently, a decrease in $C^{2(6)}$ and C^4 shielding with an increase in the volume of the alkyl substituent can be considered as steric inhibition of resonance caused by a violation of *p*–π-coplanarity: $\Delta\delta C^{2(6)}(O) = 9.89$ and $\Delta\delta C^{2(6)}(S) = 11.03$ ppm. The low-field shift of $\delta C^{2(6)}$ for alkylbenzenes bearing bulkier substituents ($\Delta\delta C^{2(6)}(C) = 2.32$ ppm) is owing to the direct steric interaction of alkyl with *ortho*-position of the benzene ring. The additional contribution of this effect to the chemical shift of $C^{2(6)}$ in the sulfides and ethers certainly increases the variation of these values and does not allow explaining the observed changes only by the violation of the *p*–π-conjugation.

With an increase in the branching of the alkyl substituent, the chemical shifts of C^4 atoms in both alkyl phenyl ethers and alkyl phenyl sulfides are also observed in a weak field. Changes in the shielding of C^4 atoms are mainly determined by the nature of the interaction between heteroatom and π-system of the benzene ring. In the above ethers and sulfides, $\Delta\delta C^4(O) = 2.27$ and $\Delta\delta C^4(S) = 3.61$ ppm, while for alkylbenzenes, δC^4 remain almost constant. Figure 6.1 clearly shows that in alkyl phenyl sulfides, there is a decrease in C^4 shielding, and hence a violation of the *p*–π-conjugation gradually augments in the series Me < Et < *i*-Pr < *t*-Bu, while for alkyl phenyl ethers, a significant reduction of C^4 shielding is characteristic only for *t*-Bu-substituent. It is also interesting that if the *para*-carbon atom in *tert*-butyl phenyl ether remains substantially shielded, the C^4 chemical shift in the *tert*-butyl phenyl sulfide approaches that of in unsubstituted benzene (δ 122.88, 129.13, and 128.50 ppm, respectively).

The comparative analysis reveals that close-to-planar conformations are much more stable for alkyl phenyl ethers, which is explained by both the larger Ph–O–R angle compared to Ph–S–R and by more intense *p*–π-conjugation. A significant low-field shift of the C^4 signal in sulfides can be associated with a violation of the molecule coplanarity, affecting only *p*–π-interaction, whereas the *d*–π-interaction, due to a different geometry of *d*-orbitals, is not changed [21], and its relative role increases.

Table 6.2 The ^{13}C NMR chemical shifts δ_C of alkyl phenyl sulfide, alkyl phenyl ethers, and alkylbenzenes [18]



R	Chemical shifts, δ, ppm											
	X = S				X = O				X = CH_2			
	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4
Me	138.58	126.12	128.56	124.52	159.93	114.01	129.47	120.61	143.98	127.82	128.33	125.67
Et	136.88	128.59	128.46	125.27	159.27	114.54	129.37	120.44	142.28	128.42	126.21	125.67
Pr^n	137.19	128.57	128.57	125.24	159.40	114.52	129.29	120.37	143.08	128.33	128.18	125.58
Bu^n	137.35	128.55	128.41	125.15					142.44	128.25	128.12	125.52
Am^n	137.42	128.52	128.43	125.13								
$C_6H^n_{13}$	137.44	128.49	128.43	125.11								
$C_7H^n_{15}$	137.45	128.48	128.40	125.10								
$C_8H^n_{17}$	137.48	128.47	128.47	125.10								
$C_9H^n_{19}$	137.50	128.47	128.43	125.07								
$C_{10}H^n_{21}$	137.49	128.47	128.40	125.06								
Am^i	137.27	128.44	128.35	125.08								
cyclo-C_3H_5					159.09	114.98	129.24	120.79				
Pr^i	135.64	131.38	128.46	126.16	158.06	115.83	129.29	120.29	141.14	128.93	127.98	125.62
Bu^s	135.67	131.59	128.46	126.16	158.42	115.91	129.30	120.32				
cyclo-C_6H_{11}	135.37	131.57	128.39	126.10								
Bu^t	132.58	137.15	127.98	128.13	155.63	123.90	128.62	122.88	139.06	130.14	127.42	125.63

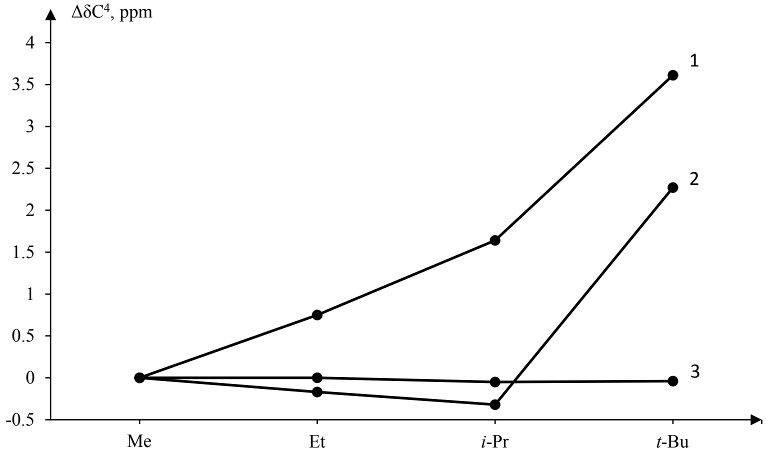


Fig. 6.1 The dependence of phenyl carbon C^4 shieldings on alkyl substituent (Et, *i*-Pr, *t*-Bu) for: *1*—PhSR, *2*—PhOR, *3*—PhCH$_2$R [$\Delta\delta(^{13}C^4) = \delta(^{13}C^4_R) - \delta(^{13}C^4_{Me})$]

The ^{13}C NMR analysis of conformational equilibrium in alkyl phenyl sulfides is described in Sect. 6.2.

The quantum-chemical calculations have revealed that density of the π-electron charge on a carbon atom is connected with its chemical shift by a relation $\delta(^{13}C) = 160(q_\pi - 1)$ [22]. This allows evaluating the excess π-electron charges (q_π) in *para*-position of the aromatic ring in alkyl phenyl ethers and alkyl phenyl sulfides, which, relative to unsubstituted benzene, are equal [18]:

The q_π values and their ratios for the same alkyls in oxygen- and sulfur-containing compounds indicate that the intensity of the *p*–π-conjugation is always predominant in alkyl phenyl ethers. Noteworthy, in *tert*-butyl phenyl sulfide, the contribution of the *p*–π-conjugation to shielding of C^4 ceases to prevail, obviously due to violation of the *p*–π-conjugation and its partial compensation by the *d*–π-acceptor interaction. However, such an assessment of the *p*–π-conjugation should be considered rather rough which is explained by the very nature of the ratio used as well as by the assumptions made.

This model of interaction between alkyl substituent with the conjugated system heteroatom/benzene ring in alkyl phenyl sulfides is confirmed by the close relationship of C^4 chemical shift with the isosteric constants of the combined substituents $E_s^o(CH_2R)$ characterizing the steric effect of the SR substituent [18]:

$$\delta C^4 = (123.9 \pm 0.1) - (2.0 \pm 0.1) E_s^o(CH_2R); r = 0.99; s = 0.17, n = 9.$$

In the series of alkylbenzenes, the correlation of chemical shift of the ***para***-carbon atom with the steric constants of the alkyl substituent R is not observed:

$$\delta C^4 = (124.5 \pm 0.2) - (1.5 \pm 0.2) E_S^o(R), r = 0.94; s = 0.40; n = 10.$$

δC^4 Values of alkyl phenyl sulfides correlate with hyperconjugation constants more satisfactory ($\Delta n = n_H + 0.4 n_C$, where n_H and n_C are the number of H and C atoms in the α-position) [18]:

$\delta C^4 = (129.8 \pm 0.5) - (1.9 \pm 0.2)\Delta n$; $r = 0.96$, $s = 0.35$.

However, since Δn is connected with the number of H and C atoms at substituent α-carbon, it also describes steric interactions, and the satisfactory correlation is achieved for E_s^o and Δn in the case of alkyl substituents [15].

In the series of alkyl phenyl ethers, the effect of resonance steric inhibition is significant only for *tert*-butyl phenyl ether (see Fig. 6.1). Therefore, a correlation of the chemical shifts of *ortho*- and *para*-carbon atoms with $E_s^o(CH_2R)$ constants is expectedly not observed.

Analysis of the ^1H and ^{13}C NMR spectra of aryl vinyl ethers and sulfides [23, 24] by comparing the chemical shifts with Hammett constants σ reveals that the sensitivity parameter value for sulfides appears to be slightly higher. Consequently, it is concluded that the sulfur atom is a better transmitter of electronic effects than the oxygen atom. The better transfer of substituents effects through sulfur atom is explained by the participation of *d*-orbitals in the interaction, thus creating additional possibilities for transmittance of substituent polar effects between two unsaturated fragments. In some alkyl phenyl ethers and sulfides, as well as alkyl vinyl ethers and sulfides [15, 25], ^{13}C NMR chemical shifts of sulfur-containing compounds are also more sensitive to the structure of the substituent, though this is not related to the so-called through-conjugation, but is mainly due to conformational factors.

The ^{13}C NMR spectra [26, 27] of a wide range of alkyl aryl sulfides RC_6H_4SAlk have been studied and peculiarities of the alkyl groups (Me, Et, *i*-Pr, and *t*-Bu) effect on the shielding of ^{13}C nuclei in 3- and 4-substituted alkyl aryl sulfides have been established (Table 6.3).

The variation of alkyls from Me to *t*-Bu in all the above compounds increases the shielding of the C^1 and $C^{3(5)}$ nuclei and deshielding of $C^{2(6)}$ and C^4. The range of changes of C^1, $C^{2(6)}$, and C^4 chemical shifts in the series is quite large: 6.2–4.6, 11.1–8.9, and 4.4–2.0 ppm, respectively, the measurement accuracy being $\delta C \pm 0.02$ ppm and higher. The changes in chemical shifts of $C^{3(5)}$ carbon range not so significantly (0.8–0.3 ppm).

Table 6.3 The ^{13}C NMR chemical shifts of alkyl aryl sulfides

R	Alk	Chemical shifts, δ, ppm			
		C^1	$C^{2(6)}$	$C^{3(5)}$	C^4
1	2	3	4	5	6
H	Me	138.6	126.1	128.6	124.5
	Et	136.9	128.5	128.6	125.3
	Pr^i	135.6	131.4	128.5	126.2
	Bu^t	132.6	137.2	128.0	128.1
	Δ	6.0	–11.1	0.6	–3.6
4-Me	Me	134.7	127.4	129.9	135.5
	Et	133.6	130.1	129.9	135.6
	Pr^i	132.5	134.1	129.8	136.7
	Bu^t	130.1	137.9	129.6	138.5
	Δ	4.6	–10.5	0.3	–3.0
4-MeO	Me	128.9	129.7	114.5	158.0
	Et	126.7	132.7	114.4	158.7
	Pr^i	125.4	135.3	114.2	159.2
	Bu^t	123.5	138.6	113.8	160.0
	Δ	5.4	–8.9	0.7	–2.0
3-MeO	Me	140.0	112.1 118.5	159.9 129.6	110.3
	Et	138.4	114.0 120.5	159.9 129.6	110.9
	Pr^i	137.1	116.8 123.3	159.7 129.4	111.9
	Bu^t	133.8	122.5 129.3	159.1 128.8	114.3
	Δ	6.2	–10.4 –10.8	0.8 0.8	–4.0

(continued)

Table 6.3 (continued)

R	Alk	Chemical shifts, δ, ppm			
		C^1	$C^{2(6)}$	$C^{3(5)}$	C^4
1	2	3	4	5	6
4-F	Me	133.9	128.9	115.9	161.0
	Et	132.0	131.8	115.8	161.6
	Pr^i	130.7	134.8	115.7	162.1
	Bu^t	128.3	139.2	115.3	163.1
	Δ	5.6	–10.3	0.6	–2.1
3-F	Me	142.6	113.3 122.7	163.9 131.2	112.2
	Et	140.8	115.3 124.5	163.8 131.3	112.8
	Pr^i	139.7	117.6 127.1	163.6 131.3	113.8
	Bu^t	135.9	124.2 133.9	163.0 130.9	116.5
	Δ	6.7	–10.9 –11.2	0.9 0.3	–4.3
4-Cl	Me	137.2	127.2	128.5	130.2
	Et	135.6	129.7	128.6	131.2
	Pr^i	134.3	132.6	128.5	132.2
	Bu^t	131.2	138.3	128.2	134.6
	Δ	6.0	–11.1	0.3	–4.4
4-NO_2	Me	150.0	124.5	125.9	145.5
	Et	148.8	125.8	124.5	145.6
	Pr^i	148.0	128.5	124.6	146.0
	Bu^t	142.9	137.5	124.1	148.6
	Δ	7.1	–13.0	1.8	–3.1

If the intramolecular effect of the alkyl groups is limited to induction, hyperconjugate, and steric ones, then the correlation analysis faces an issue of searching and interpreting the multiparameter regression equations connecting δC with the corresponding structural constants of the substituents, for example [28]:

$$\delta\left({}^{13}\mathrm{C}\right) = a_0 + a_1\sigma* + a_2\Delta n + a_3E_{\mathrm{s}}^{\mathrm{o}}.$$

However, the non-orthogonality of structural constants for alkyl groups [15, 29] makes interpretation of the above dependencies even at high correlation coefficients rather arbitrary due to uncertainty of the a_{n} coefficients and does not allow contributions of various structural effects to be evaluated. At the same time, a rigorous theoretical calculation of the ^{13}C shielding constants in such multielectron systems as substituted alkyl aryl sulfides is difficult, and its results are difficult to interpret in terms of well-known phenomenological models describing the effects of substituents. In this situation, it seems encouraging to use factor analysis (the method of principal components), which, without revealing the physical meaning of the factors controlling the experimental parameters, permits to estimate their number and relative importance.

Mathematically, the method of principal components [30] is reduced to the problem of finding eigenvectors and eigenvalues of the scattering matrix. The eigenvalues represent variances of factors, and the set of eigenvectors is the orthogonal transformation matrix (matrix of factors)

$$\mathrm{V} = \mathrm{BX},$$

where X is a matrix of initial data; B is a matrix of factors; V is a matrix of factor values. The method of principal component extracts the matrix of orthogonal factors with the greatest variance from the matrix of initial data by the linear transformation. Factors with zero or close to zero variance are discarded. The δC^1, δC$^{2(6)}$, and δC^4 chemical shifts values, given in Table 6.3, are the elements of the matrix of initial data X (X = H, 4-Me, 3-MeO, 4-MeO, 4-F, 4-Cl). This matrix has six lines (six series of compounds with different substituents) and 12 columns (four alkyl groups and three positions in the ring, 4 × 3 = 12) [26]. The δ(^{13}C$^{3(5)}$) values are analyzed due to the small range of changes.

The component analysis enables to transform a matrix of the initial data X into a matrix of factor values (Table 6.4), whose elements (V_i) can be interpreted as factor values for the alkyl substituents under discussion. The analysis of the factor values shows that the used δ(^{13}C) set is formally described by two factors (V_1 and V_2), which are 97% responsible for changing the entire variance. Factor V_1 clearly divides the selected part of the matrix V into three parts corresponding to the position of nuclei in the benzene ring: δC^1, δC$^{2(6)}$, and δC^4. The main information about the effect of alkyls on δC^1, δC$^{2(6)}$, and δC^4 can be retrieved from the factor V_2, whose contribution in the series from Me to *t*-Bu for δC$^{2(6)}$ increases, and for δC^1 it decreases. Consequently, augmentation of factor V_2 contribution leads to shielding of C^1 nuclei and deshielding of C$^{2(6)}$ and C^4 nuclei. Thus, analysis of Alk

Table 6.4 Matrix of factor values [26]

δC	R	V_1	V_2	V_3	V_4	V_5	V_6
C^1	Me	–4.46	300.67	–110.74	36.95	–74.97	–25.88
	Et	–4.78	297.20	–109.10	35.84	–73.74	–25.30
	Pr^i	–4.79	294.45	–108.01	35.34	–73.07	–25.05
	Bu^t	–3.73	283.44	–105.68	34.56	–71.77	–24.77
$C^{2(6)}$	Me	13.06	279.70	–96.69	38.84	–73.25	–24.78
	Et	13.92	285.51	–93.54	39.73	–74.90	–25.31
	Pr^i	14. 22	292.49	–95.55	39.67	–76.32	–25.60
	Bu^t	12.12	303.06	–99.58	41.64	–78.83	–25.94
C^4	Me	44.87	300.64	–106.70	50.59	–93.28	–24.43
	Et	44.67	301.97	–107.15	51.34	–83.60	–24.62
	Pr^i	44.30	303.92	–107.61	51.35	–83.85	–24.80
	Bu^t	42.97	308.02	–108.88	51.58	–84.21	–23.08
	%	60.292	96.640	99.818	99.978	99.998	100.00

effect on the chemical shifts of the benzene ring carbons in the alkyl aryl sulfides should take into account only one statistically significant factor (V_2).

Factor V_2 can be distinguished in one sense or another by correlating its values with induction, resonance, or steric Alk constants. However, in view of the aforementioned non-orthogonality of different constant scales for alkyl groups, such a solution would be inconsistent. Therefore, it should be done within the framework of certain model representations.

For comparison, it is appropriate to discuss the effect of a large number of alkyl substituents on chemical shifts of the benzene ring carbons in the alkylbenzenes of the two series, PhAlk and $PhCH_2Alk$ (Tables 6.2 and 6.5). The latter are the compounds that do not contain lone pairs or vacant orbitals, capable of resonant interaction, in the bridge between Alk and the benzene ring.

The increase of C^1 shielding in $C_6H_5CH_2Alk$ (from Me to *t*-Bu) confirms the ideas about the induction effect of these groups. However, in C_6H_5Alk, where even

Table 6.5 The ^{13}C NMR chemical shifts of some alkylbenzenes[a] [26]

Alk	Chemical shifts, δ, ppm							
	C_6H_5Alk				$C_6H_5CH_2Alk$			
	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4
Me	137.5	129.3	128.3	125.4	143.9	127.8	128.3	125.6
Et	143.9	127.8	128.3	125.6	142.3	128.4	128.2	125.6
Pr^i	148.4	126.2	128.3	125.7	141.1	122.9	128.0	125.6
Bu^t	150.3	124.9	127.9	125.2	139.1	130.1	127.4	125.6
Δ[b]	–12.8	4.4	0.4	0.5	4.8	–2.3	0.9	0

[a]Relative to Me_4Si; [b]Δ is difference between δC_{Me} and $\delta C_{Bu\text{-}t}$

stronger induction effect of Alk on C^1 is expected, shielding of the latter occurs in the opposite way. Information on the induction effect of Alk could be obtained from $\delta C^{3(5)}$, but the range of their changes in $C_6H_5CH_2Alk$ (~0.9 ppm) is more than 2 times higher than that in C_6H_5Alk (~0.4 ppm), which contradicts the data on transmittance of the induction effect. When the volume of the alkyl substituent increases, $C^{2(6)}$ signals are shifted to a strong field in C_6H_5Alk series, while for $C_6H_5C\underline{\mathbf{H_2}}Alk$ they are displaced to a weak field. The δC^4 values in C_6H_5Alk vary slightly (~0.5 ppm), while in $C_6H_5C\underline{\mathbf{H_2}}Alk$ they almost remain constant. It should be noted that shielding of C^4 nuclei is in all cases stronger than in unsubstituted benzene ($\delta C = 128.5$ ppm). Thus, it can be concluded that the alkyl groups are mainly characterized by a steric effect, determined by their volume and branching, as well as by the π-polarizing effect, which depends slightly on the type of alkyl substituent.

The C_6H_5SAlk molecules exist in solutions in the preferable conformations, which differ in the dihedral angle (φ) between planes of Csp^2–S–Csp^3 bond and the benzene ring.

In methyl phenyl sulfide, the averaged angle φ, estimated based on the Kerr constants, is 23° [31]. According to photoelectron spectroscopy data, the amount of non-planar conformer in alkyl aryl sulfides with Me, Et, *i*-Pr, and *t*-Bu substituents is 10, 60, 85, and 95%, respectively [32]. Since only one from two lone pairs at a sulfur atom in sulfides can participate in the *p*–π-conjugation [33, 34], a strong dependence of the *p*–π-conjugation on conformation should be observed in alkyl aryl sulfides.

In alkyl phenyl sulfides (see Table 6.2), the trends in changes of δC^1 and $\delta C^{2(6)}$ are the same as in $C_6H_5CH_2Alk$. Noteworthy, the range of changes in $C^{2(6)}$ chemical shifts in 3- and 4-substituted aryl sulfides RC_6H_4SAlk is significantly larger (11.1–8.9 ppm) than in alkylbenzenes $PhCH_2Alk$ (2.3 ppm). But most importantly, in alkyl aryl sulfides, an increase in the volume of alkyl substituents causes a significant deshielding of C^4 atoms. Apart from the violation of the *p*–π-interaction of the sulfur atom with the benzene ring, it is difficult to suggest any other mechanism responsible for the deshielding of these atoms. A reason for the violation of the *p*–π-interaction is a change in the conformation of alkyl aryl sulfides, which occurs due to an increase in steric interactions between position 2(6) and the alkyl group in the series Me < Et < *i*-Pr < *t*-Bu.

Thus, changes in δC^1 and $\delta C^{2(6)}$ chemical shifts are resulted from two simultaneous effects: direct steric effect and effect of *p*–π-conjugation violation. Both effects are defined by the volume of the alkyl groups, and their contributions are formally indistinguishable. Changes in δC^4 are a direct consequence of the steric violation of the *p*–π-conjugation of the sulfur atom with the benzene ring. Apparently, factor V_2 reflects both of these effects of the alkyl group, and there is no need to consider any other interactions. Therefore, the equations connecting chemical shifts δC^1, $\delta C^{2(6)}$, and δC^4 with steric constants (isosteric steric constants $E_S^o(CH_2Alk)$ [28]), approximately describing the steric effect of the SAlk groups as a whole, can serve for quantitative evaluation of the alkyl substituents effect on the specified spectral parameters. Of particular interest are the dependences $\delta C^4 =$

Table 6.6 The parameters of correlation equations $\delta C^4 = a_0 + a_1 E_s^o(CH_2Alk)$

$\delta\ C^4_{(R)}$	a_0	a_1	r	s_0
$\delta\ C^4_{(H)}$	123.9	–2.1 ± 0.1	0.990	0.17
$\delta\ C^4_{(4-Me)}$	134.8	–1.8 ± 0 2	0.987	0.27
$\delta\ C^4_{(4-OMe)}$	157.9	–1.1 ± 0.1	0.982	0.20
$\delta\ C^4_{(3-OMe)}$	109.6	–2.3 ± 0.2	0.991	0.29
$\delta\ C^4_{(4-F)}$	160.8	–1.2 ± 0.1	0.990	0.09
$\delta\ C^4_{(4-Cl)}$	129.6	–2.5 ± 0.1	0.996	0.16
$\delta\ C^4_{(4-F)}$	111.3	–2.6 ± 0.1	0.988	0.14
$\delta\ C^4_{(4-NO_2)}$	144.6	–1.9 ± 0.1	0.936	0.32

$a_0 + a_1 E_s^o(CH_2Alk)$ (Table 6.6). Comparison of the sensitivity constants a_1 in these dependencies shows that the response of δC^4 to the change in Alk substantially depends on the nature of the substituent R. The series with acceptor substituents (R = 3-MeO, 4-Cl, 4-NO_2) are more sensitive to the effects of Alk than the series, in which the π-donor effect of R (4-MeO, 4-F, 3-F, and 4-Me) prevails. The methyl group does not have a significant resonant effect. Nevertheless, in the position 4, it substantially polarizes the benzene ring via π-induction mechanism [35].

A good linear dependence is observed between δC^i values of different series of compounds [36]. For example:

$$\delta C^1_{(4-Cl)} = (-0.1 \pm 0.1) + (1.0 \pm 0.1)\delta C^1_{(H)}, r = 0.999, s = 0.05;$$

$$\delta C^{2(6)}_{(4-Cl)} = (0.1 \pm 0.1) + (1.0 \pm 0.1)\delta C^{2(6)}_{(H)}, r = 0.999; s = 0.08;$$

$$\delta C^4_{(4-C1)} = (0.1 \pm 0.1) + (1.2 \pm 0.1)\delta C^4_{(H)}, r = 0.999, s = 0.04.$$

The trends of $\delta C^{3(5)}$ change are also similar, but they cannot be represented quantitatively due to the small range of changes in these values (0.4–0.6 ppm). From these equations, it follows that in C_6H_5SAlk and 4-ClC_6H_4Alk, alkyl substituents equally affect the shielding of ^{13}C nuclei of the aromatic fragment. Moreover, the ratio of populations of planar and non-planar forms at the corresponding substituents is approximately the same. Only a slight increase in sensitivity of δC^4 (Δ = 4.39 ppm) in 4-ClC_6H_4Alk compared to δC^4 in C_6H_5SAlk (Δ = 3.61 ppm) indicates some minor differences (the sensitivity coefficient in correlation equation δC^4 is 1.2).

Such differences evidence the dependence of RC_6H_4SAlk conformation not only on the type of Alk, but also on the substituent R. When Alk = *t*-Bu, alkyl aryl sulfides with any R have a non-planar gauche-form ($\varphi \approx 90°$) due to steric hindrances to coplanarity, but for small alkyl groups (Me or Et), acceptor R improves coplanarity of the molecules by enhancing the *p*–π-conjugation of the sulfur atom with the benzene ring, while with π–donor R, this conjugation is weakened by a competing interaction. Therefore, the variation of Alk from Me to *t*-Bu in series with acceptor R leads to significant changes in shielding of C^4 nuclei and steric inhibition of the *p*–π-conjugation of sulfur S atom with the benzene ring becomes more pronounced.

In order to check the above assumptions, ^{13}C NMR spectra of 1-alkylthio-2,4,6-trimethylbenzenes have been studied (Table 6.7) [26, 37]. The presence of two methyl groups in positions 2 and 6 of these alkyl aryl sulfides, regardless of the type of SAlk groups, creates significant hindrances to coplanarity and, accordingly, to *p*–π-conjugation of the sulfur atom with the benzene ring. Therefore, the change of Alk from Me to *t*-Bu does not almost alter the shielding of C^4 nuclei (the δC^4 range is ~0.1 ppm). An increase in the volume of Alk from Me to *t*-Bu in a series of these compounds changes $\delta C^{2(6)}$ by 2.5 ppm, which corresponds to the range of $\delta C^{2(6)}$ changes in $PhCH_2Alk$ (2.3 ppm) and indicates the steric nature of this effect. The $\delta C^{3(5)}$ values in these compounds are constant.

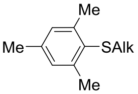
Measurement of the $\delta^{13}C$ of organyl phenyl sulfides, containing unsaturated and heteroatomic substituents at sulfur atom (Table 6.8), has shown that $\delta C^{2(6)}$ and δC^4 of the ring in such compounds approximately reflect the induction effect of the R groups:

$$\delta C^{2(6)} = (128.5 \pm 0.3) + (3.2 \pm 0.4)\sigma *, r = 0.946, s = 0.56, n = 9;$$

$$\delta C^4 = (125.9 \pm 0.2) + (1.4 \pm 0.2)\sigma *, r = 0.902, \ \mathrm{s} = 0.34, n = 9.$$

The ^{33}S NMR studies of sulfides did not come into common use due to the fact that the sulfur nucleus has a relatively large quadrupole moment, which, in asymmetrical environments, leads to very broad lines. Consequently, the sulfur resonance is difficult to be detected and characterized quantitatively [7]. Dicoordinated sulfur has a low electronic symmetry. The S resonance lies upfield with respect to the SO_4^{2-} signal, and chemical shifts of saturated cyclic sulfides are in the

Table 6.7 The ^{13}C NMR chemical shifts of 1-alkylthio-2,4,6-trimethylbenzenes [26]



Alk	Chemical shifts[a], δ, ppm						
	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	Me-$C^{2,6}$	Me-C^4	C_{Alk}
Me	133.3	142.2	129.2	137.6	21.3	21.9	18.5
Et	133.5	142.9	129.2	137.6	21.3	22.3	19.6, 15.2
Pr^i	130.6	143.1	129.2	137.6	21.3	22.5	39.0, 23.6
Bu^t	129.4	144.9	129.2	137.7	21.4	23.5	48.7, 32.0

[a] Relative to Me_4Si

Table 6.8 The ^{13}C NMR chemical shifts of organic phenyl sulfides PhSR

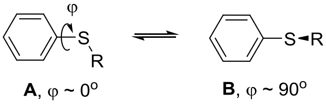
Structure	Chemical shifts, δ, ppm					σ^*
	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	R	
$C_6H_5SCH_2CH = CH_2$	136.12	129.36	128.45	125.68	136.12 (CH_2 =), 117.04 (CH =), 36.79 (SCH_2)	0.18
$C_6H_5SCH = CH_2$	134.31	130.31	128.79	126.74	132.04 (SCH =), 114.67 (CH_2 =)	0.40
$C_6H_5SC_6H_5$	135.57	130.62	128.79	126.53		0.60
$C_6H_5SCH_2C_6H_5$	136.49	129.04	128.04	126.70	137.08 (C^1), 128.45 ($C^{2(6)}$), 128.45 ($C^{3(5)}$), 125.67 (C^4)	0.215
$C_6H_5SCH_2CH_2OH$	135.60	128.76	128.76	125.75	60.42 (OCH_2), 35.59 (SCH_2)	0.198
$C_6H_5SCH_2CH_2Cl$	134.27	129.68	128.85	126.43	42.21 (CH_2Cl), 35.63 (SCH_2)	0.385
$C_6H_5SCH_2CH_2Br$	133.98	129.71	128.70	126.37	35.56 (SCH_2), 29.81 (CH_2Br)	0.26
$C_6H_5SCH_2CH_2CN$	133.67	129.92	129.14	126.85	118.37 (CN), 29.23 (SCH_2), 17.28 (CH_2)	0.80
$C_6H_5SCH_2SC_6H_5$	134.83	129.67	128.54	126.35	39.42	
$C_6H_5SC(O)Me$	129.03	134.20	128.93	128.18	192.00 (CO), 29.72 (Me)	1.65
$C_6H_5SC(O)CCl_3$	129.83	133.98	129.06	125.46	185.54 (CO), 94.70 (CCl_3)	

range −460 to −300 ppm with the exception of thiirane (−573 ppm) [38]. The observed line widths vary from 2000 to 20,000 Hz, and the signals become undetectable as the molecular size increases. Apart from a series of saturated cyclic sulfides, the only reported values are δS −428 ($w_{1/2}$ 3300 Hz) for dimethyl [38] and δS −390 ($w_{1/2}$ 19,800 Hz) [11] for methyl phenyl sulfides. It is clear that the introduction of an aryl group results in a higher chemical shift for methyl phenyl sulfide.

The ^{33}Sulfur NMR chemical shieldings have been determined at the correlation-including density functional theory scaled B3LYP/6-311+G(nd,p)//B3LYP/6-311+G(d,p) and modified MP2/6-311+G(nd,p) estimated infinite order Møller–Plesset levels with n = 2 for sulfur [39]. The calculations span the range of sulfur shieldings and show agreement with the experiment of about 3% of the shielding range.

6.1.3 Direct Spin-Spin Coupling Constants ^{13}C–^{13}C of Alkyl Aryl Sulfides

According to a number of works (see, for example, [32, 40]), alkyl phenyl sulfides exist in an equilibrium mixture of two conformers, planar (**A**) and orthogonal (**B**), which are transformed into each other upon rotating the alkyl substituent by 90° relative to the C^{1}–S bond.



An increase in the branching of the alkyl radical shifts the equilibrium toward orthogonal conformer. This is clearly manifested in the change of NMR parameters characterizing the phenyl group of alkyl phenyl sulfides (^{1}H and ^{13}C chemical shifts, ^{1}H–^{1}H, and ^{13}C–^{1}H spin-spin coupling constants [18, 41, 42]). The introduction of acceptor substituents into the *para*-position of the benzene ring in sulfides enhances the *p*–π-conjugation of sulfur with the aromatic fragment and promotes coplanarity of molecules, while the electron-donating groups have the opposite effect [31, 34, 43, 44].

The ^{13}C–^{13}C spin-spin coupling constants have been obtained by analyzing C-satellite the ^{13}C–{^{1}H} satellite NMR spectra [44]. The experimental values of the direct carbon–carbon constants for a series of organyl phenyl sulfides are given in Table 6.9.

The shift of conformational equilibrium toward the orthogonal conformer, which occurs with an increase in branching at the α-carbon atom coupled with sulfur atom [18, 32, 42, 44, 45], is accompanied by a decrease in spin-spin coupling constants (SSCC) $^{1}J_{1,2}$, due to the reduction of the additional positive contribution of lone electron pair of the sulfur atom to the direct constant between the carbon nuclei. $^{1}J_{2,3}$ and $^{3}J_{2,5}$ SSCC are changed in a similar manner (with an increase in the

Table 6.9 Experimental values of ^{13}C–^{13}C spin-spin coupling constants in the benzene ring of organyl phenyl sulfides [45]

Structure	^{13}C-^{13}C spin-spin coupling constants, J, Hz				
	$^1J_{1,2} = {}^1J_{1,6}$	$^1J_{2,3} = {}^1J_{5,6}$	$^1J_{3,4} = {}^1J_{4,5}$	$^3J_{1,4}$	$^3J_{3,6} = {}^3J_{2,5}$
PhSMe	59.8	56.5	56.0	9.7	8.7
PhSEt	59.5	56.2	56.0	9.7	
$PhSPr^n$	59.6		56.0	9.9	
$PhSPr^i$	59.2	55.5	56.0	9.8	8.4
$PhSBu^n$	59.6		55.9	9.8	
$PhSBu^s$	59.3			9.7	9.0
$PhSBu^t$	58.6	54.0		10.1	8.1
$PhSCH_2CH = CH_2$	59.7		56.5		
$PhSCH = CH_2$	60.0	55.7	56.1		
$PhSC_6H_{11}$-*cyclo*	59.8			10.4	7.7
PhSPh	59.9		55.8	9.8	8.4
$PhSCH_2CH_2Br$	59.6		56.5	9.7	8.5

effective volume of the alkyl substituent), while $^3J_{1,4}$ remains constant and $^3J_{1,4}$ gradually augments.

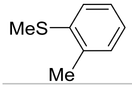
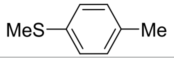
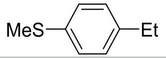
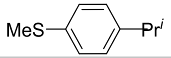
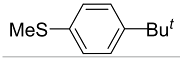
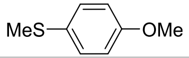
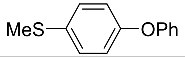
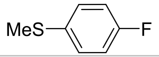
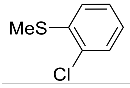
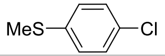
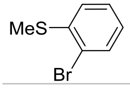
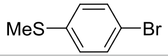
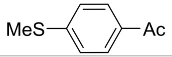
The data on ^{13}C–^{13}C SSCC of aromatic compounds are abundant in literature [46–48]. The additivity of the substituent effect on ^{13}C–^{13}C SSCC in aromatic sulfides is studied in [49] using a statistically representative series of compounds. The direct ^{13}C–^{13}C SSCC of substituted aromatic sulfides are calculated from the values of the corresponding constants of monosubstituted benzenes [46, 47] and methyl phenyl sulfides [45] and the direct ^{13}C–^{13}C constant in unsubstituted benzene ($^1J = 55.95$ Hz [50]).

Table 6.10 shows experimental values of the direct carbon–carbon constants and their deviations from those calculated according to the proposed additive scheme for 13 aryl methyl sulfides with different substituents in the benzene ring. In some cases, the presence of a strong spin coupling between the interacting isotopes of the ^{13}C nucleus ($\Delta J < 1$ Hz) does not allow measuring some carbon–carbon constants due to the difficulty of observing the multiplet external components of the corresponding AB-system in the satellite spectrum.

From Table 6.10, it can be seen that the proposed additive scheme enables to predict the direct ^{13}C–^{13}C SSCC in aryl methyl sulfides with an accuracy of no less than ± 1 Hz regardless of the type of substituents in the benzene ring, except for specific intramolecular interaction of closely located substituents.

Thus, the additive schemes for SSCC calculation, widely employed in NMR [51–56], not only permit to address specific issues of complex spectra interpretation, but also allow to understand the nature of intramolecular interactions of substituents.

Table 6.10 ^{13}C–^{13}C spin-spin coupling constants in the benzene ring of aryl methyl sulfides[a, b]

Structure	$^1J_{1,2}$	$^1J_{1,6}$	$^1J_{2,3}$	$^1J_{3,4}$	$^1J_{4,5}$	$^1J_{5,6}$
	58.9 (–1.9)	61.8 (1.5)	58.4 (0.9)	56.7. (0.2)	[56.3]	56.3 (–0.5)
	60.6 (0.5)	60.6 (0.5)	57.5. (0.5)	57.3 (0.3)	57.3 (0.3)	57.5 (0.5)
	60.1 (0.3)	60.1 (0.3)	56.5 (–0.5)	57.4 (0.3)	57.3 (0.3)	56.5 (–0.5)
	60.0 (0.2)	60.0 (0.2)	[57.1]	57.7 (0.3)	57.7 (0.3)	[57.1]
	60.2 (0.6)	60.2 (0.6)	[57.2]	58.4 (0.5)	58.4 (0.5)	[57.2]
	60.0	60.0	59.1. (0.9)	67.8 (0.7)	67.8 (0.7)	59.1 (0.9)
	60.3 (0.4)	60.3 (0.4)	57.5 (–0.2)	68.4 (0.5)	68.4. (0.5)	57.5 (–0.2)
	60.3 (0.3)	60.3 (0.3)	[57.1]	71.6 (0.8)	71.6 (0.8)	[57.1]
	67.9 (–1.1)	60.1 (0.5)	66.0 (0.3)	55.5 (–0.3)	[56.1]	[56.6]
	60.4 (0.5)	60.4 (0.5)	[56.3]	[65.2]	[65.2]	[56.3]
	66.8 (–0.7)	59.8 (1.1)	65.1 (0.9)	55.6 (0.7)	56.7 (0.6)	56.7 (0.1)
	60.7 (0.8)	60.7 (0.8)	56.4 (1.0)	64.3 (0.6)	64.3 (0.6)	56.4 (1.0)
	59.1 (0.1)	59.1 (0.1)	57.2 (0.3)	58.2 (0.4)	58.2 (0.4)	57.2 (0.3)

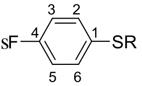
[a] In parentheses, the deviations of the experimental values of $^{1}\boldsymbol{J}_{i,j}$ constants from those calculated by the additive scheme are given; [b] in square brackets, the values of constants calculated according to the additive scheme are given

6.1.4 ^{1}H, ^{13}C, ^{19}F NMR Spectra of Organyl 4-Fluorophenyl Sulfides

A structural feature of organyl 4-fluorophenyl sulfides is the presence of two, capable of conjugation, heteroatoms (S and F) at the unsaturated fragment. Analysis of the ^{1}H, ^{13}C, and ^{19}F NMR spectra of a large series of organyl-4-fluorophenylsulfides allows obtaining additional data on the electronic and spatial structure of these compounds [27, 57, 58].

