*Russian Journal of Organic Chemistry, Vol. 41, No. 5, 2005, pp. 631–648. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 5, 2005, pp. 647–664.*


**REVIEW**

# Synthesis, Structure, and Physicochemical Characteristics of Thiols

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Received June 21, 2004

**Abstract**—Data on thiols structure, physicochemical characteristics, and synthetic procedures for preparation are systematized and generalized.

## 1. INTRODUCTION

Thiol are among the simplest classes of the organosulfur compounds playing important part in many chemical transformations. This is primarily due to the presence of a sulfur atom, a reactive center of variable valency, and also the S–H bond whose rupture can result in generation of thiyl radicals, thiolate anions, and sulfenyl cations operating as relatively stable and highly reactive intermediates. Thiols also play important role in many biochemical processes. For instance, cysteine is a component of proteins that operate in the biochemical redox processes and in the capture of free radicals [1]. The presence of this aminoacid rest ensures formation of disulfide bridges fixing the conformation of proteins and polypeptides by building up a cystine fragment. The cystamine enters into disulfide exchange with the newly synthesized proteins containing thiol groups [2]. Gluta-thione tripeptide with a thiol group is present in a relatively high concentration in the intercellular space of the living organisms [3]. It preserves the thiol groups in proteins, destroys peroxides and free radicals, and performs the coenzyme function. Glutathionespermidine takes part in the growth control and in metabolism of nucleic acids [4]. The coenzyme A (COA) containing an active mercapto group catalyzes acyl groups transfer in the biosynthesis of fatty acids and biotin [5]. Certain dithiols, in particular, dihydrolipoic acid, take part in the photosynthesis and the metabolism in mitochondria [6, 7]. The conversion of the green form of sulfomyoglobin into the red form is believed [8] to result from transformation of a thioepoxy group into a thiol one.

The natural occurrence of thiols is relatively rare due to their ready oxidation to disulfides. Thiols naturally form mostly as metabolic products of various natural compounds. For instance, it was remarked that the methionine cleavage by corinoforms provided methanethiol [9]. The methanethiol was also isolated from green Hungarian turnip *Brasica oleracea* (*Cruciferae*) [10]. From the essential oil of *Ferula assafoetida* 2-butyl-2-propene-1-thiol was isolated as the corresponding disulfide [11], and from the asparagus juice was separated asparagusic acid [12]. Apart from the fine organic synthesis and chemistry of naturally occurring compounds some thiols find wide application in the rubber industry [13], in the polymer chemistry [14, 15], in the medicine [17] and the other branches of economy indicating the practical importance of thiols.

The stable high interest in the thiol chemistry stimulated the publication of a number of reviews [12, 18–20] describing the advances in this field within a certain period.

Ivan Vasil'evich Koval' was born in 1942 in a settlement Podgorodnoye, Dnepropetrovsk oblast'. He graduated from Dnepropetrovsk Institute of Chemical Technology in 1967, sustained the Candidate of Sciences thesis in 1970, and the Doctor of Sciences thesis in 1987. In 1995 he was elected Full Member of the Ukainian Technological Academy. He is the Head of the Chair of Chemical Processing of Macromolecular Compounds in the Ukrainian State University.

Scientific interests of I.V. Koval include organoelemental chemistry and chemistry of macromolecular compounds. His main achievement was the discovery, development of generation methods, and comprehensive investigation of properties of α-sulfenyl-*N*-anions. He is the author of over 200 scientific publications, among them 20 are reviews on the current problems in the organoelemental chemistry.

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However since the last published review a lot of new findings were revealed that required summing up. This is the goal of the present publication.

## 2. STRUCTURE AND PHYSICOCHEMICAL CHARACTERISTICS OF THIOLS

### *Bond energy and spectral characteristics of thiols*

Dissociation energy of S–H and C–S bonds in thiols is sufficiently large and equals to 318.8–448.5 and 238.1–355.2 kJ mol$^{-1}$ respectively [20]. However these bonds are less strong than O–H and C–O bonds in the oxygen analogs of thiols, alcohols (377.0–437.6 and 373.2–405.8 kJ mol$^{-1}$ respectively). In the series of aliphatic thiols the bond energy of S–H tends to grow and that of C–S tends to decrease with increasing length of the alkyl chain. The strength of these bonds is considerably affected by the conjugation of the sulfur $\pi$-electrons with the p-electrons of an aromatic system ($\pi,\pi$-conjugation) as shows the decrease in the bond energy of S–H bond and enhanced bond energy of C–S bond in going from aliphatic to aromatic thiols. The angle CSH in the methanethiol molecule is $100.3 \pm 0.2°$ [12]. Inasmuch as the sulfur atom is less electronegative than oxygen the thiols unlike alcohols are less prone to form hydrogen bonds as confirmed by IR and $^1$H NMR spectra. The reduced affinity of thiols to the hydrogen bonds formation results in their greater volatility compared to alcohols (alkanethioles have boiling points by 40–60°C lower that those of the corresponding alcohols), and also in lower solubility of thiols in water.

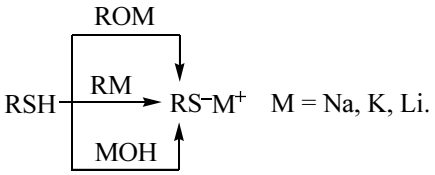
The thiol complexes with shift-reagents are less stable than those of the corresponding alcohols, and therefore the induced shifts of the SH group protons are smaller than the analogous values for the hydroxy group protons [12].