The shielding of C^1 carbon atoms bonded with the SR group (Table 6.11) is determined by at least three factors: inductive, resonant, and steric. The relative role of each of these effects on the carbon chemical shift is difficult to estimate because

Table 6.11 The ^{1}H and ^{13}C NMR chemical shifts of 4-fluorophenyl organyl sulfides



Structure	Chemical shifts, δ, ppm						Spin-spin coupling constants, J_{CF}, Hz			
	^{1}H NMR		^{13}C NMR							
	$H^{2(6)}$	$H^{3(5)}$	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	C^1-F	$C^{2(6)}$-F	$C^{3(5)}$-F	C^4-F
1	2	3	4	5	6	7	8	9	10	11
4-FC_6H_4SMe	7.11	6.86	133.94	128.88	115.85	161.00	2.8	7.6	21.7	243.8
4-FC_6H_4SEt	7.23	6.87	132.07	131.84	115.84	161.58	3.0	7.8	21.8	245.3
4-$FC_6H_4SPr^n$	7.21	6.84	132.32	131.87	115.82	161.56	3.6	7.9	21.8	245.6
4-$FC_6H_4SPr^i$	7.29	6.88	130.71	134.83	115.66	162.07	3.4	8.1	21.9	247.0
4-$FC_6H_4SBu^n$	7.21	6.85	132.43	131.68	115.79	161.51	3.3	7.5	21.8	245.5
4-$FC_6H_4SBu^i$	7.20	6.83	132.64	131.68	115.73	161.35	3.3	8.0	22.0	245.7
4-$FC_6H_4SBu^t$	7.42	6.90	128.30	139.18	115.27	163.06	3.3	8.5	21.6	249.1
4-$FC_6H_4SAm^n$	7.20	6.84	132.43	131.64	115.76	161.47	3.5	8.1	22.4	246.0
4-$FC_6H_4SAm^i$	7.21	6.85	132.28	131.46	115.70	161.34	3.4	7.7	21.7	245.4
4-$FC_6H_4SC_6H^n_{13}$	7.20	6.84	132.40	131.66	115.73	161.47	3.5	7.5	21.8	245.7
4-$FC_6H_4SC_7H^n_{15}$	7.20	6.84	132.46	131.61	115.75	161.41	3.4	8.0	21.5	245.9
4-$FC_6H_4SC_8H^n_{17}$	7.20	6.84	132.40	131.59	115.71	161.42	3.4	7.8	21.7	246.4
4-$FC_6H_4SC_9H^n_{19}$	7.20	6.84	132.39	131.63	115.70	161.43	3.2	7.8	21.6	246.0
4-$FC_6H_4SC_6H_{11}$-*cyclo*	7.29	6.86	130.33	134.87	115.59	162.06	3.5	8.0	21.4	246.8
4-$FC_6H_4SCH = CH_2$	7.26	6.91	128.98	133.07	116.15	162.13	3.3	8.1	21.7	247.8
4-$FC_6H_4SCH_2CH = CH_2$	7.25	6.86	131.0	132.73	115.70	161.66	3.4	8.0	21.9	246.2
4-$FC_6H_4SCH_2CH_2OH$	7.25	6.86	130.88	132.25	116.08	161.69	3.2	8.3	21.8	246.0
4-$FC_6H_4SCH_2CH_2Cl$	7.30	6.90ara>	129.49	133.31	116.17	162.02	3.2	7.9	22.0	247.3
4-$FC_6H_4SCH_2CH_2Br$	7.28	6.90	129.10	133.21	116.06	161.85	2.9	8.0	21.7	247.2

(continued)

Table 6.11 (continued)

Structure	Chemical shifts, δ, ppm						Spin-spin coupling constants, J_{CF}, Hz			
	^{1}H NMR		^{13}C NMR							
	$H^{2(6)}$	$H^{3(5)}$	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	C^1-F	$C^{2(6)}$-F	$C^{3(5)}$-F	C^4-F
1	2	3	4	5	6	7	8	9	10	11
4-$FC_6H_4SCH_2CH_2CN$	7.35	6.94	129.05	133.65	116.41	162.18	3.2	8.0	21.8	246.7
4-FC_6H_4SPh	7.20	6.80	130.14	133.89	116.14	162.01	3.1	7.8	21.7	247.8
4-$FC_6H_4SCH_2Ph$	6.98	6.73	130.82	132.77	115.47	161.75	3.5	7.8	21.8	247.1
4-$FC_6H_4SCH = CHPh$-*cis*	7.30	6.82	130.06	131.89	116.05	161.78	3.5	7.9	22.3	247.1
4-$FC_6H_4SCH = CHPh$-*trans*	7.30	6.82	130.02	131.99	116.05	161.78	3.6	7.9	22.3	247.1
(4-$FC_6H_4S)_2CH_2$	7.30	6.88	129.88	133.48	115.96	162.14	3.4	8.2	22.1	247.7
(4-$FC_6H_4SCH_2)_2$	7.23	6.91	129.98	132.72	115.80		3.8	8.1	21.6	
4-$FC_6H_4SCH_2NEt_2$	7.36	6.86	132.32	131.87	115.82	161.56	3.6	7.9	21.8	245.6
4-FC_6H_4SAc			123.78	136.59	116.27	163.26	3.5	8.6	22.2	249.2
4-$FC_6H_4SC(O)CH_2Cl$			122.03	136.69	116.56	163.49	3.3	8.8	22.2	250.2
4-$FC_6H_4SC(O)CCl_3$			120.95	136.44	116.61	163.54	3.5	8.6	22.3	252.2
4-$FC_6H_4SC(O)Ph$			123.25	137.21	116.34		3.6	8.4	21.5	

this atom is located close to the variable substituent. It should only be noted that an increase in the electron-donating ability of alkyls enhances the shielding of ^{1}C atoms: replacement of the methyl group with the *tert*-butyl one shifts C^1 signal to a strong field by 5.64 ppm.

The change in $C^{3(5)}$ chemical shifts in the studied series of organyl 4-fluorophenyl sulfides has a similar character, but their range is much smaller. The $C^{2(6)}$ chemical shifts are very sensitive to the variation of the substituent ($\Delta\delta C^{2(6)} = 10.30$ ppm), but the character of their changes is opposite to those expected from the induction effect of alkyl groups. Section 6.1.2 shows that changes in shielding of $C^{2(6)}$ in alkyl aryl sulfides are determined by two main factors: direct steric effects of the thioalkyl substituent and the 3*p*–π-hindrances, enhancing in the series Me → Et → *i*-Pr → *t*-Bu, to the conjugation of the sulfur atom with the benzene ring [18]. Since both effects are controlled by the steric parameters of the alkyl group, the dependence of $C^{2(6)}$ chemical shifts on $E_s^o(CH_2R)$ isosteric constants, approximately reflecting the spatial characteristics of the alkyl group, provides a quantitative estimation of the contribution of both mechanisms to the $C^{2(6)}$ shielding:

$$\delta C^{2(6)} = 128.2 - (5.8 \pm 0.3)E_s^o(CH_2R); r = 0.992, s_o = 0.43.$$

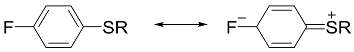
Good correlation between $\delta C^{2(6)}$ and steric constants of the alkyl substituents is not observed:

$$\delta C^{2(6)} = 129.5 - (4.3 \pm 0.8)E_s^o(R); r = 0.906, s_o = 1.43.$$

The ^{1}H NMR chemical shifts of $H^{2(6)}$ also expectedly augment as the branching of substituents increases (Table 6.11).

The most reliable information on the redistribution of π-electron density in the studied compounds has been obtained by analyzing the changes in $^{13}C^4$ and ^{19}F chemical shifts.

The C^4 atom in 4-FC_6H_4SMe (161.00 ppm) is shielded slightly stronger than in fluorobenzene (163.3 ppm) [59] due to the donor 3*p*–π-conjugation of sulfur with the benzene ring.



Unlike $C^{2(6)}$ carbons, C^4 atoms are not directly affected by the steric effects of the SR group. Therefore, a decrease in shielding of their nuclei in the studied series of compounds (Table 6.11) is associated only with the violation of ***p***–π-coplanarity and, hence, 3***p***–π-conjugation.

Steric inhibition of resonance in 4-fluorophenylsulfides is slightly less ($\Delta\boldsymbol{\delta}C^4 = 2.06$ ppm) than in the unsubstituted sulfides ($\Delta\boldsymbol{\delta}C^4 = 3.61$ ppm) owing to the ability of the fluorine atom to undergo a competitive resonance ($\sigma_{\mathbf{F}}^{\mathbf{o}} = -0.32$ [59]). In addition, it is possible that redistribution of the charge between C and F atoms somewhat “levels” the changes in shielding of C^4 carbon atom. The shielding of C^4 nuclei in the series Me → Et → ***i***-Pr → ***t***-Bu decreases gradually. The C^4

chemical shift in $FC_6H_4SBu^t$ (163.06 ppm) is almost the same as the chemical shift in C_6H_5F (163.3 ppm).

Thus, the values and nature of changes in C^4 chemical shift leave no doubt that in 4-FC_6H_4SR an increase in the volume of alkyl substituents leads to steric inhibition of the *p*–π-conjugation of the sulfur atom with the benzene ring. The dependence of C^4 chemical shift on steric constants $E_s^o(CH_2R)$ allows the contribution of resonance steric inhibition to the shielding of carbon nuclei to be evaluated:

$$\delta C^4 = 160.8 - (1.2 \pm 0.1)E_s^o(CH_2R), r = 0.990, s_o = 0.09, n = 10.$$

With steric constants of the alkyl substituents, the correlation is much worse:

$$\delta C^4 = 161.1 - (0.8 \pm 0.2)E_s^o(R), r = 0.875, s_o = 0.33, n = 12.$$

To estimate the effect of structural factors of the electron-withdrawing substituent R on intensity of intramolecular interaction between the R group and other fragment of the aromatic system, the values of $C^{2(6)}$ and C^4 chemical shifts are compared with the substituent constants. The obtained correlation dependences show that in sulfides 4-FC_6H_4SR (R is the electron-withdrawing substituent) the substituents effects are satisfactorily described by the induction effect [1]:

$$\delta C^{2(6)} = 132.15 + 2.59\sigma*, r = 0.970, s_o = 0.33, n = 9;$$

$$\delta C^4 = 161.54 + 1.01\sigma*, r = 0.976, s_o = 0.11, n = 9.$$

The SSCC values between C and F nuclei (J_{C-F}) naturally decrease with an increase in the number of bonds between the interacting nuclei. For the studied compounds, SSCC through two, three, and four bonds ($C^{3(5)}$–F, $C^{2(6)}$–F, C^1–F) slightly change (Tables 6.11 and 6.12). The H^2–H^3, H^2–F, and H^3–F SSCC are 8.5 ± 0.2, 5.3 ± 0.2, and 8.4 ± 0.2 Hz, respectively.

Theoretical concepts on the nature of SSCC for fluorine are less developed than for protons, mainly due to the complexity of electron configuration of the fluorine atom [61].

It has been reported [62] that if the spin-spin coupling between the nuclei of directly bound atoms is determined mainly by the Fermi contact interaction, then SSCC values are proportional to the contribution of *s*-character of the chemical bond. The calculation of $J_{F\text{-}F}$ and $J_{H\text{-}F}$ constants for a number of fluorine-containing compounds shows that, although spin-orbital coupling makes some contribution, the contact Fermi interaction has a decisive role for the constant [60]. If this is also true for the C–F constant in fluorobenzenes, then it should be expected that SSCC of C^4–F in the studied compounds will also depend on *s*-character of the bond between the C^4 and F atoms, which, according to the conclusions made from the analysis of ^{19}F chemical shifts, should change significantly depending on the steric effect of SR substituent. Indeed, with an increase in the branching of the alkyl and, consequently, with a decrease in the *p*–π-conjugation between the sulfur atom and

Table 6.12 The ^{19}F NMR spectra of 4-fluorophenyl organyl sulfides

No.	Structure	Chemical shifts, δ, ppm		Spin-spin coupling constants, J_{HF}, Hz		Constants of substituents [60]	
		δ ^{19}F	$\Delta\delta$ ^{19}F^{a}	$^{3}J^{3}_{H\text{-}F}$	$^{4}J^{2}_{H\text{-}F}$	Field (F)	Resonance (R)
1	2	3	4	5	6	7	8
1	4-FC$_6$H$_4$SMe	45.09	4.30	8.4	5.4	–0.04	–0.13
2	4-FC$_6$H$_4$SEt	46.36	3.03	8.25	5.3	–0.05	–0.10
3	4-FC$_6$H$_4$SPr^{n}	46.23	3.16	8.25	5.25	–0.06	–0.08
4	4-FC$_6$H$_4$SPr^{i}	47.59	1.80	8.5	5.4		
5	4-FC$_6$H$_4$SBu^{n}	46.17	3.22	8.25	5.15		
6	4-FC$_6$H$_4$SBu^{i}	46.11	3.28	8.3	5.4		
7	4-FC$_6$H$_4$SBu^{t}	49.44	0.05	8.5	5.6		
8	4-FC$_6$H$_4$SAm^{n}	46.17	3.22	8.15	5.2		
9	4-FC$_6$H$_4$SAm^{i}	46.18	3.21	8.25	5.26		
10	4-FC$_6$H$_4$SC$_6$H$^{n}_{13}$	46.17	3.22	8.25	5.3		
11	4-FC$_6$H$_4$SC$_7$H$^{n}_{15}$	46.16	3.23	8.4	5.15		
12	4-FC$_6$H$_4$SC$_8$H$^{n}_{17}$	46.16	3.23	8.15	5.3		
13	4-FC$_6$H$_4$SC$_9$H$^{n}_{19}$	46.16	3.23	8.3	5.2		
14	4-FC$_6$H$_4$SC$_6$H$_{11}$-*cyclo*	47.40	1.99	8.4	5.15		
15	4-FC$_6$H$_4$SCH = CH$_2$	48.24	1.15	8.3	5.4	0.07	–0.08
16	4-FC$_6$H$_4$SCH$_2$CH = CH$_2$	47.08	2.31	8.4	5.3		
17	4-FC$_6$H$_4$SCH$_2$CH$_2$OH	47.32	2.07	8.4	5.2		
18	4-FC$_6$H$_4$SCH$_2$CH$_2$Cl	48.34	1.05	8.4	5.2		
19	4-FC$_6$H$_4$SCH$_2$CH$_2$Br	48.43	0.96	8.4	5.1		
20	4-FC$_6$H$_4$SCH$_2$CH$_2$CN	48.91	0.48	8.2	5.2		
21	4-FC$_6$H$_4$SPh	48.23	1.16	8.4	5.3	0.08	–0.08
22	4-FC$_6$H$_4$SCH$_2$Ph	47.40	1.99	8.2	5.3	–0.08	–0.01
23	4-FC$_6$H$_4$SCH = CHPh-*cis*	47.90	1.49	8.2	5.2	0.06	–0.12
24	4-FC$_6$H$_4$SCH = CHPh-*trans*	48.18	1.21	8.5	5.2		
25	(4-FC$_6$H$_4$S)$_2$CH$_2$	48.66	0.73	8.3	5.1		
26	(4-FC$_6$H$_4$SCH$_2$)$_2$	47.72	1.67	8.2	5.1		
27	4-FC$_6$H$_4$SCH$_2$NEt$_2$	46.88	2.51	8.4	5.3		
28	4-FC$_6$H$_4$SAc	50.90	–1.51	8.5	5.5	0.32	0.20
29	4-FC$_6$H$_4$SC(O)CH$_2$Cl	51.85	–2.46	8.1	5.2		
30	4-FC$_6$H$_4$SC(O)CCl$_3$	53.24	–3.85	8.1	5.1		
31	4-FC$_6$H$_4$SC(O)Ph	50.94	–1.55	8.4	5.2	0.30	0.16

[a] Relative to C$_6$H$_5$F (δ 49.39 ppm)

the benzene ring, SSCC of C^4–F augments (Table 6.11). This indicates an increase in the *s*-character of the C^4−F bond.

With the violation of the 3*p*–π-conjugation, C^4–F SSCC increases and, starting with R = *n*-Pr, $^{1}J^{4}_{C-F}$ values are slightly higher than in FC_6H_5 (245.3 Hz [63]). This is considered as an argument in favor of the significance of induction and/or *d*-orbital interaction in fluorophenyl sulfides [57].

For oxygen analogs, in molecules of which the RO substituent is characterized by stronger, compared to RS, π-donating properties, $J^{4}_{C\text{-}F}$ is much lower (for 4-fluoroanisole, it is 237 Hz [61]).

In organyl 4-fluorophenyl sulfide, $^{1}J^{4}_{C\text{-}F}$ varies linearly with $^{13}C^4$ and ^{19}F chemical shifts:

$$\delta\left(^{13}\mathrm{C}^4\right) = 64.7 + 0.4J^4_{\mathrm{C}} - \mathrm{F}, r = 0.93, s_o = 0.2, n = 29;$$

$$\delta\left(^{13}\mathrm{F}\right) = 207.2 + 0.8J^4_{\mathrm{C}} - \mathrm{F}, r = 0.95, \mathrm{s_o} = 0.3, \mathrm{n} = 29.$$

This confirms that the changes in C^4 and ^{19}F chemical shifts and C^4–F SSCC are due to a single mechanism of interaction of substituents in the molecules of the compounds studied.

The remoteness of the fluorine atom from the organylthio group creates additional possibilities for studying the nature of the electron interaction of sulfur with the benzene ring using the ^{19}F NMR technique. This method has been widely used to evaluate the electronic effects of substituents in fluorobenzene derivatives owing to the high sensitivity of ^{19}F shielding to changes in polarity of the C−F σ-bond, π-charge on F atom, and order of the C−F π-bond [64].

Character of $\delta(^{19}F)$ change for a number of organyl 4-fluorophenyl sulfides indicates the predominance of the contribution of interaction between lone electron pair of a sulfur atom and π-electrons of the benzene ring. So, despite the fact that the alkylthio group in terms of its induction effect represents an electron-acceptor, the ^{19}F nuclei are more shielded in aromatic sulfides (Table 6.12, R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, *n*-Am, *i*-Am, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}, *n*-C_9H_{19}, *cyclo*-C_6H_{11}) than in the fluorobenzene molecule [$\delta(^{19}F)$ in fluorobenzene is taken as zero, therefore the signals lying in a strong field have positive values, while those in a weak field have negative values].

A decrease in the shielding of fluorine nuclei is associated with a decrease in 3*p*–π-conjugation. The ^{19}F chemical shift in 4-FC_6H_4SBu-*t* (–0.05 ppm) practically coincides with $\delta(^{19}F)$ in fluorobenzene.

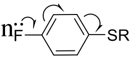
The dependence of ^{19}F chemical shift on the steric constants $E_s^o(CH_2R)$ allows estimating the contribution of steric inhibition of resonance in the shielding of fluorine nuclei:

$$\delta\left(^{19}\mathrm{F}\right) = 4.7 + (2.4 \pm 0.1)E^{\mathrm{o}}_{\mathrm{s}}(\mathrm{CH_2R}); r = 0.991; s = 0.19, n = 10.$$

Since the established effect of steric factors on the p–π-conjugation (steric inhibition of resonance [65]) is determined by the contribution of the entire alkylthio moiety, the correlation with steric constants of alkyl substituents is much worse:

$$\Delta\delta\left({}^{19}\mathrm{F}\right) = 4.1 + (1.8 \pm 0.4)E_{\mathrm{s}}^{\mathrm{o}}(\mathrm{R}), r = 0.891, s = 0.65, n = 12.$$

Obviously, the most significant violation of coplanarity should be expected in *tert*-butyl 4-fluorophenyl sulfide, for which the contribution of donor *p*–π-conjugation to ^{19}F shielding ceases to be noticeable.

In 4-FC$_6$H$_4$SR sulfides with electron-withdrawing substituents, the polar conjugation  acts in the same direction as the *d*–π-interaction and – *I*-substituent effect. Therefore, it can be assumed that the introduction of an electron-withdrawing substituent can enhance the *d*–π-interaction in the –C$_6$H$_4$S-fragment and, at the same time, decrease the π-electron density on fluorine atom.

To evaluate the dependence of acceptor interaction (conditionally *d*–π) in 4-FC$_6$H$_4$SR sulfides on the *I*-effect of the substituent, a series of aromatic sulfides with the maximum range of σ* values of the substituent R (Table 6.12) [66].

As can be seen from Table 6.12, δ(^{19}F) value monotonically increases upon transition from allyl to acyl 4-fluorophenyl sulfide. Since this is due to a decrease in the negative charge on the F atom, it can be assumed that the electron-withdrawing properties of the S atom enhance with the increase in the electron-withdrawing character of the substituent.

Figure 6.2 shows the correlation between difference in chemical shifts of ^{19}F NMR signals and Taft σ*-constants for substituents R with –*I* effects in 4-FC$_6$H$_4$SR sulfides. This straight line is described by the correlation equation:

$$\Delta\delta\left({}^{19}\mathrm{F}\right) = 2.28 - (2.30 \pm 0.01)\sigma*, r = 0.947, s = 0.35, n = 11.$$

The dots corresponding to sulfides, in the molecules of which can exist an acceptor interaction (*d*–π type) between vacant (nonbonding) orbitals of S atom and the π-electrons of the benzene ring, vinyl or carbonyl groups, fit well on the straight line describing the linear correlation between δ(^{19}F) molecules of 4-FC$_6$H$_4$SR series from σ*-constant of the acceptor substituent. This may mean that no other electronic effects, apart from induction one, are transmitted through the sulfur atom in the considered series.

This conclusion is confirmed by calculation of two-parameter dependence of δ(^{19}F) value on the field (*F*) and resonant (*R*) Sven–Lepton constant of substituent R [67] (Table 6.12):

$$\begin{aligned}\Delta\delta\left({}^{19}\mathrm{F}\right) &= -1.99 + (9.59 \pm 3.84)F + (3.81 \pm 4.72)R; R = 0.939, s_{\mathrm{o}}\\ &= 0.34, n = 9.\end{aligned}$$

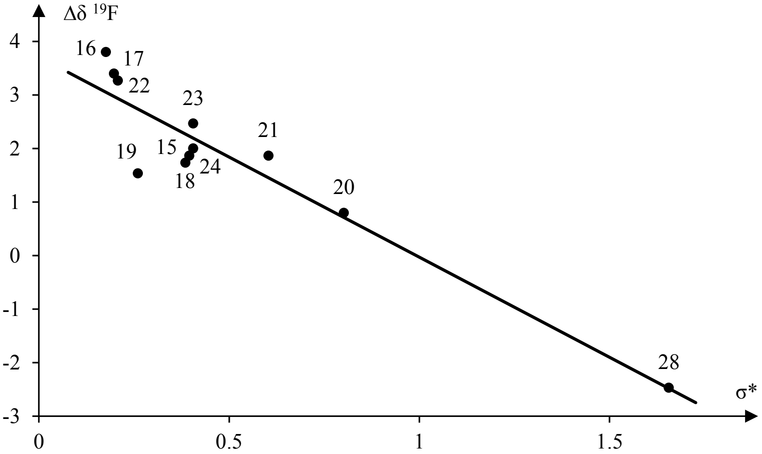


Fig. 6.2 Correlation between Δδ ^{19}F values and induction *-constants of electron-withdrawing substituents in 4-FC_6H_4SR (the numbering of compounds corresponds to Table 6.12)

The above equation indicates the statistical uncertainty of Δδ(^{19}F) sensitivity coefficients to structural effects *F* and *R*. However, the obtained correlation, although not completely statistically certain, may be due to the absence of a noticeable effect of the resonant effects of substituent R on ^{19}F shielding in the studied series of organyl fluorophenyl sulfides.

From the obtained data, it can be seen that the shielding of ^{19}F nuclei expectedly decreases with an increase in the electron-withdrawing ability of substituent R. At the same time, despite the large –*I*-effect of the considered substituents, ^{19}F nuclei in sulfides No. 16–25 (Table 6.12) are shielded significantly stronger than in fluorobenzene. The noticeable electron-donating character of the RS group (R is the electron-withdrawing substituent) is mainly owing to conjugation between the S atom and the benzene ring in the sulfides.

The measurement of ^{19}F chemical shifts in organyl 3-fluorobenzyl sulfides, 3-$FC_6H_4CH_2SR$, has shown that the effect of alkyl radicals on the ^{19}F shielding is very weak and is mainly determined by steric factors (R = *t*-Bu, *cyclo*-C_6H_{11}, Table 6.13). The δ(^{19}F) values in 3-fluorobenzyl thioacylates (R = Ac, $COCH_2Cl$, $COCl_3$) are low-field shifted by 0.5–1.2 ppm, which is probably due to the electron-withdrawing character of the acyl fragment.

Thus, the effect of the electron-withdrawing substituent at the sulfur atom on changes in chemical δ(^{19}F) shifts is inconsistent with the concept of *d*–π-conjugation in the ground electronic state of the studied aromatic sulfides.

Table 6.13 The ^{19}F NMR chemical shifts in 3-fluorobenzyl organyl sulfides

Structure	$\delta(^{19}F)^a$, ppm	Structure	$\delta(^{19}F)^a$, ppm
$3\text{-}FC_6H_4CH_2SMe$	–1.30	$3\text{-}FC_6H_4CH_2SC_6H_{11}$-*cyclo*	–0.90
$3\text{-}FC_6H_4CH_2SEt$	–1.30	$3\text{-}FC_6H_4CH_2SCH_2CH_2Cl$	–0.90
$3\text{-}FC_6H_4CH_2SPr$-*n*	–1.30	$3\text{-}FC_6H_4CH_2SCH_2CH_2OH$	–1.00
$3\text{-}FC_6H_4CH_2SPr$-*i*	–1.30	$3\text{-}FC_6H_4CH_2SCH_2CO_2H$	–1.10
$3\text{-}FC_6H_4CH_2SBu$-*t*	–1.50	$3\text{-}FC_6H_4CH_2SAc$	–0.80
$3\text{-}FC_6H_4CH_2Amr$-*n*	–1.30	$3\text{-}FC_6H_4CH_2SC(O)CH_2Cl$	–0.70
$3\text{-}FC_6H_4CH_2SCH_2Ph$	–1.20	$3\text{-}FC_6H_4CH_2SC(O)CCl_3$	–0.10

[a] Relative to C_6H_5F (δ 49.39 ppm)

6.1.5 NMR Spectra of Alkyl Aryl Sulfoxides

A priori, the methylsulfinyl group might be expected to show resonance properties, which is somewhat a blend of lone pair donation and *d*-orbital acceptance. On the basis of dipole moments [68], ^{19}F NMR [69], and pK_a values [4] however, the *d*-orbital acceptance properties are considered to be predominant. For methyl phenyl sulfoxide, like for alkyl phenyl sulfides, the shielding effects relative to benzene (128.7 ppm) are observed at the $C^{2(6)}$ and C^4 carbons (Table 6.14). The influence of fluorine substituents on the MeSO carbon chemical shift is negligible. This suggests a minor amount of conjugation between the phenyl ring and the sulfur atom [20]. The δ values of the benzene ring C^1 carbons depend on the steric influence of alkyl groups. When the branching of the alkyl substituent changes from Me to *t*-Bu, chemical shifts of C^1 carbon atoms decrease by 6.2 ppm.

The ^{13}C NMR spectra of typical representatives of the alkyl benzyl sulfoxides indicate that the benzene ring carbons exhibit nearly identical chemical shifts [1]. This evidences that there is no conjugation between the sulfur atom and the benzene ring.

The ^{33}S spectra of a very limited number of sulfoxides have been reported [7]. The literature data reveal significant differences, often due to the various experimental conditions used in the acquisition of the spectra and also to large errors in the case of broad signals, especially at low magnetic fields. The ^{33}S nucleus is significantly deshielded with respect to sulfides (δS −20 and −459 ppm for DMSO and dimethyl sulfide, respectively). The ^{33}S NMR chemical shifts of cyclic sulfoxides range from 32 to −213 ppm [38], and signals are significantly broader than in the corresponding sulfides. Evidently, when one sulfur lone pair is used to bond an oxygen atom, the electron density around the sulfur nucleus decreases, due to the electronegativity of the oxygen atom and a loss in symmetry of the electron distribution.

6.1.6 ^{13}C, ^{17}O and ^{33}S NMR Spectra of Alkyl Aryl Sulfones

Electro-optical studies (Kerr constants) of alkyl phenyl sulfones have shown that the optimal orientation of the aryl ring in aryl methyl sulfone [70, 71] and aryl *tert*-butyl sulfone [72] is a skewed one with the rotation angle of the C_{Ar}–S bond at Alk = Me ~ 58 ± 13°, and at Alk = *t*-Bu ~ 73 ± 13°. Photoelectron spectra also indicate that the alkyl substituents do not significantly affect the conformation of alkyl phenyl sulfones [73, 74].

In this sense, the ^{33}S NMR spectra of sulfones are of independent interest, though data on such spectra for organosulfur compounds are very scarce [7, 8] due to the low content of ^{33}S (0.76%) and the significant quadrupole moment of this nucleus ($-0.55 \cdot 10^{-28}$ cm^{2}) that causes weak sensitivity of ^{33}S NMR ~ $2 \cdot 10^{-3}$ relative to ^{1}H nuclei). The quadrupole moment of the ^{33}S nuclei leads to short times of the spin-lattice and spin-spin relaxation, which results in a strong broadening of the signal. However, in sulfones, due to the high symmetry of the electronic environment, the gradient of the electric field at ^{33}S nucleus decreases, the relaxation of ^{33}S nuclei becomes slower, and, consequently, the signal narrows. Therefore, modern pulsed spectrometers provide observation of the ^{33}S signals in sulfones at acceptable costs of instrument time.

The ^{13}C, ^{17}O, and ^{33}S NMR spectra of a series of alkyl aryl sulfones $RC_6H_4SO_2Alk$ (Alk = Me, Et, *i*-Pr, *t*-Bu; R = H, Cl) have been studied [36, 75]. The analysis of changes in shielding of all nuclei (^{13}C, ^{17}O, and ^{33}S) that constitute the skeleton of the molecule allows establishing the main trends in the influence of the alkyl group on electron density redistribution (Table 6.15). Of particular interest are the ^{33}S NMR spectra, which directly indicate shielding of sulfur nuclei (Table 6.15).

Table 6.14 The ^{13}C NMR chemical shifts of alkyl 4-fluorophenyl and alkyl benzyl sulfoxides

No.	Structure	Chemical shifts[a], δ, ppm ($J_{C\text{-}F}$, Hz)					
		C^{1}	$C^{2(6)}$	$C^{3(5)}$	C^{4}	CH_2	R
1	$4\text{-}FC_6H_4SOMe$	130.98	134.16 (8.0)	116.86 (22)	163.31 (245.61)		20.83
2	$4\text{-}FC_6H_4SOPr^{i}$	132.05	128.00	116.91	164.93 (248.12)		44.74 16.20
3	$4\text{-}FC_6H_4SOBu^{t}$	124.70	138.01 (8)	116.93 (22)			47.46 27.49
4	$PhCH_2SOMe$	131.06	129.31	129.98	129.20	58.70	29.78
5	$PhCH_2SOEt$	131.68	129.27	130.93	128.50	57.94	45.06 6.79
6	$PhCH_2SOPr^{i}$	130.14	130.85	130.85	128.39	55.60	44.66 16.82
7	$PhCH_2SOBu^{t}$	134.19	129.17	130.95	128.23	53.34	53.66 23.02

[a] Relative to Me_4Si

Table 6.15 The ^{13}C, ^{17}O, and ^{33}S NMR spectra of alkyl phenyl and alkyl 4-chlorophenyl sulfones

Structure	Chemical shifts, $\delta^{13}C$, ppm^a ($J_{C\text{-}F}$, Hz)					δ $^{17}O^b$ $(w_{1/2})^c$, ppm (Hz)	δ $^{33}S^d$ $(w_{1/2})^c$, ppm (Hz)
	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	Alk		
$PhSO_2Me$	140.89	126.96	129.42	133.61	43.61	155(630)	316 (210)
$PhSO_2Et$	138.47	128.02	129.60	133.98	49.74 7.22	143 (900)	324 (460)
$PhSO_2Pr^i$	136.99	128.72	129.33	133.72	54.52 15.22	133 (460)	333 (1100)
$PhSO_2Bu^t$	134.90	130.09	129.09	133.94	59.04 23.02	125 (1400)	330 (1500)
$4\text{-}ClC_6H_4SO_2Me$	139.49	128.95	129.81	140.41	44.50	156 (610)	313 (350)
$4\text{-}ClC_6H_4SO_2Et$	137.65	130.03	129.73	140.31	50.55 7.38	148 (1100)	324 (900)
$4\text{-}ClC_6H_4SO_2Pr^i$	136.00	130.70	129.58	140.34	55.63 15.67	136 (600)	336 (1000)
$4\text{-}ClC_6H_4SO_2Bu^t$	134.29	132.07	129.13	140.34	59.89 23.59	130 (1000)	342 (800)
$4\text{-}FC_6H_4SO_2Me$	138.49 (2.93)	131.19 (8.93)	117.11 (23.82)	166.23 (253.07)	44.40	154.5 (125)	316.4 (85)
$4\text{-}FC_6H_4SO_2Pr^n$	136.98 (2.93)	131.93 (10.42)	117.17 (23.82)	166.35 (253.07)	58.01 17.28 13.02	145.3 (200) 146.4	324.7 (150)
$4\text{-}FC_6H_4SO_2Pr^i$	134.71 (2.93)	132.81 (8.93)	117.11 (22.33)	166.46 (253.07)	55.82 15.83	133.4 (170)	333.3 (180)
$4\text{-}FC_6H_4SO_2Bu^i$	137.90 (2.98)	131.66 (10.42)	117.14 (22.33)	166.29 (253.07)	63.83 24.82 22.69	145.5 (200)	322.5 (160)
$4\text{-}FC_6H_4SO_2Bu^t$	132.81 (2.93)	134.14 (8.93)	116.84 (23.82)	166.52 (254.56)	60.08 23.66	126.7 (180)	339.7(200)

[a] Relative to Me_4Si; [b] Relative to H_2O; [c] Line width of signal at half-weight; [d] Relative to CS_2

As follows from Table 6.15, the alkyl substituents deshield ^{33}S nuclei in alkyl aryl sulfones in the series Me < Et < i-Pr < t-Bu. A similar effect of the alkyl substituents on the shielding of the nuclei is observed for dialkyl ethers [76], sulfones [77, 78], selenides [78], and tellurides [79]. Apparently, an increase in the steric parameters of alkyl groups worsens the spherical symmetry of the electron shell of SO_2 atoms, which, due to the growth of the paramagnetic contribution, leads to shielding of SO_2 nuclei (comparison with chemical shifts reported to the SO_4^{2-} signal may be made using the equation $\delta_S(Na_2SO_4) = \delta_S(CS_2) - 332$).

The influence of the alkyl groups alternates along a chain of atoms that form the skeleton of alkyl phenyl sulfone molecules. So, the shielding of ^{17}O nuclei of the SO_2 group and C^1 nuclei of the aromatic fragment, i.e., nuclei of atoms directly coupled with sulfur, increases symbatically with the deshielding of the ^{33}S nuclei (Fig. 6.3). In turn, the shielding of $C^{2(6)}$ nuclei occurs symbatically with an increase in the shielding of C^1 nuclei (Fig. 6.4). The shielding of $C^{3(5)}$ and C^4 nuclei changes

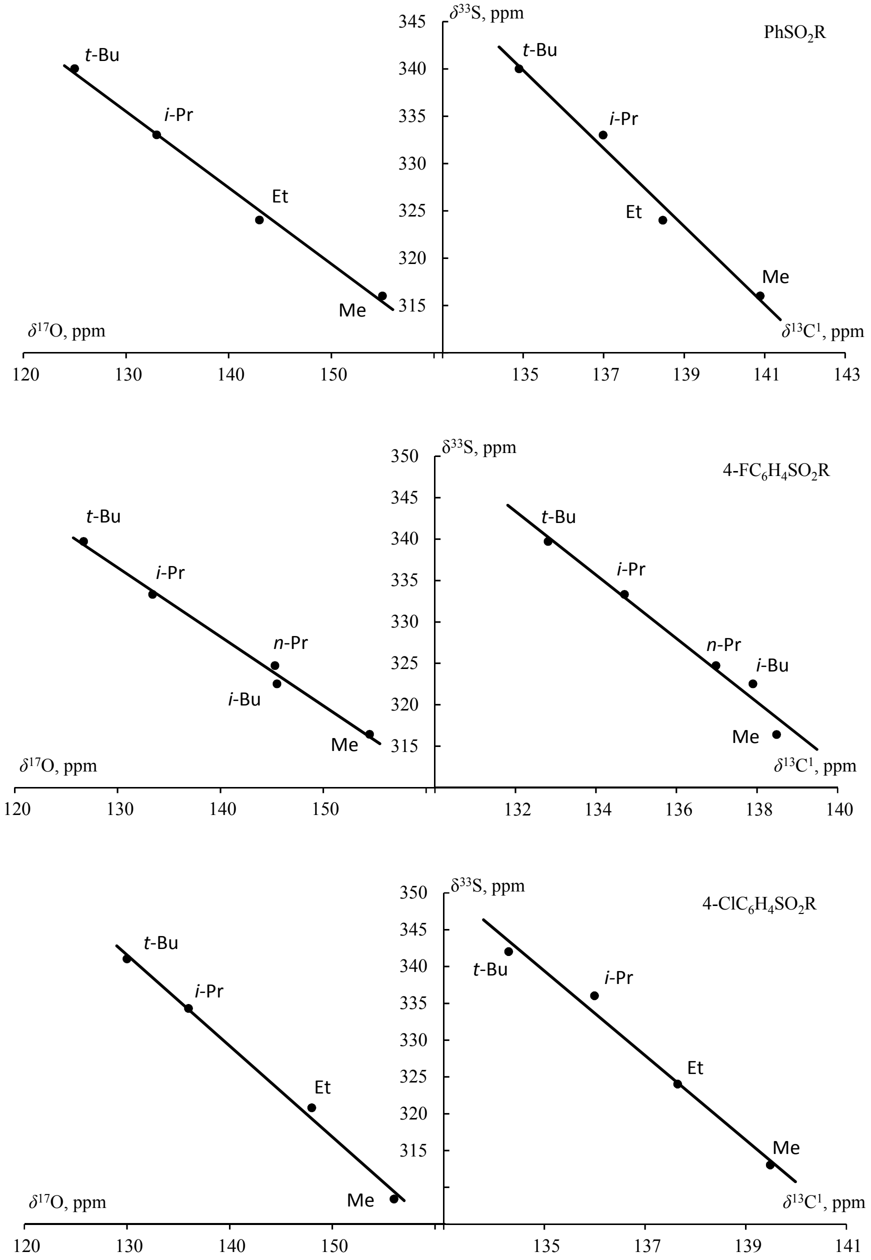


Fig. 6.3 Interrelation of chemical shifts $\delta(^{13}C^1)$, $\delta(^{17}O)$, and $\delta(^{33}S)$ in $PhSO_2Alk$, 4-$FC_6H_4SO_2Alk$, and 4-$ClC_6H_4SO_2Alk$

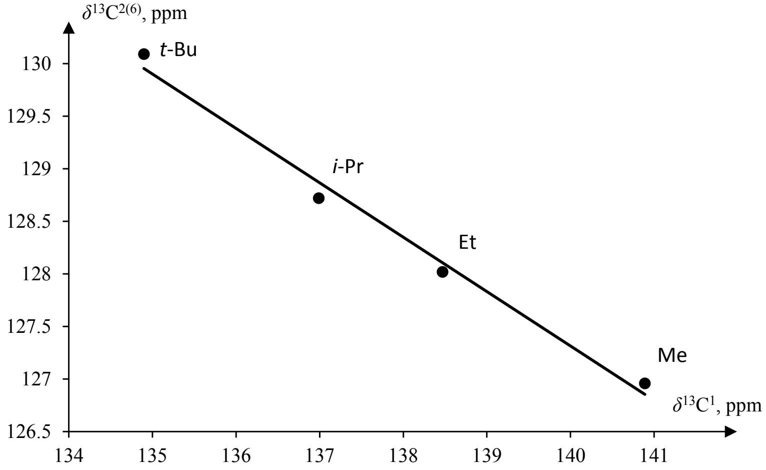


Fig. 6.4 Linear dependence of chemical shifts $\delta(^{13}C^1)$ and $\delta(^{13}C^{2(6)})$ in alkyl phenyl sulfones $PhSO_2A_{LK}$

slightly (Table 6.15). Thus, alkyl substituents in the series from Me to *t*-Bu in alkyl aryl sulfones are characterized by the alternating effect, which is damped along the chain and practically does not extend further to the 3(5) position. This effect is manifested in the deshielding of the odd atom nuclei and shielding of the even atom nuclei.