Thiols possess lower affinity to protons than alcohols. The rates of a proton transfer to thiols and of their reaction with trifluoromethanesulfonic acid are $10^4$–$10^5$ times slower than the analogous rates for alcohols, in conformity to the Pearson HSAB principle [12]. The stretching vibrations of S–H bonds in the IR spectra of alkanethiols appear in the region 2560–2592 cm$^{-1}$, and those of thiols of aromatic series in the region 2538–2568 cm$^{-1}$ [20]. In the electronic spectra of the alcoholic solutions of ethanethiol and thiophenol the following absorption maxima are observed [$\lambda_{max}$ (log $\varepsilon$)]: 195 (3.15), 225 (2.2) and 210 (4.08), 246 (3.76), 280 (2.64) respectively [20]. The proton signal of the thiol group in the $^1$H NMR spectra of thiols is observed as a singlet in the region $\delta$ 1.5–3.5 ppm. The thiol group in cyclohexanethiols is located mostly in the equatorial position [12]. The effective charges on atoms and bond orders in methanethiol and its carbanion were calculated by CNDO/2 method [21]. The force constants of S–H and C–S bonds were evaluated from the spectral data and quantum-chemical calculations for methanethiol and the other aliphatic thiols [22].

### *Acid Properties of Thiols, Generation of Thiolate Anions*

Thiols are stronger acids than alcohols due to more polar of S–H bonds compared to O–H bonds because of the greater *s*-character of the central atom. Therewith the acidity of thiols as SH-acids varies in a relatively wide range depending on the nature of groups attached to sulfur (see table) [21].

As seen from the table, the acidity of arenethiols is higher than that of alkanethiols because of greater S–H bond polarity due to $\pi,\pi$-conjugation. The introduction of strong electron-withdrawing groups into the aromatic ring additionally increases the S–H bond polarity and consequently the thiol acidity, therefore certain thiols relatively easily undergo dissociation in polar solvents yielding thiolate anions. However the genetation of thiolate anions is preformed as a rule with the use of alkali metals alcoholates, organometallic compounds, or organic and inorganic bases [21].

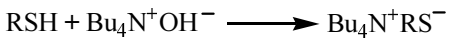



With thioles unstable in basic media (for instance, $CF_3SH$, $C_6F_5SH$) as a source of the corresponding thiolate anions may serve their mercury salts, e.g., $Hg(SCF_3)_2$ [21]. Apart from alkali metals and mercury thiolates the other metal thiolates are also known. For instance, a synthesis of indium(III) thiolates was described [23] affording the target products in 96–98% yield. The process occurred by boiling indium(III) isopropylate with three equiv of the corresponding thiol in benzene for 4 h with aseotropic removal of 2-propanol in the course of the reaction.

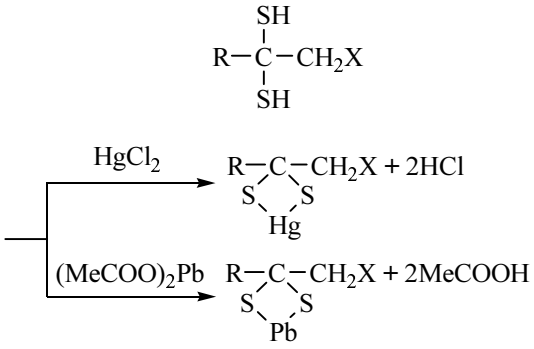
$$3RNHC(O)CH_2SH + In(OPr\text{-}i)_3 \longrightarrow [RNHC(O)CH_2S]_3In$$

The reaction of thioles with tetraalkylammonium hydroxide in organic solvents (benzene, toluene, methanol,

etc.) at 6–10°C afforded tetraalkylammonium thiolates [24].

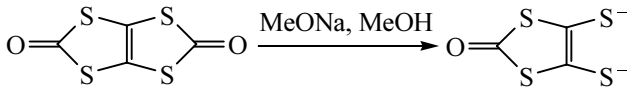


Also mercury(II) and lead(II) dithiolates are known. They arise in the reaction of geminal dithiols with mercury(II) chloride or lead(II) acetate in methanol [25, 26].

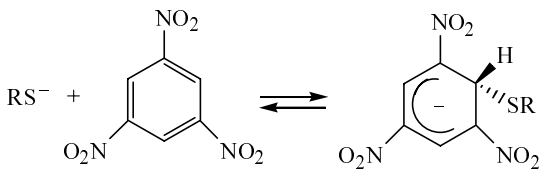


X = Cl, Br, F.

Among unsaturated thiolate anions acetylenethiolate [27], 1,1-ethylenedithiolate [28], and ethylenetetrathiolate [29] anions were described. Inasmuch as the thioles with a thiol group linked to an *sp*- or $sp^2$-hybriduzed carbon are unstable, the unsaturated thiolate anions are generated by other alternative methods involving as a rule a nucleophilic cleavage of labile C–S bonds in various compounds of bivalent sulfur, as, for instance, in generation of a dithiolate anion [29].