A similar alternating effect of the alkyl groups on chemical shifts of the aromatic fragment carbons is also observed in alkyl phenyl sulfides [80] (see Table 6.3 in Sect. 6.1.2). The ranges of $\delta(^{13}C^1)$ changes in alkyl phenyl sulfones (5.99 ppm) and alkyl phenyl sulfides (6.00 ppm) practically coincide. Significantly larger differences are found in the changes of $\delta(^{13}C^{2(6)})$ and $\delta(^{13}C^4)$ chemical shifts. The alterations in δC^4 in alkyl phenyl sulfides indicate a redistribution of electron density due to the violation of the *p*–π-conjugation of the sulfur atom with the aromatic ring owing to conformational factors [73, 80]. In sulfones, $\delta(^{13}C^4)$ values do not almost alter upon variation of the alkyl substituents (range of variation $\leq$ 0.32 ppm), which evidences the absence of a noticeable effect of electronic (induction and resonance) effects of alkyls on the charge distribution in the benzene ring [73].

If in sulfones, the range of $\delta(C^{2(6)})$ changes (3.13 ppm), as it was shown above, is affected only by the direct alternating effect of the alkyl substituents, in sulfides, an additional deshielding contribution of the substituents from Me to *t*-Bu appears, which is associated with the conformational violation of *p*–π-conjugation, and the range of $\delta(^{13}C^{2(6)})$ changes reaches 11.03 ppm. Since both effects are caused by one reason, i.e., the branching of the alkyl radical, and coincide in sign, there is a correlation between these values in the discussed series of sulfides and sulfones.

$$\delta C^{2(6)}_{SO_2} = (92.58 \pm 3.49) + (0.27 \pm 0.03)\delta C^{2(6)}_{S}, r = 0.99I, s = 0.22.$$

The range of $\delta(^{13}C^{3(5)})$ changes in $PhSO_2Alk$ (0.53 ppm) and PhSAlk (0.58 ppm) is almost the same.

Thus, in alkyl phenyl sulfones, changes in the shielding of ^{33}S, ^{17}O и ^{13}C nuclei are determined by the effect (alternating in sign and damping along the chain of atoms) of alkyl substituents from Me to *t*-Bu. In contrast to sulfones, in alkyl aryl sulfides, the shielding of $C^{2(6)}$ nuclei is affected by the additional violation of the *p*–π-interaction of lone electron pairs of the sulfur atom with the aromatic ring due to conformational changes, which is crucial for alternations in the shielding of C^4 nuclei.

In alkyl 4-chlorophenyl sulfones, $4\text{-ClC}_6H_4SO_2Alk$, the alkyl substituents in the series Me < Et < *i*-Pr < *t*-Bu deshield the ^{33}S nuclei, as well as the ^{13}C nuclei of the CH_2 group in isostructural alkylbenzenes, $PhCH_2Alk$. There is a good linear correlation between the chemical shifts of ^{33}S and $^{13}C(CH_2)$ (Fig. 6.5). The effect of alkyl groups on atomic nuclei directly coupled with them is steric in nature, since it depends only on the branching of alkyls at the C_α atom.

An increase in steric compression (repulsive interaction of an alkyl radical with a hydrogen atom in *ortho*-position of the phenyl moiety) of alkyl substituents in the series from Me to *t*-Bu onto S atom bonded with them apparently deforms the electron shell of the latter, which leads to deshielding owing to the shift of electron charge localization center.

Similar conclusions have been drawn from the analysis of the ^{13}C NMR spectra of alkyl-4-fluorophenylsulfones (see Table 6.15).

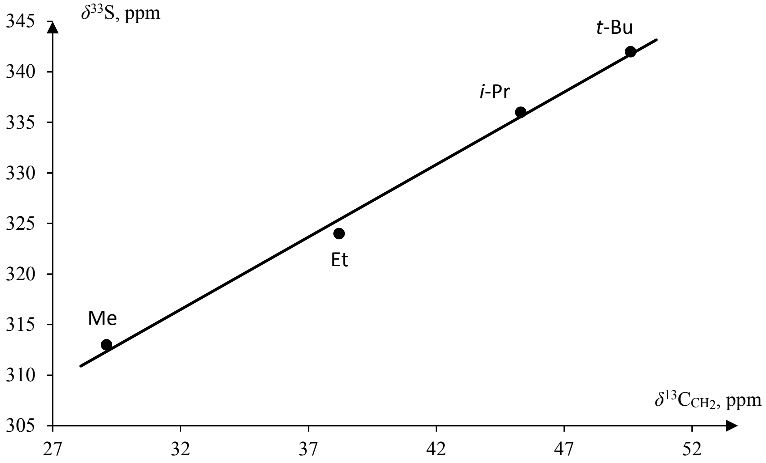


Fig. 6.5 Linear dependence of ^{33}S chemical shifts in $4\text{-ClC}_6H_4SO_2Alk$ and $^{13}C(CH_2)$ in $PhCH_2Alk$

Table 6.16 The ^{13}C NMR chemical shifts of alkyl benzyl sulfones

No.	Structure	Chemical shifts, δ^a, ppm ($J_{C\text{-}F}$, Hz)					
		C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	CH_2	R
1	$PhCH_2SO_2Me$	129.44	129.34	132.00	129.29	58.76	39.45
2	$PhCH_2SO_2Et$	130.01	129.31	131.71	129.15	58.62	46.41 6.58
3	$PhCH_2SO_2Pr^i$	129.74	129.26	131.84	129.09	56.14	52.31 15.52
4	$PhCH_2SO_2Bu^t$	129.17	128.99	132.33	128.90	52.69	59.83 23.74
5	$4\text{-}FC_6H_4CH_2H_4SO_2Me$	126.45	133.73 (8.93)	116.28 (22.33)	163.68 (245.63)	59.90	39.58
6	$4\text{-}FC_6H_4CH_2H_4SO_2Et$	126.04 (2.94)	133.73 (8.93)	116.13 (20.84)	163.62 (245.63)	57.53	46.44 6.57
7	$4\text{-}FC_6H_4CH_2H_4SO_2Pr^i$	125.74	133.88 (8.93)	116.10 (20.84)	163.59 (245.63)	54.99	52.42 15.47
8	$4\text{-}FC_6H_4CH_2H_4SO_2Bu^t$	125.27	134.35 (8.93)	115.86 (20.84)	163.65 (245.63)	51.65	59.65 23.72

^{a}Relative to Me_4Si

Table 6.16 shows the ^{13}C NMR chemical shifts of alkyl benzyl sulfones, which indicate that the introduction of a methylene spacer between SO_2R^2 and aromatic fragment prevents the conjugation of sulfogroup with the benzene ring. Structurally different alkyl groups in alkyl benzyl sulfones cause significantly smaller changes in the chemical shifts δ of the carbon atoms C^1, $C^{2(6)}$, and C^4 in the series of unsubstituted ($PhCH_2SO_2R$) and fluorine-substituted ($4\text{-}FC_6H_4CH_2SO_2R$) alkyl benzyl sulfones.

Comparison of the ^{13}C NMR spectra of methyl-, ethyl-, isopropyl-, and *tert*-butyl benzyl sulfones (Table 6.16, entries 1–4) with those of the corresponding alkyl 4-fluorobenzyl sulfones (Table 6.16, entries 5–8) reveals that fluorine atom in the benzene ring shields C^1 and $C^{3(5)}$ nuclei and deshields $C^{2(6)}$. The ^{13}C NMR chemical shifts of the CH_2 group in both series of sulfones decrease regularly, depending on the nature of the SO_2R radical in the order Me > Et > *i*-Pr > *t*-Bu.

A detailed analysis of the ^{13}C, ^{17}O, and ^{33}S NMR spectra of aryl methyl sulfones, $4\text{-}RC_6H_4SO_2Me$ (R = H, Me, MeO, Cl, Br, NO_2), is described (Table **6.16**) [81]. For comparison, the effect of substituents in the ring on the shielding of ^{13}C, ^{17}O, and ^{77}Se nuclei in isostructural series of aryl methyl ethers [44, 82, 83] and selenides [44, 84] is considered. For aryl methyl sulfides, sulfoxides, and sulfones, ^{13}C NMR spectra are studied [44, 85]. Due to the low sensitivity of the ^{33}S NMR method, it is impossible to detect the ^{33}S signals in alkyl aryl sulfides and sulfoxides.

The δC^1, δC^3, and δC^4 values of the aromatic ring atoms in $4\text{-}RC_6H_4SO_2Me$, presented in Table 6.16, correlate well with δ^{13}C of the corresponding atoms in monosubstituted benzenes (Table 6.18, Eqs. 1–3). Similar dependences are also established for aryl methyl ethers, sulfides, and selenides [44]. In the equations for

Table 6.17 The ^{13}C, ^{17}O, and ^{33}S NMR spectra of aryl methyl sulfones

Structure	^{13}C Chemical shift, δ^a, ppm					δ ^{17}O^b $(\nu_{1/2})^c$, ppm (Hz)	δ ^{33}S^d $(\nu_{1/2})^c$, ppm (Hz)
	C^1	C$^{2(6)}$	C$^{3(5)}$	C^4	Me		
4-$MeOC_6H_4SO_2Me$^{e}	132.69	129.61	115.05	163.60	44.41	160 (90)	306 (180)
4-$MeC_6H_4SO_2Me$^{f}	138.24	127.07	129.90	144.20	43.90	155 (740)	317 (530)
$PhSO_2Me$	140.89	126.96	129.42	133.61	43.61	155 (630)	316 (210)
4-$ClC_6H_4SO_2Me$	139.49	128.95	129.81	140.41	43.50	156 (610)	313 (350)
4-$BrC_6H_4SO_2Me$	140.08	129.06	132.47	127.73	43.53	156 (740)	312 (650)
4-$NO_2C_6H_4SO_2Me$	146.04	128.87	124.65	150.45	43.16	163 (840)	322 (160)

[a]Relative to Me_4Si; [b]Relative to H_2O; [c]Line width of signal at half-weight; [d]Relative to CS_2; [e]δ ^{13}C (MeO) 56.17 ppm; [f]δ^{13}C(Me) 21.11 ppm

δC^1, the coefficients a_1 are significantly different with good statistical parameters of the regression equations (see Table 6.18, Eqs. 3–7). In the ethers, the sensitivity of $\delta(^{13}C^1)$ to the effect of *para*-substituents is noticeably lower ($a_1 \approx 0.77$) than in monosubstituted benzenes. In sulfoxides ($a_1 \approx 1.10$) and sulfones ($a_1 \approx 0.90$), it is close to 1, while in sulfides ($a_1 \approx 1.46$) and selenides ($a_1 \approx 1.48$), it is much higher.

A similar dependence of changes in sensitivity of $\delta(^{13}C^1)$ on the effect of *para*-substituents is found for aryl vinyl ethers, sulfides, and selenides [86]. This is related to the general problem of the nonadditive influence of substituents on the chemical shifts of carbon nuclei in the aromatic ring of disubstituted benzenes (see, for example, [87]). The induction and resonance effects of 4-R substituents on chemical shift C^1 in the series of 4-RC_6H_4X compounds (X = H, OMe, SMe, S(O) Me, SO_2Me, and SeMe) can be estimated using regression equations of the type $\delta C^1 = \rho_o + \rho_I\sigma_I + \rho_R\sigma_R{}^o$ (Table 6.19). The sensitivity of δC^1 to the induction effect in the series of substituted benzenes, ethers, sulfoxides, and sulfones, taking into account the standard deviation of the coefficients ρ_I, is approximately the same. Chemical shifts in aromatic sulfides and selenides are more sensitive to the substituent effects. The resonance effect of 4-R on δC^1 at X = H, S(O), and SO_2 is also almost the same. However, as compared with monosubstituted benzene (R = H),

Table 6.18 Correlation dependences $\delta(^{13}C(X)) = a_o + a_1\delta(^{13}C(H))$ in compounds 4-RC_6H_4X (X = H, OMe, SMe, S(O)Me, SO_2Me, SeMe)

No. of equation	C atom	X	a_o	a_1	*r*	*s*
1	C^4	SO_2	8.91 ± 7.18	0.97 ± 0.05	0.994	0.51
2	C^3	SO_2	10.18 ± 0.98	0.93 ± 0.01	0.999	0.12
3	C^1	SO_2	26.02 ± 3.09	0.90 ± 0.02	0.999	0.26
4[a]	C^1	SO	4.79 ± 6.15	1.10 ± 0.05	0.996	0.52
5[b]	C^1	O	60.88 ± 4.72	0.77 ± 0.04	0.990	0.60
6[b]	C^1	S	–48.60 ± 7.31	1.46 ± 0.06	0.995	0.75
7[b]	C^1	Se	–56.29 ± 8.79	1.48 ± 0.07	0.992	1.08

[a]Calculated according to [85]; [b]Calculated according to [44]

Table 6.19 Correlation dependences $\delta C^1 = \rho_o + \rho_I\sigma_I + \rho_R\sigma_R^o$ in compounds 4-RC_6H_4X (X = H, OMe, SMe, S(O)Me, SO_2Me, or SeMe) [88]

No. of equation	X	ρ_o	ρ_I	ρ_R	r	s
1[a]	H	128.40 ± 0.57	5.74 ± 11.28	21.00 ± 1.70	0.992	0.78
2[b]	O	159.99 ± 0.15	4.57 ± 0.33	14.73 ± 0.44	0.999	0.20
3[b]	S	138.09 ± 0.20)	10.47 ± 0.44	26.87 ± 0.59	0.999	0.27
4[c]	SO	146.22 ± 0.37	7.21 ± 0.82	22.85 ± 1.10	0.997	0.50
5	SO_2	I40.66 ± 0.69	5.05 ± 1.55	18.68 ± 2.06	0.986	0.94
6[b]	Se	131.92 ± 0.24	11.03 ± 0.55	29.89 ± 0.73	0.999	0.33

[a]Calculated according to [83]; [b]Calculated according to [44]; [c]Calculated according to [85]

the resonance effect of 4-R substituents on δC^1 in ethers is noticeably weaker, and, on the contrary, in sulfides and selenides, it is stronger. The sequence of the increase in δC^1 sensitivity toward the induction and resonance effects of 4-R substituents in the series of ethers < sulfides < selenides corresponds to an increase in the polarizability of atoms in the sequence O < S < Se.

The values of δS chemical shifts in 4-$RC_6H_4SO_2Me$ indicate the growth of shielding in the case of electron-donating substituent 4-MeO and deshielding for electron-withdrawing group 4-NO_2. The δS values correlate with the induction and resonance constants of 4-R substituents:

$$\begin{aligned}\delta\left(^{33}\mathrm{S}\right) &= (317.80 \pm 1.25) + (0.12 \pm 2.19)\sigma_I + (25.33 \pm 3.87)\sigma_R^o; R\\ &= 0.967, s_o = 1.78, n = 6.\end{aligned}$$

Induction member in this dependency is insignificant. Changes in $\delta(^{33}S)$ can be described only by the resonant constants of the substituents, which reflects the participation of the SO_2 group in the resonant interaction with the aromatic ring:

$$\delta\left(^{33}\mathrm{S}\right) = (317.84 \pm 0.78) + (25.35 \pm 3.36)\sigma_R^o; R = 0.967, s_o = 1.54, n = 6.$$

In the corresponding dependences for oxygen atoms $\delta(^{17}O)$ in methyl aryl ethers (calculated according to [83]) and selenium atoms $\delta(^{77}Se)$ in methyl aryl selenides (calculated according to [84]), the induction member is determined statistically quite well.

$$\begin{aligned}\delta\left(^{17}\mathrm{O}\right) &= (150.76 \pm 1.20) + (16.89 \pm 2.66)\sigma_I + (30.48 \pm 3.07)\sigma_R^o; R\\ &= 0.979, s_o = 2.07, n = 11;\end{aligned}$$

$$\begin{aligned}\delta\left(^{77}\mathrm{Se}\right) &= (202.71 \pm 1.25) + (31.46 \pm 2.97)\sigma_I + (49.72 \pm 2.74)\sigma_R^o; R\\ &= 0.995, s_o = 1.96, n = 9.\end{aligned}$$

The δC^4 values of carbon atoms in monosubstituted benzenes adequately reflect the charge value on this atom. In the $PhSO_2Me$ molecule, δC^4 (133.61 ppm) is noticeably higher than δC in benzene (128.5 ppm), i.e., the SO_2 group acts as an acceptor relative to the aromatic ring. This is confirmed by the values of the Hammett ($\sigma = 0.68$) and resonance ($\sigma_R^o = 0.12$) constants of the SO_2Me group. X-ray emission spectroscopy has shown that vacant 3*d*-orbitals of S atom in sulfones participate in chemical bonding [89].

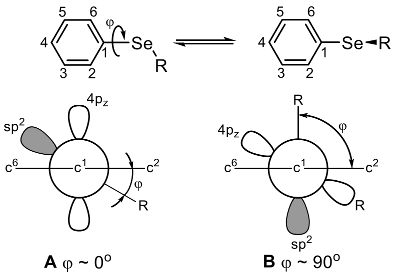
The ^{33}S and ^{17}O nuclei in $PhSO_2Me$ are considerably shielded compared to Me_2SO_2 [$\delta(^{33}S) = 323$ ppm, $\delta(^{17}O) = 164$ ppm]. This effect could be interpreted as an increase in the electron density on ^{33}S in unsaturated molecules due to the acceptor (3*d*–π type) interaction of the sulfur atom with the aromatic ring. It should be underlined that in the isostructural compounds containing CH_2 group or O atom, instead of SO_2 moiety, the substitution of Me by Ph does not shield, but, on the contrary, deshields ^{13}C and ^{17}O. Replacement of both Me groups in Me_2SO_2 with Ph leads to even greater shielding of ^{33}S (in $PhSO_2Ph$ $\delta(^{33}S) = 305$–312 ppm [90]), which is explained by conjugation of the vacant orbitals of S atom with an aromatic ring [77, 90].

However, such an interpretation ignores the fact that in ketones, as well as in sulfones, the replacement of the Me group by an aromatic ring enhances the shielding of ^{13}C and ^{17}O in carbonyl group (see, for example, [88, 91]). Apparently, the shielding of $\delta(^{33}S)$ and $\delta(^{17}O)$ of the SO_2 group in unsaturated sulfones compared to the saturated ones, as well as the shielding of $\delta(^{13}C)$ and $\delta(^{17}O)$ of the carbonyl group in the corresponding ketones, evidences the π-acceptor interaction of the $S = O$ or $C = O$ bonds with unsaturated fragments. The conjugation of nonbonding orbitals (conditionally, of 3*d*-type) of S atom in sulfones with unsaturated fragments is not excluded, but it is not mandatory for the explanation of the observed effect.

Thus, an analysis of the ^{13}C, ^{17}O, and ^{33}S NMR spectra testifies to a general acceptor character of the SO_2 group effect on unsaturated fragments. This effect can be rationalized without any ideas on the dominant role of 3*d*–π-conjugation.

6.1.7 Conjugation Effects and Conformational Structure in Aromatic Selenides

Aromatic selenides are characterized by a low energy barrier of rotation around the C_{Ar}–Se bond and constitute a convenient model for studying the electronic interaction of the Se atom with the aromatic π-system. The degree of this interaction is determined by a ratio of planar **A** and orthogonal **B** conformers (by analogy with ethers [92, 93] and sulfides [32, 40, 94, 95]).



The *p*–π-interaction is due to the orbital overlapping of unhybridized $4p_z$-lone pair of selenium and π-system of the aromatic ring, which is maximal in the planar conformer **A** and, for geometric reasons, is impossible in the orthogonal conformer **B**.

A shift of equilibrium toward the orthogonal conformer weakens the *p*–π-interaction. This is manifested in the deshielding of C^4 atom of the benzene ring [96]. This permits to evaluate the conformational equilibrium and degree of the *p*–π-interaction in the series of alkyl phenyl selenides [18]. Another NMR parameter, sensitive to the discussed interaction, is the one-bond ^{13}C–^{13}C coupling constant in the aromatic system. The decrease of this constant with an increase in the amount of conformer **B** is mainly owing to the “removal” of an additional positive contribution of sp^2-hybridized lone pair of the heteroatom to $^1J_{1,2}$ value [49].

Tables 6.20 and 6.21 show the data of the NMR spectra of some alkyl phenyl selenides. As seen from Table 6.20, the nature of the alkyl substituent insignificantly influences the chemical shifts of the benzene ring protons.

Figure 6.6 depicts the changes of the most informative (in terms of evaluation of *p*–π-interaction degree and conformational structure) NMR parameters, $\delta(^{13}C^4)$ and ^{13}C–^{13}C CCSS, for alkyl phenyl selenides, PhSeAlk (Alk = Me, Et, *i*-Pr, *t*-Bu) (Table 6.21), and for isologous series of ethers and sulfides [45, 51, 49].

Table 6.20 The ^1H NMR chemical shifts of alkyl phenyl selenides

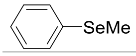
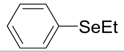
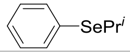
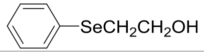
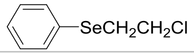
Structure	Chemical shifts, δ, ppm	
	Ph	R
	7.28–6.93	2.00 (Me)
	7.30–6.87	2.66 (CH_2), 1.12 (Me)
	7.33–6.97	3.22 (CH), 1.20 (Me_2)
	7.38–6.89	4.40 (OH), 3.58 (CH_2O), 2.82 (CH_2Se)
	7.04–6.60	3.49 (CH_2Cl), 3.00 (CH_2Se)

Table 6.21 The ^{13}C NMR spectra of alkyl phenyl selenides [97]

Structure	Chemical shifts, δ^{a}, ppm					^{13}C-^{13}C spin-spin coupling constants, J, Hz		
	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	R	$^1J_{1,2}$	$^1J_{2,3}$	$^1J_{3,4}$
PhSeMe	132.22	130.30	129.25	126.19	7.03 (Me)	58.3		56.3
PhSeEt	130.80	132.62	129.49	127.03	21.18 (CH_2), 15.72 (Me)	58.5	56.8	56.0
PhSePr^i	130.37	135.01	129.55	127.84	33.79 (CH), 24.39 (2Me)	58.1	54.8	55.7
PhSeBu^n	131.45	132.62	129.68	127.09	32.85(CH_2Se), 27.57 (CH_2), 23.38 (CH_2), 13.80 (Me)	58.4		55.3
PhSeBu^s	130.21	135.18	129.65	127.91	47.52 (CH), 30.94 (CH_2), 21.90 (Me), 12.48 (Me)	58.2	55.8	56.4
PhSeBu^t	128.90	138.71	129.37	127.53	42.93 (C), 32.34 (3Me)	57.8		55.6
$PhSeC_6H_{11}$-*cyclo*	130.04	134.96	129.49	127.72	43.24 (C^1), 34.74 ($C^{2(6)}$), 27.20 (C^4), 26.29 ($C^{3(5)}$)	58.1	54.8	56.0
$PhSeCH_2CH = CH_2$	130.56	133.23	129.34	127.29	30.54 (CH_2), 116.81 (CH_2 =), 134.93 (CH =)	58.6	54.9	55.7
$PhSeCH_2Ph$	131.14	133.15	129.32	127.29	32.00 (CH_2), 138.85 (C^1), 129.17 ($C^{3(5)}$), 128.65 ($C^{2(6)}$), 127.08 (C^4)	58.5		

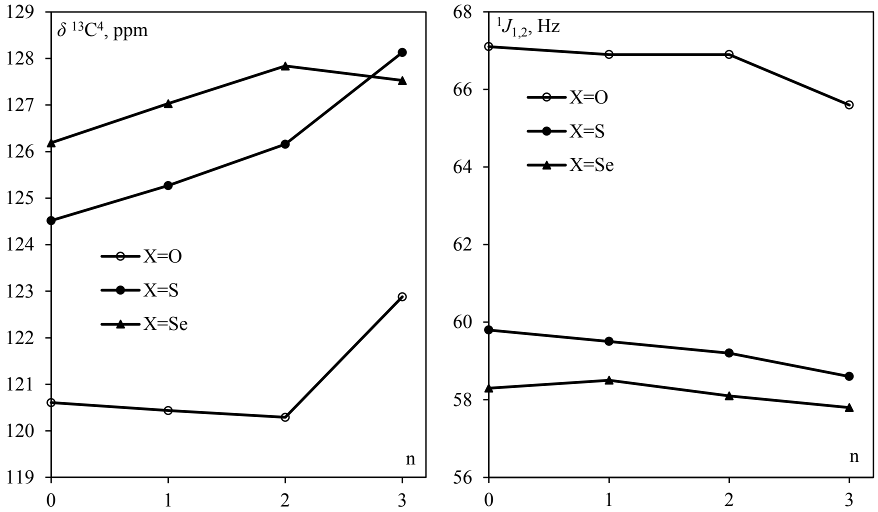


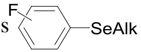
Fig. 6.6 Dependence of chemical shift $\delta(^{13}C^4)$ and ^{13}C–^{13}C SSCC ($^1J_{1,2}$) of alkyl phenyl ethers, sulfides, and selenides $PhXCMe_nH_{3-n}$ (X = O, S, Se) on the number of methyl groups at α-carbon atom of the alkyl group

As can be seen from the above data, in alkyl phenyl selenides, unlike the corresponding sulfides, there is no steric inhibition of conjugation (*p*–π-interaction) with an increase in the effective volume of the second substituent, which usually manifests itself in augmentation of chemical shift C^4 and a decrease in CCSS $^1J_{1,2}$. However, alkyl phenyl selenides (Table 6.21) are not conformationally homogeneous. A decrease in the ^{13}C–^{13}C constant ($^1J_{1,2}$) by 0.6–0.8 Hz with enhancing the branching of the α-carbon atom of the alkyl substituent in this series of compounds corresponds to an increase in the proportion of the orthogonal conformer by 40–50% [45].

The incomplete steric inhibition of conjugation in *tert*-butyl phenyl selenide is confirmed by the value of C^4 chemical shift (127.53 ppm), which corresponds to the shielding of the phenyl group C^4 atom by ~1 ppm relative to unsubstituted benzene. The weak π-donating properties of the Se atom with respect to the phenyl group in this selenide can be explained by quite high content (~30–50%) of the planar conformer A. In the corresponding sulfide *t*-BuSPh, the sulfur atom does not exhibit π-donating properties toward the aromatic ring, since $\delta(^{13}C^4)$ chemical shift is equal to 128.57 ppm, which indicates an ~100% content of the orthogonal conformer in this compound [32, 40, 45, 94, 95].

Table 6.22 demonstrates the parameters of the ^{13}C NMR spectra of some alkyl aryl selenides containing a substituent in the ring. The values of ^{13}C–^{13}C SSCC in the aromatic fragment, like in sulfides, are strictly additive (Fig. 6.7). The average deviation of the ^{13}C–^{13}C SSCC (calculated by the additive scheme) from the experimental values is less than 0.6 Hz. It points to the absence of noticeable conformational changes induced by the second substituent (F) in the benzene ring.

Table 6.22 The ^{13}C NMR spectra of alkyl aryl selenides



No.	Structure	^{13}C chemical shifts, δ, ppm (J_{CF}, Hz)						^{13}C-^{13}C spin-spin coupling constants, J, Hz					
		C^1	C^2	C^3	C^4	C^5	C^6	$^1J_{1,2}$	$^1J_{2,3}$	$^1J_{3,4}$	$^1J_{4,5}$	$^1J_{5,6}$	$^1J_{1,6}$
1	3-FC$_6$H$_4$SeMe	135.16 (6.4)	116.65 (21.0)	163.41 (247.6)	113.06 (23.0)	130.98 (7.3)	125.84 (0)		71.0	71.0			58.4
2	4-FC$_6$H$_4$SeMe	127.23 (2.6)	113.12 (7.3)	116.60 (21.6)	162.21 (244.5)	116.60 (21.6)	113.12 (7.3)	59.4	55.7	71.5	71.5	56.2	59.4
3	3-FC$_6$H$_4$SeEt	133.52 (8.0)	118.62 (20.9)	163.24 (249.0)	113.67 22.5)	130.87 (8.0)	127.75 (3.2)	60.7	70.9	70.9	56.8	55.7	58.5
4	4-FC$_6$H$_4$SeEt	125.39 (3.2)	134.49 (7.2)	116.45 (21.7)	162.57 (245.8)	116.45 (21.7)	134.49 (7.2)	59.0	55.7	71.3	71.3	55.7	59.0
5	4-FC$_6$H$_4$SePr^i	124.79 (0)	137.79 (8.0)	116.41 (20.9)	163.06 (247.4)	116.41 (20.9)	137.79 (8.0)	58.5	56.4	71.3	71.3	56.4	58.5

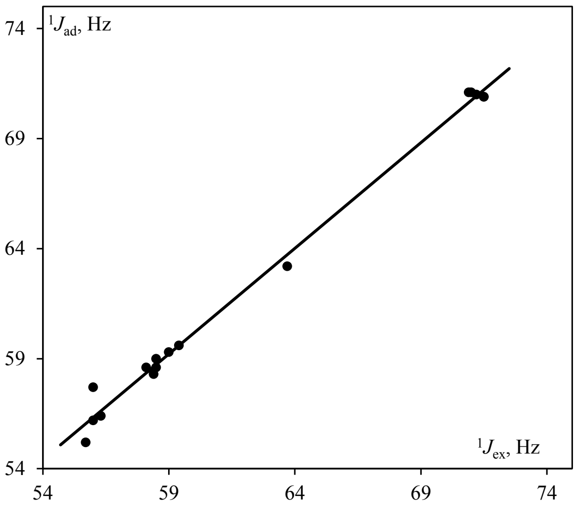


Fig. 6.7 Dependence of calculated additive $^1J_{ad}$ and experimental $^1J_{exp}$ values of ^{13}C–^{13}C SSCC in the benzene ring of alkyl aryl selenides

The potential functions of internal rotation around the Csp^2−Se bond in methyl phenyl selenide were obtained by quantum-chemical calculations in the HF/3-21G (*d*), HF/6-31G(*d*), MP2(*f*)/6-31G(*d*), and B3LYP/6-31G(*d*) approximations [98, 99]. The calculations were performed using variable torsion angle φ (between planes of the benzene ring and the Csp^2−Se−Csp^3 bonds) from 0° to 90° with 15° step. Ab initio quantum-chemical calculations indicate that the minimum of the potential function of internal rotation around the Csp^2−Se bond in the methyl phenyl selenide molecule is in the region of the orthogonal conformation, and the maximum is in the region of the planar form. The barrier to rotation around the Csp^2−Se bond, corrected for the zero-point energy, is estimated to be 10.25 and 6.41 kJ/mol (MP2(f)/6-31(d) and B3LYP/6- 31G(d) methods, respectively) [98]. This result disagrees with the experimental (electron diffraction) data on the methyl phenyl selenide conformation in the gas phase (φ 40 ± 13° [100]) and with the data obtained by measuring the Kerr constants in solution (φ 32° [101]). In terms of the NBO approach, the selenium lone electron pairs are nonequivalent. One of them is essentially a *p*-orbital, and the other is a hybrid orbital with ~74% contribution of the *s*-constituent in the orthogonal conformation. The efficiency of the n–π-interaction of Se with the *p*-system depends on the angle between the symmetry axis of the lone electron pair (*p*-orbital) and that of the p_π-orbital of the adjacent carbon atom of the aromatic ring. As a result, the intramolecular interactions and electron density distribution in methyl phenyl selenide are largely determined by its conformation. In the orthogonal conformation, the selenium atom is almost unable to resonance interaction with the aromatic ring (energy of n–π*-interaction is 3.6 kJ/mol) [99]. This is experimentally confirmed by the ^{13}C NMR spectra.

6.1.8 ^{13}C NMR Spectra of Thiobenzoates and Alkyl Benzyl Sulfides

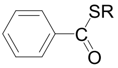
As follows from Sect. 6.1.2, in alkyl phenyl sulfides, PhSAlk, a change in the structure of Alk in the series Me, Et, *i*-Pr, and *t*-Bu leads, for steric reasons, to a decrease in the amount of planar conformer (90, 40, 15, and 5%, respectively [32]). Consequently, in these compounds, the shielding of carbon nuclei in the *ortho*- and *para*-positions is observed. As a result, the *p*–π-conjugation of the lone electron pairs of the sulfur atom with π-system of the aromatic ring weakens [18]. Alkyl substituent has a similar effect on the redistribution of π-electron density in other series of RC_6H_4SAlk [57].

This section discusses the influence of alkylthio groups on the shielding of ^{13}C nuclei of an aromatic ring, separated from these groups by a bridge, capable of (C=O group) or incapable of (CH_2) transmitting π-electronic effects [97].

A characteristic feature of the ^{13}C NMR spectra of thiobenzoates, PhC(O)SR, is that the introduction of various substituents R to S atom has little effect on ^{13}C chemical shifts of the benzene ring (Table 6.23).

The $\delta(^{13}C^1)$ values of the phenyl ring carbons coupled directly to the substituent correspond to the group electronegativity of the latter. With an increase in the branching of the alkyl substituent from Me to *t*-Bu, C^1 chemical shifts change insignificantly.

Table 6.23 The ^{13}C NMR chemical shifts of *S*-substituted thiobenzoates



Structure	Chemical shifts, δ, ppm						σ*
	C = O	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	R	
PhC(O)SH	189.91	136.44	127.74	128.45	133.52		0.49
PhC(O)SMe	190.37	136.90	126.96	128.32	132.87	11.30 (Me)	0.00
PhC(O)SEt	190.24	137.16	127.09	128.32	132.87	14.81 (Me), 23.13 (CH_2)	–0.1
PhC(O)SPr^i	189.91	137.22	127.02	128.19	132.68	23.06 (Me), 34.43 (CH)	–0.19
PhC(O)SBu^t	189.91	136.45	127.74	128.45	133.52	29.82 (Me), 54.36 (C)	–0.30
PhC(O)CH_2Ph	189.53	137.42 136.58	127.09	128.26 128.78	132.87	32.94 (CH_2)	0.215
PhC(O)SPh	187.31	136.70	127.28	128.65 128.26	124.82 132.87		0.60
PhC(O)SCH_2CH_2Cl	189.33	136.31	127.22	128.45	133.39	30.93 (CH_2S), 42.43 (CH_2Cl)	0.385
PhC(O)SCH_2CH_2OH	191.21	136.64	127.80	128.39	133.52	31.38 (CH_2S), 61.08 (CH_2OH)	0.198
PhC(O)SCH_2SC(O)Ph	188.81	136.25	127.15	128.26	133.07	27.55 (CH_2)	
PhC(O)SC_2H_4SC(O)Ph	189.27	136.70	127.15	128.19	132.87	28.72 (CH_2)	

It is worthwhile to note that $\delta C^{3(5)}$ chemical shift is less sensitive toward the substituents in the *meta*-position of the benzene ring. The range of changes in $\delta(^{13}C^{2(6)})$ and $\delta(^{13}C^{4})$ values in the discussed series of compounds is also small.

Some conclusions about the electronic structure of the studied compounds allow the values and nature of changes in $\delta^{13}C$ of the carbonyl group carbons to be analyzed.

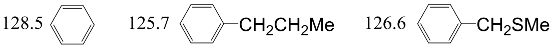
The relationship between $\delta^{13}C$ of the carbonyl group and the values of Taft induction constants (σ^*) is described by the following equations:

$$\delta\left(^{13}C_{C=O}\right) = 190.23 + 0.94\sigma*, r = 0.91, s = 0.16, n = 10.$$

The approximate linear dependences obtained ($r = 0.91$) indicate that alkyl substituents influence the chemical shift of the carbonyl group carbon mainly according to the induction mechanism.

In thiobenzoates, containing electron-withdrawing groups or benzene ring at the S atom, conjugation effects also take place along with the induction effect. This is evidenced by the chemical shifts of the carbonyl group for benzyl, phenyl, and 2-chloroethyl S-esters of thiobenzoic acid, the values of which deviate from the correlation straight line.

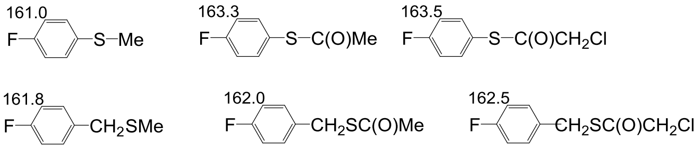
The C^4 shielding in alkyl benzyl sulfides ($PhCH_2SR$ and $4\text{-}FC_6H_4CH_2SR$) permits to evaluate π-charge in the *para*-position of the benzene ring [102] and indicates the π-polarization of the aromatic fragment by $–CH_2SR$ groups (δ, ppm relative to TMS):



Like in alkylbenzenes, this is due to the π-induction effect [35].

Analysis of the ^{13}C NMR spectra (Tables 6.24 and 6.25) shows that the CH_2SR groups act as weak π-donors relative to the aromatic part of the molecule due to the π-induction effect. The change of structurally different alkyls in benzyl sulfides causes significantly smaller changes in δC^1, $\delta C^{2(6),}$ and δC^4 (Table 6.24) than in PhSR [18] and $4\text{-}FC_6H_4SR$ [57].

The effect of acceptor substituents at the sulfur atom on the shielding of ^{13}C ring nuclei also is also lesser than in the corresponding aryl organyl sulfides (Table 6.24, see, for example, δC^4):



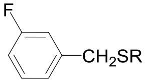
These results completely confirm the idea about the absence in alkyl benzyl sulfides of both π-electron interactions of the aromatic ring and sulfur atom and the sterically caused conformational heterogeneity in the considered series with different alkylthio groups.

Table 6.24 The ^{13}C NMR chemical shifts of benzyl organyl sulfides

Structure	Chemical shifts, δ^a, ppm					
	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	CH_2	R
$PhCH_2SMe$	138.22	128.15	128.70	126.63	38.15	14.58 (Me)
$PhCH_2SEt$	138.60	128.12	128.65	126.51	35.79	25.04 (CH_2), 14.40 (Me)
$PhCH_2SPr^i$	138.64	128.03	128.56	126.38	35.00	33.83 (CH), 23.10 (Me)
$PhCH_2SBu^t$	138.47	127.09	128.64	126.20	33.20	42.00 (C), 30.79 (Me)
$4\text{-}FC_6H_4CH_2SMe$	134.11	130.26	114.97	161.75	37.44	14.46 (Me)
$4\text{-}FC_6H_4CH_2SEt$	134.74	130.41	115.14	161.74	35.13	25.19 (CH_2), 14.41 (Me)
$4\text{-}FC_6H_4CH_2SPr^i$	135.60	130.55	115.33	162.00	34.42	34.42 (CH), 23.24 (Me)
$4\text{-}FC_6H_4CH_2SBu^t$	135.03	130.77	115.09	162.17	32.34	42.48 (C), 30.60 (Me)
$4\text{-}FC_6H_4CH_2SC(O)Me$	134.64	131.02	115.53	162.01	35.15	29.71 (Me), 192.35 (C = O)
$4\text{-}FC_6H_4CH_2SC(O)CH_2Cl$	133.69	131.23	115.83	162.49	33.17	48.31 (CH_2), 193.59 (C = O)

^{a13}C-^{19}F spin-spin coupling constants are $^1J^4_{CF}$ 244–246, $^2J^{3(5)}_{C\ F}$ 20–22, $^3J^{2(6)}_{C\ F}$ 7–9, $^4J^1_{CF}$ 3–5 Hz

Table 6.25 The ^{13}C NMR chemical shifts of 3-fluorobenzyl organyl sulfides



Formula	Chemical shifts, δ^a, ppm							
	C^1	C^2	C^3	C^4	C^5	C^6	CH_2	R
$3\text{-}FC_6H_4CH_2SMe$	141.26	115.62	162.80	113.64	129.77	124.63	37.75	14.66
$3\text{-}FC_6H_4CH_2SEt$	141.62	115.59	162.83	113.55	129.71	124.53	35.46	25.29 14.35
$3\text{-}FC_6H_4CH_2SPr^i$	141.73	115.54	162.82	113.54	129.68	124.39	34.23	34.67 23.04
$3\text{-}FC_6H_4CH_2SBu^t$	141.53	115.72	162.56	113. 36	129.57	124.58	32.94	42.46 30.80
$3\text{-}FC_6H_4CH_2SC(O)Me$	140.66	115.71	162.72	114.02	130.01	125.62	32.79	29.77
$3\text{-}FC_6H_4CH_2SC(O)CF_3$	139.85	116.07	162.50	114.17	129.77	125.00	32.08	
$3\text{-}FC_6H_4CH_2SC(O)CCl_3$	137.53	115.72	162.38	114.81	130.19	124.51	35.25	

^{a13}C- ^{19}F spin-spin coupling constants are $^1J^3_{CF}$ 244-248, $^2J^2_{CF}$ 21-23, $^3J^1_{CF}$ 6-9, $^3J^5_{CF}$ 8-10, $^4J^6_{CF}$ 0-2 Hz

6.2 Effects of Conjugation of the Sulfur Atom

6.2.1 Alkyl Aryl Sulfides

6.2.1.1 Electronic Spectra

A number of works have been devoted to the conjugation effects of the sulfur atom in aromatic sulfides, just to mention a comprehensive review [103]. In this section, we did not attempt to analyze in detail the literature data on the UV spectra of alkyl aryl sulfides. However, some of these data will be used to discuss the results obtained for a series of aromatic sulfides with a regularly changing structure.