Thiolate anions are weaker bases than alcoholate anions. The estimation of thiolate anions basicity from the proton acidity scale employing the equilibria $RS^- + H^+ \leftrightarrows RSH$ and $RO^- + H^+ \leftrightarrows ROH$ gave the following basicity sequence: $MeO^- > EtS^- > PhO^- > PhS^-$ [12]. However with respect to CH-acids with the use of equation



Thiols p$K_a$ values[a]

| Thiol | p$K_a$ |
|---|---|
| $C_2H_5SH$ | 10.60 |
| $C_3H_7SH$ | 10.65 |
| $C_4H_9SH$ | 10.65 |
| $C_5H_{11}SH$ | 10.70 |
| $C_6H_{13}SH$ | 10.70 |
| $C_7H_{15}SH$ | 10.72 |
| $C_8H_{17}SH$ | 10.75 |
| $C_6H_5CH_2SH$ | 10.40 |
| 8-Mercaptoquinoline | 8.40[b] |
| $4\text{-}CH_3C_6H_4SH$ | 8.03 |
| $C_6H_5NHCOCH_2SH$ | 7.98 |
| $C_2H_5OCOCH_2SH$ | 7.93[b] |
| $C_6H_5SH$ | 7.76 |
| $4\text{-}ClC_6H_4SH$ | 6.96 |
| $4\text{-}NO_2C_6H_4SH$ | 5.90 |
| $2\text{-}NO_2C_6H_4SH$ | 5.26 |
| $2,4\text{-}(NO_2)_2C_6H_3SH$ | 3.94 |
| $C_6Cl_5SH$ | 4.23 |
| $CH_3COSH$ | 4.33[b] |
| $2,4,6\text{-}(NO_2)_3C_6H_2SH$ | 4.13[c] |

[a] Data of potetiometric titration in 48% ethanol.

[b] In water.

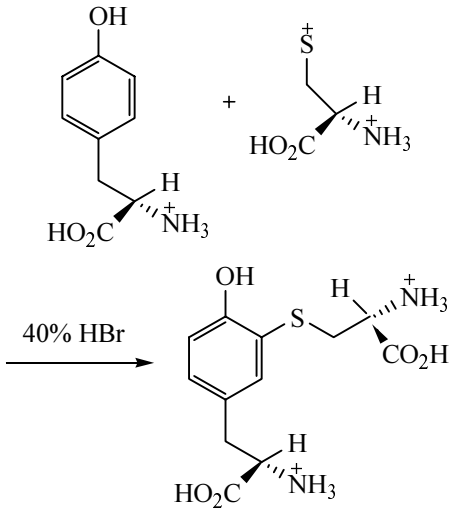
[c] In DMF.

the following series was obtained: $EtS^- > MeO^- > PhS^- > PhO^-$.

With respect to CH-acids the thiophenolate anion is $10^3$ times weaker base than the hydroxide anion due to the lower solvation degree of the former [12]. However the nucleophilic properties of the thiolate anions exceed both those of alkoholate and hydroxide anions. For instance, the nucleophilicity constant in the reaction with methyl fluoride equals for the hydroxide anions to 4.2, and for the thiolate anion to 5.1 [12]. The nucleophilicity constant in reaction with 2.4-dinitrochlorobenzene is 2.9 for methylate anion versus 5.0 for thiophenolate anion [12]. The stronger nucleophilic character of the less basic thiolate anion compared to the corresponding alkoxide anion may be ascribed to greater polarizability of sulfur than that of oxygen, and also to more energetically favorable transition state involving the thiolate anion since it is additionally stabilized by participation of the sulfur *d*-orbitals. On the other hand, it cannot be excluded that the oxygen atom in a protic solvent is involved in a strong hydrogen bond, and this fact results in reducing its nucleophilicity. In most reactions the thiols take part as thiolate anions.

*Generation of Sulfenyl Cations*

Instances of spontaneous sulfenyl cation formation are extremely seldom since the formal cleavage of a hydride ion from thiols is energetically unfavorable. However in some reactions sulfenyl cations $RS^+$ are involved as intermediates. As an example can be cited the reaction between *L*-tyrosine and *L*-cysteine in a boiling 40% hydrobromic acid [12]. The assumed mechanism of the reaction consists in electrophilic substitution in the aromatic ring of phenol involving a sulfenyl cation.




The generation from aromatic thiols of chiral electrophilic reagents being essentially arylsulfenyl cations was reported in [30].

*Generation of Thiyl Radicals*

The homolysis of the S–H bond in thiols yields thiyl radicals that play extremely important part in various chemical reactions [19, 31], in particular, in the polymerization proceses [32]. The homolysis of the S–H bond in thiols can be performed by photochemical [19, 33], radiation [19], thermal [19, 31], and chemical [19, 34] effect. The chemical procedure is the most widely applied. Here the thiyl radicals form in reaction with radical initiators: peroxides, diazo compounds etc. Sometimes in order to obtain thiyl radicals the thiols are converted into thio derivatives with a highly labile bond [S–E] that under the reaction conditions suffers homolysis to furnish thiyl radicals [34].

$$RSH + NO^+ \longrightarrow RSNO + H^+$$

$$RSNO \longrightarrow RS^{\bullet} + NO^{\bullet}$$

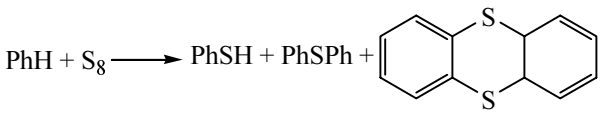
R = Alk, Ar.