The electronic absorption spectra of alkyl phenyl sulfides (Table 6.26) [104] show only one well-resolved band in the region of 250–260 nm, the characteristics of which agree well with literature data [105]. This band is attributed to the ^1L_a-type (the first primary band) and is due to the A_{1g}–B_{1u} transition [106, 107]. Apart from this band, the spectra demonstrate additional absorption bands at 210–220 and 280–300 nm in the form of peaks and bends, the character of which strongly depends on the alkyl substituent at the sulfur atom. For instance, a barely noticeable bend at 214 nm for methyl phenyl sulfide (No. 1, Table 6.26) is gradually transformed into a band with a clearly pronounced maximum at 220 nm for *tert*-butyl phenyl sulfide (No. 4, Table 6.26). In the region of 280–300 nm, the opposite picture is observed: an increase in the volume of alkyl substituents at sulfur atom leads to the gradual disappearance of weakly resolved bends at 285 and 294 nm. In the spectrum of methyl phenyl sulfide, a shoulder at 240 nm appears from the short-wave side of the main absorption band. The absorption in the region of 280–300 nm can be attributed to the π-π*-transition of the A_{1g}–B_{2u} type (secondary ^1L_b band).

The character of electronic spectra of alkyl aryl sulfides depends on the nature of the solvent. In the series of alkyl phenyl sulfides (No. 1–4, Table 6.26), the replacement of hexane with ethanol does not lead to a significant change in intensity and position of the ^1L_a-bands, but causes a noticeable hypsochromic shift of the ^IL_b-band, accompanied by a hypochromic effect.

In the UV spectra (solutions in *n*-hexane) of alkyl 4-fluorophenyl sulfides, 4-FC_6H_4SR (No. 6–9, Table 6.26), two absorption bands are observed at 250 and 290 nm. The first ^1L_a-type band is quite intense, but its intensity drops by more than 1.5 times on going from methyl to isopropyl 4-fluorophenyl sulfide. The weak absorption (ε 900) at 289 nm (^1L_b-band) in this series of compounds also decreases by ~2 times. In the spectrum of methyl 4-fluorophenyl sulfide, a bend at ~240 nm is detected from the short-wave side on the wing of the intense band. For these compounds, like for alkyl phenyl sulfides PhSR, the character of the spectral curve in the region of 210–220 nm and the bands at 290 nm strongly depend on the structure of the alkyl substituent. So, in the spectrum of methyl 4-fluorophenyl sulfide in the region of 210–220 nm, the absorption intensity monotonously decreases with the increase of the wavelength, and the bend appears only at 216 nm. In the spectrum of ethyl 4-fluorophenyl sulfide, this bend becomes more pronounced, and its intensity increases. The spectrum of isopropyl 4-fluorophenyl sulfide shows a well-resolved bend at 216 nm, the intensity of which is almost two times higher than that of the band at 256 nm. This trend is violated for the

Table 6.26 Electronic spectra of alkyl aryl sulfides

No.	Structure	Hexane		EtOH		HClO$_4^a$	
		^1L_a	^1L_b	^1L_a	^1L_b	^1L_a	^1L_b
		λ (ε)	λ (ε)	λ (ε)	λ (ε)	λ (ε)	λ (ε)
1	PhSMe	214 (9100) 240 (6200) 254 (9900)	285 (2100) 294 (1770)	214 (10,200) 240 (6700) 254 (11,200)	283 (930) 293 (480)		
2	PhSEt	215 (10,600) 256 (10,300)	285 (960) 293 (500)	215 (9300) 255 (9100)			
3	PhSPr^i	216 (9200) 257 (6400)	295(sh)	215 (8800) 257 (6200)			
4	PhSBu^t	220 (15,200)	268 (2860)	219 (13,000)	264 (3050)		
5	$PhCH_2SBu^t$	208 (12,900)	255 (380) 261 (320) 267 (220)	207 (14,600)	255 (440) 261 (370) 267 (300)		
6	4-FC_6H_4SMe	216 (3900) 240 (4600) 252 (6200)	289 (900)	240 (5000) 252 (6900)	288 (910)	246 (6080)	283 (840)
7	4-FC_6H_4SEt	216 (4900) 254 (5000)	292 (660)	252 (5300)	290 (670)	247 (4800)	285 (560)
8	4-$FC_6H_4SPr^i$	216 (7400) 256 (3800)	295 (520)	255 (4050)	292 (460)	248 (3000)	292 (320)
9	4-$FC_6H_4SBu^t$	219 (10,100)	265 (1280)	219 (9400)	261 (1250)	230 (4300) 228 (6270)^b	270 (590) 288 (300) 270 (690)^b 286 (420)^b
10	2,4,6-$Me_3C_6H_2SMe$	225 (9400)	267 (2100)	224 (10,300)	266 (2500)		
11	2,4,6-$Me_3C_6H_2SEt$	225 (12,400)	267 (2000)	225 (12,000)	266 (2700)		
12	2,4,6-$Me_3C_6H_2SPr^i$	227 (13,300)	268 (2900)	225 (12,900)	267 (2760)		
13	2,4,6-$Me_3C_6H_2SBu^t$	233 (12,500)	275 (1400)	234 (12,000)	274 (1090)		

^{a}In 57% $HClO_4$ solution; ^{b}In 70% $HClO_4$ solution long-wavelength band. If in the spectrum of methyl 4-fluorophenyl sulfide, a band with a pronounced maximum at 289 nm (ε 900) is recorded, then in the spectrum of isopropyl 4-fluorophenyl sulfide, only a weak bend appears, the intensity of which is by 2 times less. When hexane is replaced by ethanol, the intensity of both bands increases insignificantly, and the bands themselves shift slightly to the short-wave region. When 57% $HClO_4$ is used as a solvent, the absorption intensity in the study area decreases, and the spectral curve undergoes a hypsochromic shift, which is apparently due to the binding of a lone electron sulfur atom (the ability of alkyl aryl sulfides to form H-bonds is quite strong [108]).

The spectrum of *tert*-butyl 4-fluorophenyl sulfide (in *n*-hexane solution) contains an intense band at 219 nm and a band of medium intensity at 265 nm with traces of the vibrational structure. The electronic spectrum of this compound is most sensitive to the effects of the medium. In ethanol, the intensity of both bands decreases, and they are shifted to the short-wave region. In solutions of 57–70% $HClO_4$ in the region of 210 nm, instead of a clearly defined band, only a weakly pronounced bend is observed. At the same time, a weak absorption is detected at 288 nm and a band appears at 230 nm, which is absent in the UV spectra of this sulfide recorded in organic solvents. Moreover, with an increase in the concentration of $HClO_4$ from 57% to 70%, this band shifts to the short-wave region by 2 nm, and its intensity augments significantly. The band in the region of 230 nm in strongly acidic solutions of alkyl aryl sulfides should apparently be attributed to the transition associated with the partial transfer of π-electron density to the vacant orbitals of the sulfur atom. Obviously, the formation of sulfonium salts (the appearance of a positive charge on sulfur atom) is accompanied by a decrease in the energy of the vacant orbitals.

From the above analysis, it follows that in the spectra of alkyl aryl sulfides, the parameters of ^1L_a- and ^1L_b-bands obtained in inert solvents (that is, when the intermolecular interactions play a negligible role in the system molecule of the absorbing substance/solvent) are quite sensitive to nature of the substituent at the sulfur atom. Changes in the absorption spectra of alkyl aryl sulfides with an increase in the effective volume of the alkyl substituent are determined by the steric interaction of the alkyl group with hydrogen atoms in the *ortho*-positions of the aromatic ring. The character of these changes suggests an increasing role of the steric effect in the Me < Et < *i*-Pr < *t*-Bu series (Fig. 6.8), which leads to a decrease in the *p*–π-interaction of the sulfur atom with the benzene ring [109, 110], the efficiency of which depends on the degree of the molecule coplanarity. The strongest steric hindrances to the *p*–π-conjugation should be expected in the case when R = *t*-Bu. Therefore, the spectral characteristics of aryl *tert*-butyl sulfides should be comparable with those of compounds, in which steric inhibition of the *p*–π-conjugation involves, for example, aryl sulfides, where the sulfur atom is blocked from both sides by alkyl groups in the position 2(6). Indeed, in terms of ^1L_a and ^1L_b-bands, *tert*-butyl phenyl sulfide more resembles mesityl methyl sulfide (No. 10, Table 6.26) than the genetically related methyl phenyl or ethyl phenyl sulfides.

In this regard, it is pertinent to compare the UV spectra of *tert*-butyl phenyl sulfide with those of *tert*-butyl benzyl sulfide (No. 4, 5, Table 6.26), in which the *p*–π-interaction between the sulfur atom and the benzene ring cannot be realized due to the separation of these fragments by the methylene group (Fig. 6.9).

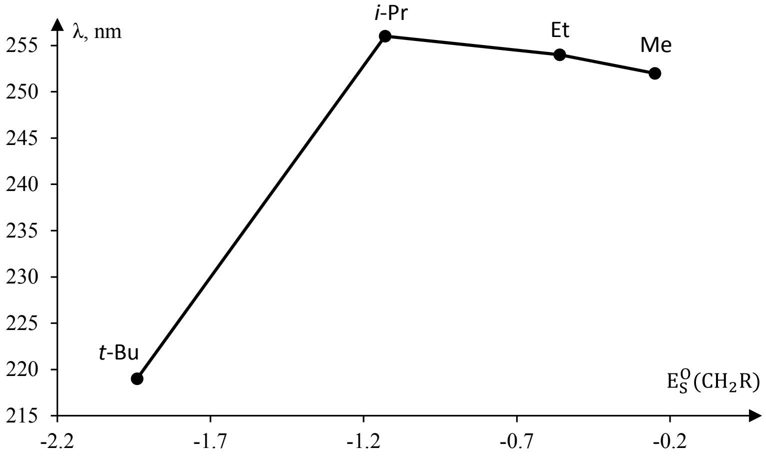
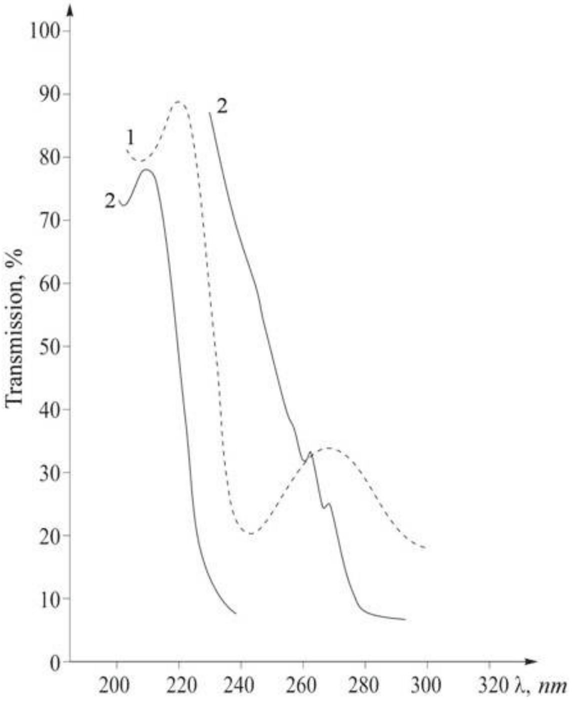


Fig. 6.8 Dependence of λ_{max} values of ^1L_a-absorption bands in the spectra of 4-FC_6H_4SR on $E_s^o(CH_2R)$ constants

Fig. 6.9 UV spectra of hexane solutions: *tert*-butyl phenyl sulfide (*1*); *tert*-butyl benzyl sulfide (*2*)



Comparison of the absorption spectra of these compounds allows us to admit the presence of some additional interaction between the sulfur atom and the benzene ring in *tert*-butyl phenyl sulfide. In accordance with the orbital classification proposed for molecules with a non-planar conformation [111], it can be assumed that in this case, the transition from the level of lone electron pair of the sulfur atom to the loosening π-orbital occurs.

As it already has been mentioned, with a variation of the alkyl substituent, shapes of ^1L_a and ^1L_b-bands of alkyl aryl sulfides change gradually. A barely noticeable bend in the region of 214 nm (^1L_a-band, R = Me) becomes more pronounced in aryl *tert*-butyl sulfides with an increase in steric requirements of the alkyl substituent and leads to the appearance of a band with a clearly defined maximum at 220 nm. Simultaneously, changes occur in the region of the ^1L_b-band. This feature of the UV spectra of alkyl aryl sulfides does not exclude the presence of the *d*–π-interactions between the S atom and the benzene ring, which competes with the *p*–π-interaction. At the same time, as the steric requirements of the alkyl substituent augment, the contribution of the *d*–π-interaction grows [110, 112].

It is obvious that the effects of *p*–π- and *d*–π-conjugations in the UV spectra of aryl sulfides are manifested in the same manner, causing a bathochromic shift of the benzene absorption and an increase in its intensity, although the effect of *d*–π-conjugation is less significant as compared to *p*–π-conjugation. Thus, from a formal point of view, the spectral manifestation of the *d*–π-conjugation is similar to the *p*–π-conjugation.

It is known that the efficiency of *p*–π-conjugation in unsaturated heteroatom compounds strongly depends on the conformation of the molecules. The compounds of PhSR type are characterized by a decrease in the π-donating ability of sulfur atom relative to the aromatic ring with an increase in the volume of the alkyl group [18, 21, 110, 113–115] associated with rotation of the SR fragment around the C_{Ph}–S bond due to steric repulsion of the alkyl from hydrogen atoms in the position 2(6) of the benzene ring. Another explanation is possible: in such compounds, there is an equilibrium between a conformer with a parallel or almost parallel orientation of the orbital axis of lonely electron pair and p_Z-orbital axis of the nearest carbon atom of the unsaturated fragment (planar form **A**) and a conformer, in which the axis of heteroatom orbital of the lone electron pair lies in the plane of the benzene ring (non-planar form **B**). An increase in steric hindrances shifts the equilibrium toward form **B**. Such methods as NMR, the Kerr effect, and in some cases IR spectroscopy do not separately record the characteristics of planar and non-planar forms, but give some averaged parameters, the changes of which in a series of compounds may be due to (i) alteration in the effective angle between the S–R bond axis and the plane of the benzene nucleus [116] and (ii) population of forms **A** and **B**. The study of photoelectron spectra of alkyl phenyl sulfides has shown [32, 40] that these compounds exist in the form of the above two conformers, wherein, according to a rough estimate [32], the contribution of planar form n_A gradually decreased by ~93% (PhSMe) to 10% (PhSBu^t) (Table 6.27). A more thorough investigation of the contribution of planar n_A and non-planar *nB* forms for methyl phenyl sulfides (79 and 21%, respectively) [40] has revealed that the content of form **B** in a mixture of conformers increases with augmenting the temperature. These data are in good agreement with "the effective" conformation of methyl phenyl sulfide obtained using the Kerr effect, in which the dihedral angle φ between the ring plane and S–Me bond is 23° [31] and 30–40° [116]. Based on the average value of $\varphi = 30°$ and assuming that the contribution of planar form is proportional to $cos^2\ \varphi$, and non-planar to $\sin^2\ \varphi$, the content of planar form **A** ($n_A = \cos^2 30°$) is found to be 0.75 [94].

According to a theoretical analysis of the dependence between p–π-conjugation in the UV spectra on the degree of coplanarity of heteroatom p-orbital and carbon p_z-orbital of the unsaturated system [117, 118], the planar conformer should contain an intense absorption band at 250 nm, which is caused by an electronic transition in the π-system including the benzene ring and lone electron pair of the heteroatom. Since in the non-planar conformer, p–π-conjugation is absent owing to the orthogonality of orbitals of the heteroatom lone electron pair and orbitals of the phenyl ring, conformer B should contain a weak band approximately in the same spectral region. This band is associated with the forbidden transition $A_{1g}\rightarrow B_{2u}$ in the benzene ring. The oscillator force f and extinction coefficient ε of this band for alkyl phenyl sulfides are estimated to be 0.01 (f_B) and 300 (ε_B). Such estimation is made using the analysis of the shape and intensity of similar bands in the spectra of *tert*-butyl phenyl sulfide and its 2, 6-dimethyl-substituted analog. For form **A**, the band related to the transition $A_{1g}\rightarrow B_{2u}$ is observed in a longer wavelength region (~285 nm) and has a higher intensity. Thus, the intensity of the discussed UV absorption bands is connected with the content of conformers by the following relationship:

$$\varepsilon = \varepsilon_A \cdot n_A + \varepsilon_B(1-n_A),$$

$$f = f_A \cdot n_A + f_B(1 - n_A)$$

In the spectra of alkyl phenyl sulfides, the oscillator force and extinction coefficient of an intense band (250–270 nm) and a weak band with a vibrational structure (~285 nm) consistently decrease with the increasing volume of the alkyl group. The band of the non-planar conformer **B** is overlapped by an intense band of form **A** and is not separately observed (Table 6.27). Using the data on conformational structure of methyl phenyl sulfide ($n_A = 0.79$, $n_B = 0.21$ [40]) and the values of the oscillator force and extinction coefficient ($f_B = 0.01$, $\varepsilon_B = 300$ [94]), obtained from analysis of its UV spectrum, the ε_A and f_A values are determined by the above equations. These parameters have been employed to establish the conformational composition n_A and n_B of other alkyl phenyl sulfides. It is assumed that the conformational composition of compounds does not change upon transition from the gas phase to a diluted solution in cyclohexane, and the parameters ε_A and f_A are the same for all members of this series, since intensity of the corresponding band in the UV spectrum is determined by the interaction of a sulfur lonely electron pair with the phenyl fragment, and the change in inductive effect of the alkyl groups has almost no effect on this pair. The obtained n_A values [94] are in good agreement with the estimation of this value made in the paper [32] (see Table 6.27).

Table 6.27 Parameters of UV[a] spectra and population of planar conformation of alkyl phenyl sulfides PhSR

Structure	Wavelength λ, nm		Extinction ε, L·mol^{-1}·cm^{-1}		Oscillator force f		Content of planar conformer, n_A	
	[94]	[21]	[94]	[21]	[94]	[21]	[94]	[32]
PhSMe	254 284 294	254 252 293	10,000	10,100	0.167	0.155	0.79[b]	0.93
PhSEt	256 284 292	256 283 292	8200 1300 500	7750 900 450	0.144	0.143	0.66	0.85
PhSPr^i	258 294	257 293	5600 200	5770 250	0.11	0.081	0.44	0.60
PhSBu^t	267	268	1500	1290	0.021	0.018	0.07	0.10

[a]Cyclohexane was used as a solvent; [b]According to [40]

6.2.1.2 ^{13}C NMR Spectra

Chemical shifts in the ^{13}C NMR spectra can also be successfully applied to the analysis of the dynamic equilibrium of conformers [119]. For this purpose, it is convenient to use the values of δC^3 and δC^4 chemical shifts of the aromatic ring, taking into account a linear relationship of these values with populations of forms **A** and **B** calculated from the UV spectra:

$$\delta\left({}^{13}C^3\right) = n_A \delta C^3_A + (1 - n_A)\delta C^3_B,$$

$$\delta\left({}^{13}C^4\right) = n_A \delta C^4_A + (1 - n_A)\delta C^4_B.$$

It is assumed that the conformational composition and chemical shifts of carbon atoms in the positions 3 and 4 of the benzene ring of alkyl phenyl sulfides are similar in a diluted cyclohexane solution and in a pure liquid (i.e., in the absence of a solvent), which is confirmed by close values of δC^3 and δC^4 as well as difference ($\delta C^4 - \delta C^3$) for pure methyl phenyl sulfide and its solution in $CDCl_3$ (see Table 6.2, Sect. 6.1.2).

If to suppose that δC^4_A, δC^3_A and δC^4_B, δC^3_B are constant for the whole series of alkyl phenyl sulfides (thereby ignoring the change in the induction effect of different alkyl groups on δC), then it can be possible to determine these values by the above equations, taking the experimental values of ^{13}C chemical shifts and content of conformers (found from the UV spectra) for any pair of compounds:

δC^4_A	δC^4_B	δC^3_A	δC^3_B	$[\delta C^4 - \delta C^3]_A$	$[\delta C^4 - \delta C^3]_B$
123.5 ± 0.2	128.5 ± 0.4	128.8 ± 0.2	128.1 ± 0.2	–5.2 ± 0.4	0.5 ± 0.4

Table 6.28 The ^{13}C NMR chemical shifts of alkyl phenyl sulfides calculated from conformational composition [94]

R	Pairs of alkyl phenyl sulfides	δC^4, ppm	δC^3, ppm	$\delta C^4 - \delta C^3$, ppm
Me	Et/Pr^i	124.76	128.51	–3.5
	Et/Bu^t	124.68	128.60	–4.1
	Pr^i/Bu^t	124.40	128.93	–4.6
Et	Me/Pr^i	125.13	128.57	–3.4
	Me/Bu^t	125.15	128.49	–3.4
	Pr^i/Bu^t	125.07	128.76	–3.7
i-Pr	Me/Et	126.63	128.31	–1.7
	Me/Bu^t	126.25	128.31	–2.1
	Et/Bu^t	126.34	128.32	–2.0
t-Bu	Me/Et	128.90	128.01	0.88
	Me/Pr^i	128.01	128.41	–0.32
	Et/Pr^i	127.73	128.04	0.14

To check the correctness of chemical shifts C^4_A, C^3_A and C^4_B, C^3_B evaluated for one of the pairs of compounds, for calculations, δC^3 and δC^4 of the third compound taking into account its conformational composition, determined from the UV spectra, have been used. Similarly, the differences in chemical shifts for each conformer are calculated and checked (Table 6.28):

$$\delta C^4 - \delta C^3 = n_A\left[\delta C^4 - \delta C^3\right]_A + (1 - n_A)\left[\delta C^4 - \delta C^3\right]_B.$$

A similar calculation of the chemical shifts of alkyl phenyl sulfides C^3, C^4 and the difference (δC^4–δC^3) is performed on the basis of the calculated values of chemical shifts of conformers **A** and **B** (Table 6.29). In all cases, there is a good agreement between the calculated and experimental values, which confirms the correctness of the discussed characteristics and the validity of the initial positions, on the basis of which the equations, connecting the parameters of the UV and ^{13}C NMR spectra with the conformational composition, are derived.

Thus, all the considered approaches provide a consistent picture of the changes in the conformational composition in the series of alkyl phenyl sulfides. Alterations in the UV spectra of these compounds are well described if to take into account the presence of equilibrium between conformers. The C^4 chemical shifts of conformer **A** are smaller than those of conformer **B**, which indicates the donor effect of sulfur in form A. The $\boldsymbol{\delta C^4 - \delta C^3}$ values of conformers **A** and **B** allow estimating the donor-acceptor ability of the alkylthio group in both conformations using the dependency reported in [120]. For example, for alkyl phenyl sulfides $(\sigma^o_R)_A = 0.05$ $[\boldsymbol{\delta C^4 - \delta C^3}]_A = -0.26 \pm 0.02$, which evidences the strong donor properties of

Table 6.29 Comparison of ^{13}C chemical shifts of PhSR determined experimentally[a] [13] and calculated from conformational composition [94]

Structure	δC^4, ppm	δC^3, ppm	$\delta C^4 - \delta C^3$, ppm
PhSMe	124.61 (124.52)	128.58 (128.56)	–4.0 (–4.1)
PhSEt	125.11 (125.27)	128.61 (128.46)	–3.5 (–3.2)
PhSPr^i	126.40 (126.16)	128.31 (128.46)	–1.9 (–2.3)
PhSBu^t	128.21 (128.13)	128.15 (127.98)	–0.1 (+0.1)

[a] Given in parenthesis

SAlk. In conformer B, the value of $(\sigma_R^o)_B = 0.025 \pm 0.02$ is so small that it is hardly possible to speak about any significant π-acceptor effect of the SAlk group in this conformation.

Therefore, in conformation **A**, sulfur exhibits pronounced donating properties, whereas in conformation **B**, the acceptor effect of sulfur is close to zero.

6.2.2 Alkyl Aryl Sulfoxides and Sulfones

The electronic spectra of alkyl aryl sulfoxides and alkyl aryl sulfones are less studied compared to the spectra of the corresponding sulfides. The simultaneous presence of such fragments as Ar, S=O, and O=S=O in these molecules is a factor determining peculiarities of their spectral characteristics.

In the spectra of alkyl 4-fluorophenyl sulfoxides (recorded in *n*-hexane and ethanol), two absorption bands with maxima at 203–205 and 236–252 nm are observed (Table 6.30) [121]. The long-wavelength shoulder of the band at 203–205 nm shows a bend in the region of ~214 nm (ε = 7000–9000). There is a weak indistinctly pronounced band at ~270 nm (ε ~ 700), which decreases with the increasing volume of the alkyl substituent. Upon transition from hexane to ethanol, in the spectra of sulfoxides, a hypsochromic shift $n \rightarrow \pi^*$ of the S=O absorption band appears.

Table 6.30 Electronic spectra of alkyl 4-fluorophenyl sulfoxides

Structure	Hexane		EtOH	
	λ, nm (ε)		λ, nm (ε)	
	I band	II band	I band	II band
4-$FC_6H_4S(O)Me$	202 (5840)	245 (3720)	205 (7150)	245 (1990)
4-$FC_6H_4S(O)Et$	203 (9650)	252 (3770)	205 (10,700)	250 (5130)
4-$FC_6H_4S(O)Pr^n$	203 (7160)	248 (3100)	203 (9400)	242 (5400)
4-$FC_6H_4S(O)Pr^i$	204 (16,420)	248 (6450)	204 (10,800)	242 (4770)
4-$FC_6H_4S(O)Bu^t$	203 (24,000)	228 (14,000)	205 (18,000)	236 (11,000)

Table 6.31 Electronic spectra of alkyl 4-halophenyl sulfones

No.	Formula	Hexane		EtOH	
		λ, nm (ε)		λ, nm (ε)	
		I band	II band	I band	II band
1	$4\text{-FC}_6\text{H}_4\text{SO}_2\text{Me}$	218 (7850)	258 (320)	218 (8460)	258 (350)
2	$4\text{-FC}_6\text{H}_4\text{SO}_2\text{Et}$	217 (5425)	259 (213)	218 (6950)	259 (270)
3	$4\text{-FC}_6\text{H}_4\text{SO}_2\text{Pr}^n$	219 (9730)	260 (276)	219 (10,100)	260 (310)
4	$4\text{-FC}_6\text{H}_4\text{SO}_2\text{Pr}^i$	217 (7560)	259 (540)	217 (10,520)	258 (350)
5	$4\text{-FC}_6\text{H}_4\text{SO}_2\text{Bu}^i$	218 (5485)	260 (256)	218 (10,860)	260 (332)
6	$4\text{-FC}_6\text{H}_4\text{S(O)Bu}^t$	215 (9360)	257 (266)	217 (9048)	257 (360)
7	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{Me}$			227 (21,000)	266 (390)
8	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{Et}$			228 (16,100)	266 (520)
9	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{Pr}^n$			228 (14,200)	267 (510)
10	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{Pr}^i$			229 (12,700)	268 (410)
11	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{Bu}^n$			228 (13,200)	266 (470)
12	$4\text{-ClC}_6\text{H}_4\text{S(O)Bu}^t$			229 (23,000)	268 (800)
13	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{Am}^n$			228 (15,400)	267 (560)
14	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{C}_6\text{H}^n_{13}$			228 (16,200)	267 (570)
15	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{C}_7\text{H}^n_{15}$			228 (13,400)	267 (510)
16	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{C}_8\text{H}^n_{17}$			228 (15,600)	267 (550)
17	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{C}_9\text{H}^n_{19}$			228 (14,500)	266 (470)
18	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{C}_{10}\text{H}^n_{21}$			228 (14,500)	267 (530)
19	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{C}_{11}\text{H}^n_{23}$			228 (16,700)	267 (530)
20	$4\text{-ClC}_6\text{H}_4\text{SO}_2\text{C}_{12}\text{H}^n_{25}$			228 (14,000)	266 (480)

The spectrum of methyl phenyl sulfone contains two absorption bands at 217 and 264 nm. The bathochromic shift of the bands in comparison with benzene (200 and 256 nm) is explained by the conjugation effect [122]. In the spectra of alkyl 4-fluorophenyl sulfones, there are also two bands with maxima at 215–219 nm and 258–260 nm (Table 6.31, No. 1–6). In contrast to the corresponding sulfoxides, the long-wavelength band is weak and has a clearly pronounced vibrational structure. Upon transition from hexane to ethanol, no noticeable changes are detected in the spectra of these sulfones. An increase in the length and branching of the alkyl chain causes a slight bathochromic shift and a hyperchromic effect of the absorption bands.

The spectra of alkyl 4-chlorophenyl sulfones (Table 6.31, No. 7–20) also contain two absorption bands. The introduction of a chlorine atom into the *para*-position of the benzene ring causes the bathochromic shift of both absorption bands relative to methyl phenyl sulfone by 11 and 3 nm, respectively. In this case, the short-wave band turns out to be most sensitive to substitution.

The long-wavelength band with a maximum at 267 nm, like in the case of benzene, retains a vibrational structure ($\Delta\nu \sim 900\ \text{cm}^{-1}$), corresponding to the pulse vibrations of the benzene ring in the electron-excited state [123]. The varying of alkyl substituents at the sulfonyl group does not significantly affect the position of the bands and their intensity.

Both bands in the alkyl 4-chlorophenyl sulfones are bathochromically shifted "benzene" bands at 200 and 256 nm, which correspond to π–π*-transitions, and belong to $A_{1g} \rightarrow B_{1u}$ and $A_{1g} \rightarrow B_{2u}$ types, respectively.

6.3 Relative Basicity of Alkyl Aryl Sulfides and Some of Their Analogs

6.3.1 Alkyl Phenyl Sulfides

The relative basicity of various classes of organic compounds, including sulfides, can be evaluated using IR spectroscopy [124]. The relative basicity is commonly assessed as a shift in frequency of stretching vibration Δν(OH) of the O-H bond of phenol when the latter forms H-complexes with the corresponding weak base. Thus, IR spectroscopic studies of H-complexes allow indirectly evaluating the conjugation effects of organosulfur compounds in molecules [125]. For example, it has been established [126] that the most significant changes in the relative basicity of *α,β*-unsaturated sulfides CH_2=CHSR are caused by the induction effect of substituents at the sulfur atom, while the contributions of the *p*–π- and *d*–π-conjugation effects are much smaller. The relative basicity of *α,β*-unsaturated sulfides has been compared to that of their analogs containing a phenyl group instead of the vinyl moiety.

To evaluate the structural effects of PhSR sulfides on their relative basicity (and, consequently, on their reactivity), the ability of these compounds to participate in the formation of H-bonding with phenol (in CCl_4 medium) has been studied using IR spectroscopy [108, 127–129]. Since the formation of H-bonds proceeds with a minimum redistribution of electron density in a weak base (in particular, it does not require heteroatom rehybridization), it is assumed (in accordance with the generally accepted point of view [130]) that the Δν(OH) value is proportional to the hydrogen bond formation energy O–H···S (and, hence, to the electron-donating ability of sulfide) and reflects, ultimately, the change in electron density at the basicity center under the influence of variable substituents.

The results obtained show that in the IR spectra of phenol/phenyl sulfide/CCl_4 triad, three absorption bands are observed in the region of the OH group stretching vibrations (Fig. 6.10). The first one (from the high-frequency side) corresponds to the vibrations of the phenol "free" OH group, the second is attributed to the vibrations of the OH group bonded with the π-electron system of the benzene sulfide ring (H-complex of the π-type), and the third band is assigned to vibrations of the OH group coupled with a lone electron pair of the sulfur atom (H-complex of *n*-type). The assignment of absorption bands to these two types of H-complexes is confirmed by close values of these bands frequency to those of H-complexes of phenol with ethylbenzene (Δν(OH) = 47 cm^{-1}), where only a π-type complex can

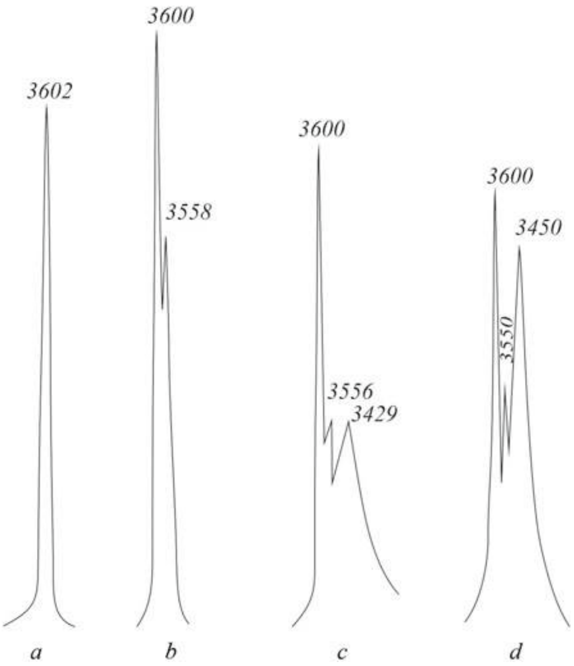


Fig. 6.10 IR spectra of phenol/CCl_4 (**a**), phenol/CCl_4/benzene (**b**), phenol/CCl_4/methyl phenyl sulfide (**c**), phenol/CCl_4/methyl phenyl ether (**d**) solutions

be formed, and with *n*-amyl cyclohexyl sulfide (Δν(OH = 255 cm^{-1}), where only the *n*-type complex can be formed.

For H-complexes of alkyl phenyl- and dialkyl sulfides (Table 6.32), the absorption bands of bound phenol have a simple structure, which indicates the absence of Δν(OH) value distortions, sometimes arising in phenol complexes with strong electron donors [131]. The presence of “free” OH group in the spectra evidences a small value of the complex formation constant of sulfides with phenol.

The relationship between Δν(OH) values for *n*-complexes and induction Taft constants (σ^*) of substituents at sulfur atom for PhSR compounds is described by the following equation:

$$\Delta\nu(\mathrm{OH}) = (219 \pm 7) - (78 \pm 12)\sum\sigma*, r = 0.965, s = 4.9, n = 15.$$

It should be underlined that Δν(OH) values of not only phenyl sulfides, but also other sulfides are placed on the correlation straight line [126, 132]. The quite satisfactory correlation (*r* = 0.965) suggests that the hyperconjugation and steric effects of substituents at sulfur atom do not play a decisive role in the formation of H-complexes of O-H···S type. The relationship between substituent R and sulfur atom in PhSR molecules is limited mainly to induction interaction.

Thus, if to take Δν(OH) value as a measure of relative basicity, then, based on the obtained results and literature data [126, 129, 132, 133], it can be concluded that alkyl phenyl sulfides compared to structurally close ethers [13, 134] are stronger *n*-

Table 6.32 Δν(OH) Values in IR spectra of H-complexes of sulfides PhSR and RSR with phenol

No.	Structure	Δν (OH) (n-complex), cm^{-1}	$\Sigma\sigma^*$	Reference
1	PhSMe	171 172	0.60	[108] [126]
2	PhSEt	183 180	0.50	[108] [119]
3	$PhSPr^n$	175	0.485	[108]
4	$PhSPr^i$	192	0.41	[108]
5	$PhSBu^n$	177	0.47	[108]
6	$PhSBu^i$	181	0.475	[108]
7	$PhSBu^s$	188	0.39	[108]
8	$PhSBu^t$	200	0.30	[108]
9	$PhSAm^n$	174	0.438	[108]
10	$PhSAm^i$	188	0.438	[108]
11	$PhSC_6H_{13}^n$	180		[108]
12	$PhSC_7H_{15}^n$	178		[108]
13	$PhSC_8H_{17}^n$	185		[108]
14	$PhSC_9H_{19}^n$	180		[108]
15	$PhSC_{10}H_{21}^n$	179		[108]
16	$PhSCH{=}CH_2$	142 122 140	1.0	[108] [126] [132]
17	$PhSC_6H_{11}$-*cyclo*	195	0.4	[108]
18	PhSPh	149	1.20	[108]
19	$PhSCH_2Ph$	179	0.815	[108]
20	$PhSCH_2CH_2Cl$	143	0.985	[108]
21	$PhSCH_2CH_2Br$	153	0.86	[108]
22	$PhSC_3H_6Br$	167	0.693	[108]
23	MeSMe	223 227	0.0	[108] [126]
24	EtSEt	242	–0.20	[108, 126]
25	$Pr_2^n S$	248 245	–0.23	[108] [126]
26	$Pr_2^i S$	262 256	–0.38	[108] [126]
27	Bu_2^nS	255 248 250	–0.26	[108] [126] [132]
28	Am_2^iS	263	–0.324	[108]
29	$(PhCH_2)_2S$	166 179 160	0.43	[108] [126] [132]
30	$Am^nSC_6H_{11}$-*cyclo*	255	–0.362	[108]

bases. However, in the aliphatic series, an inverse relationship is observed: the basicity of dialkyl sulfides is significantly lower than that of their oxygen analogs [135]. This contradiction cannot be explained by the contribution of the substituent induction effect, since the latter should have a stronger influence on less electronegative sulfur atom (cf. [136]), thus decreasing electron-donating properties of aromatic sulfides. Apparently, a possible reason for the higher basicity of alkyl phenyl sulfides (compared to isostructural ethers) is a weaker p–π-interaction of the lone electron pair of the sulfur atom with π-system of the benzene ring in contrast to oxygen analogs [137]. On the other hand, the stronger basicity of alkyl phenyl sulfides with respect to their oxygen analogs can also be owing to d–π-conjugation between the sulfur atom and the benzene ring, which increases the effective negative charge on the sulfur atom. To clarify this issue, the relative basicity of saturated sulfides has been studied (Table 6.32, compounds No. 23–30). Statistical processing of the obtained results shows that the parameter Δν(OH) correlates with the induction Taft constants of substituents R:

$$\Delta\nu(\mathrm{OH}) = (220 \pm 4) - (119 \pm 14)\sum\sigma^*, r = 0.991, s = 4.7, \mathrm{n} = 8.$$

Thus, in the series of saturated sulfides, the substituents at the sulfur atom also affect the relative basicity mainly through the induction mechanism.

Generally, the correlation processing of Δν(OH) values for aliphatic and aromatic sulfides reveals that the common linear dependence of Δν(OH) on the sum of substituent induction constants $\sum\sigma^*$ is expressed quite unambiguously:

$$\Delta\nu(\mathrm{OH}) = (225 \pm 4) - (90 \pm 3)\sum\sigma^*, r = 0.985, s = 6.8, \mathrm{n} = 23.$$

Analysis of the relative basicity data (Δν (OH)) demonstrates that no other electronic effects, apart from induction one, are observed in the studied series of sulfides as well as in vinyl sulfides [126].