The character and structure of groups attached to sulfur in the thiol affect significantly the enthalpy of formation of thiyl radicals [19, 35]. For instance arenethiyl radicals possess higher value of the formation enthalpy as compared to that of alkanethiyl radicals; the formation enthalpy for the benzenethiyl radical equals to $237.6 \pm 9$ kJ mol$^{-1}$ [19]. The enthalpy of formation in the series of alkanethiyl radicals diminishes with the growing length and branching of the alkyl chain from 129.7 kJ mol$^{-1}$ for methanethiyl to 61.8 kJ mol$^{-1}$ for butanethiyl and 46 kJ mol$^{-1}$ for 2-methyl-1-propanethiyl radicals [19]. The electron affinity of thiyl radicals is higher than that of oxyl radicals due to the presence of vacant *d*-orbitals in the sulfur atom. The stabilization energy of thiyl radicals is notably lower than that of oxyl radicals. For instance, the stabilization energy of benzenethiyl and benzeneoxyl radicals amonts respectively to 39.6 and 72.2 kJ mol$^{-1}$ [20]. By MNDO method the molecular and electronic structures were calculated for $MeS^{\bullet}$ and $EtS^{\bullet}$ radicals which possess $C_s$-symmetry [20].

## 3. METHODS OF THIOL SYNTHESIS

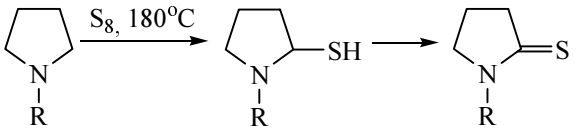
*Synthesis from Elemental Sulfur and Its Inorganic Derivatives*

The application of sulfur to the thiol synthesis is not yet widely used due to its relatively low reactivity. The latter fact is caused by its existence in the polymeric cyclic form, and additional energy is necessary for the cleavage of the ring [36]. Therefore the reactions involving sulfur as a rule require the use of highly reactive reactants or drastic process conditions. Several procedures of thiols preparation with the use of sulfur were developed. One among them consists in reaction of hydrocarbonds with sulfur. For instance, in reaction of sulfur with butane carried out at 125–135°C under the pressure of 12–24 kg/cm$^2$ in the presence of $AlCl_3$ within 2–6 h a mixture was obtained [37] of hydrogen sulfide, 2-methyl-1-propanethiol, and various sulfides. In the presence of $AlCl_3$ benzene reacted with sulfur at heating along Friedel–Crafts process yielding a mixture of thiophenol, diphenylsulfide, and thianthrene.



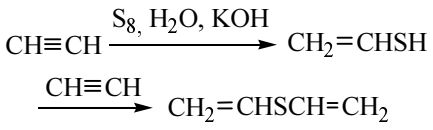

The reaction of sulfur with *N*-alkylpyrrolidines at 180°C in 9 h afforded in high yield 2-mercapto-*N*-alkyl-

pyrrolidines that under the process conditions transformed into the corresponding thiones [37].

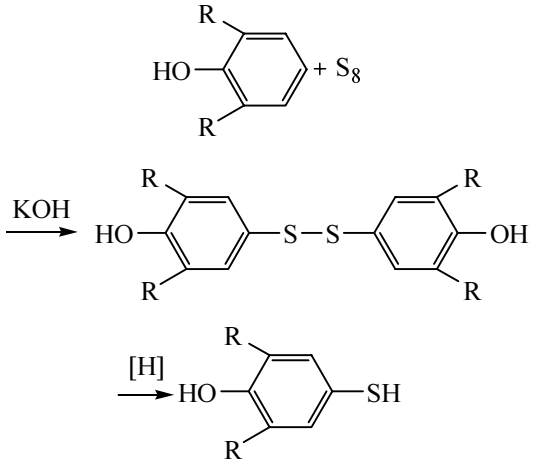


R = Me, Bu

The reaction between sulfur and acetylene in the presence of KOH affords ethenethiol that further undergoes vinylation into divinyl sulfide [20].

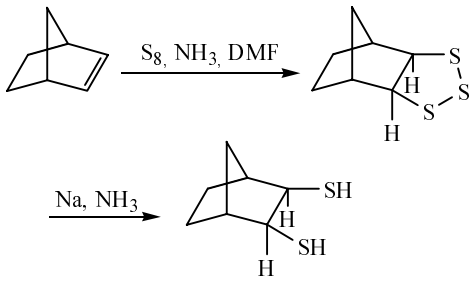


Sometimes the reactions of sulfur with hydrocarbons furnish di- and polysulfides which then are easily reduced to thiols. One of these reactions occurs between sulfur and dialkylphenols [20].

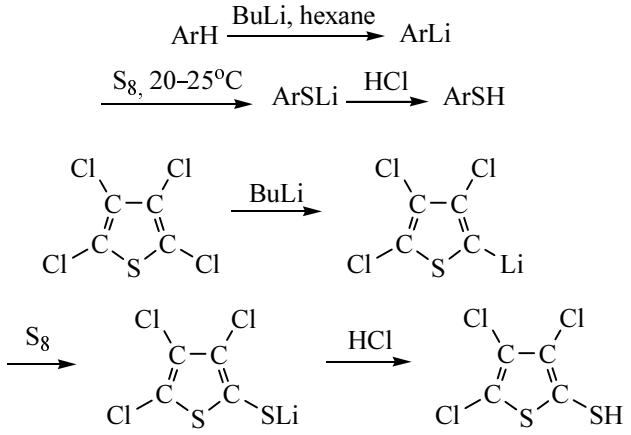


R = Me, Et, *t*-Bu.

The reaction of sulfur with norbornene resulted in formation of the corresponding trisulfide that was reduced with sodium in liquid ammonia to give dithiol [20].



A wider application, especially recently, found another procedure of thiol preparation consisting in treating sulfur with organolithium compounds in inert solvents (hexane, benzene, etc.). For instance, this method was successfully used for preparation of some aromatic [38–43] and heterocyclic [44] thiols.

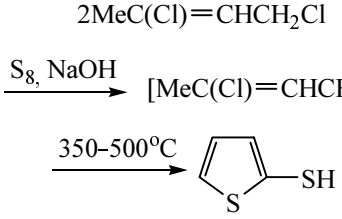


Ar = 2,6-$(MeO)_2C_6H_3$, 2-$HSC_6H_4$, 1,3,5-$(t\text{-}Bu)_3C_6H_2$, 2-HC(O)-4-$MeC_6H_3$, 2-HC(O)-4-$ClC_6H_3$.

Thiols can be obtained by reaction of sulfur mixed with sodium sulfide [12] or hydroxide with highly reactive halo derivatives of arenes or aliphatic hydrocarbons, and also with diazonium salts. The disulfides thus formed can be converted into the corresponding thiols without isolation from the reaction mixture.

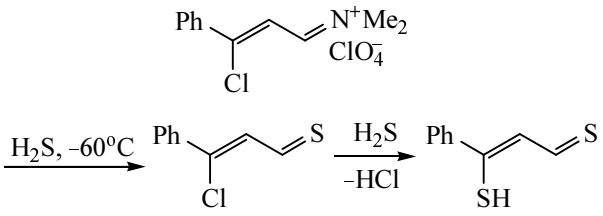
Ar = 2-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_4$.

Ar = Ph, 4-$MeC_6H_4$, 4-$ClC_6H_4$ etc.

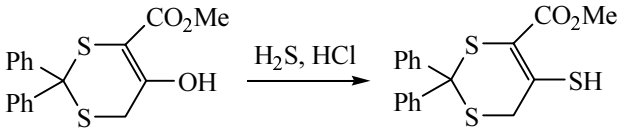


A reaction was described of 1,2,3-trichloropropane with sulfur in hydrazine hydrate affording Tiokol that was

subjected to reductive cleavage with hydrazine hydrate followed by acidifying with HCl to obtain trithioglycerol [45]. Among the inorganic sulfur derivatives the hydrogen sulfide is often applied to build up a thiol function. One procedure is based on substitution of halogens, hydroxy, methoxy, cyano, and other easily departing groups by SH under the treatment with $H_2S$. For instance, a reaction was described [46] between 2-chlorothiophene with the hydrogen sulfide occurring at 400–700°C. The replacement of a chlorine by a thiol group in 4-fluorochlorobenzene under treatment with $H_2S$ in the gas phase also was carried out under fairly stringent conditions [47]. Although the yield of the 4-fluorothiophenol is small and a side process giving bis(4-fluorophenyl) sulfide accompanies the target reaction this method may be considered as preparatively interesting. Under relatively mild conditions 3-phenyl-3-chloropropenylideneammonium perchlorate reacted with the hydrogen sulfide affording 3-phenyl-3-chloropropenethial that by the second $H_2S$ molecule was converted into unstable 3-mercapto-3-phenylpropenethial [48].

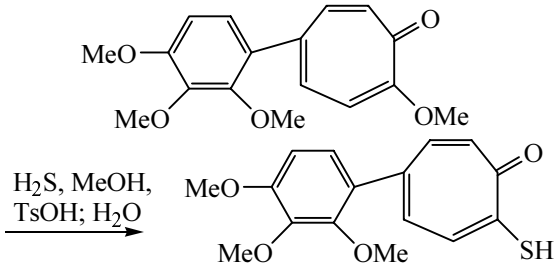



At treatment of 5-hydroxy-4-methoxycarbonyl-2,2-diphenyl-1,3-dithian-4-ene with $H_2S$ in anhydrous THF in the presence of HCl the hydroxy group is replaced by SH [49].

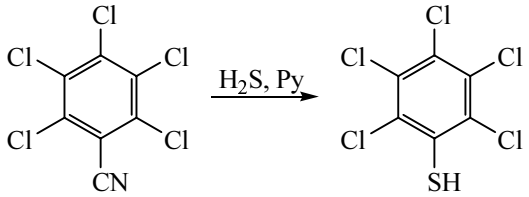



The replacement of the glycoside hydroxy group by SH in the *D*-glucose with the use of $H_2S$ occurred under relatively rigid conditions (150°C, $H_2O$) [12]. The exchange for SH of the hydroxy group in alcohols is successfully performed applying $P_4S_{10}$ [12].

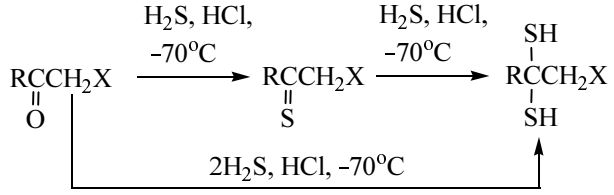
The replacement of a methoxy group by SH in a haptatriene ring of a colchicines analog was described [50] effected by hydrogen sulfide in methanol in the presence of *p*-toluenesulfonic acid.




One of the preparative procedures for pentachlorothiophenol synthesis consists in substitition by SH group of a cyano group in the pentachlorobenzonitrile. This substitution is performed with $H_2S$ in the presence of pyridine [12].