6.3.2 Alkyl Aryl Sulfides

It is believed that evaluation of the electron-donating ability in the formation of H-complexes, based on values of Δν(OH) shift, is no less adequate than the use of thermodynamic basicity (pK_a values) [130, 138], and can characterize the electron density distribution in donor molecule in the ground state. The contribution of induction and mesomeric effects of Alk and RC_6H_4 substituents on the electron-donating ability of sulfur atom has been evaluated using the alkyl aryl sulfides RC_6H_4SAlk as an example [139]. As a measure of the electron-donating properties, a shift of the absorption band of stretching vibration Δν(OH) of phenol during the formation of a hydrogen bond with the RC_6H_4SAlk sulfides is accepted.

Table 6.33 Δν(OH) Values for H-complexes of RC_6H_4SAlk sulfides with phenol [139]

No.	Structure	(Δν(OH) of H-complex, cm^{-1}	$\Sigma\sigma^*$
1	PhSMe	171 (172^a)	0.6
2	$3\text{-}MeC_6H_4SMe$	174	0.53
3	$4\text{-}MeC_6H_4SMe$	184 (173^b)	0.45
4	$4\text{-}MeC_6H_4SEt$	191	0.35
5	$4\text{-}MeC_6H_4SPr^i$	194	0.26
6	$4\text{-}MeC_6H_4SBu^t$	202	0.15
7	$3\text{-}FC_6H_4SMe$	151	0.95
8	$4\text{-}FC_6H_4SMe$	158	0.77
9	$4\text{-}FC_6H_4SEt$	171	0.67
10	$4\text{-}FC_6H_4SPr^i$	177	0.58
11	$4\text{-}FC_6H_4SBu^t$	184	0.47
12	$4\text{-}ClC_6H_4SMe$	151 (151^b)	0.87
13	$3\text{-}BrC_6H_4SMe$	150	0.98
14	$4\text{-}BrC_6H_4SMe$	152	0.87
15	$4\text{-}IC_6H_4SMe$	152	0.87

[a]According to [142]; [b]According to [141]

The Δν(OH) values (Table 6.33) significantly depend on the character of the alkyl and aryl substituents. This dependence is of fundamental nature, since the Δν (OH) values are connected by well-known relations with the energy characteristics of H-bonds [140, 141].

The Δν(OH) values for RC_6H_4SAlk sulfides (Table 6.33) are linearly related to the total induction effect of the substituents ($\sum\sigma^*$), which indicates the additivity of the substitution effects in this series.

$$\Delta\nu(\mathrm{OH}) = (213 \pm 6) - (68 \pm 4)\sum\sigma^*, r = 0.990, s = 2.7, n = 15.$$

Such additivity points to the fact that the S atom is not directly involved in the resonant interaction with R substituents in the benzene ring, and the main cause of the changes in Δν(OH) values is the inductive effect of the Alk and RC_6H_4 substituents.

The correlation processing of the data on the electron-donating ability of R_2S, PhSR [108], and RC_6H_4SAlk [139] shows that all the studied compounds can be divided into two groups. For each of them, there is a pronounced relationship between Δν(OH) and $\sum\sigma^*$. For alkyl aryl sulfides (No. 1–10, 16, 17, 20–22, Table 6.32; No. 2–15, Table 6.33):

$$\Delta\nu(\mathrm{OH}) = (216 \pm 2) - (72 \pm 4)\sum\sigma^*, r = 0.975, s = 4.0, n = 29;$$

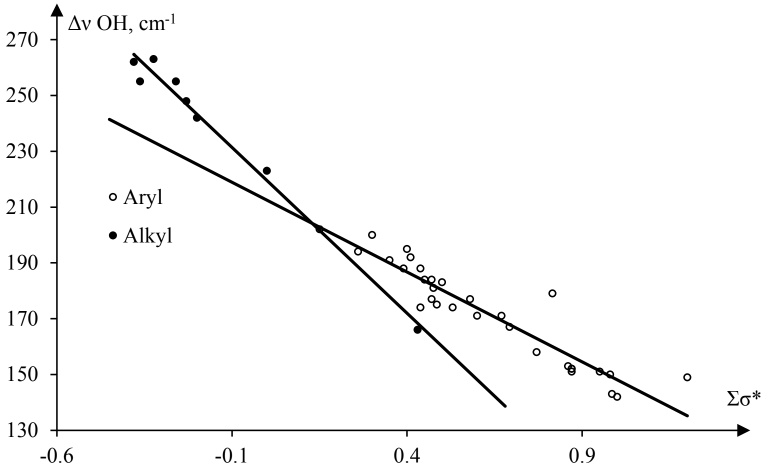


Fig. 6.11 Correlation of Δν(OH) (cm^{-1}) with $\sum\sigma^*$ constants of substituents in the series of dialkyl and alkyl aryl sulfides

For dialkyl sulfides (№ 23–30, Table 6.32):

$$\Delta\nu(\mathrm{OH}) = (220 \pm 4) - (119 \pm 14)\sum\sigma^*, r = 0.991, s = 4.7, n = 8.$$

The straight lines characterizing these dependences intersect at a point when at $\sum\sigma^* = 0$ (Fig. 6.11). At the same time, the right branch of the straight line corresponding to the first equation for aromatic sulfides is located higher than the straight line corresponding to aliphatic sulfides.

The reasons for this phenomenon still remain obscure. Traditionally, it could be explained by the *d*–π-interaction in the $-\mathrm{C_6H_4S}-$ fragment due to the presence of low-lying vacant 3*d*-orbitals at the S atom [137].

The presence of a partial positive charge on sulfur atom (for example, owing to the attachment of electron-withdrawing substituent to it) leads to contraction of its vacant orbitals that facilitates their overlapping with the π-system of the adjacent benzene ring. With an increase in the positive charge, the vacant orbitals of the sulfur atom are contracted strongly and their participation in the *d*–π-interaction becomes more noticeable. Thus, electron-withdrawing substituents make some contribution to the enhancement of the *d*–π-conjugation between the π-electron cloud of the benzene ring and sulfur atom, which apparently increases the electron density at the basicity center (sulfur atom), thus augmenting the electron-donating ability of the corresponding sulfide. On the other hand, the induction effect of electron-withdrawing substituents (–*I*-effect) does reduce the electron-donating ability of both aliphatic and aromatic sulfides.

In ArSR sulfides, the induction effect of Ar and R substituents and the *d*–π-conjugation effect act cooperatively with the conjugation effect of sulfur lone electron pair with π-system of the benzene ring, resulting in a deficit of electron density on S atom. The juxtaposition of these three divergent effects can be apparently explained by a small excessive (compared with saturated analogs) negative charge on the sulfur atom in aromatic sulfides with electron-withdrawing substituents.

It is common knowledge that owing to *d*–π-conjugation, sulfur atom exhibits π-electron-acceptor properties with respect to the benzene ring coupled with it [143]. A reduction of π-electron density on the benzene ring expectedly leads to a decrease in its electron-donating properties. The enhancement of the *d*–π-interaction of the sulfur atom with the benzene ring is accompanied by a further decrease in the π-electron-donating ability of the latter.

It has been established that the relative π-electron-donating ability of the benzene core of thioanisole ($\Delta\nu(\mathrm{OH}) = 44\ \mathrm{cm}^{-1}$) is less than that of anisole ($\Delta\nu(\mathrm{OH}) = 50\ \mathrm{cm}^{-1}$) and even ethyl benzene ($\Delta\nu(\mathrm{OH}) = 47\ \mathrm{cm}^{-1}$). Noteworthy, in sulfides PhSR, the transition from R = Me ($\Delta\nu(\mathrm{OH}) = 44\ \mathrm{cm}^{-1}$) to R = *t*-Bi ($\Delta\nu(\mathrm{OH}) = 32\ \mathrm{cm}^{-1}$) is accompanied by a decrease in π-electron-donating ability of the benzene ring, which apparently indicates a relatively small, but increasing (from Me to *t*-Bu) acceptor role of the vacant orbitals of the sulfur atom [113]. This result is in agreement with the published data [144] that in terms of the decreasing π-electron-donating ability of forming H-bonds with thiophenol, the studied aromatic compounds are located in the series: methyl phenyl ether > benzene > methyl phenyl thiol. The position of thiol in this series, established by ^{1}H NMR method, is due to a reduction of π-electron density on its benzene ring owing to *d*–π-conjugation with the sulfur atom.

The above regularities in the change of electron-donating properties of aromatic sulfides under the electronic effects of substituents at sulfur atom are explained by the hypothesis of the *d*–π-interaction. Naturally, this is not the only possible explanation. Along with the concept of vacant *d*-orbitals, there are opposite points of view in the literature [145]. At the same time, the data of ^{13}C NMR study [146] testify that for assessing the nature of the interaction between the sulfur atom and π-system of the benzene ring, it is not necessary to employ the concept of the *d*–π-effect in aromatic sulfides.

To conclude, it should be noted that the elucidation of all electronic and steric effects that cooperatively act in aromatic sulfides and define their macrocharacteristics, such as basicity, requires further experimental studies and quantum-chemical analysis using modern basis sets.

6.3.3 Oxygen and Selenium Analogs of Aromatic Sulfides

It is known that organoelementcompounds of group VI of the periodic system are fairly strong electron donors due to the presence of lone electron pairs capable of coordination.

While the literature contains extensive data [147, 148] on the electron-donating characteristics of ethers and sulfides, including aromatic ones, the information on the basic properties of selenides is scarce [135, 149]. In addition, the interpretation of the results obtained in some cases is contradictory [125].

The electron-donating properties of a series of selenides, PhSeAlk and R_2Se, have been studied by the IR spectroscopy method [150]. By analogy with similar works, the $\Delta\nu(OH)$ value is taken as a measure of the electron-donating properties, i.e., frequency shift of the stretching vibrations of phenol hydroxyl (relative to "free" phenol molecules) observed during the formation of phenol complex with the hydrogen bond. The formation of H-complexes is not accompanied by the cleavage of covalent bonds in the reacting molecules and their deep rearrangement. Therefore, the strength of H-bonds of type O–H···Se reflects the value of electron density on Se atom in the ground state of selenide, that is, ultimately its electron-donating properties [138].

Table 6.34 shows the data on the electron-donating ability of selenides (in units of $\Delta\nu(OH)$ shift of phenol as a proton donor) as well as $\Delta\nu(OH)$ values for H-complexes of O–H…O [134] and O–H…S [108] types for comparing the relative electron-donating ability of O, S, and Se atoms in isostructural compounds.

The $\Delta\nu(OH)$ values for alkyl phenyl selenides are 168–193 cm^{-1} (Table 6.34), which are significantly higher than $\Delta\nu(OH)$ values for structurally similar ethers (except for Alk = *t*-Bu), but coincide up to a measurement error (±3–5 cm^{-1}) with the $\Delta\nu(OH)$ for the corresponding sulfides [151]. At the same time, in *tert*-butyl phenyl chalcogenides, a regular decrease in $\Delta\nu(OH)$ values is observed upon transition from oxygen to selenium, which corresponds to a decrease in the electron

Table 6.34 $\Delta\nu(OH)$ Values in IR spectra of H-complexes of *n*-type of RXAlk with phenol [150]

No.	Structure	$\Delta\nu(OH)$, cm^{-1}			$\Sigma\sigma^*$
		X = O	X = S	X = Se	
1	PhXMe	150	171	168	0.6
2	PhXEt	155	183	178	0.5
3	$PhXPr^n$	159	175	178	0.485
4	$PhXPr^i$	168	192	178	0.41
5	$PhXBu^n$	162	177	177	0.47
6	$PhXBu^i$	165	181	177	0.475
7	$PhXBu^t$	212	200	189	0.3
8	$PhXAm^n$	165	174	181	0.438
9	$PhXC_6H_{11}$-*cyclo*	170	195	193	0.34
10	$PhXCH_2Ph$	136	179	174	0.815
11	PhXPh	103	149	147	0.12
12	EtXEt	282	242	234	–0.2
13	$(Pr^n)_2X$	285	248	238	–0.23
14	$(Pr^iX)_2$	297	262	252	–0.38
15	$(Bu^nX)_2$	287	255	240	–0.26

density on Se. A similar trend takes place in the series of dialkyl chalcogenides R_2O, R_2S, R_2Se: the transition from oxygen to sulfur and selenium reduces the electron-donating properties of the compound. Thus, for alkyl phenyl chalcogenides, the electron-donating ability decreases in the order Se > S > O, while in the series of dialkyl chalcogenides, the reverse sequence is observed: O > S > Se.

As for the effect of substituents at selenium atom on the electron-donating properties of selenides, here, like in the case of phenol H-complexes with ethers and sulfides, a linear correlation between the Δν(OH) values and the sum of Taft induction constants ($\sum \sigma^*$) for these substituents at Se atom is present:

$$\Delta\nu(\mathrm{OH}) = (219 \pm 12) - (84 \pm 5) \sum \sigma^*, r = 0.998, \mathrm{s} = 2.1, n = 13.$$

An exception is diphenyl selenide and benzyl phenyl selenide, whose points noticeably deviate from the regression line toward higher basicity. Therefore, the corresponding Δν(OH) values are not included in the correlation.

The high values of correlation coefficient r (0.998) and angular coefficient ρ (84 ± 5) in the correlation equation suggest that the formation of electron-donating properties of selenides occurs without the noticeable participation of the vacant orbitals of selenium atom. The fact that the dependence $\Delta\nu(\mathrm{OH}) = f(\sum \sigma^*)$ covers both aromatic and saturated selenides indicates a rather weak p–π-conjugation in the PhSe group (Fig. 6.12).

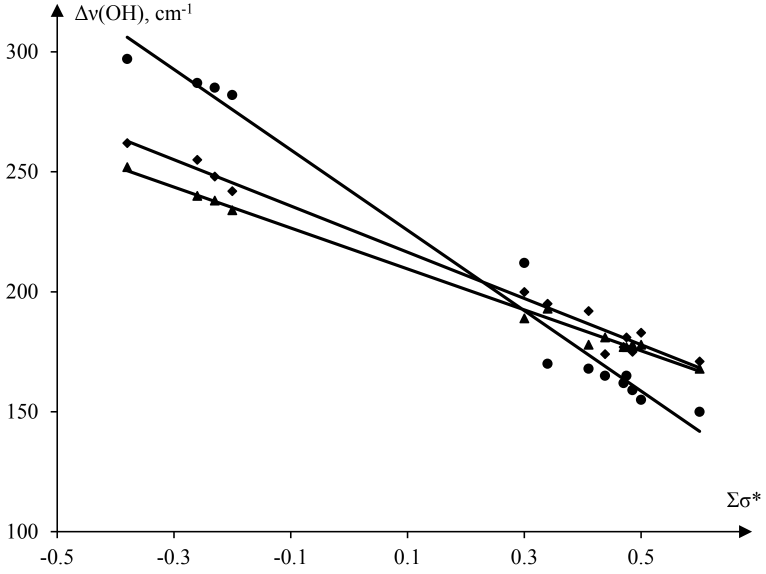


Fig. 6.12 Correlation of Δν (OH) values with $\Sigma\sigma^*$ substituent constants in the series of alkyl phenyl ethers (●), alkyl phenyl sulfides (■), and alkyl phenyl selenides (▲)

The above regularities in the substituent effects of alkyl phenyl and dialkyl chalcogenides on the electron-donating ability of the chalcogen atom may be due to the different contribution of the conjugation of lone electron pair at chalcogen atom with π-system of the benzene ring to the electron density of the molecule. *P*–π-Conjugation of a chalcogen atom with the benzene ring significantly decreases the electron density on the chalcogen atom and, hence, reduces Δν(OH) values owing to the diminishing ability of lone electron pair orbital of the chalcogen to intermolecular overlapping of the proton donor H atom with of 1*s*-orbital [152].

As follows from the ^{13}C NMR spectroscopic data [146], the ability of heteroatoms to *p*–π- conjugation decreases in the sequence O > S > Se. Therefore, it should be expected that, in the series of alkyl phenyl chalcogenides, the chalcogen atoms, in terms of their electron-donating properties, should be placed in the reverse order: O < S < Se. On the other hand, for each group of the periodic system, the basicity with respect to proton acids, H-bond donors, decreases monotonously (from top to bottom) in [135]. For alkyl compounds of group VI, the basicity order O > S > Se > Te coincides with that obtained for organic chalcogenides R_2X. Almost identical electron-donating ability of sulfides and selenides is explained [153] by the close electronegativity values of S and Se atoms. These observations relative to alkyl phenyl chalcogenides can be rationalized if to take into account the electronegativity values of phenyl moiety and the fact that the *p*–π-conjugation in sulfides is somewhat stronger than in selenides.

The *p*–π-conjugation of a heteroatom with the benzene ring is determined by the steric conditions that control the overlapping of the orbitals of lone electron pair with $2p_Z$-orbitals of neighboring carbon [154]. Therefore, steric inhibition of *p*–π-conjugation should lead to an increase in the electron-donating ability of the chalcogen atom. *tert*-Butyl phenyl chalcogenides exist in non-planar *gauche*-form due to steric hindrances to coplanarity [32]. In sulfides and selenides, the conjugation of heteroatom lone electron pair with π-system of the benzene ring is almost completely violated. This conclusion is consistent with the nature of change in the Δν(OH) values for *tert*-butyl phenyl chalcogenides in the order O > S > Se.

6.4 Electronic Effects in *S*-Aryl Thioacylates and 2-(Arylthio)ethyl Acylates

The data of the ^{13}C and ^{19}F NMR spectra of some representatives of the synthesized *S*-aryl thioacylates ArSC(O)R are given in Table 6.35. The introduction of various substituents to the S atom does not almost affect the ^{13}C and ^{19}F chemical shifts of the aromatic fragment, and substituents in the benzene ring have little influence on chemical shifts of the carbonyl group carbon. Measurement of the ^{13}C NMR chemical shifts of organyl phenyl sulfides has shown that $\delta C^{2(6)}$ and δC^4 of the ring in such compounds approximately reflect the induction effect of the R groups (see Sect. 6.1.2).

Table 6.35 The ^{13}C and ^{19}F NMR chemical shifts of *S*-aryl thioacylates ArSC(O)R

Formula	Chemical shifts, δ, ppm						
	δ ^{13}C						δ ^{19}F
	C^1	$C^{2(6)}$	$C^{3(5)}$	C^4	C = O	R	
PhSC(O)Me	129.0	134.2	128.9	128.2	192.0	29.7	
$\mathrm{PhSC(O)CCl_3^a}$	129.8	134.0	129.1	125.5	185.9	94.7	
PhSC(O)Ph	127.6	135.0	129.3	128.6	189.7	136.6 127.4 129.1 133.5	
$\mathrm{4\text{-}MeC_6H_4SC(O)Ph}$	123.9	135.0	130.1	139.7	190.4	136.8 127.5 128.7 133.5	
$\mathrm{4\text{-}FC_6H_4SC(O)Me}$	124.5	137.1	116.7	163.9	193.2	29.8	–1.51
$\mathrm{4\text{-}FeC_6H_4SC(O)Et}$	124.4	137.4	116.8	164.0	197.4	37.2 9.6	–1.73
$\mathrm{4\text{-}FC_6H_4SC(O)Pr}^{j}$	124.4	137.4	116.7	163.9	200.0	43.2 19.3	–2.18
$\mathrm{4\text{-}FC_6H_4SC(O)Bu}^{t}$	124.5	137.7	116.7	163.9	203.4	47.3 27.5	–1.15
$\mathrm{4\text{-}FC_6H_4SC(O)CH_2Cl}$	123.0	137.7	117.2	164.3	192.3	48.5	–2.56
$\mathrm{4\text{-}FC_6H_4SC(O)CCl_3}$	122.9	138.4	118.6	165.5	[b]	[b]	–3.85
$\mathrm{4\text{-}FC_6H_4SC(O)Ph}$	123.2	137.2	116.3	[b]	189.9		–1.55
$\mathrm{4\text{-}ClC_6H_4SC(O)Bu}^{t}$	128.4	137.4	132.9	123.8	203.2	47.4 27.4	
$\mathrm{4\text{-}ClC_6H_4SC(O)Ph}$	128.3	137.6	139.2	96.3	189.0	137.1 128.0 129.8 134.8	
$\mathrm{4\text{-}AcC_6H_4SC(O)Me}$	134.3	134.9	129.5	138.4	192.5 197.3	30.4 (26.7)	
$\mathrm{4\text{-}AcC_6H_4SC(O)Ph}$	133.4	135.4	129.7	127.7	188.7 197.5	136.7 134.8 129.3 (28.8)	

[a] The spectrum was recorded at 60 °C; [b] Signals of low intensity

The regularities in the mutual influence of the aryl fragment and carbonyl group, separated by a sulfur atom, are of special research interest for elucidating the nature and mechanism of transfer of substituent electronic effects through the S atom.

To study the electron conductivity of the S atom in the ground state of $\mathrm{RC_6H_4SC(O)Me}$ molecules, the effect of substituents R on the frequency of stretching vibrations of the C=O group in the IR spectra of thioacetic acid aryl esters has been analyzed [155–157].

Table 6.36 The frequency of stretching vibrations of the carbonyl group $\nu_{(C=O)}$ in IR spectra of *S*-aryl and *S*-alkyl thioacetates [155]

No.	Structure	$\nu_{(C=O)}$, cm^{-1}	σ^*
1	PhSC(O)Me	1717	0.6
2	$3\text{-MeC}_6H_4SC(O)Me$	1715	0.53
3	$4\text{-MeC}_6H_4SC(O)Me$	1712	0.45
4	$3\text{-MeOC}_6H_4SC(O)Me$	1718	0.66
5	$4\text{-MeOC}_6H_4SC(O)Me$	1713	0.44
6	$4\text{-FC}_6H_4SC(O)Me$	1721	0.77
7	$4\text{-ClC}_6H_4SC(O)Me$	1721	0.87
8	$4\text{-BrC}_6H_4SC(O)Me$	1722	0.86
9	$4\text{-IC}_6H_4SC(O)Me$	1722	0.87
10	MeSC(O)Me	1698^a	0
11	EtSC(O)Me	1697	–0.1
12	$Pr^nSC(O)Me$	1796	–0.115
13	$Bu^nSC(O)Me$	1695^b	–0.13
14	$PhCH_2SC(O)Me$	1696	0.215
15	$2,4,6\text{-Me}_3C_6H_2SC(O)Me$	1715	–

[a]According to [158]; [b]According to [159]

The stretching vibration $\nu_{(C=O)}$ is very characteristic and in the spectrum of thioesters RSC(O)Me, it is observed as an intense band at 1695–1722 cm^{-1} (Table 6.36).

A spectral peculiarity of thioesters $RC_6H_4SC(O)Me$ is that the introduction of various substituents R into the benzene ring has little effect on the position of the absorption band of the carbonyl group.

Since the substituents R in positions 3 and 4 of the benzene ring of thioacetates $RC_6H_4SC(O)Me$ are spatially removed from the C=O group, their mass does not affect the $\nu_{(C=O)}$ vibration [160], and the kinematic interactions of the C=O group with the vibration of substituents R are absent. Therefore, the observed changes in frequency can only be attributed to the electronic effects of these substituents. The regularities of the frequency $\nu_{(C=O)}$ change in carbonyl-containing compounds MeC(O)X, where X is atoms or groups containing elements of periods II and III, have been studied [161].

Analysis of $\nu_{(C=O)}$ dependence on the substituent constants shows that the employment of usual Hammett constants, resonant, or electrophilic constants does not provide even an approximate correlation between these values, while the induction Taft constants σ^* allow deducing an equation that is applicable for both aryl- and alkyl esters of thioacetic acids:

$$\nu_{(C=O)} = 1698.3 + 28.3\sigma^*; r = 0.971, s = 2.78, n = 14.$$

The point corresponding to *S*-benzyl thioacetate (No. 14) deviates significantly from the correlation straight line (Fig. 6.13). It is not excluded that this deviation is due to the contribution of the geminal conjugation effect, characteristic of benzyl sulfides, to the frequency $\nu_{(C=O)}$ [126, 162, 142].

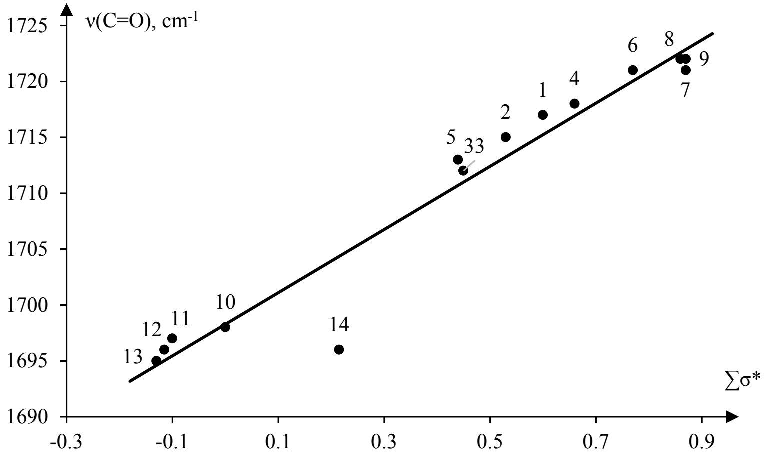


Fig. 6.13 Correlation dependence of stretching vibrations frequency $\nu_{(C=O)}$ (cm^{-1}) on substituent induction constants σ^* in RSCOMe (the numbers correspond to Table 6.36)

Exclusion of *S*-benzyl thioacetate from series (No. 14) improves the correlation:

$$\nu_{(C=O)} = 1699.4 + 27.2\sigma*; r = 0.994, s = 1.19, n = 13.$$

Thus, the above correlation analysis indicates the absence of direct polar conjugation between substituents R and SC(O)Me group in RSC(O)Me compounds. The lack of this effect in thioacetic acid esters is also confirmed by the data on dipole moments of aryl thioacetates having electron-donating and electron-withdrawing substituents in the *para*-position [163]. From this, it follows that the role of 3*d*-orbitals in electron interactions involving sulfur atom in aryl thioesters is exaggerated (*cf.* [164]).

The ^{1}H NMR spectra of 2-(4-fluorophenylthio)ethyl acylates are given in Table 6.37. The nature of the substituents in the acylate function has no noticeable effect on chemical shifts of the benzene ring and the CH_2S group protons. Alkyl groups from Me to *t*-Bu, unlike the electron-withdrawing functions CF_3 and CCl_3, do not almost influence on the shielding of the CH_2O protons. In the latter case, chemical shifts of the CH_2O protons are by ~0.3 ppm low-field shifted as compared with 2-(4-fluorophenylthio)ethyl acetate (4.22 and 4.27 ppm *vs.* 3.90 ppm).

In the IR spectra of 2-(4-fluorophenylthio)ethyl acylates, the absorption bands of skeletal vibrations of the aromatic ring appear at 1580–1593 cm^{-1}; bending C–H vibrations of 1, 4-disubstituted benzene correspond to a band at 820–833 cm^{-1}. The absorption band of the C=O group stretching vibrations is observed at 1720–1787 cm^{-1}, the signal of the C−O−C band appears at ~1220 cm^{-1}, while a weak band at 693–620 cm^{-1} is assigned the C−S bond vibration. A frequency-stable

Table 6.37 The ^1H NMR chemical shifts of 2-(4-fluorophenylthio)ethyl acylates [165]

No.	Structure	Chemical shifts, δ, ppm				
		H^2 (6)	H^3 (5)	CH_2O	CH_2S	R
1	$4\text{-}FC_6H_4SCH_2CH_2OC(O)Me$	7.00	6.68	3.90	2.83	1.20 (Me)
2	$4\text{-}FC_6H_4SCH_2CH_2OC(O)Et$	7.04	6.76	4.00	2.90	2.18 (CH_2) 1.08 (Me)
3	$4\text{-}FC_6H_4SCH_2CH_2OC(O)Pr^i$	7.04	6.72	4.00	2.83	2.26 (CH) 1.12 (Me)
4	$4\text{-}FC_6H_4SCH_2CH_2OC(O)Bu^t$	6.99	6.67	3.91	2.83	1.1 (Me)
5	$4\text{-}FC_6H_4SCH_2CH_2OC(O)CH_2Cl$	7.02	6.70	4.04	2.88	3.73 (CH_2Cl)
6	$4\text{-}FC_6H_4SCH_2CH_2OC(O)CCl_3$	7.16	6.80	4.27	3.07	
7	$4\text{-}FC_6H_4SCH_2CH_2OC(O)CF_3$	7.05	6.73	4.22	3.00	

band at 1153 cm^{-1} belongs to the stretching vibration of the C−F bond. The absorption bands of CF_3, CCl_3 stretching vibrations in acyl groups are detected in the region of 990–1153 cm^{-1} and 520–570 cm^{-1}.

6.5 ^{35}Cl NQR Spectra

6.5.1 Alkyl 4-Chlorophenyl Sulfides

The ^{35}Cl NQR study of a series of alkyl 4-chlorophenyl sulfides ClC_6H_4SR [166] has shown that there is no definite relationship between their frequencies and σ-constants of substituents R. The ^{35}Cl NQR spectra of alkyl 4-chlorophenyl sulfides and 4-chlorophenyl thiocarboxylic acid [R = C(O)R^1] (Tables 6.38 and 6.39) confirm the absence of a similar dependence for the whole $4\text{-}ClC_6H_4SR$ series [167]. Nevertheless, the NQR frequencies of alkyl 4-chlorophenyl sulfides, $4\text{-}ClC_6H_4S(CH_2)_nH$, first increase linearly (to n = 6) with the growth of n number, and then (at n = 7–12) remain almost constant (ν^{77} 34.95 MHz, Fig. 6.14). A satisfactory linear correlation ($\nu^{77} = 34.566 + 0.116n$, $r = 0.987$) is observed between ν^{77} values and the number of methylene groups n (n = 1–6). This correlation cannot be explained by the electron effect of substituents R on chlorine atom, transmitted through the system of separating bonds. As is known [65, 168, 169], the electron-donating properties of $(CH_2)_nH$ substituents, characterized by their induction constant, increase with the growth of the number of methylene groups to n = 2–3, while for n > 3, they remain almost constant and are determined by the electron-donating properties of the polymethylene chain ($\sigma^*(CH_2)_n$ –0.13) [169]. In accordance with this, in $4\text{-}ClC_6H_4S(CH_2)_nH$ series, the NQR frequency should decrease with increasing n (to n = 3), and then (if n > 3) it should be almost intact, which is not true. The observed unexpected increase in the NQR frequency

Table 6.38 The ^{35}Cl NQR frequencies at 77°K (ν^{77}) of $4\text{-}ClC_6H_4S(CH_2)_nH$ and signal-to-noise ratio (s/n) in their NQR spectra

No.	Structure	ν^{77}, MHz	s/n
1	$4\text{-}ClC_6H_4S(CH_2)_1H$	34.654[a]	7
2	$4\text{-}ClC_6H_4S(CH_2)_2H$	34.832	5
3	$4\text{-}ClC_6H_4S(CH_2)_3H$	34.892	11
4	$4\text{-}ClC_6H_4S(CH_2)_4H$	35.039	6
5	$4\text{-}ClC_6H_4S(CH_2)_5H$	35.188	5
6	$4\text{-}ClC_6H_4S(CH_2)_6H$	35.220	7
7	$4\text{-}ClC_6H_4S(CH_2)_7H$	35.152	7
8	$4\text{-}ClC_6H_4S(CH_2)_8H$	34.706	8
9	$4\text{-}ClC_6H_4S(CH_2)_9H$	35.232	8
10	$4\text{-}ClC_6H_4S(CH_2)_{10}H$	34.706	6
11	$4\text{-}ClC_6H_4S(CH_2)_{11}H$	35.293	5
12	$4\text{-}ClC_6H_4S(CH_2)_{12}H$	34.709	4

[a] Frequency of ^{35}Cl NMR almost coincides with that of given in [166]

Table 6.39 The ^{35}Cl NQR frequencies at 77°K (ν^{77}) of $4\text{-}ClC_6H_4SR$ compounds and signal-to-noise ratio (s/n) in their NQR spectra

Structure	ν^{77}, MHz		s/n
$4\text{-}ClC_6H_4SPr^i$	34.828		11
$4\text{-}ClC_6H_4SBu^t$ [a]	34.551	I phase	12
	34.706	II phase	4
	34.936		4
	34.551	III phase	4
	34.706		3
	34.945		3
	34.716	IV phase	5
	34.818		5
$4\text{-}ClC_6H_4SC(O)Ph$	34.806		3
	34.891		3
$4\text{-}ClC_6H_4SC(O)Me$[b]	34.965		10

[a] In [166], ^{35}Cl NMR frequencies of 3 lines (34.548, 34.704 and 34.944 MHz) are given; [b] Frequency of ^{35}Cl NMR almost coincides with that of given in [166]

(approximately 0.6 by MHz) with growth in the number n to 6 is apparently due to the effect of the crystal field associated with the spatial arrangement of the alkyl chain.

For $4\text{-}ClC_6H_4S(CH_2)_nH$ with n $\geq$ 7 for even n values, the NQR frequency is lower than for odd ones, like in the series $Cl(CH_2)_nH$ [169]. The NQR frequencies with even values of n = 8, 10, 12, within the measurement error limits, are almost the same (ν^{77} = 34.708 ± 0.002 MHz). NQR frequencies are almost the same for odd values of n = 7, 9, 11 (ν^{77} = 35.22 ± 0.07 MHz).

There are the most contradictory opinions about the nature of the alternation effect (see, for example [169]). Thus, it is stated that this effect is due to the different

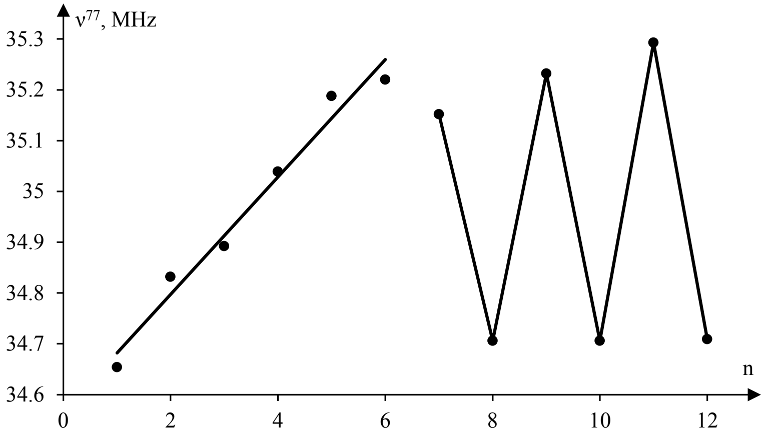


Fig. 6.14 Dependence of ^{35}Cl NQR frequencies of 4-$ClC_6H_4S(CH_2)_nH$ (ν^{77}) on the number of methylene groups (n)

types of crystalline structure of $X(CH_2)_nY$ compounds with even and odd values of n. For alkanes C_nH_{2n+2}, this difference is proved by X-ray diffraction studies. The different melting points of the neighboring members of the homologous series are explained by the alternation of the crystalline structure of these compounds [170]. A similar, but much weaker and irregular alternation of melting points is also observed in the series of alkyl aryl sulfides, 4-$ClC_6H_4S(CH_2)_nH$ (Fig. 6.15). However, changes in NQR frequencies cannot be rationalized by different crystalline structures of compounds, since alternation of some physical and chemical properties of homologs is also manifested in the liquid state [168], for example, alternation $X(CH_2)_nY$ reactivity [171]. Obviously, the difference of crystalline structure is not the cause of the alternation effect, but rather its consequence.

The NQR spectra of all 4-ClC_6H_4SR compounds (Tables 6.38 and 6.39), except for R = *t*-Bu and C(O)Ph, consist of single lines. When R = C(O)Ph, the NQR spectrum contains two lines of identical intensity. 4-$ClC_6H_4SBu^t$ can crystallize in four modifications. Consequently, it is possible to record four types of spectra differing in the number of lines and in their frequencies (Table 6.38). If for this compound to consider the arithmetic mean value of the NQR frequencies of all four modifications, then the dependence of NQR frequencies of $ClC_6H_4SCMe_nH_{3-n}$ on the induction constants of the CMe_nH_{3-n} substituents has the same form (Fig. 6.16) as for RC(O)Cl and 4-$RC_6H_4CH_2Cl$ with the same values of R [172]. Upon transition from n = 0 to n = 2, the NQR frequency increases in all three series of compounds, while at n = 3 it has a noticeably lower value than that could be expected based on the ratio of induction constants of substituents R = CH_nMe_{3-n}. Within the framework of existing ideas about electronic effects, this decrease can be explained by the so-called σ,σ-conjugation (hyperconjugation of a methyl group with a sulfur atom [172]).

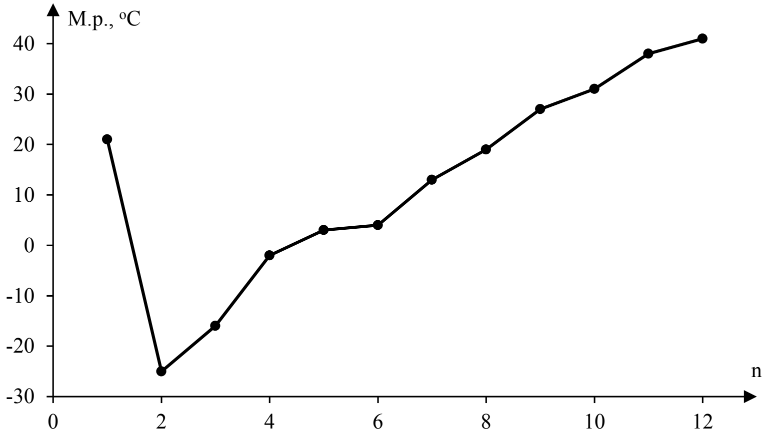


Fig. 6.15 Dependence of m.p. of 4-$ClC_6H_4S(CH_2)_nH$ on the number of methylene groups (n)

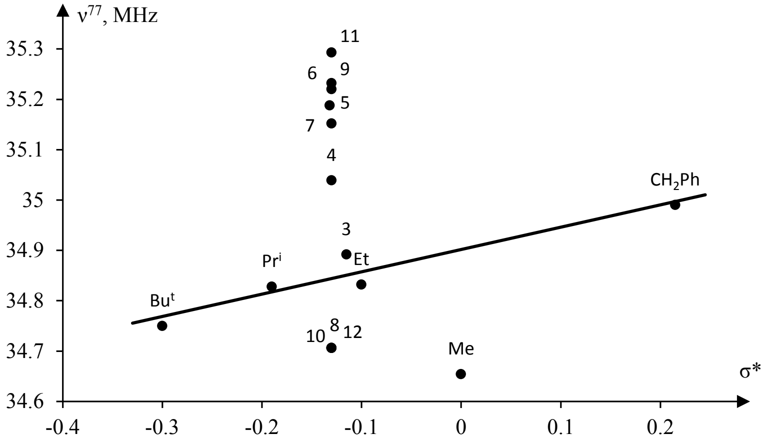


Fig. 6.16 The dependence of ^{35}Cl NQR (ν^{77}) frequencies of 4-ClC_6H_4SR on substituent R induction constants (σ^*)

The ν^{77} values of lower alkyl 4-chlorophenyl sulfides 4-ClC_6H_4SR with short-chain alkyl substituents (R = Et, *n*-Pr, *i*-Pr, *t*-Bu) and CH_2Ph increase linearly with augmenting the substituent R induction constant ($\nu^{77} = 34.605 + 3.13\sigma^*$, $r = 0.954$, $s = 0.07$). At the same time, the ν^{77} values of alkyl 4-chlorophenyl sulfides $ClC_6H_4S(CH_2)_nH$ with long-chain alkyl substituents (n = 4–7, 9, 11) lie above the correlation straight line $\nu^{77} = f(\sigma^*)$, and those of sulfides with n = 1, 8, 10, 12 are located below it (Fig. 6.16).

The NQR frequencies of 4-$ClC_6H_4SCOR^1$ with R^1 = Me и Ph are close to those of alkyl 4-chlorophenyl sulfides. This confirms a weak transmittance of the substituents electron effect in 4-ClC_6H_4SR through the C_6H_4S [166].