Another way of building up a thiol function with the use of $H_2S$ consists in its addition to the multiple bonds C=O, C=S, and C=C. For instance, it was mentioned that hydrogen sulfide addition across C=O and C=S bonds in haloketones [51] and halothioketones [52] afforded unstable geminal dithiols in 83–94% yield




R = Me, Ph; X = Cl, Br, F.

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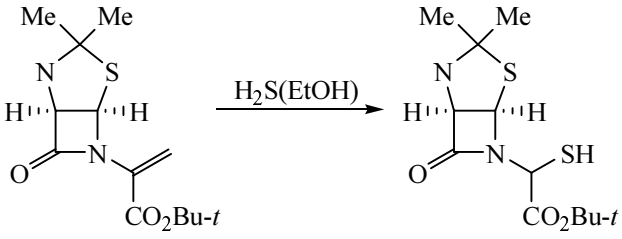
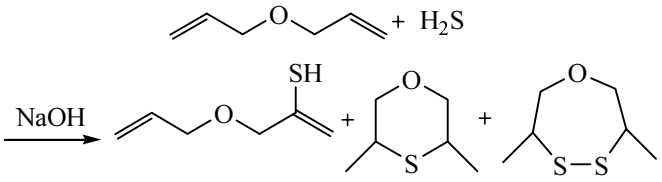
The addition of $H_2S$ to the C=C bond of methylpropene in the presence of sulfuric acid resulted in 2-methyl-2-propanethiol [20].

$$Me_2C{=}CH_2 + H_2S \xrightarrow{H_2SO_4} Me_3CSH$$

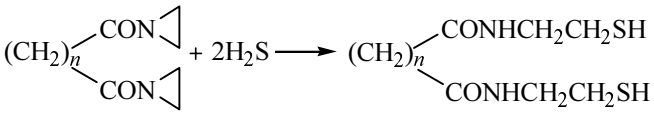
This procedure of creating a thiol function was successfully used in one of the key stages of the synthesis of the close analog of cephalosporin [53].



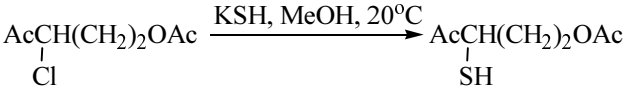
When the reagent molecule contains several active double bonds alongside with thiol also other products may form, as for instance, in reaction between $H_2S$ and diallyl ether [54].



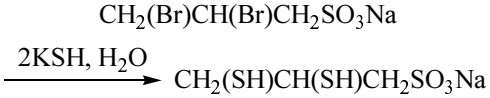
Examples are known of thiol function formation by cleavage of unstable rings effected by hydrogen sulfide. For instance, aziridine ring in bis-*N*-ethylenimides of azelaic and sebacic acids was reported to open at treatment with $H_2S$ resulting in linear bis(2-mercaptoethyl)diamides of the corresponding acids [55].



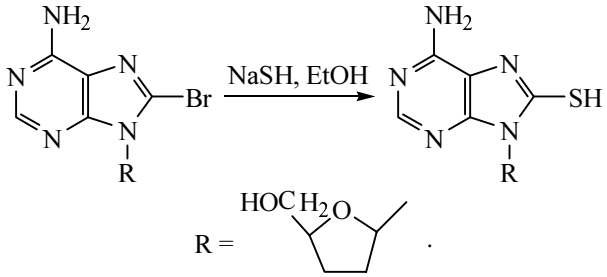
Among the other inorganic sulfur compounds potassium and sodium hydrogen sulfides are very often used to introduce the thiol function. These compounds relatively readily react under mild conditions with halogen derivatives replacing the halogen by a thiol group. Basing on these reagents quite a number of preparative methods for thiol synthesis were developed widely used in the fine organic synthesis [56]. For instance, the synthesis of thiamine hydrochloride includes a stage [57] of chlorine substitution by a thiol group in 1-acetyl-3-acetoxy-1-chloropropane effected by KSH in methanol at 20°C within 1 h affording 1-acetyl-3-acetoxy-1-propanethiol in a quantitative yield.



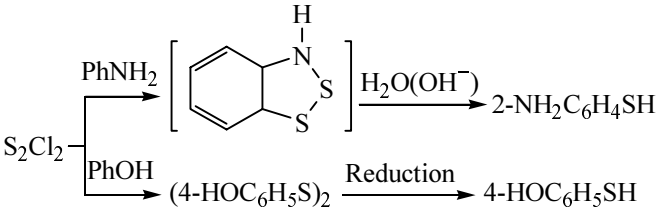
The refined procedure for unithiol synthesis [58] in order to introduce two thiol groups utilized a reaction of sodium 2,3-dibromopropane-1-sulfonate with KSH in water solution.



A classic method of 5-mercaptopyrimidinenucleosides synthesis involves a reaction between the corresponding bromo derivatives with sodium hydrogen sulfide in dimethylacetamide [53]. A similar procedure was applied to preparation of 8-mercapto-2,3-didesoxyadenosine [59]: The 8-bromo-2,3-didesoxyadenosine was boiled in alcohol with sodium hydrogen sulfide for 2 h.

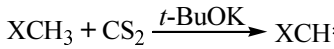


The sodium hydrogen sulfide on polymer support was utilized in the synthesis of thiols from alcohols carried out in acetonitrile in the presence of trifluoroacetic anhydride [60]. Thiols were obtained in 68–88% yields. In the preparation of 2-amino- and 4-hydroxythiophenols the sulfur monochloride was frequently used [12].