6.5.2 Alkyl 4-Chlorophenyl Sulfoxides and Sulfones

The high sensitivity of the NQR frequencies toward changes in the electron distribution near the indicative atom (^{35}Cl) allows one to study such fine effects as the alternation of electron density in molecules of type $X(CH_2)_nY$, peculiarities of the electronic influence of alkyl groups R = $CH_nMe_{3\text{-}n}$ (n = 0–3) [168, 172, 173]. These effects are clearly manifested in the ^{35}Cl NQR spectra of alkyl-4-chlorophenylsulfides 4-ClC_6H_4SR [167]. The ^{35}Cl NQR spectra of analogs of these compounds containing four- and hexavalent sulfur atom, 4-$ClC_6H_4S(O)R$ (R = $CH_nMe_{3\text{-}n}$) and 4-$ClC_6H_4SO_2R$ [R = $(CH_2)_nH$ and $CH_nMe_{3\text{-}n}$], are singlet in nature [174]. Due to a stronger electron-withdrawing effect of the S(O)R and SO_2R groups, the ^{35}Cl NQR frequencies of alkyl 4-chlorophenyl sulfoxides and sulfones are generally higher than those of similar sulfides (Tables 6.40 and 6.41; Figs. 6.17 and 6.18).

An increase in the number of methylene groups n in the alkyl radical R = $(CH_2)_nH$ is clearly manifested in the ^{35}Cl NQR spectra of 4-$ClC_6H_4SO_2R$. In this case, the NQR frequencies change regularly, despite the fact that a part of the molecule that is quite remote from the indicative chlorine atom is altered. Starting from n = 9, the ^{35}Cl NQR frequencies of these compounds alternate around the mean value $\nu \approx 35.25$ MHz, whereas in the series 4-$ClC_6H_4S(CH_2)_nH$, similar oscillations around the mean value $\nu \approx 34.95$ MHz begin at n = 7 (Fig. 6.17). For the compounds of each of these series, in the case of even values of n, the ^{35}Cl NQR frequencies are close to each other, but lower than for odd ones. The regularity of changes in the ^{35}Cl NQR frequencies of the initial members of

Table 6.40 The ^{35}Cl NQR frequencies at 77 K (ν^{77}) of 4-$ClC_6H_4SO_2(CH_2)_nH$ and signal-to-noise ratios in their NQR spectra

No.	Structure	ν^{77}, MHz	s/n
1	4-$ClC_6H_4SO_2(CH_2)_1H$	34.807	4
2	4-$ClC_6H_4SO_2(CH_2)_2H$	35.328	5
3	4-$ClC_6H_4SO_2(CH_2)_3H$	35.288	4
4	4-$ClC_6H_4SO_2(CH_2)_4H$	34.709	4
5	4-$ClC_6H_4SO_2(CH_2)_5H$	35.610	6
6	4-$ClC_6H_4SO_2(CH_2)_6H$	35.650	3
7	4-$ClC_6H_4SO_2(CH_2)_7H$	34.986	
8	4-$ClC_6H_4SO_2(CH_2)_8H$	35.041	4
9	4-$ClC_6H_4S(CH_2)_9H$	35.483	8
10	4-$ClC_6H_4S(CH_2)_{10}H$	34.980	15
11	4-$ClC_6H_4S(CH_2)_{11}H$	35.470	7
12	4-$ClC_6H_4S(CH_2)_{12}H$	34.998	6

Table 6.41 The ^{35}Cl NQR frequencies at 77 K (ν^{77}) of alkyl 4-chlorophenyl sulfoxides and sulfones and signal-to-noise (s/n) ratio in their NQR spectra [174]

Structure	ν^{77}, MHz	s/n
4-$ClC_6H_4S(O)Me$	35.013	3
4-$ClC_6H_4S(O)Pr^i$	35.092	3
4-$ClC_6H_4S(O)Bu^t$	35.080	9
4-$ClC_6H_4SO_2Me$	34.807	4
4-$ClC_6H_4SO_2Et$	35.328	5
4-$ClC_6H_4SO_2Pr^i$	35.188	20
4-$ClC_6H_4SO_2Bu^t$	35.129	15

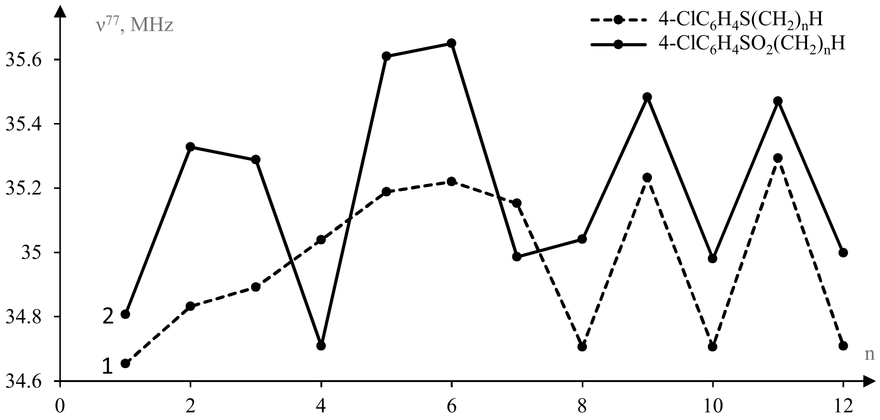


Fig. 6.17 The dependence of ^{35}Cl NQR frequencies of 4-$ClC_6H_4SO_2(CH_2)_nH$ (*1*) and 4-$ClC_6H_4S(CH_2)_nH$ (*2*) of the number n

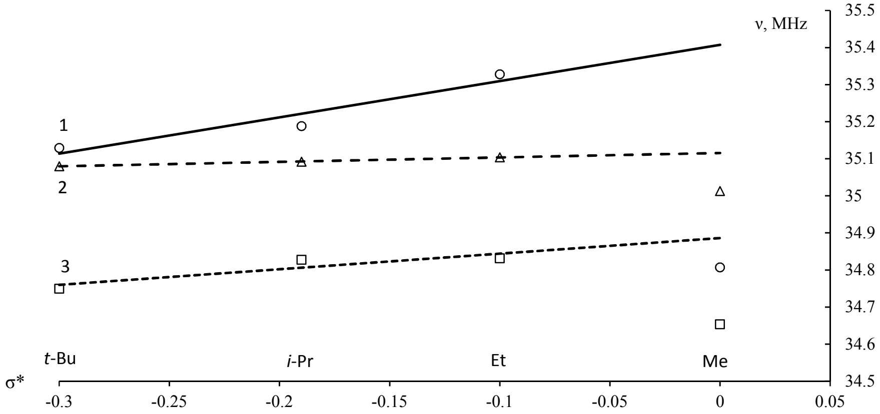


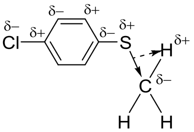
Fig. 6.18 Correlation of ^{35}Cl NQR frequencies of 4-$ClC_6H_4SO_2R$ (1), 4-$ClC_6H_4S(O)R$ (2) and 4-ClC_6H_4SR (3) with σ*-constants of R = CMe_nH_{3-n} substituents [174]

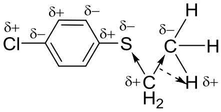
$4\text{-ClC}_6\text{H}_4\text{SO}_2(\text{CH}_2)_n\text{H}$ series (n = 1–9) is more complex than for n > 9 and for $4\text{-ClC}_6\text{H}_4\text{S}(\text{CH}_2)_n\text{H}$ sulfides (Fig. 6.17).

The values of these frequencies at n = 1, 4, 7, and 10 are significantly lower than for other values of n. In this case, the NQR frequencies of two neighboring members of the series n (2, 3 and 5, 6 and 8, 9 and 11) are close to each other (Fig. 6.17). Such character of oscillation is obviously caused by peculiarities of electrostatic through-space interaction of non-coupled atoms of the polymethylene chain, which cannot be linear in these molecules.

The ^{35}Cl NQR frequencies of $4\text{-ClC}_6\text{H}_4\text{SO}_2\text{CMe}_n\text{H}_{3\text{-}n}$ increase on going from n = 0 to n = 1 and 2, i.e., with a decrease in the induction electron-donating effect of the $\text{CH}_n\text{Me}_{3\text{-}n}$ alkyl groups (Fig. 6.18). The same regularity of changes in the ^{35}Cl NQR frequencies with increasing n in R = $\text{CH}_n\text{Me}_{3\text{-}n}$ is observed for compounds of the series $4\text{-ClC}_6\text{H}_4\text{SR}$ [167], ClC(O)R, $4\text{-ClCH}_2\text{C}_6\text{H}_4\text{R}$ [172], etc. However, this pattern is not valid for the NQR frequency of the compounds from all the above series with n = 3 (R = Me). Its value is significantly lower than that of the frequency expected from the induction effect of the methyl group. The nature of changes in the ^{35}Cl NQR frequencies of $4\text{-ClC}_6\text{H}_4\text{S(O)CH}_n\text{Me}_{3\text{-}n}$ sulfoxides (compound with n = 2 does not crystallize) is similar upon transition from n = 0 to n = 3 (Fig. 6.18).

Lowering the ^{35}Cl NQR frequency of MeC(O)Cl compared with EtC(O)Cl, $4\text{-MeC}_6\text{H}_4\text{CH}_2\text{Cl}$, etc. is explained by the polarization of the end C–C bond under the action of the charge of the methyl geminal hydrogen and by the transfer of such interaction along the chain of atoms [173]. The ^{35}Cl NQR frequencies of $4\text{-ClC}_6\text{H}_4\text{SR}$, $4\text{-ClC}_6\text{H}_4\text{SC(O)R}$, and $4\text{-ClC}_6\text{H}_4\text{SO}_2\text{R}$ are lower at R = Me than at R = Et.





The regular change in the ^{35}Cl NQR frequencies of compounds from these series with an increase of n for R = $\text{CH}_n\text{Me}_{3\text{-}n}$, i.e., when its induction effect is altered, indicates that in the above molecules, this effect is transferred to the chlorine atom.

6.6 $^{79/81}$Br NQR Spectra of Alkyl 4-Bromophenyl Sulfides

In bromine-containing compounds, the peculiarities of electronic effects of the alkyl groups (polarization of a chemical bond under the action of a partial charge of the geminal atom directly through the field and the transfer of such effect along the chain of atoms) are more pronounced than in chlorine-containing compounds. This is due to the greater polarizability of the Br atom compared to Cl [173]. To obtain additional information about the mechanism of atomic interaction in alkyl aryl sulfides, the ^{79}Br and ^{81}Br NQR spectra of alkyl 4-bromophenyl sulfides have been recorded [175].

Table 6.42 The $^{79/81}$Br NQR frequencies at 77 K (ν^{77}) of $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_n\text{H}$ and signal-to-noise ratio (s/n) in their NQR spectra [175]

n	ν^{77} (^{79}Br), MHz	s/n	ν^{77} (^{81}Br), MHz	s/n
1	269.670	60	225.280	60
2	268.081, 268.700	5.5	223.930, 224.550	15, 15
4	273.450	20	228.450	20
5	274.280	7	229.110	8
6	274.810	60	229.590	9
7	275.020	40	229.740	35
8	270.120	120	225.680	80
9	275.480	20	230.150	30

The ^{79}Br and ^{81}Br NQR spectra of alkyl 4-bromophenyl sulfides $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_n\text{H}$ (n = 1, 2, 4–9) (Table 6.42), $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_n\text{CH(CH}_3)_2$ (n = 0–2), and $4\text{-BrC}_6\text{H}_4\text{SCH}_m\text{(CH}_3)_{3\text{-m}}$ (m = 0–3) (Table 6.43) are singlet, except for of $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_2\text{H}$, which shows doublet signals. In the spectrum of $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_9\text{H}$, the line is slightly broadened. Obviously, it is an unresolved doublet. We failed to record the NQR spectrum of $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_3\text{H}$.

The $^{\mathbf{79/81}}$Br NQR frequencies of $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_n\text{H}$, unlike chlorine-containing compounds, decrease on going from n = 1 to n = 2 in accordance with the more electron-donating properties of the ethyl group compared to the methyl (Table 6.42). The same ratio of NQR frequencies at n = 1 and 2 is observed for esters $4\text{-BrC}_6\text{H}_4\text{O(CH}_2)_n\text{H}$ {$\nu(^{79}\text{Br}) = 271.371$ and 266.818 MHz} and $4\text{-ClC6H4O(CH}_2)_n\text{H}$ {$\nu(^{35}\text{Cl}) = 34.753$ and 34.381 MHz} [176]. The ^{79}Br and ^{81}Br NQR frequencies of $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_n\text{H}$ series increase almost linearly with growth of n from 4 to 7, and with a further increase in the number n they alternate (Table 6.42). Like in the series of chlorine-containing analogs [167], the frequencies with even n values are lower than with odd ones (Fig. 6.19).

Thus, the nature of changes in the $^{79/81}$Br NQR frequencies and, consequently, the electron density of halogen atom of the studied alkyl 4-bromophenyl sulfides with increasing n number is the same as in the chlorine-containing analogs. The only exceptions are compounds with n = 2. The amplitude of the ^{79}Br and ^{81}Br NQR frequency oscillations for compounds of $4\text{-BrC}_6\text{H}_4\text{S(CH}_2)_n\text{H}$ series is significantly higher than that of the ^{35}Cl NQR of chlorine-containing analogs. For the

Table 6.43 The $^{79/81}$Br NQR frequencies at 77 K (ν^{77}) of $4\text{-BrC}_6\text{H}_4\text{SR}$ and signal-to-noise ratio (s/n) in their NQR spectra [175]

R	ν^{77} (^{79}Br), MHz	s/n	ν^{77} (^{81}Br), MHz	s/n
$\text{CH(CH}_3)_2$	271.590	40	226.890	90
$\text{C(CH}_3)_3$	268.530	100	224.300	90
$\text{CH}_2\text{CH(CH}_3)_2$	268.990	2	224.710	2
$\text{(CH}_2)_2\text{CH(CH}_3)_2$	271.170	15	226.530	40

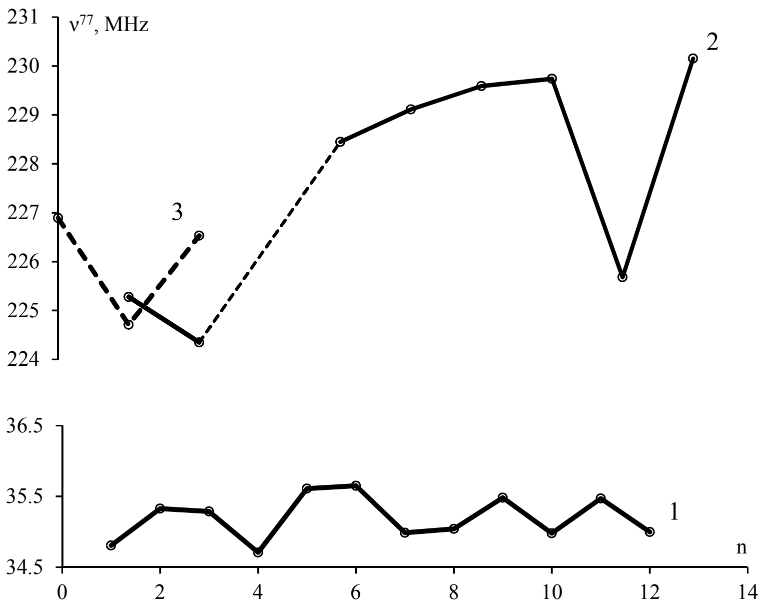


Fig. 6.19 The dependence of ^{35}Cl NQR frequencies of 4-ClC$_6$H$_4$S(CH$_2$)$_n$H (*1*) and ^{81}Br of 4-BrC$_6$H$_4$S(CH$_2$)$_n$H (*2*) and 4-BrC$_6$H$_4$S(CH$_2$)$_n$CH(Me)$_2$ (*3*) on the number n

latter, it is –0.5 MHz [167]. For compounds of 4-BrC$_6$H$_4$S(CH$_2$)$_n$H series, the experimental data is limited in number. However, it can be assumed that, if for chlorine-containing analogs, the amplitude of NQR frequencies oscillation at other values of n will be approximately the same as at n = 7–9 (–5.1 MHz), then we can state that the ratio of oscillation amplitudes in bromine- and chlorine-containing analogs (~10.2) is close to the ratio of Starks' shifts dν/dE$_z$ of halogen atoms (~12.5) bonded with the aromatic ring dν/dE$_z$ = 480 and 38.5 Hz•(kV/cm)$^{-1}$ for ^{79}Br and ^{35}Cl, respectively [177, 178]. Given that the dν /dE$_z$ values characterize polarizability of the corresponding atoms, close ratios of the oscillation amplitudes of the NQR frequencies of alkyl 4-bromo- and 4-chlorophenyl sulfides and dν/dE$_z$ values for Br and Cl atoms can confirm the correctness of the explanation of the oscillation effect by chemical polarization under the action of geminal atom charge directly through the field and by the transfer of such effect along the chain of atoms [173]. Since bromine and chlorine-containing analogs of YC$_6$H$_4$S(CH$_2$)$_n$H series differ only in halogen Y atoms, the oscillation amplitudes of their NQR frequencies are determined mainly by the polarizability of these halogen atoms. This polarizability is proportional to the polarization of the chemical bond in which the halogen atom participates [179].

The $^{79/79}$Br NQR frequencies of 4-$BrC_6H_4S(CH_2)_nCH(CH_3)_2$ oscillate with a consecutive increase in the number n from 0 to 2. The amplitude of this oscillation is 2 times less than for 4-$BrC_6H_4S(CH_2)_nH$. Unlike the latter, for 4-$BrC_6H_4S(CH_2)_nCH(CH_3)_2$, the NQR frequencies for even n are higher than for odd ones (Fig. 6.19).

The dependence of the ^{35}Cl NQR frequencies of 4-ClC_6H_4SR on the substituent induction constants R = $CH_m(Me)_{3-m}$ has the same character as for compounds from RC(O)Cl and 4-$RC_6H_4CH_2Cl$ series [167, 172, 173]; upon going from m = 0 to m = 2, the NQR frequency correlates with the substituent R induction constants (i.e., it increases). The NQR frequency of compounds with m = 3 deviates from this correlation to a low-frequency region. Such a change in the ^{35}Cl NQR frequencies of these compounds is in accordance with the concept of bond polarization under the action of a partial charge of a geminal atom directly through the field and the transfer of such an effect along the chain of atoms [166]. Upon transition from m = 0 to m = 1, the ^{79}Br and ^{81}Br NQR frequency of $BrC_6H_4SCH_m(CH_3)_{3-m}$ also increases (Table 6.43). However, with a further increase in m (to m = 2), it decreases significantly (Tables 6.42 and 6.43), in contrast to the corresponding compounds of 4-ClC_6H_4SR, RC(O)Cl, and **4**-$RC_6H_{\boldsymbol{4}}CH_{\boldsymbol{2}}Cl$. series. When m = 3, the NQR frequency $\boldsymbol{\nu}^{\boldsymbol{77}}$ is lower than with m = 1 (Tables 6.42 and 6.43). Thus, the dependence of the $^{79/81}$Br NQR frequencies of 4-$BrC_6H_{\boldsymbol{4}}SCH_m(CH_3)_{3-m}$ is similar to that of RC(O)Cl, 4-$RC_6H_4CH_2Cl$, and 4-ClC_6H_4SR except for m = 2, which, apparently, is due to the peculiarities of 4-$BrC_{\boldsymbol{6}}H_4SCH_2CH_3$ conformation.

Despite the fact that upon varying the number n in 4-$BrC_6H_4S(CH_2)_nH$ or 4-$BrC_6H_4S(CH_2)_nCMe_3$, as well as the number m in 4-$BrC_6H_4SCH_m(Me)_{3-m}$, the changes occur relatively far from the indicative Br atom, and the electron density of this atom is altered regularly (with rare exceptions).

6.7 X-Ray Fluorescent Spectra of Aromatic Thiols and Sulfides

SK_β-Fluorescence spectra are successfully employed for the conformational analysis of aryl thiols and alkyl aryl sulfides. These spectra are characteristic and are relatively easy to interpret. To study the electronic structure and conjugation of sulfur compounds, the following parameters are used: energy of the short-wave maximum A^1, which corresponds to the transition from the nonbonding level of sulfur lone electron pair to its K-vacancy (EA^1, eV); splitting level of sulfur nonbonding electron pair n_S (Δ_{13}), and the full width of the spectrum at the half height of the main maximum (S, eV) [37, 73, 97, 180–182].

The efficiency of p–π-conjugation in the series of alkyl aryl sulfides substantially depends on the geometry of molecules: the highest conjugation is observed for planar conformation (dihedral angle $\varphi \sim 0°$), while it is almost absent in the orthogonal ($\varphi \sim 90°$) conformation. The spectral parameters observed by ^{13}C

NMR, electron diffraction, UV, IR, and other methods are explained both by the superposition of planar and orthogonal conformers (with varying weight fractions) and by ideas about an effective conformation, which changes depending on the substituents coupled with sulfur atom [73, 74, 94, 180, 183, 184]. The photoelectron spectra of methyl phenyl sulfide [40] and vinyl methyl sulfide [185], recorded at 20–600 °C, show both conformations of the studied molecules, the population of less stable orthogonal conformer being naturally increased with the growth of temperature.

Figure 6.20 demonstrates that in the planar conformation favorable for n_s–π-conjugations, the n_s level splits into two: n_s–b_1 (maximum *A'* in SK_β-spectra) and $n_s + b_1$ (maximum *A''*) (*b*). In the orthogonal conformation, n_s–b_1-interaction is absent, and e_{1g} level of the benzene ring remains degenerate (*d*). Comparative efficiency of n_s–π-conjugations in a series of similar compounds can be characterized by the Δ_{13} parameter [180, 182, 186].

In the SK_β-fluorescence spectrum of H_2S, the intense short-wave peak *A* corresponds to the transition from sulfur lone electron pair (n_S) to $1s_S$ vacancy, and the maxima *B* and *C* correspond to transitions from the S–H σ-bond levels (Fig. 6.21) [180, 181, 186]. The SK_β-spectrum of PhSH indicates the presence of effective n_S–b_1-conjugation. Consequently, peak *A* significantly decreases in intensity and splits into two ones (*A′* and *A″*) corresponding to the formation of a combination of populated loosening n_S–π- and binding $n_S + \pi$-orbitals. The weak flaw at 2467.8 eV, coinciding in position with the maximum *A* in the spectrum of hydrogen sulfide, is apparently attributed to n_S level in a small admixture of the orthogonal conformer [180, 181, 186].

The SK_β-fluorescent spectrum of MeSPh evidences a more efficient (in comparison with thiophenol) n_S–b_1-conjugation, which is confirmed by a higher population of the planar conformer (Fig. 6.22a). The interaction of the phenyl moiety with a level of sulfur lone electron pair n_S occurs via the formation of binding and loosening molecular orbitals $n_S \pm \pi_R$. In the series of alkyl phenyl sulfides, the efficiency of n_S–π_R-conjugation is characterized by the following X-ray spectral parameters: 1) the value of level n_S splitting (Δ_{13}); 2) the energy of short-wave maximum $E_{A'}$; 3) the full width of SK_β spectrum (*S*); 4) the ratio of maxima intensity *B* (the most intense in the band of σ-levels) and *A*' (*A*).

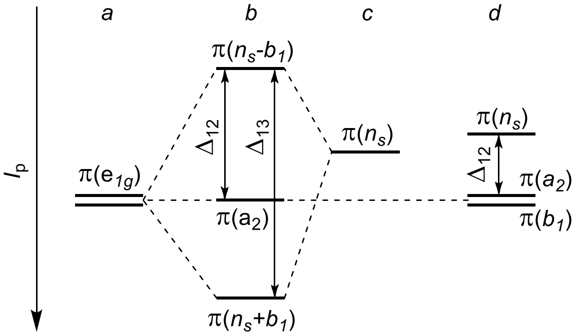


Fig. 6.20 Interaction of π-levels in benzene (**a**), alkyl aryl sulfides (**b**, **d**), and dialkyl sulfides (**c**)

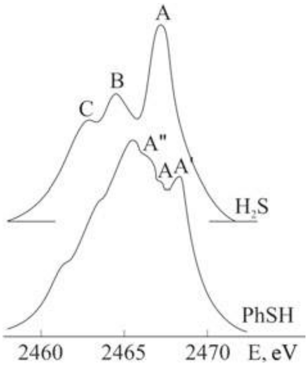


Fig. 6.21 SK_β-Fluorescence spectra of H_2S and PhSH

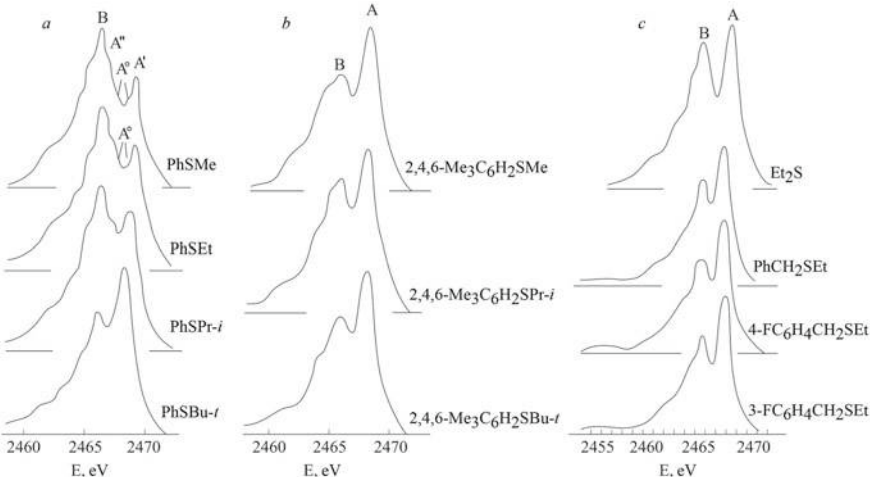


Fig. 6.22 SK_β-Fluorescence spectra of alkyl phenyl (**a**), alkyl 2,4,6-trimethyl phenyl (**b**), and benzyl ethyl sulfides (**c**)

Enhancement of the n_S–π_R-interaction should increase the loosening character of high occupied molecular orbital (HOMO), which is manifested in the short-wavelength shift of the maximum of $\boldsymbol{A'}$. However, a degree of the HOMO loosening is more correctly attributed not to a change in energy $\boldsymbol{E_{A'}}$, but to alterations in difference $\Delta E_A = E_{A'} - E_A$, where E_A is the energy of $n_S \rightarrow 1s_S$ transition, which arises if n_S level would exist in the molecule. The energy of $1s_S$ and n_S levels is defined mainly by the charge values on sulfur atom [187, 188], which are linearly related to the values of SK_α line shifts, ΔSK_α [189]. The analysis of some sulfides

(**n** = 13), for which ΔSK_α values are found and the energies of $n_S \rightarrow 1s_S$-transitions are determined, allows the following correlation relation to be derived [182]:

$$E_A(\text{eV}) = (2468.38 \pm 0.04) + (0.056 \pm 0.006)\Delta SK_\alpha(\text{eV} \cdot 100), r = 0.938, s = 0.12.$$

The relatively small correlation coefficient ($r = 0.938$) is apparently due to the rather low accuracy of E_A values measurement (± 0.1 eV). The ΔSK_α values for alkyl aryl and alkyl benzyl sulfides, the corresponding charge values on sulfur atom q_S (determined using the functional correspondence between the experimental ΔSK_α values and q_S values calculated for a number of model objects by electronegativity equalization [189]), as well as E_A and ΔE_A values , are given in Table 6.44.

An increase in the efficiency of n_S–π_R-interaction should lead to broadening of the SK_β-spectrum S. However, for a more correct comparison of parameter S with the efficiency of the considered conjugation, it is necessary to subtract a value corresponding to the σ-interactions of the sulfur atom with medium from S.

The parameters Δ_{13} and ΔE_A, obtained from the analysis of the SK_β spectra of alkyl aryl sulfides, can characterize the p–π-interaction in individual conformers, while ΔS and intensity I relate to the effective conformation of the studied sulfides. As follows from the spectral data, in methyl-, ethyl-, and isopropyl phenyl sulfides, the conformation, in which effective (n_S–b_1)-interaction occurs, is populated. The efficiency of the p–π-interaction in this conformation decreases in the order Me > Et > *i*-Pr, which indicates an increase in the dihedral angle φ in this series. This leads to the situation, when maxima, the distance between which is less than 0.5 eV, are not resolved. Since for this conformation in both sulfides, the change in the energy difference is $\Delta E_A = 0.0$ eV, and the value of splitting level n_S $\Delta_{13}(\text{R} = \text{Me}) = \Delta_{13}(\text{R} = \text{Et})$ is 0.6 eV, it can be concluded that the dihedral angles φ in these sulfides are approximately equal to each other and close to 90°. The SK_β spectra of methyl and ethyl phenyl sulfides (Fig. 6.22a) contain also two low-intense maxima A^o, which should be assigned to low-populated, substantially less coplanar conformation. In the SK_β-spectrum of isopropyl phenyl sulfide, traces of a less conjugate conformation are not detected due to the significant width of the partial spectral lines ($\sim$1.3 eV). In *tert*-butyl phenyl sulfide, all spectral parameters indicate the absence of (n_S–b_1)-interaction, and all molecules in this sulfide are located in a conformation close to orthogonal. Thus, the observed rotational isomerism of alkyl phenyl sulfides can be formally described by one effective conformation, the coplanarity of which decreases with the increasing volume of the alkyl substituent in the series Me > Et > *i*-Pr > *t*-Bu.

The values of Δ_{13}, ΔE_A, I parameters and the general shape of the SK_β-spectra of alkyl mesityl sulfides testify to the absence of (n_S–b_1)-interaction (Table 6.44, Fig. 6.22b) [182]. This evidences that these sulfides are in close-to-orthogonal conformation. The latter, apparently, does not flatten due to the steric effect in the

Table 6.44 X-ray spectral parameters of the comparative efficiency of π-conjugation and charge characteristics of the sulfur atom in alkyl organyl sulfides [182]

No.	Structure	ΔSK_α, eV•100, relative to S_8	q_S, e•100	E_A,[a] eV, relative to 2468.0 (± 0.1) eV	ΔE_A, (± 0.1) eV	Δ_{13}, (± 0.1) eV	S, eV	ΔS, eV	I_B/I_A	I
1	Et_2S	–6.1(9)[b]	–9 (2)[b]	0.2	0	0	4.4	0	0.88	1.0
2	PhSMe	–2.3(4)	–4(1)	[0.2]	0.7/0[c]	2.3/0.6[c]	5.3	0.9	1.43	1.7
3	PhSEt	–5.2(4)	–8(2)	[0.1]	0.7/0[c]	1.7/0.6[c]	5.1	0.7	1.30	1.5
4	$PhSPr^i$	–6.8(10)	–10 (2)	[0.0]	0.5	1.4	4.9	0.6	1.20	1.4
5	$PhSBu^t$	–4.6(14)	–7(3)	[0.1]	–0.1	0.0	4.0	– 0.3	0.73	0.8
6	2,4,6-$Me_3C_6H_2SMe$	–4.6(7)	–7(2)	[0.1]	0.1	0	5.3	0.9	0.72	0.9
7	2,4,6-$Me_3C_6H_2SPr^i$	–5.8(9)	–9(2)	[0.0]	0.1	0	4.7	0.3	0.81	0.9
8	2,4,6-$Me_3C_6H_2SBu^t$	–5.5(11)	–8(3)	[0.1]	–0.1	0	4.2	– 0.1	0.72	0.8
9	$PhCH_2SMe$	–5.7(9)	–9(2)	0	0	0				
10	3-$FC_6H_4CH_2SMe$	–4.0(6)	–6(2)	0	0	0				
11	4-$FC_6H_4CH_2SMe$	–5.8(11)	–9(3)	0	0	0				

[a] E_A values were calculated according to the correlation equation $E_A = (2468.38 \pm 0.04) + (0.056 \pm 0.006)\Delta SK_\alpha$; [b] In parentheses, there is given the root-mean-square error in the last significant digit taken for the 95% confidence interval according to the Student's test; [c] Data relates to the less planar conformer

ortho-methyl groups. The observed changes in ΔS parameter should be attributed to differences in σ-interaction Alk–SAr.

For alkyl vinyl sulfides, the efficiency of n_S–π_R-interactions and coplanarity of the predominantly populated conjugated conformation decreases in the order Me > Et > *i*-Pr > *t*-Bu. However, as compared with alkyl phenyl sulfides (R = Me, Et, *i*-Pr, *t*-Bu), these changes occur in a much smaller range.

Separation of SR and the aromatic fragment by the methylene group prevents the *p*–π-conjugation of the sulfur atom with the ring. This is clearly evidenced from the SK_β-fluorescence spectra of $PhCH_2SEt$, $4\text{-}FC_6H_4CH_2SEt$, and $3\text{-}FC_6H_4CH_2SEt$ (Fig. 6.22c) [73]. The short-wave intense maximum *A* corresponds to the transition from the non-binding level of sulfur lone electron pair to the *K*-vacancy, and the maxima *B* and *C* relate to transitions from the C–S σ-bond levels [73, 190]. Peak *A* remains unchanged in the above compounds and is similar to peak *A* in Et_2S.

All four parameters of the *p*–π-interaction efficiency (Table 6.44) indicate the absence of the *p*–π-conjugation of the sulfur atom with the phenyl ring in alkyl benzyl sulfides.

In the $S\boldsymbol{K}_\beta$-spectra of alkyl phenyl sulfoxides and sulfones (Fig. 6.23, Table 6.45), an additional short-wave maximum D appears (compared to the corresponding sulfides), which is attributed to transitions from levels, formed due to the ***p***–π-interaction of 3***p***-atomic orbitals of sulfur with 2***p***-atomic orbitals of oxygen. Therefore, the degree of the ***p***–π-conjugation of S with the phenyl ring in sulfoxides and sulfones decreases in comparison with the corresponding sulfides. A high positive charge on S atoms, detected in sulfoxides and sulfones, indicates a

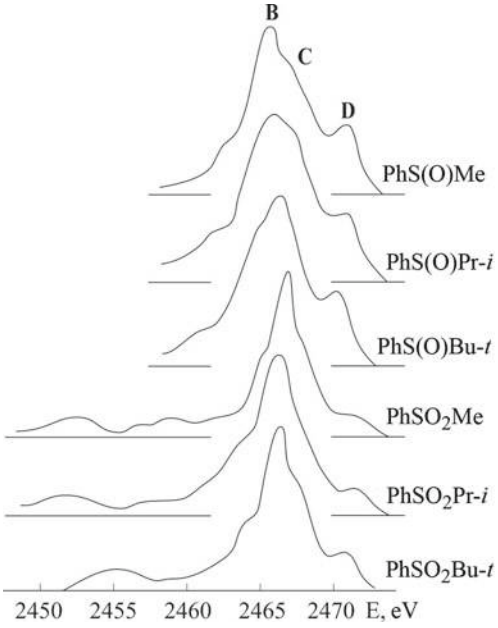


Fig. 6.23 SK_β-Fluorescence spectra of alkyl phenyl sulfoxides and sulfones

Table 6.45 X-ray spectral characteristics of the electronic structure of alkyl phenyl sulfoxides and sulfones

No.	Structure	ΔSK_α, eV•100, relative to S_8	$q_{S,}$ e•100	Positions[a] of maxima in SK_β-spectra, eV (± 0.1)			*S*, eV
				B	C	D	
1	PhS(O)Me	36(1)	40(1)	2.9	1	2.3	4.8
2	$PhS(O)Pr^i$	36(1)	40(1)	2.3	1	2.0	5.3
3	$PhS(O)Bu^t$	36(1)	40(1)	2.0		2.0	4.7
4	$PhSO_2Me$	81(1)	69(1)	1.5		3.0	2.7
5	$PhSO_2Pr^i$	80(1)	68(1)	2.0		2.9	3.9
6	$PhSO_2Bu^t$	80(1)	68(1)	1.8		2.5	3.5

[a] Positions of maxima are given relative to energy of maximum A in SK_β-spectrum of Me_2S (2468.2 eV)

significant transfer of electron density from S to O atom. The electron density on the S atom in ***tert***-butyl sulfoxide and sulfone (No. 3 and 6, Table 6.45) is increased as compared to their analogs, which can be explained by the donor effect of ***t***-Bu radical with respect to the positively charged S atom [73].

The investigations of the S*L*-fluorescence spectra, including $3d \rightarrow 2p$ and $3\ s \rightarrow 2p$ transitions, allow electron density on vacant 3*d*-orbitals of S atom to be reliably detected. Systematic X-ray spectral analysis of wide series of sulfur-containing compounds, including almost all types of chemical interactions known for S atom, shows that the 3*d*(S)-population linearly depends on the SK_α-shift and can be manifested only if sulfur atom contains some critical positive charge: $\Delta SK_\alpha \geq +0.10$ eV (rel. S_8) [190]. In alkyl phenyl sulfides, the charge on the sulfur atom is significantly less than this value, which testifies to the absence of a noticeable population of their 3*d*-orbitals (Table 6.44, No. 2–5). The S*L*-fluorescence spectra of alkyl phenyl sulfides (R = Me, Et, i-Pr, t-Bu) are identical to those of Ph_2S and Me_2S. In alkyl phenyl sulfoxides and to a still greater extent in alkyl phenyl sulfones, the charge on the S atom is quite sufficient for the population of 3*d*-orbitals, which is confirmed by the S*L*-fluorescence spectra of these molecules (Table 6.45).

Thus, the X-ray fluorescence permits to obtain new reliable information about the conjugation effects of the S atom in various valence states, as well as SO and SO_2 groups with a benzene ring.

6.8 Theoretical Studies of the Structure and Electronic Properties of Aromatic Thiols and Their Derivatives

An important geometric characteristic of thiophenol is the torsion angle φ between the plane of the benzene ring and $C_{sp}2{-}S{-}H$ bond, characterizing the molecular conformation. Most experimental studies revealed the absence of conformational isomerism in the thiophenol molecule. Molecular orbital computations [191] of the internal barrier found predominantly twofold barriers, but with a large range of values: 14.8 (STO-3G); −6.8 (3–21G); −4.5 (3–21G*); −4.4 (6–31G); −2.7 kJ/mol (6–31G*); a negative sign indicates that the orthogonal conformer is most stable. The contrast with the experimental indications is disconcerting. Nonempirical Hartree–Fock approximations with 6-311F(d) and 6-311G(p, d) basis sets [192] showed that the minimum energy occurs at a torsion angle near 38°. The barrier to the transition to the planar conformation is 0.430 kJ/mol, and to the orthogonal is 0.633 kJ/mol.

Single-determinant Hartree–Fock treatment with the 6-31G(d), 6-31G(d,p), 6-31++G(d,p), DZV, 6-311G(d,p), and TZV basis sets, as well as the allowance for correlation energy in terms of the Møller–Plesset second-order perturbation theory and DFT computational schemes (Becke 3LYP hybrid functional) estimate $C_{sp}2{-}S$ torsional potential functions for thiophenol [193]. The MP2(fc)/6-31G(d), MP2(fc)/6-31G(d,p), and Becke 3LYP/6-311G(d,p) results suggest free rotation about the $C_{sp}2{-}S$ bond. It should be noted that the efficient conformation of the molecule is a conjugated one. Interaction of lone electron pairs of sulfur and the ring π system in different conformations was considered using the natural bond orbital procedure.

It is established that in thiophenol, the interaction of n_p sulfur atom with the π-system is estimated to be 87.15 kJ/mol at $\varphi = 0^o$ and 47.53 kJ/mol at $\varphi = 45^o$. At $\varphi = 90^o$, the interaction of n_p sulfur atom with the antibonding orbitals of the π-system is less than 2 kJ/mol. Therefore, in the conformation with a torsion angle φ of 45º, the *p–π*-interaction of the lone electron pair of the nitrogen atom with the π-system of the ring is quite effective, although it is by ~2 times less effective than in the planar conformation. In the orthogonal conformation, the *p–π*-interaction is almost absent.