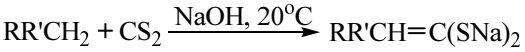


It was reported that $NaBH_2S_3$ was applied to the synthesis of phenylmethanethiol [12], $Na_2S_2O_3$ to the preparation of 8-mercaptopurinenucleosides [61], and $Li_2S$ to the synthesis of thio-α-amino acids [62].

To build up two thiolate groups attached to an unsaturated carbon a reaction of carbon disulfide with compounds containing active methyl [63] or methylene [64] groups is successfully used.



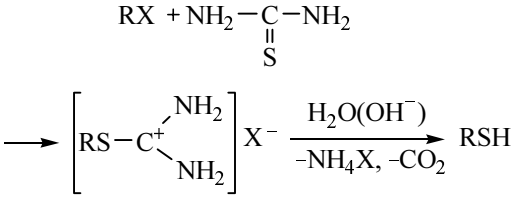
X = 4-phenylbenzoyl, 2-thienylcarbonyl.



R = R' =CN, $CO_2Et$, Ac; R = CN, R' =$CO_2Et$; R = Ac, R' = $CO_2Et$.

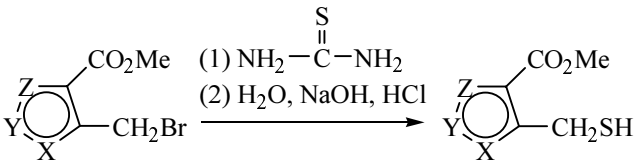
*Hydrolytic methods of thiol synthesis* are based on reactions of compounds with labile halogen atoms or highly reactive functional groups with reagents containing thiol or thione groups (transfer agents for SH groups)

followed by hydrolytic cleavage of a C–S bond in the formed intermediate product. To these procedures belongs the already classic method widely used in the laboratory routine of thiols synthesis applying thiourea. In such an event a mixture of halo derivatives and thiourea is heated in a polar solvent (water, alcohol, acetone, etc.) to obtain an isothiouronium salt that on hydrolysis in an alkaline medium yields the thiol.

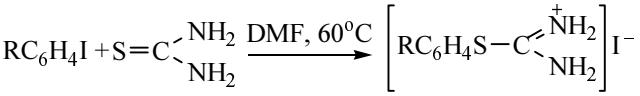


X = Cl, Br, I.

This method was applied to preparation of 3,5-dihydroxyphenylmethanethiol [65], ω-ferrocenylalkanethiols $Fc(CH_2)_nSH$ ($n$ = 6, 8, 11) [66], 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-propanethiol [67], 1,3-dithiols [68], methyl 6-mercapto-3,3,4,4,5,5,6,6-octadeuterohexanoate [69], 2,3,4,6-tetra-*O*-acetyl-1,5-dithia-β-*D*-glucopyranose [70], *N*-(dihydroxyborylphenyl)-5-mercaptopentaneamide [71], some pyridinethiols [72], and their N-oxides [73]. The reaction of the appropriate bromomethyl derivatives with thiourea in acetone afforded a series of heterocyclic thiols in 80–90% yields [74].



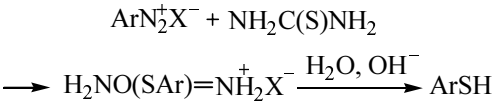
X = Y = CH, Z = S; X = S, Y = Z = CH; X = Z = CH, Y = S; X = O, Y = Z = CH; X = Y = CH, Z = O.



R = H, *p*-Me, *o*-Me, *p*-MeO, *p*-$NH_2$, *p*-Cl, *p*-Br.

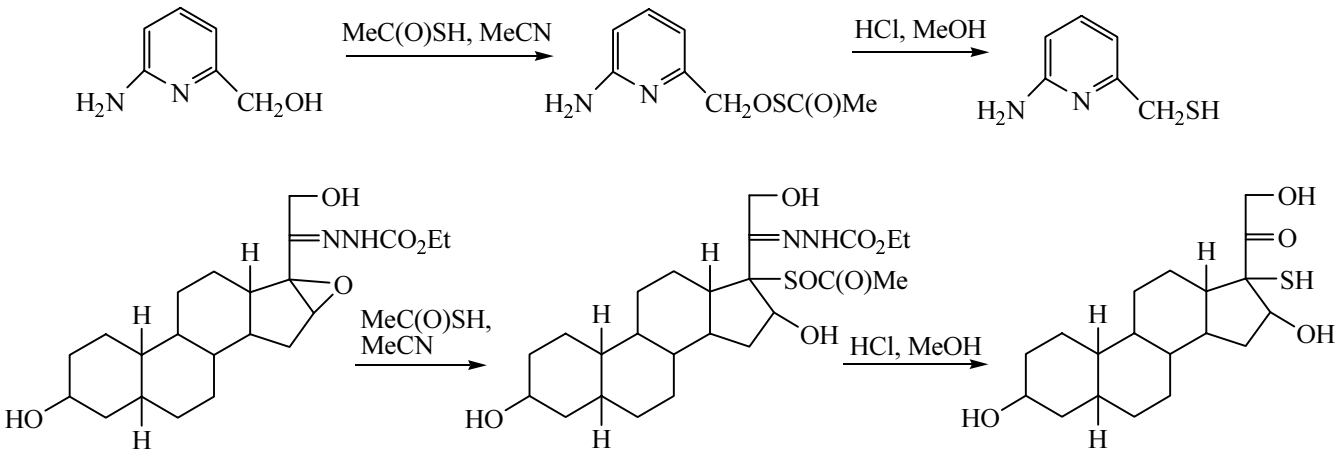
In reactions of inactivated aryl halides with thiourea it was suggested [75] to use a catalytic complex of Ni(II) that formed *in situ* from the bis(triethylphosphine)nickel chloride and sodium cyanoborohydride. At the use of this complex arenethiols were obtained even from aryl halides with electron-donor groups in the benzene ring [75].