The most important conformational characteristic of alkyl aryl sulfides is the torsion (dihedral) angle between the planes of the benzene ring and $C_{sp}2{-}S{-}C_{sp}3$ bonds. The extreme case of non-planar conformation is the orthogonal form (φ 90 and 270º). The molecular conformation is governed by two major factors: *n–π*-conjugation of the sulfur lone electron pairs with the system of the aromatic ring, stabilizing the planar form, and the steric interactions of the *ortho*-hydrogen atoms of the ring with the hydrogen atom of the alkyl group, preventing the realization of the planar structure. Most experimental studies (Sects. 6.1, 6.2, 6.7) revealed the presence of two conformers, planar and orthogonal. Despite different estimates of the population of the orthogonal conformer, obtained by different methods, all these prefer the planar conformer as the most energetically favorable.

The results of quantum-chemical calculations are characterized by greater discrepancies concerning the most favorable conformer of methyl phenyl sulfide. MNDO and nonempirical Hartree–Fock approximations with D95*, 6-31G*, 6-31G**, 6-31++G**, and 6-311G** basis sets together with Moeller–Plesse calculations (MP2, MP3, MP4) with account taken of electronic correlation give preference to the orthogonal conformer [99, 194, 195]. Semiempirical calculations (AM, PM3) and nonempirical methods with the use of STO-3G and STO-3G* basis sets [196], as well as BLYP, B3LYP, and B3P86 calculations, predict greater stability of the planar conformer and confirm free rotation of the fragments around the $C_{sp}2{-}S$ bond [194, 195]. The by 6-311++G(3d,p) calculations with and without accounting for electronic correlation evidence also the coplanar orientation of the C −S−C fragment and the benzene ring [197], which agrees with the most experimental studies. Comparison of the experimental dipole moment of methyl phenyl sulfide with those calculated by the B3LYP and MP2 procedures with the use of various basis sets shows a good reproducibility with most of the latter. The best agreement was achieved with the B3LYP/6-311 ++G(3df,p) basis set.

The potential functions of internal rotation around the $C_{sp}{}^2{-}S$ bond in the compounds 4-RC_6H_4SMe (R = NH_2, OMe, Me, H, F, Cl, CN, NO_2) are studied by ab initio quantum-chemical calculations taking into account the correlation energy for all the electrons (MP2/6-31G*) and in the approximation of the density functional theory (B3LYP/6-31G*) [198]. As the electron-donor power of the *p*-substituents decreases and their electron-acceptor power grows, the molecular conformation changes in the sequence orthogonal-free rotation-planar.

In 4-RC_6H_4SMe molecules, electron-donor *para*-substituents destabilize the planar conformation, and electron-acceptor *para*-substituents stabilize it. This is reflected in the profile of the potential functions of internal rotation and in the heights of barriers to rotation around the $C_{sp}{}^2{-}S$ bond. As the electron-donating power of *p*-substituents is made weaker and their electron-withdrawing power is enhanced, the molecular conformation changes in the order orthogonal-free rotation-planar. As compared to the MP2/6-31G* method, calculations in the B3LYP/6-31G* approximation overestimate the stability of the planar form. The HF/6-31G* calculations overestimate the stability of the orthogonal conformation of the molecules in question [54], and the results of AM1 and PM3 semiempirical calculations suggest the planar structure of these molecules, with the rotation barrier height varying from 5.3 (NH_2) to 17.8 (NO_2) kJ/mol (AM1 [196]).

The interaction of the sulfur lone electron pairs with the aromatic ring is studied by the natural bond orbital method. The major factors responsible for braked rotation around the $Csp^2{-}S$ bond are the $n_\pi{-}\pi^*$-conjugation of the sulfur lone electron pairs with the aromatic ring, stabilizing the planar conformation, and the steric interactions of the Me group with the *ortho*-H atoms of the aromatic ring, preventing the realization of the planar structure. The nonhybridized lone electron pair efficiently interacts with the antibonding π* orbitals of the aromatic fragment only in the conformations close to planar, with the interaction energy growing as the electron-withdrawing power of *para*-substituents gets stronger and their electron-donating power weakens. Therefore, changes in the energy of the n_π–π*-interaction under the influence of *para*-substituents affect the relative contribution of the electronic and steric factors and hence the kind of the energetically favorable conformation. The higher conformational lability of 4-RC_6H_4SMe molecules compared to 4-RC_6H_4OMe molecules is due to less efficient, compared to the O atom, n_π–π*-interaction of the S atom with the aromatic fragment and to a stronger steric hindrance to the formation of the planar structure (smaller CSC bond angles compared to COC angles).

The effect that the conformational changes occurring upon replacement of *para*-substituents exert on the electron density redistribution is demonstrated. In the 4-RC_6H_4SMe series, as in the 4-RC_6H_4OMe series, the replacement of *para*-substituents in the ring (going from electron donors to electron acceptors) decreases the electron density on the heteroatom (O or S) and on H_{Me} atoms and increases the electron density on the C_{Me} atoms. Changes in the molecular conformation affect the charge distribution to a greater extent than does the replacement of substituents (going from NH_2 to NO_2) within the same conformation. The wider range of charge variation for atoms of the SMe group, compared to the OMe group, is due to the higher polarizability of the thioaromatic fragment and the conformational changes in the 4-RC_6H_4SMe molecules, indicated by the electronic effects of the *para*-substituents. Thus, in 4-RC_6H_4SMe, the conformational distortion of the n_π-π*-interaction plays an essential role in the electron density redistribution.

Ab initio MO calculations (3-21G*//3-1G* basis set) for methyl phenyl sulphoxide have shown [199] that in the energy profile for rotation around the $C_{sp}2$−S bond one minimum is present and corresponds to the S=O bond which is nearly eclipsed with the phenyl ring (twist angle 7.3°). Two energy minima are found for methyl 2-fluorophenyl sulfoxide in the more stable conformation; the S−O bond is coplanar with the ring and *anti* with respect to the *ortho* fluorine substituent. In the less stable ground state, the lone pair of the sulfur atom settles in the nodal plane of the π-electron cloud of the phenyl ring. This conformation is structurally close to the conformational ground state of 2,6-difluorophenyl derivative. The energy barrier for internal rotation corresponds to the S−C bond of the methyl sulphinyl group eclipsed with one *ortho* C–H bond. A significantly higher twist of the S−O bond with respect to the ring was found in the 2,6-difluorophenyl sulfoxide. These results from calculations are in qualitative agreement with the conclusions of a multinuclear NMR experimental study [200] carried out on a number of ring-substituted methyl phenyl sulphoxides. The ground-state conformation of these molecules is thus strictly dependent on the degree of substitution of the *ortho*-positions of the phenyl ring, and only to a minor extent, if at all, on the substituents on the other positions of the ring.

The preferred conformations of the methylsulphinyl group in a number of phenyl methyl sulphoxides substituted in the phenyl ring with one, two, or three fluorine atoms have been studied by employing a multinuclear NMR approach [201]. From the ^1H, ^{13}C, and ^{17}O chemical shifts of the methylsulphinyl group, and the torsional angles obtained either from MO calculations [199] or experimental determinations for a number of the compounds, empirical correlations have been derived which enabled us to extract the preferred orientation of the S−O bond or of the methyl group relative to the phenyl ring in all the molecules examined. For a limited number of the compounds, the structure of the preferred conformer is satisfactorily close to the solid-state structure found in an independent study carried out with X-ray diffraction. The twist of the S−O bond relative to the phenyl ring changes as a function of the number of *ortho* substituents, being highest when two substituents are present. The lowest twist, torsional angle nearly zero, was found in *ortho*-monosubstituted compounds and the S−O bond is oriented toward the opposite side with respect to the substituent. Analyses were also carried out of the conformational dependence of long-range $^nJ_{(HF)}$ and $^nJ_{(CF)}$ coupling constants, where the first nucleus in the parentheses refers to the methylsulphinyl group. The behavior of these coupling constants as a function of internal rotation around the exocyclic C−S bond was derived from semi-empirical INDO MO FPT calculations, and scaled interpolating equations were derived in order to reproduce the experimental results. It thus emerges that $^5J_{(HF)}$, $^4J_{(CF)}$, $^5J_{(CF),}$ and $^6J_{(CF)}$ are conformationally dependent and show, experimentally, significant changes. These parameters can be usefully employed for the conformational analysis of methyl phenyl sulphoxides.

The solid-state crystal and molecular structure of a number of ring-substituted methyl phenyl sulfoxides, containing mainly fluorine substituents, has been obtained by X-ray analysis [202]. The conformation, found for the molecules, has geometrical features very close to those of the most stable conformer predicted by ab initio MO calculations. In those compounds without *ortho* substituents, the S=O bond is only slightly twisted from being coplanar with the ring plane, while a larger twist is present when both *ortho*-positions are substituted. In the presence of one *ortho* substituent, the S=O bond adopts an anti-orientation and is almost coplanar with the ring. With the unsymmetrically substituted derivatives, two conformers are possible and in the case of *ortho* substitution, the energy difference (18–24 kJ/mol) is large enough to have crystals only of the lower energy conformer. When the ortho-positions are both free, the energy difference is quite low (0.6 kJ/mol) and both conformers are found in the same crystal.

The potential functions of internal rotation about the $C_{sp}2{-}S$ bonds for $PhSOCX_3$ and $PhSO_2CX_3$ species (X = H or F) have been obtained at the MP2 (full)/6–31 + G(d) level of ab initio theory [203]. It is found that the spatial structures with the plane of $C_{sp}{}^2{-}S{-}C_{sp}{}^3$ bonds, which is near perpendicular to the benzene ring plane, are the energy-favorable conformations. The values of the rotational barrier about the $C_{sp}{}^2{-}S$ bond are equal to 21.2 kJ/mol (PhSOMe), 29.0 kJ/mol ($PhSOCF_3$), 20.4 kJ/mol ($PhSO_2Me$), and 28.2 ($PhSO_2CF_3$). On the basis of the Natural Bond Orbital (NBO) analysis results, it has been revealed that the double S=O bond is a strongly polarized covalent σ-bond, whereas π-bond electrons practically are localized on the oxygen atom. The S=O bond order for aromatic sulfoxides and sulphones is mainly caused by hyperconjugational interactions according to the LP(O) $\rightarrow \sigma^*(S{-}C_{ipso})$ and LP(O) $\rightarrow \sigma^*(S{-}C_Y)$ mechanisms. In sulphones, there is also the additional mechanism of hyperconjugational interactions such as $LP(O^1 \rightarrow \sigma^*(S{-}O^2)$ and $LP(O^2) \rightarrow \sigma^*(S{-}O^1)$. With the replacement of one hydrogen atom on the $-CX_3$ group, the charge loss of the unsubstituted benzene molecule increases: $-SOCH_3 < -SO_2CH_3 < -SOCF_3 < -SO_2CF_3$. The substitution of the $-CH_3$ group for the $-CF_3$ group weakly influences the charge value on the sulfur atom but affects the acceptor characteristics of the substituent to a greater extent than the variation of the sulfur atom coordination.

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7 Some Areas of Application of Aromatic Thiols and Their Derivatives

The application areas of aromatic thiols and their derivatives are ever-expanding. To cover all these areas, a special monograph would be required. Here we will only briefly discuss some recent trends in the use of these compounds. Also, selected examples (in some cases, unpublished ones) of practical application of aromatic thiol derivatives, the synthesis of which was discussed in previous chapters, for modifying technical oils and in analytical chemistry, will be considered.

7.1 Versatile Reagents

Currently, organic sulfides and polysulfides find application in the composition of various compounds, where they are present as arylthio fragments, often essentially changing the characteristics of a material or a biologically active drug. For instance, in the review [1], the properties of sulfur containing plastics, such as sulfides, polysulfides, and vinyl sulfides including those with aromatic fragments, are discussed. Such polymers have a high refractive index, good impact resistance and are perfectly processed, which allows them to be recommended for the manufacture of contact lenses.

In recent years, interest in the application of addition reactions of thiols, including aromatic ones, to the double (less often to the triple) bonds to produce polymeric materials with improved properties is rapidly growing. Such addition proceeds in the absence of metal catalysts. Its implementation requires radical initiators or ultraviolet radiation. Sometimes for this purpose, it is enough only heating. As a rule, the processes are quantitative and highly regioselective. By

I. A. Aliyev et al., *Aromatic Thiols and Their Derivatives*,
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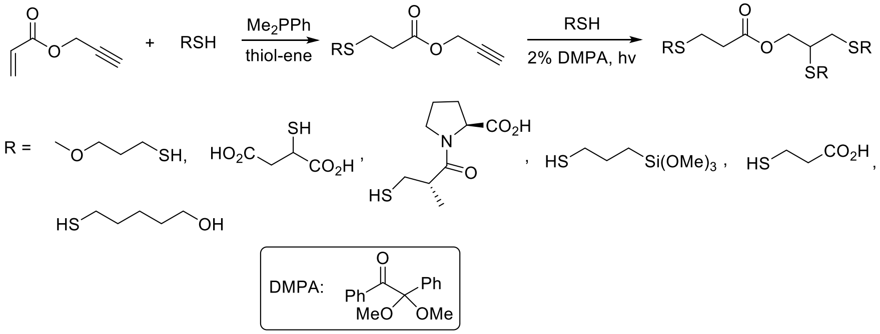
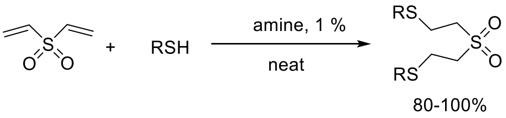
analogy with the cycloaddition of azides to acetylenes [2], these processes are referred to as thiol-ene click reactions (thiol-ene click chemistry). Unexpectedly, the addition reactions of thiols to unsaturated compounds are going mainstream: over the past decade, numerous reviews have been devoted to this topic [3–7].

A facile synthesis of polyfunctional materials involves consecutive reactions of nucleophilic addition of thiols to the triple bonds and radical addition to the double bonds, catalyzed by phosphines and radical initiators, respectively [8].

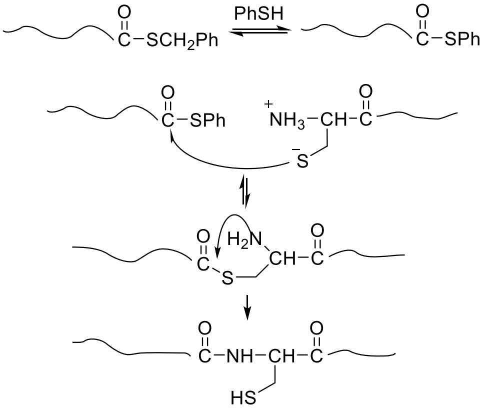


Activated alkenes (methacrylates, fumarates, maleimides, etc.) also easily interact with thiols under nucleophilic conditions. NEt_3 or other amines are used as catalysts [9].

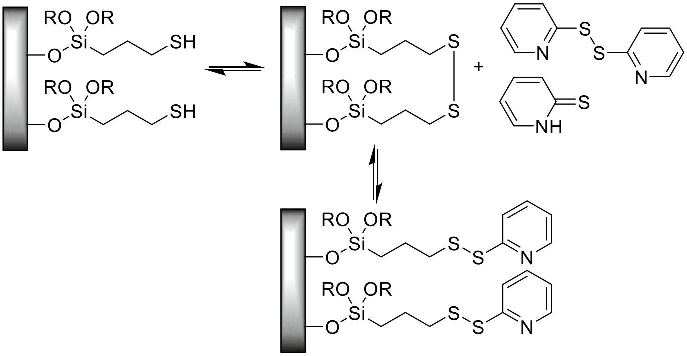


amine: DABCO, imidazole, 1-methlimidazole, 4-dimethylaminopyridine

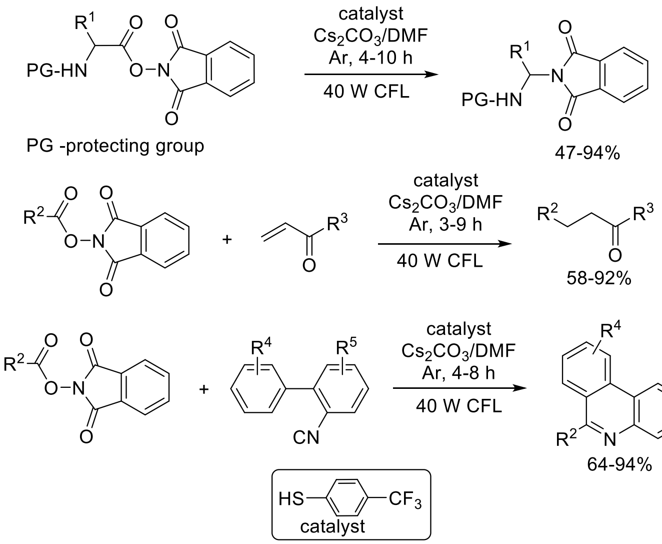
In situ transthioesterification reactions are widely employed in the chemical synthesis of proteins. In native chemical ligation, unprotected peptide thiocarboxylates react with a second peptide containing an *N*-terminal cysteine residue. The application of aromatic thiols owing to easy transthioesterification allows reducing the thiol group of cysteine and synthesizing peptides. Model synthesis of a barnase chain consisting of 110 amino acids has shown that the usage of thiophenol as an additive ensures a fast selective reaction delivering the target product bound by an amide bond [10].



Compounds containing disulfide bonds are used for the preparation of self-assembled monolayers, which have found vast applications as surface coatings, in micro- and nano-fabrication, molecular electronics, sensors, etc. [11]. A successful reaction scheme for obtaining reactive disulfide bonds on silicon surfaces derivatized with mercapto groups has been demonstrated [12]. The thiopyridyl group is employed to protect the thiol group to be utilized for the immobilization of thiol-containing molecules to the surface.

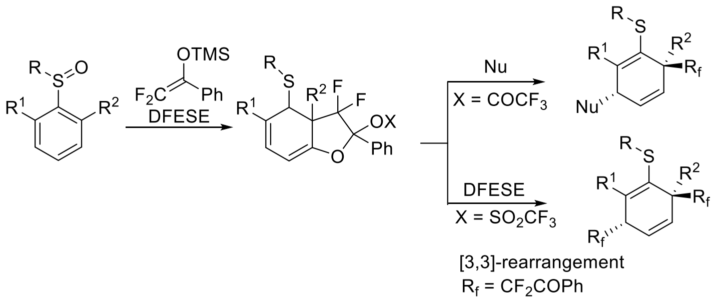


Thiophenols are effective organocatalysts for redox-decarboxylation of *N*-acetoxyphthalimides and coupling of the latter with alkenes or substituted 2-isocyanobiphenyls [13]. The reactions proceed at room temperature in DMF under the action of visible light (a 40 W fluorescent lamp).



The key stage of these reactions involves one-electron transfer from the arylthiolate, formed under the action of Cs_2CO_3, to the phthalimide moiety, excited by light radiation. In the absence of a thiol, the reactions are not effective. This interesting discovery provides a new and environmentally friendly strategy for the photo-reductive transformation of organic molecules in visible light.

Dearomatization is a powerful strategy that enables the direct conversion of readily available 2-D arenes to value-added 3-D alicyclic architectures in a step-economical manner. The dearomatization protocol has great potential in the synthesis of natural products and bioactive compounds. The dearomatization of aryl sulfoxides with difluoroenol silyl ether (DFESE) using a rearrangement/addition protocol has been described. Through the choice of appropriate sulfoxide activators (Tf_2O or TFAA), one or two difluoroalkyl groups according to the demand could be incorporated into the dearomatized products. Remarkably, both the mono- and dual-difluoroalkylation processes exhibit excellent functional group compatibility and regioselectivity for asymmetric aryl sulfoxides. In addition to Et_3SiH and DFESE, other carbon and heteroatom nucleophiles are also suitable for capturing the dearomatized difluoroalkylated intermediate. The dearomatization protocol has great potential in the synthesis of natural products and bioactive compounds.



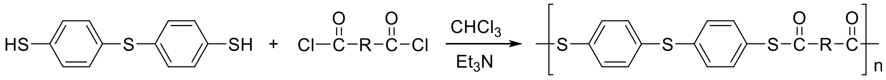
Among rapidly progressing areas of application of aromatic sulfones are synthons and auxiliary reagents for organic synthesis. This issue is covered in a comprehensive review by E.N. Prilezhaeva, in which the role of sulfones and sulfoxides, including aromatic ones, in the total synthesis of natural compounds is thoroughly analyzed [14]. The development of new methodologies for asymmetric synthesis, allowing selectively obtaining various structures in enantiomerically pure configurations, is one of the urgent challenges of organic chemistry. In this line, sulfones, especially those with aromatic radicals, start to be intensively employed to address this challenge. The main trends in application of sulfones in organocatalytic processes are summarized in reviews [15, 16].

New synthetic methods involving aryl vinyl sulfones are developed in the chemistry of natural compounds [17]. An effective strategy for forming a new C–C bond is the asymmetric Michael reaction. In the presence of metal complex catalysts (Binap•Cu и TolBinap•Cu), α,β-unsaturated sulfones add the Grignard reagents or diorganylzincates with high enantioselectivity (ee is up to 98%) [18, 19]. The Michael asymmetric *N*-isopropyl-2,2’-bipyrrolidine-catalyzed addition of aldehydes to aryl vinyl sulfones is described [20]. Three years later, the first asymmetric addition of ketones to aryl vinyl sulfones, catalyzed by amino derivative of the cinchonine alkaloid, has been implemented [21].

7.2 Advanced Polymers

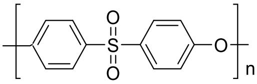
Sulfur containing polymers play a key role as materials with high chemical and thermal stability and as active components for optoelectronic and electrical devices.

Aromatic dithiols easily undergo a condensation reaction with acid dichlorides (60 °C, 0.5 h) to afford higher molecular thioesters with good performance characteristics [22, 23]. For instance, bis(mercaptophenyl)sulfide and acyl dichloride polythioesters (Mw 39000–185000) possess high thermal resistance [22]. Similar polycondensation of 4,4’-biphenyldithiol with bis(chloroanhydrides) leads to polythioesters with good adhesive properties [23].



Branched polyphenylene sulfide polymers can be employed as encapsulating matrices to stabilize nanoparticles, e.g. to obtain nanoscale palladium particles [24].

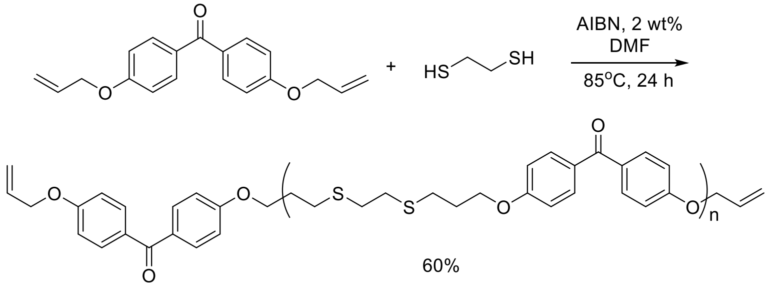
Poly(ether sulphone) (PES) is one of the most widely used and versatile high temperature thermoplastic engineering plastics, which can be employed continuously in the range of −110 to 200 °C for a long time without any substantial decline of its excellent optical transparency and mechanical properties [25]. It also exhibits good flame-retardancy, very low rate of creep, high resistance to failure by static fatigue, and dimensionally stability. All these advantages make PES a good candidate for the substrates of optoelectronic devices.



PES

Functionalized polyarylene-type polymers including polysulfones are potential candidates as the key material to attain enhanced performance and lifetime of proton exchange membrane fuel cells [26–28].

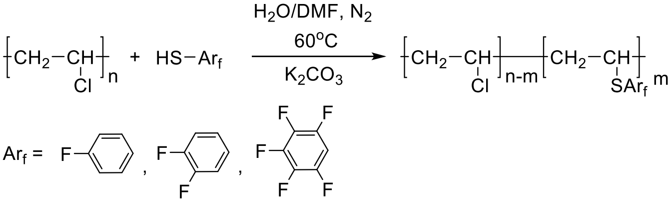
Radical thiol-ene reactions represent a convenient tool for the post-polymerization functionalization of polymers. They are also employed in the synthesis of linear macromonomers. The reactions proceed under the action of UV-irradiation or upon heating in the presence of initiators (for example, AIBN) [29].



Thiol-ene click reactions are successfully applied in the creation of new materials for medicine, in particular, for dentistry [30–32]. Modification of methacrylates improves flexural strength, shrinkage stress, depth of cure, while maintaining equivalent flexural modulus of the materials. A general strategy for the stabilization and functionalization of polymer coatings, particles, and capsules via photoinduced addition of thiols to the double bond has been developed [33]. Additional functionalization of coatings allows obtaining particles capable of binding the protein (for example, succinimide groups) or resistant to the action of the protein (acrylate functions). This opens prospects for the design of new systems for solid particles and microreactors delivery.

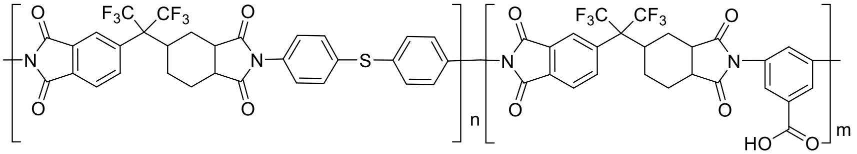
The reactions of thiol-ene coupling are successfully exploited in polymer chemistry. Application of this approach in the chemical modification of polymers allows such properties of the materials as adhesion, bioactivity, etc., to be directly controlled. Derivatives of unsaturated fatty acids, containing from one to four multiple bonds, are abundant in vegetable oils, fats, and cell membrane lipids. A special review [6] surveys a thiol-ene coupling of vegetable oils with thiols. Such a modification may be useful for the film formation of paint coatings, for example, oil paints, which are based on drying oils and unsaturated alkyd resins.

A promising practical aspect is the modification of known industrial polymers with thiols. Thus, transformation of PVC-film surface layer with fluorinated thiophenols in an inert atmosphere (H_2O/DMF, 60 °C, K_2CO_3) allows synthesizing the materials of new generation [34].



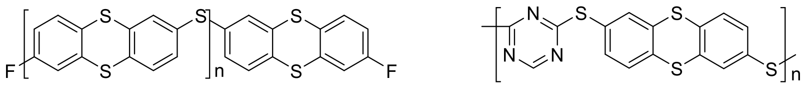
For example, due to such modification, the films treated with 4-fluorothiophenol can be used as gas-separation membranes.

Compared to commercially available transparent polymers, i.e., polymethylmethacrylate and cycloolefin polymers, the sulfur (co)polyimides containing carboxyl groups show much higher glass-transition temperatures, comparably low moisture uptake and high transmission at the sodium D-line. Furthermore, good solubility in commonly used organic solvents makes them very attractive as high-performance coating materials [35].



Achievements of new functions in advanced optical devices strongly depend on the availability of new functional materials. Recently, high refractive index polymers (HRIPs) have attracted considerable attention due to their potential applications in advanced optoelectronic fabrications. Sulfur containing substituents including linear thioether and sulfone, cyclic thiophene, thiadiazole, and thianthrene are the most commonly used groups for increasing a polymer's refractive index.

HRIPs with refractive index close to 1.80 have been developed such as thianthrene-based poly(phenylene sulfide)s [36] and poly(phenylene thioether) derived from triazines [37].

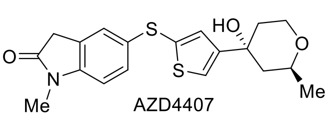


Refractive index at 633 nm:	1.802	1.770
Transmittance at 400 nm:	84%	90%
Birefringence:	0.0033	0.005

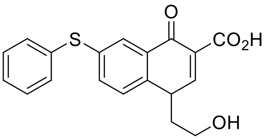
The optical crosslinked polymer of 9,9-bis(4-glycidyloxyphenyl)fluorine and 4,4-thiodibenzenethiol with high transparency over the visible region of the spectrum and thermally stable up to 290 °C has refractive index *n* = 1.707 at 590 nm and can be thermally nanoimprinted at 160 °C with nanoscale size resolution [38].

7.3 Bioorganic and Medical Chemistry

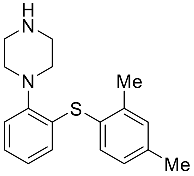
Aryl sulfides and sulfones are important compounds in biological processes and medicine.



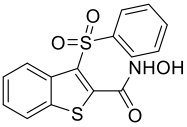
AZD4407
5-lipoxygenase inhibitor



HIV-1 integrase
inhibitor

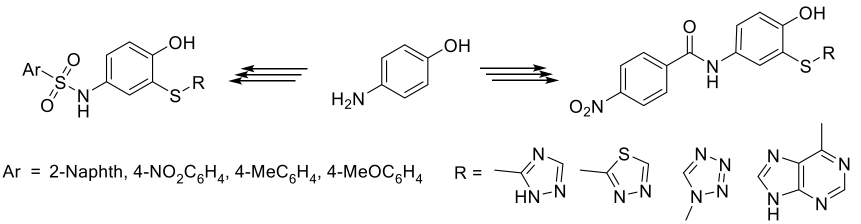


Vortioxetine (Brintellix)
antidepressant



anti-hepatitis C
virus activity

A number of new aryl amide and aryl sulfamide derivatives of 4-aminophenols have been synthesized, among which there have been found the compounds that have inhibitory activity against protein kinase and angiogenesis [39].

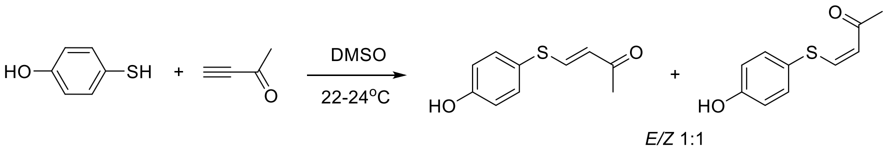


Ar = 2-Naphth, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$

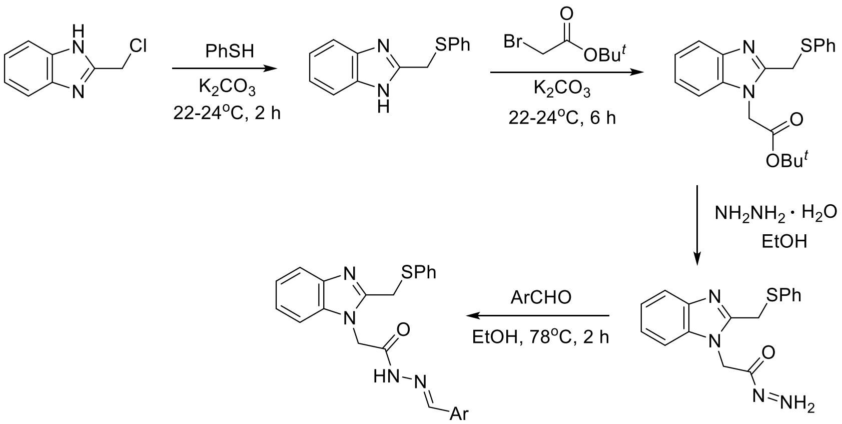
R =

To effectively inhibit AKT and ABL kinases, a compound should contain sulfonic and 1,2,4-triazole function, and the phenyl ring should bear an acceptor substituent. The screening has revealed compounds comparable in activity to the drug Pazopanib, which makes them promising agents for the treatment of cancer.

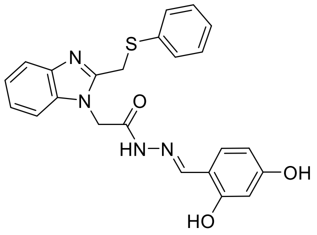
The synthesis and preliminary biological activity of (*E/Z*)-4-[4-(hydroxyphenyl) thiobut-3-ene]-2-one are described. Both isomers show significant cytotoxic activity against B16F1 mouse melanoma cells [40].

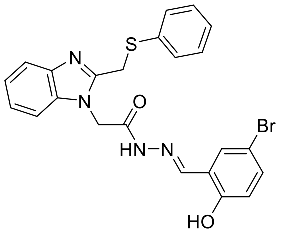


A new class of compounds exhibiting antiproliferative activity has been synthesized on the basis of acetylhydrazones with benzimidazole cycles [41].

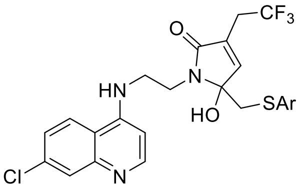


In vitro evaluation of antitumor activity against five strains of cancer cell lines has revealed that *N*-(2,4-dihydroxybenzylidene)-2-(2-(phenylthiomethyl)-1*H*-benzo [*d*]imidazol-1-yl)acetohydrazide and *N*-(5-bromo-2-hydroxybenzylidene)-2-(2-(phenylthiomethyl)-*1H*-benzo [*d*]imidazol-1-yl)acetohydrazide display excellent inhibitory activity against the tested cancer cells (IC_{50} 4-17 μM), compared with that of 5-fluorouracil 5FU and multi-kinase inhibitor sunitinib SU11248.





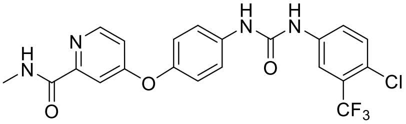
To design new antimalarial drugs, a series of novel 4-aminoquinoline 5-[(arylthio)methylene]-(2,2,2-trifluoroethyl)-γ-lactams, combining several pharmacophoric fragments in the molecule, has been synthesized [42]. The compounds exhibit good in vitro activity against Plasmodium falciparum clones (including those resistant to the known antimalarial drug chloroquine).



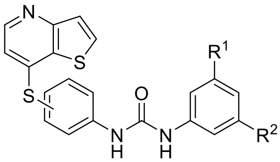
Ar = Ph, 4-Py, 2-Py, 2-pyridyl-N-oxide,
1,3-pyrazinyl, 1,2,4-reiazolyl

Fragments of aromatic sulfides are contained in a large group of compounds that are active inhibitors of enzymes as well as some biological processes. The derivatives of 3-arylthioindole prevent tubulin polymerization and growth of breast adenocarcinoma cells with activity comparable to colchicine and combretostatin A-4 [43, 44]. Sulfur containing congeners of trichostatin A are potent inhibitors of histone deacetylase (both in vitro and in vivo), and also suppress the proliferation of three cell lines with submicromolecular values of semi-inhibition concentrations (IC_{50} 0.9-2.7 μM) [45]. Non-indole melatonin analogs containing the 3-methoxyphenylthio group as a new bioisosteric counterpart of the endogenous ligand have been synthesized [46]. These compounds are found to be active melatonin receptors MT1 and MT2 agonists. Derivatives of 3-sulfonamide benzoates are described as selective inhibitors of siritin deacetylase SIRT2 [47]. Substituted sulfonamides, *N'*-(2-arylmethylthio-4-chloro-5-methylbenzylsulfonyl) guanidines, suppress the transmembrane tumor-associated isozymes IX and XII, as well as up to 35 tumor cell lines with GI_{50} in the range 2.1-5.0 μM [48]. 2-Amino-3-(phenylthio)norbonane-2-carboxylate is employed as a platform for the design of protein interaction inhibitors [49]. Some of the synthesized compounds are also capable of retarding the migration of smooth muscle cells.

Sorafenib analogs, in which the pyridine fragment is substituted with thieno[3,2-*b*]pyridine, are stronger inhibitors of the tyrosine kinase VEGFR-2. These compounds also retard the growth of human umbilical vein endothelial cells, which indicates suppression of angiogenesis [50].

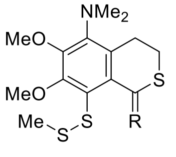


Sorafenib

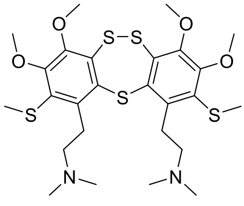


1-aryl-3-[(thieno[3,2-*b*]pyridin-7-ylthio)phenyl]urea

In recent decades, potent bioactive natural products possessing sulfur-sulfur bonds have been discovered, such as antifungal polycarpamine family [51] and Lissoclinotoxins [52, 53]. The inhibitory effect of Lissoclinotoxin F on cervical cancer has been verified [53].



Polycarpamine B (R = O)
Polycarpamine C (R = S)
(anti-fungus)

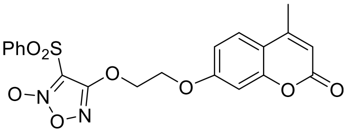


Lissoclinotoxin F

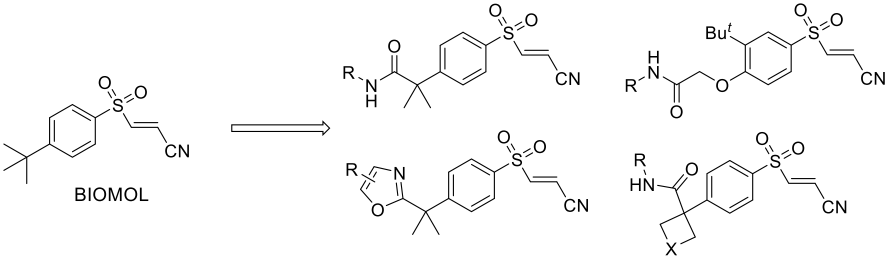
The disulfide bond shows unique chemical and biophysical properties, which distinguish it as one of the key structural elements of bioactive proteins and peptides, important drugs, and other materials. Structurally simple aryl alkyl disulfides have been found to inhibit *β*-ketoacyl-acyl carrier protein synthase III, or FabH, a key enzyme in type II fatty acid biosynthesis, and that may lead to the development of effective antibacterials for MRSA and anthrax infections [54].

Derivatives of aryl and hetaryl thiols exhibit antioxidant properties in biological systems. They are capable of interacting with free radicals of unsaturated fatty acids and peroxides. It has been shown [55] that diphenyl disulfides containing alkyltelluro groups in *ortho*-, *meta*-, or *para*-positions can be easily reduced in situ to the corresponding alkyl tellurothiophenols, which can bind peroxide radicals more efficiently than α-tocopherol. Tris-(2-carboxyethyl)phosphine cocatalyst reduces disulfide and telluroxide, thus ensuring a continuous catalytic cycle.

High biological activity of aromatic sulfones gives free rein to the search for new drugs derived from these compounds. Particular attention is paid to the antitumor activity of aromatic sulfones. In particular, the hybrid structures of phenylsulfonylfuroxan and coumarin, coupled by different spacers, possess high cytotoxicity against cancer cells. Overall, the NO-releasing capacity and the inhibition of ERK/MAPK pathway signaling may explain the potent antineoplastic activity of these compounds [56]. In a series of sixteen structures synthesized, a compound with 1,2-dioxyethylene spacer displays high proliferative activity relative to four cancer cell lines, including cisplatin-resistant A2780/CDDP.

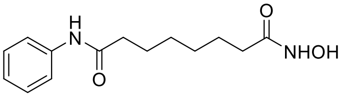


(2*E*)-3-[(4-*tert*-Butylphenyl)sulfonyl]acrylonitrile (BIOMOL) retards the metastasis of malignant tumors [57, 58]. Some new amide aryl sulfotnyl acrylonitriles demonstrate improved inhibition of intra-abdominal cancer in two clinically relevant murine models of ovarian and pancreatic cancer spread and metastasis, thus highlighting their potential clinical use as an adjunct to surgical resection of cancers [59].

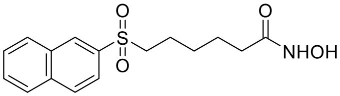


4-(Aryloyl)phenylmethylsulfones possess a large antitumor potential [60].

Substituted hydroxamates represent a well-known class of histone deacetylase (HDAC) inhibitors. Therefore, they are often used for the targeted synthesis of new biologically active molecules. A series of sulfur containing hydroxamates, showing a wide spectrum of antitumor activity, has been synthesized on a basis of known inhibitor of histone deacetylase SAHA (Vorinostat) [45]. The efficiency of *N*-hydroxy-6-(naphth-2-ylsulfonyl)hexanamide (HDAC H40) in the treatment of prostate cancer is comparable to that of SAHA and is of clinical importance in cancer chemotherapy [61].



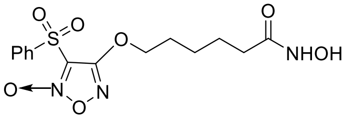
SAHA (Varinostat)



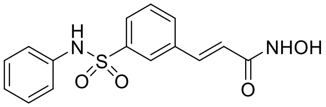
HDAC H40

This strategy is employed to synthesize a new series of hydroxamates coupled with 3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide by an alkylene or oxyalkylene linkers [62]. Evaluation of biological activity of these compounds has revealed that they are HDAC inhibitors and exhibit NO-donating activity. In addition, 4-[(6-hydroxyamino)-6-oxohexyl]-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide shows a much higher antiproliferative activity in vitro against human erythroleukemia cell as compared to the SAHA drug.

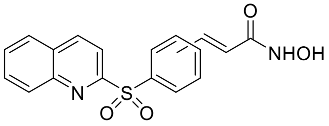
A series of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides is synthesized and their antitumor activity against four cancer cell strains is evaluated [63]. *N*-Hydroxy-3-[3-([quinolin-2-ylsulfonyl)phenyl]prop-2-enamide retards cancer proliferation with an average GI_{50} value of 0.19 µM and is more potent than the well-known drugs SAHA and PXD101. In in vivo studies, this compound inhibits the HCT116 xenograft tumor growth in 58.8% of cases. The activity of regioisomeric *N*-hydroxy-3-[4-([quinolin-2-ylsulfonyl)phenyl]prop-2-enamide is lower, but comparable to that of SAHA and PXD101 (GI_{50} 0.62 µM). Besides, these compounds are able to suppress histone deacetylase. A significant role in biological activity is played by the sulfonic linker.



4-[(6-Hydroxyamino)-6-oxogenyl]-3-(phenylsulphonyl)-
1,2,5-oxadiazole-2-oxide [62]

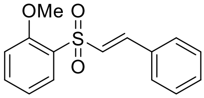


PXD101

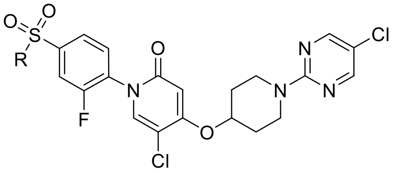


N-Hydroxy-3-(quinolin-2-yl-
sulphonylphenyl)prop-2-enamide [63]

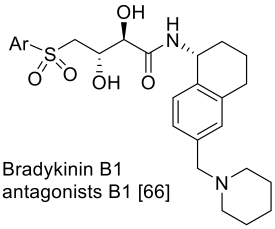
Derivatives of aryl vinyl sulfones demonstrate a plethora of activity in inducing the antioxidant enzyme HO-1 and are promising as a new class of neuroprotectors for the treatment of Parkinson's disease [64].



5-Chloro-4-((1-(5-chloropyrimidin-2-yl)piperidin-4-yl)oxy)-1-(2-fluoro-4-(methyl sulfonyl)phenyl)pyridin-2(1*H*)-one (BMS-903452) has been shown to act as a GPR119 receptor agonist and is considered a potential new drug for the treatment of type 2 diabetes [65]. Bradykinin B1 receptor antagonists have been found among aryl sulfones. According to the biological tests on rabbits, compounds of this class are promising as analgesics, especially for relieving chronic pain [66].

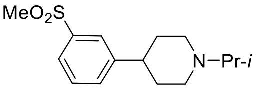


BMS-903452 [65]

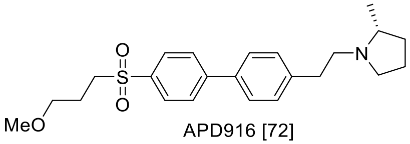


Bradykinin B1
antagonists B1 [66]

Derivatives of aromatic sulfones and sulfonamides are of great interest as regulators of the essential biological processes. They are promising inhibitors of transporting glycine GlyT1 [67], urea UT-B [68], carbonic anhydrase [69], metalloproteinases [70]. 4-[3-(Methylsulfonyl)phenyl]-1-propylpiperidine (ACR-16) has the properties of a dopaminergic stabilizer [71]. (*R*)-1-(2-(4'-(3-Methoxy propylsulfonyl)biphenyl-4-yl)ethyl)-2-methylpyrrolidine (APD916) exhibits the properties of the histamine H_3 receptor antagonist and increases wakefulness in rodents [72].



ACR-16 [71]



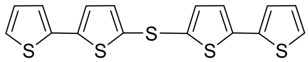
APD916 [72]

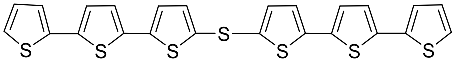
Some diaryl sulfones and aryl sulfonamides regulate various intercellular processes under physiological and pathophysiological conditions and are specific antagonists of EPAC2 [73] and metabotropic receptor 5-HT6 [74]. Bromine- and chlorine derivatives of nitrophenylsulfones inhibit the growth of *Candida albicans* cells and the expression of the APE2 leucine arylamidase gene [75]. Several diphenylsulfonyl-containing mono- and bicycloheteroaromatic acetic acids are CRTh2 receptor antagonists with nanomolar values of half-inhibition concentration (IC_{50} of 12 nM) and a long residence time (up to 21 h) [76].

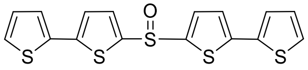
7.4 Optoelectronic Devices

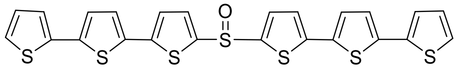
Organic electronic and optoelectronic have been the focus of a growing number of researchers particularly in the fields of physics and chemistry for more than 50 years. The main attraction of this field comes from the ability to modify the chemical structure of the organic compounds in a way that the properties of the materials could directly be affected. Currently, organic sulfur containing materials receive considerable attention due to their applications in electronic and optoelectronic devices, such as organic thin-film-transistors (OTFTs), light-emitting diodes (OLEDs), photovoltaics (OPVs), sensors, photorefractive (PR) devices, and many others.

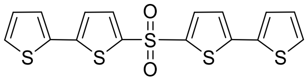
Thiophene-based materials were first applied to OLEDs in 1991 [77]. In symmetric dimers of sulfur-bridged di- and terthiophenes, the interchromophore (intradimer) electronic coupling can be modified by varying the oxidation state of the bridging sulfur from sulfide (S), to sulfoxide (SO), to sulfone (SO_2). Control of the sulfur bridge oxidation state provides the ability to tune interchromophore interactions in covalent assemblies without altering the molecular geometry or solvent polarity. This capability provides a new strategy for the design of functional supermolecules with applications in organic electronics [78, 79].

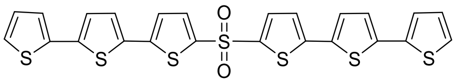




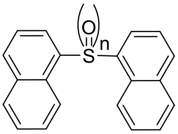


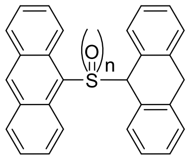


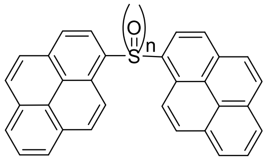




This approach was used for symmetrical sulfur-bridged chromophores, such as naphthalene [79], antracene [80], pyrene [79]. Successive oxidation of the bridging sulfur results in a systematic increase in photoluminescence quantum yield Φ_f. In most cases the sulfoxide, and in all examples the sulfone-bridged chromophores exhibit Φ_f greater than the parent arenes. The enhanced photoluminescence combined with the processability of these soluble compounds is anticipated to be useful in the fabrication of OLED devices. Furthermore, sulfone-bridged arenes are also well-known for their high mechanical and thermal stability which is also important for robust OLED operation.

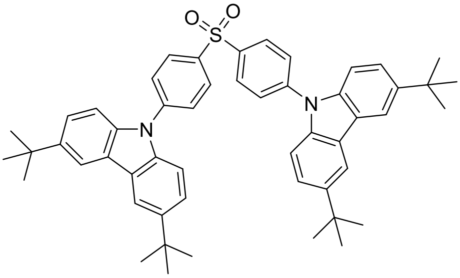




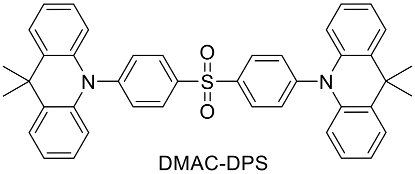


Organic light-emitting diodes (OLEDs) showing thermally activated delayed fluorescence (TADF) have emerged as cheaper alternatives to high-performance phosphorescent OLEDs with noble-metal-based dopants. However, the efficiencies of blue TADF OLEDs are still low at high luminance, limiting full-color display.

A pure blue organic light-emitting diode (OLED) based on carbazole and diphenyl sulfone demonstrates very high external quantum efficiency (EQE) of nearly 10% at low current density. Its higher EL efficiency relative to fluorescent materials with similar CIE coordinates indicates that TADF materials have great potential for OLED applications, even in the pure blue region where noble metal-based phosphors do not work well [81].

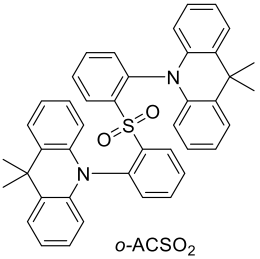


A wide variety of donor and acceptor groups have been employed in order to tune the optoelectronic properties of D−A compounds. The blue OLED containing a 9,10-dihydroacridine as a donor and diphenylsulphone as an acceptor (DMAC−DPS) has a comparable performance to today's best phosphorescent OLEDs [82, 83]. The device offers an external quantum efficiency of 19.5% and reduced efficiency roll-off characteristics at high luminance.

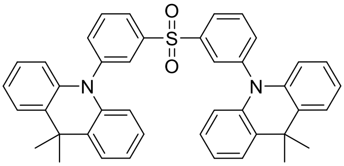


DMAC-DPS

Two new blue emitters, i.e., bis-[2-(9,9-dimethyl-9,10-dihydroacridine) phenyl]sulfone (*o*-ACSO$_2$) and bis-[3-(9,9-dimethyl-9,10-dihydroacridine) phenyl]sulfone (*m*-ACSO$_2$), with reserved fine TADF nature and simply tuned thermal and optoelectronic properties, have been synthesized by isomer engineering [84]. The meta-linking compound, i.e., *m*-ACSO$_2$, obtains the highest photoluminescence quantum yield with a small singlet − triplet energy gap, a moderate delayed fluorescent lifetime, excellent solubility, and neat film homogeneity. Due to its unique aggregation-induced emission (AIE) character, neat film-based heterojunction-like OLEDs are achievable. By inserting an excitonic inert exciton-blocking layer, the PN heterojunction-like emission accompanied by intefacial exciplex is shifted to a homojunction-like channel mainly from the AIE emitter itself, providing a new tactic to generate efficient blue color from neat films. The solution-processed nondoped sky-blue OLED employing *m*-ACSO$_2$ as emitter with homojunction-like emission ensures a maximum external quantum efficiency of 17.2%.

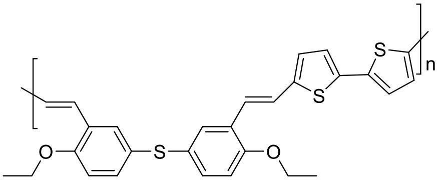


o-ACSO$_2$

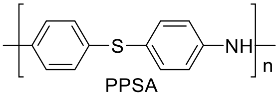


m-ACSO$_2$

Thiophene-based organic materials are among the most promising compounds with tuneable functional properties by proper molecular engineering. The optical and electrical properties of the new sulfur containing polymer on the distyryl-bithiophene π-conjugated system evidence a semiconducting behavior with a narrow optical gap, a good film quality, and a conductivity exceeding $7 \cdot 10^{-4}$ S at room temperature, which make this organic material a good candidate for molecular electronic devices [85].



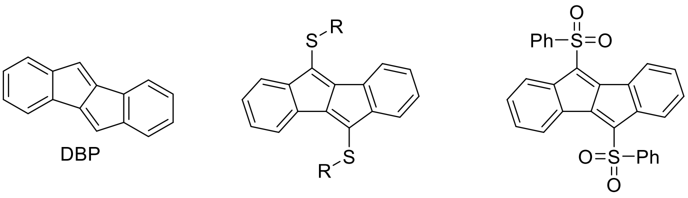
Poly(phenylenesulfidephenyleneamine) (PPSA) is a polymer consisting of alternating aniline and phenylenesulfide units that promises to combine the best electronic and structural properties of polyaniline as well as the thermal and mechanical stability of poly(phenylenesulfide). PPSA has turned out to be a promising material for hole injection into multilayer LEDs [86, 87]. It combines a low oxidation potential with a high LUMO required for preventing electron flows toward the anode.



PPSA

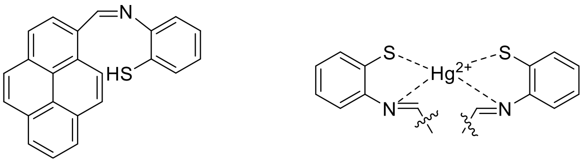
Preliminary search for the semiconductor field-effect in PPSA was carried out [88, 89]. The effects of contact resistance, surface conductivity, and gate leakage current have been demonstrated and analyzed.

Dibenzo[*a*,*e*]pentalene (DBP) is a low bandgap, organic semiconductor. The electron transport properties of thioether- and sulfone-substituted DBPs as promising candidates of n-type semiconductors in organic field-effect transistors (OFETs) are examined [90]. The molecular structures in the solid state show a one-dimensional π-stacking or herringbone packing mode with close intermolecular distances between the DBP cores. The relatively low LUMO levels of the thio-DBPs are a good requisite for n-channel conduction, especially in the case of sulfone (−3.94 eV). Two thio-DBPs and the DBP sulfone display n-channel conduction in FET measurements on well-aligned crystals with electron mobilities of up to 0.18 $cm^2 \cdot V^{-1} \cdot s^{-1}$, to date the highest reported values for n-channel conduction in DBP derivatives.



R = Bu^n, Ph, 4-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$

Pyrene-SH functionalized OTFT-based sensor for detection of Hg^{2+} ions in aquatic environments has been fabricated [91]. The OTFT sensor exhibits hole mobility of 0.28 $cm^2 \cdot V^{-1} \cdot s^{-1}$ at −60 V, a threshold voltage of −22.3 V and on/off current ratio of 10^3. OTFT sensor possesses high sensitivity to Hg^{2+} ion, indicated by increasing of drain current after exposed to different concentration of Hg^{2+} ion ranging from 1 mM to 0.01 μM. Moreover, the OTFT sensor capability for practical application is also demonstrated by sensing the present of 25 μM of Hg2 + ion in tap, drinking, and seawater samples.



7.5 Additives to Oil Products

7.5.1 Antimicrobial Additives

All petroleum oils, fuels and lubricants are destroyed by microorganisms under the conditions of high temperature and humidity. Fuel during storage, transportation, and exploitation is easily damaged by microorganisms. Biodeterioration significantly worsens physical–chemical and performance characteristics of petroleum products [92–96]. Synthesis of aggressive metabolites, primarily organic acids, increases corrosion of the metal, and destructs integrity of the fuel tanks. The accumulation of fungal biomass leads to the failure of instruments and equipment. In addition, all microbiological processes occurring in petroleum products become more pronounced in warm and humid climate (subtropics and tropics) [97]. The main microorganisms that cause biodeterioration of fuels are *Pseudomonas, Micrososcus, Mycobacterium* bacteria, as well as *Cladosporium, Aspergillus,* *Penicillum, Alternaria*, etc., fungi. It should be noted that *Ps.aeruginosa* and *Cladosporium resinae* ("kerosene fungus") are most commonly encountered in petroleum products [96].

The main method of controlling microbiological deterioration of petroleum products is based on the application of biocidal additives. However, the experience has proven that microorganisms, over time, become resistant to the biocides used. Therefore, the search for organic compounds, the introduction of which in petroleum products can protect them from the deteriorating effects of microorganisms, as well as mechanistic studies of antimicrobial substances remain an urgent challenge.

The choice of thiocarboxylic acid *S*-esters as promising inhibitors of microbiological deterioration of petroleum products is not accidental. These compounds play an important role in bioorganic synthesis [98]. Thiocarboxylate groups are contained in the structure of compounds possessing a broad spectrum of biological activity [99]. Pioneering studies of the antimicrobial activity of a series of thiocarboxylic acid *S*-aryl esters [100–102] have shown that they are active against microorganisms parasitizing petroleum products.

A variety of aliphatic and aromatic *S*-esters of thiocarboxylic acids have been tested for antimicrobial activity in petroleum fuels [103]. Most of the studied compounds (Table 7.1) are found to possess pronounced bactericidal and fungicidal properties and inhibit the growth of fungi and bacteria in kerosene at a concentration of 0.125-0.25 wt%. Comparison of the antimicrobial activity of these thioesters shows that they are more effective against the mixture of fungi (*Aspergillus niger, Cladosporium resinae, Penicillium chrysegenum Thom, Chaciomium globosum, Triknoderma viride* and yeast-like fungi *Candida tropicalis*) than against bacterial cultures.

The arylthiocarboxylate group ArSC(O) plays a significant role in antimicrobial activity. Oxygen ArOS(O)Me and carbon $ArCH_2C(O)Me$ analogs of *S*-aryl thioacetates are less active against the studied microorganisms (Table 7.1, *cf.* entries 1 and 21, 10 and 20). The antimicrobial activity of *S*-alkyl and *S*-benzyl thioacetates (entries 17-19) is significantly lower.

Substituents in the benzene ring of arylthioesters ArSC(O)R affect not only the general toxicity, but also the selectivity of bacterial and fungicidal action. The antimicrobial activity of $4\text{-}RC_6H_4SC(O)Me$ compounds, depending on substituent R in the benzene ring, decreases in the order Me > MeO > Cl > F > H > I > Br. Antimicrobial efficiency of isomeric methylphenyl thioacetates is as follows: *para* > *meta* > *ortho*.

The antimicrobial properties of thioesters ArSC(O)R strongly depend on the nature of thiocarboxylic acid. In going from thioacetic to thiopivalic acid (R = *t*-Bu), the degree of bactericidal and fungicidal action drastically decreases (*cf.* entries 10 and 12). Comparison of antimicrobial activity of butyric and isobutyric acid thioesters (entries 2, 3) shows that the compounds containing radicals of normal structure exhibit a stronger fungicidal action than their structural isomers. Substitution of Me radical with CH_2Cl or CCl_3 in arylthioacylates ArSC(O)R enhances their fungicidal activity by 1.5–2.0 times. Noteworthy, biocidal properties of these compounds with respect to misture of fungi is stronger than those of

Table 7.1 Antimicrobial activity of *S*-aryl thioacylates in kerosene

No.	Formula	Diameter of growth inhibition region of test cultures, μm	
		A mixture of bacteria in meat-and-peptone agar medium	A mixture of fungi in wort agar medium
1	$PhSC(O)Me$	16	25
2	$PhSC(O)Pr^n$	11	20
3	$PhSC(O)Pr^i$	8	6
4	$PhSC(O)CCl_3$	26	35
5	2-$MeC_6H_4SC(O)Me$	16	24
6	3-$MeC_6H_4SC(O)Me$	19	28
7	4-$MeC_6H_4SC(O)Me$	21	35
8	3-$MeOC_6H_4SC(O)Me$	18	25
9	4-$MeOC_6H_4SC(O)Me$	20	32
10	4-$FC_6H_4SC(O)Me$	20	27
11	4-$FC_6H_4SC(O)CH_2Cl$	19	40
12	4-$FC_6H_4SC(O)Bu^t$	7	4
13	4-$FC_6H_4SC(O)Ph$	6	5
14	4-$ClC_6H_4SC(O)Me$	26	31
15	4-$BrC_6H_4SC(O)Me$	11	17
16	4-$IC_6H_4SC(O)Me$	15	19
17	$Pr^nSC(O)Me$	12	13
18	$Pr^iSC(O)Me$	11	11
19	$PhCH_2SC(O)Me$	13	15
20	4-$FC_6H_4OC(O)Me$	14	13
21	$PhCH_2C(O)Me$	8	6
22	8-oxiquinoline (standard)	29	24
23	Without additive	^{b}	^{b}

[a] Concentration of additive was 0.25 wt%; [b] Intensive growth of microorganisms

8-hydroxyquinoline. Bactericidal and fungicidal activity of aromatic *S*-aryl thiobenzoates is lower and corresponds to that of benzylacetate (*cf*. entry 13 with 10 and 21).

Table 7.2 Biocidal effect of *S*-aryl thioacetates in IHP-45 cutting fluid[a]

No.	Structure	Diameter of growth inhibition region of test cultures, μm	
		A mixture of bacteria	A mixture of fungi
1	4-$FC_6H_4SC(O)Me$	32	26
2	PhSC(O)Me	40	24
3	4-$MeC_6H_4SC(O)Me$	46	50
4	4-$MeOC_6H_4SC(O)Me$	24	48
5	4-$ClC_6H_4SC(O)Me$	40	28
6	Hexachlorophene (standard)	30	[b]
7	Without additive	[b]	[b]

[a]Concentration of additive was 0.25 wt.%; [b]Intensive growth of microorganisms

The analysis of the structure-activity dependence reveals that thioacetic acid *S*-aryl esters, which contain Cl, MeO or Me-groups in the *para*-position of the benzene ring, have the highest activity. In terms of fungicidal activity, these compounds are comparable to the reference 8-hydroxyquinoline and can be recommended as biocidal additives to petroleum products.

Introduction of *S*-aryl thioacetates into the cutting fluids does not change their physical-chemical properties and performance characteristics. Table 7.2 presents the results of testing the antimicrobial action of the most active *S*-aryl thioacetates in IHP-45E cutting fluids. It is found that all the studied compounds, in contrast to hexachlorophene used as a reference, suppress both bacterial and fungal cultures. The most active turns out to be 4-methoxyphenyl thioacetate, for which the inhibition zone of microorganisms' growth is 1.5 times higher than for the reference sample.

Experiments were also carried out (in the preliminary version) to study the antimicrobial activity of $PhCH_2SC(O)Me$, 3-$MeC_6H_4SC(O)Me$, 4-$MeC_6H_4SC(O)Me$ and $PhSC(O)CCl_3$ in diesel oil (1 wt%). It is shown that all four compounds exhibit high fungicidal properties. Bactericidal properties are less pronounced. A similar result is obtained, when additives are introduced in diesel oil with antioxidant, sulfonate, and silicone additives.

7.5.2 Anti-wear and Extreme Pressure Additives to Lubricating Oils

The improvement of lubricating oil properties (mainly, lubricating power) is achieved by the introduction of special additives, primarily anti-wear and extreme pressure ones, into their composition. Lubricating power is of special importance for lubrication of high-loaded parts and assemblies, such as gears of automobiles and tractors, i.e. for transmission oils. Very often organosulfur compounds (sulfides and disulfides, xanthogenates, thio- and dithiocarbamates) are employed as such additives in lubricating compositions [104, 105].

7.5.2.1 4-Fluorothiophenol Derivatives

The compounds, containing sulfur atoms, are promising as anti-wear additives to lubricating oils operating under severe conditions (high loads, temperatures, etc.). At elevated temperatures, such additives interact with metals to form on the surface a combined film of iron sulfides, which is highly effective against seizure and has a low coefficient of friction [106, 107].

4-Fluorothiophenol derivatives, *N*,*N*-diethylaminomethyl 4-fluorophenyl sulfide, 4-fluorophenyl thiochloroacetate and (4-fluorophenylthioethyl) acetate containing ~ 15% sulfur and ~ 9% fluorine, have been tested as anti-wear and extreme pressure additives for paraffinic base oils. These compounds are easily mixed with paraffinic base oil to produce stable solutions. Anti-wear properties of sample lubricants were evaluated by the four-ball test, according to GOST 9490-7, Russia. The balls with a diameter of 12.7 mm, made of steel SH-15 (European Union's analoge 100Cr6), were used. The relative sliding speed of the friction surfaces of balls was 1500 rpm, the axial load on the balls was 3.9 MPa, test time was 60 min. Test data for different lubricants (paraffinic base oil with the additive of 4-fluorothiophenol derivatives, 3–5%) are given in Table 7.3.

All studied additives in a concentration of 3-5% increase the total wear depth (*TWD*) from 27 to 60% and reduce the wear scar diameter (*WSD*) from 0.80 to 0.48 mm, which indicates an improvement in the lubricating properties of base oil. The tested compounds almost do not differ from each other in value of the *WSD* (0.45-0.50 mm), while 4-fluorophenyl thiochloroacetate (60%) surpasses the other additives in the *TWD* value. Application of this additive (4%) increases the oil critical contact load *Pc* (from 6.9 to 9.8 MPa), which characterizes the limiting performance of lubricant layer to a certain qualitative leap, determining the transition from one lubrication mode to another. Weld point P_w also augments from 15.5 to 32.8 MPa.

7.5.2.2 Dithiocarboxylic Acid S,S'-Dibenzyl Esters

The tribological properties of compressor oil KS-19 with dibenzyl esters of dithiofumaric, dithioadipinic and dithiophthalic acids (3 wt%) have been investigated [108]. Anti-wear properties of the studied dithiocarboxylates are comparable

Table 7.3 Performance characteristics of lubrication oil modified with additives of 4-fluorothiophenol derivatives

Additive	Concentration, %	*TWV*, %	P_c, MPa	P_w, MPa	*WSD*, mm
Without additive		27	6.9	15.5	0.80
4-$FC_6H_4SCH_2NEt_2$	3	40	8.8	24.5	0.50
	5	52	9.8	30.9	0.48
4-$FC_6H_4SC(O)CH_2Cl$	4	60	9.8	32.8	0.45
4-$FC_6H_4SC_2H_4OC(O)Me$	3	40	8.8	23.5	0.48
	5	58	9.8	30.9	0.50

to those of phosphate and thiophosphate lubricating additives zink dialkyldithiophosphonate (DP-11), tricrezyl phosphane (TCP) and INKhP-21 (WSD 0.40-0.79 and 0.44-0.50 mm, respectively), and are manifested in the following order: $[PhCH_2SC(O)]_2C_2H_2 > 1,2\text{-}[PhCH_2SC(O)]_2C_6H_4 > [PhCH_2SC(O)]_2(CH_2)_4$. The addition of the most effective dithiofumaric acid dibenzyl ester to KS-19 oil (3%) reduces the wear scar by about 2.5 times (from 1.1 to 0.4 mm). When combination of dithiocarboxylate and phosphate additives is used, the ant-iwear properties of the oil are close to TAD-17 transmission oil developed at the Institute of Chemistry of Additives of the National Academy of Sciences of Azerbaijan for passenger cars.

Dithiodicarboxylic acid *S,S'*-dibenzyl esters also show antimicrobial activity against the main physiological groups of microorganisms deteriorating lubricating oils, namely against aerobic bacteria and mold fungi [109]. The experiments have demonstrated that *S*,*S*'-dibenzyl esters of dithiofumaric, dithioadipinic, and dithiophthalic acids in a concentration of 3 wt% entirely suppress the growth of bacterial and fungal microflora in hydro-reformed mineral oil. In the absence of additives, this oil was completely affected by test cultures.

Thus, dithiofumaric, dithioadipinic, and dithiophthalic acid dibenzyl esters possess not only anti-wear, but also antimicrobial properties and can be used as multifunctional additives to distillate oils.

7.6 2-(4-Ethylthiophenyl)Pyrrole as a Reagent for Palladium Determination

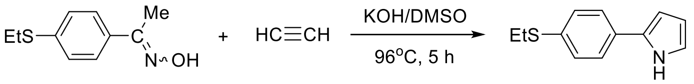
Methods for the determination of palladium are mainly based on complex formation processes. Modern analytical chemistry has a sufficient variety of reagents for palladium and a plethora of approaches to photometric and extraction-photometric determination of Pd content in various natural and industrial objects. For the photometric determination of palladium, different organic reagents containing S, N, Se, O, with which Pd forms stable compounds, are employed. These include 8-mercaptoquinoline (thioxin) [110] and some azoreagents [111–113]. Different mono- and dioximes, giving thermodynamically stable complexes with Pd, exhibit high selectivity and sufficient sensitivity [114–116]. Palladium also forms colored compounds with sulfur containing reagents [117, 118].

A simple and rapid spectrophotometric method for determination of palladium is proposed and tested in the analysis of industrial samples [113]. A blue 1:1 chelate of 2-(2-benzothiazolylazo)-5-dimethylamino-4-tolylarsonic acid with palladium can be formed even in a strongly acidic medium. The absorption maximum is at 718 nm and the molar absorptivity is 6.65×10^4 $L \cdot mol^{-1} \cdot cm^{-1}$. Beer's law is obeyed in the concentration range 0–1.6 $\mu g \cdot mL^{-1}$ Pd. Relatively large amounts of V, Cr, Mn, Cu, Fe, Nil, Zn, Mo, Si, Ag, Cd, and even noble metals such as Pt, Au, Ru, and Ir can be tolerated.

A specific method for the spectrophotometric determination of palladium with *N, N'*-diphenylbenzimidoylthiourea is described [117]. The method in new, simple, rapid, and applicable over 0.3-1.0 M HC1 and free from interferences of the precious metals i.e. Ag, Au, Pt, Ir, Rh, Ru, Os. The value of molar absorptivity of the complex in the term of Pd is 2.50×10^4 L· mol^{-1} cm^{-1} at λ_{max} 365 nm in chloroform. The detection limit of the method is 80 μg·mL^{-1} Pd. The application of the method has been tested for the analysis of the metal in catalytic material.

The simple, rapid spectrophotometric method for Pd(II) ions determination using 4-(*N*′-(4-imino-2-oxo-thiazolidine-5-ylidene)hydrazino)benzoic acid (*p*-ITYBA) is disclosed [118]. The interaction of Pd(II) ions with a reagent in water medium results in the formation of a complex. The Pd(II)-*p*-ITYBA complex shows maximum absorbance at a wavelength of 450 nm. The molar absorptivity is 4.30×10^3 L·mol^{-1}·cm^{-1}. The optimal pH for complex formation is 7.0. The developed method has a wide linearity range of 0.64–10.64 μg·mL^{-1} for Pd(II). The detection limit is 0.23 μg·mL^{-1}. It is found that Co(II), Ni(II), Zn(II), Fe(III), Cu(II), Al(III), and many anions do not interfere with the Pd(II) determination. The proposed method has been tested in the analysis of model solutions and successfully applied for the determination of palladium in catalyst. The obtained results show that this method can be used for serial determinations of palladium in various objects.

Acceleration of palladium determination and enhancement of its selectivity are the urgent challenges for analytical chemistry. 2-(4-Ethylthiophenyl)pyrrole, synthesized from 4-ethylthiophenyl ketoxime and acetylene via the Trofimov reaction [119–121] (see chapter 5) was proposed as a new complex-forming agent for extraction-photometric determination of Pd(II).



The method for quantitative determination of palladium using this reagent gives fairly accurate and reproducible results and reduces the analysis time to 4-5 min [122].

When a colorless solution of 2-(4-ethylthiophenyl)pyrrole in acetone is added to a solution of Pd(II) in hydrochloric acid, the mixture immediately turns yellows, which indicates the formation of a complex. The latter is formed in a wide range of acidity from 6 M HCl to pH 5 (optimally pH 1). Photometric determination of Pd (II) content is carried out after a single 30-second extraction of the complex from 0.1 *M* HCl solution with isobutyl alcohol. For determination, an absorption band of the complex in the visible region of the spectrum at λ 415 nm is used. With a single extraction of *i*-BuOH, palladium is isolated by 95-100%, as evidenced by the disappearance of the maximum in the analyzed spectral region. The reagent itself is colorless and absorbs only in the ultraviolet region of the spectrum (λ 306 nm, molar absorptivity is 3.3×10^4 L·mol^{-1}·cm^{-1}).

Beer's law is observed over the concentration range of 0.5–5.0 μg Pd/mL extract at 415 nm (Fig. 7.1). The molar absorptivity was calculated to be 7.20×10^3 $L{\cdot}mol^{-1}{\cdot}cm^{-1}$.

The reaction of Pd(II) with 2-(4-ethylthiophenyl)pyrrole is selective with respect to platinum and the related macroelements (Fe, Ni, Co). The analysis tolerates 50-fold amounts of Pt(IV) and W(VI), 100-150-fold amounts of Ag(I), Al(III), and Th(IV), 250300-fold amounts of Fe(III), Ni(II), Co(II), Mn(II), Zn(II), Re(VI), and 1000-fold amounts of Pb(II), Bi(III), and U(VI). In the presence of 10-50-fold molar amounts of 14 ions, the relative standard deviation during 5 parallel determinations is 0.02–0.04.

The application of the method has been tested for the analysis of the metal in catalytic material. The relative standard deviation of Pd(II) determination in the catalyst is 0.03–0.04, which is quite consistent with the metrological capabilities of photometry (Table 7.4).

The analytical characteristics and comparative selectivity of methods for determination of palladium by photometric methods [113, 117, 118] show that 2-(4-ethylthiophenyl)pyrrole has significant advantages over the known reagents: it provides high expressivity and selectivity of Pd(II) determination in the presence of large amounts of many elements.

General procedure for Pd(II) determination by the reaction with 2-(4-ethylthiophenyl)pyrrole. An aliquot of a Pd(II) solution containing 5, 10, 20, 30, 40, 50 μg of Pd(II) was placed into a separation, and 2 ml of $\mathbf{1{\cdot}10^{-3}}$ M solution of reagent in acetone was added. 1-2 Drops of 1 M NaOH solution was added for more intense yellow coloring, the volume was increased to 10 mL with 0.1 M HCl

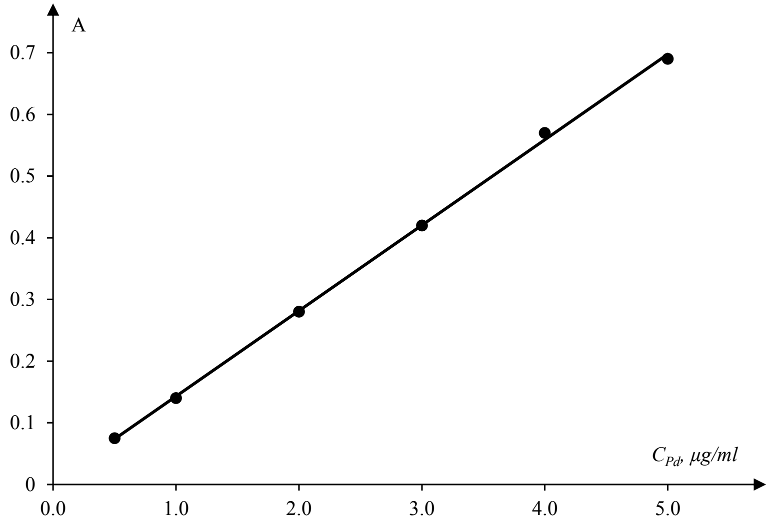


Fig. 7.1 Calibration plot of Pd(II) with 2-(4-ethylthiophenyl)pyrrole (pH 1, l = 2.0 cm)

Table 7.4 Determination of Pd(II) in the catalyst PK-404 ($n = 9$, $r = 0.95$)

Aliquote, mL	Content of Pd(II), μg		S_r
	Polarographic determination	Photometric determination	
1.5	23.2	23.0 ± 0.9	0.04
2.0	31.0	30.0 ± 1.0	0.03
3.0	46.5	46.0 ± 1.4	0.03

solution, 10 mL of isobutyl alcohol was added and the formed complex was extracted for 30 s. The optical density of the extract was measured on a FEC-56 M photoelectrocolorimeter at 415 nm (light filter No. 3) in a cuvette $l = 20$ mm against the background of *i*-BuOH.

Determination of Pd(II) in catalyst PK-404.A sample of catalyst (0.10 g) was dissolved in a mixture (30 mL) of concentrated HCl and water (1:1) upon slight heating. After cooling, the solution was placed into a flask (100 mL), so that to reach 0.1 M HCl. To 2 mL of a 1×10^{-3} M 2-(4-ethylthiophenyl)pyrrole solution in acetone, an aliquot of the Pd(II) sample solution was added and treated as described above.

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Conclusion

The present monograph covers, along with traditional (classical) methods for the synthesis of aromatic thiols and their derivatives, new approaches to the formation of the carbon-sulfur bond. These approaches are based on the use of transition metals and their complexes to activate the starting reagents, usually aromatic halides, which do not demonstrate high reactivity in classical reactions.

Original papers, reviews, patents, and dissertations are analyzed; some of them belong to the authors of the monograph. At the same time, the authors tried to accurately cite and discuss the works of other research teams devoted to various aspects (synthetic, physical-chemical, theoretical, and applied) of chemistry of aromatic thiols and their derivatives.

The interest in aromatic thiols and their derivatives is not diminishing. The number of publications devoted to aromatic organosulfur compounds, including aryl thiols, sulfides, disulfides, sulfoxides, and sulfones, as well as their functional derivatives, is noticeably increasing in the world literature. The investigations into the formation of the C−S bond using metal-complex catalysis are progressing especially dynamically.

During the preparation of this monograph, a review on the transition metal-catalyzed synthesis of aryl thiols from aryl halides has appeared [1]. An efficient synthesis of aromatic thiols from aryl iodides and sodium sulfide in the presence of a copper catalyst and 1,2-ethanedithiol was developed [2]. The synthesis of aromatic sulfides via cross-coupling of aryl thiols with aryl chlorides in the presence of a catalytic system nickel phosphite/phosphine was published [3]. An environmentally friendly method for the synthesis of aromatic sulfides based on aerobic Co-catalyzed oxidation of the CH bonds with thiols in water was proposed. The reaction tolerates aromatic thiols with electron-donating (methyl, methoxy, amino) and electron-withdrawing (chlorine, bromine) substituents [4]. The works in this direction were summarized in the review, which described the latest advances in the metal-catalyzed *S*-arylation of thiols by aryl halides in aqueous media [5].

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High yields of unsymmetrical aromatic sulfides were attained when studying the reaction of arylsulfonyl chlorides with aryl iodides in the presence of Mn as a reducing agent [6].

The reaction of aryl halides with sodium sulfonates in the presence of a nickel catalyst afforded diaryl sulfones in high yields [7]. Derivatives of aromatic sulfones possessing high antibacterial activity were obtained under conditions of green chemistry from *para*-methylaminophenols using sulfinic acids [8].

A radical reaction of aryl thiols with cleavage of the strained C−C bond of [1.1.1]propellane proceeds as a click-chemistry process to furnish new building blocks and drug precursors [9]. The investigations in the field of ene-thiol click-chemistry keep developing. Using this reaction, an approach to bioconjugation of colloidal nanoparticles with a high enzymatic activity has been elaborated [10].

An effective synthesis of aryl vinyl sulfides by the vinylation of aryl thiols using calcium carbide as a source of acetylene was developed [11]. The same methodology was used to obtain aryl vinyl sulfides and 1,2-bis(arylthio)ethenes from aryl disulfides [12].

The search for new synthetic possibilities of aromatic thiols and their derivatives continues. An unexpected reaction of aromatic and heteroaromatic thiols with α-hydroxypyrrolines, proceeding via substitution of the hydroxyl function for the aryl(hetaryl)thio group, was found. The substitution easily occurs in the presence of trifluoroacetic acid in acetonitrile. The acid protonates the nitrogen atom adjacent to the hydroxyl substituent, which increases the electrophilicity of the α-position of the pyrroline ring [13]. This new type of vicarious substitution of the hydroxyl group has opened a facile route to the previously unknown dihydropyrrole derivatives, promising drug precursors.

The cross-coupling of aryl thiols with secondary phosphine sulfides and -selenides in the CCl_4/Et_3N system provides an efficient synthesis of the corresponding dithiophosphinates [14] and thioselenophosphinates [15].

Homolytic fragmentation of aryl sulfides was observed during their direct laser flash photolysis in the presence of oxygen [16].

The authors hope that the synthetic methods and main reactions of aromatic thiols and their derivatives, summarized in the monograph, the formulated regularities and correlation dependences of reactivity on their structure, will be of help to the experts working in the field of chemistry and technology of organosulfur compounds.

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