Aromatic thiols also can be prepared by the thiourea reaction with arenedizonium salts that also affords isothiouronium salts [12].



The thioacetic acid is very often used as a transfer agent for the thiol group, not only because of its availability but apparently due to the readiness of acetyl group elimination. Several methods were developed for acetylthio group introduction into organic compounds. These procedures involve a substitution of halogen [76, 77] or hydroxy group by acetylthio group in the presence of triphenylphosphine [78, 79' or alkali [80, 81], an addition of the thioacetic acid to the C=C bonds of unsaturated compounds [82, 83], or opening of an epoxy ring effected by the thioacetic acid [84–86].

The acetyl fragment is removed by acid [77, 85] or alkaline [87] hydrolysis. The relative ease of the thiol group introduction by the use of the thioacetic acid, and



also plausible thiol yields by this procedure led to application of these methods also to the chemistry of natural compounds, for example, substitution of a thiol group for the hydroxy one in 2-hydroxymethyl-6-aminopyridine [80] and for the epoxy ring in 3β,21-dihydroxy-20-ethoxycarbonylhydrazono-16α,17α-epoxy-5α-pregnane.

In the synthesis of a series of mercaptoalcohols [88] the potassium xanthate was used as thiol group transfer agent, and the ethoxycarbonyl group was eliminated by acid hydrolysis or by reduction with lithium aluminum hydride.

$$Me_2CHCH(Br)CO_2H \xrightarrow[\text{(2) HCl, } H_2O;\ \text{(3) } NaBH_2,TiCl_4,\ 0^oC]{\text{(1) EtOC(S)SK, NaOH, } H_2O,\ 20^oC,\ 100^oC;} Me_2CHCH(SH)CH_2OH$$

$$Me_2CHCH(I)C(O)H \xrightarrow[\text{(2) } LiAlH_4]{\text{(1) EtOC(S)SK, } 20^oC;} Me_2CHCH(SH)CH_2OH$$

$$Me_2CC(O)CH_2Br \xrightarrow[\text{(2) } LiAlH_4]{\text{(1) EtOC(S)SK, } 20^oC;} Me_2CHCH(OH)CH_2SH$$

Recently the thiol group transfer was frequently carried out by triphenylsilanethiol that added to terminal alkenes in the anti-Markownikoff fashion giving S-(triphenylsilyl)thio compounds. The latter are relatively readily hydrolyzed in the presence of trifluoroacetic acid affording the corresponding thiols in a 45–86% yield [89].

$$RCH{=}CH_2 + Ph_3SiSH \longrightarrow RCH_2CH_2SSiPh_3 \xrightarrow{CF_3CO_2H} RCH_2CH_2SH$$

R = 4-$BrC_6H_4$, 4-$MeOC_6H_4$, 4-MeOCO etc.

With minor reservations the conversion of phenols into thiols involving Newman–Kwart rearrangement [20] should be also regarded as a hydrolytic preparation method (Scheme 1).

### *Cleavage of C–S Bond in Sulfides*

The reductive cleavage of the C–S bond in sulfides effected by various reagents is a well known classic method of thiol synthesis extensively used nowadays. The procedure is most often applied to the chemistry of naturally occurring compounds where the sulfide function may play the role of a protective group. As a rule the sulfides suffering the reductive cleavage tend to predominant rupture of one of the two C–S bonds; therewith the ease of the C–S cleavage decreses in the series alkynyl > vinyl > allyl > benzyl [90]. Sulfides containing a benzyl group are often subjected to the reductive cleavage. For instance, a synthesis was described [91] of new thioindigo derivatives with terminal Cθντεз SH groups. One of the stages in this synthesis was benzyl fragments elimination by reductive cleavage of the C–S bonds in the intermediate sulfide by the treatment with hydrazine hydrate (Scheme 2).

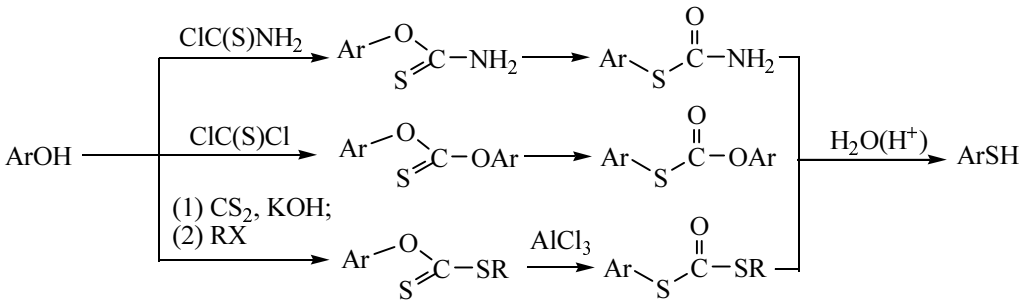
The hydrazine hydrate in alkaline medium was also used to reduce Thiokols to alkanethiols [92] and alkanedithiols [93].

In the synthesis of 3-(dimethylaminomethyl)-1,3-dithiols the reductive cleavage of the C–S bonds was performed with sodium in 1-butanol [94].

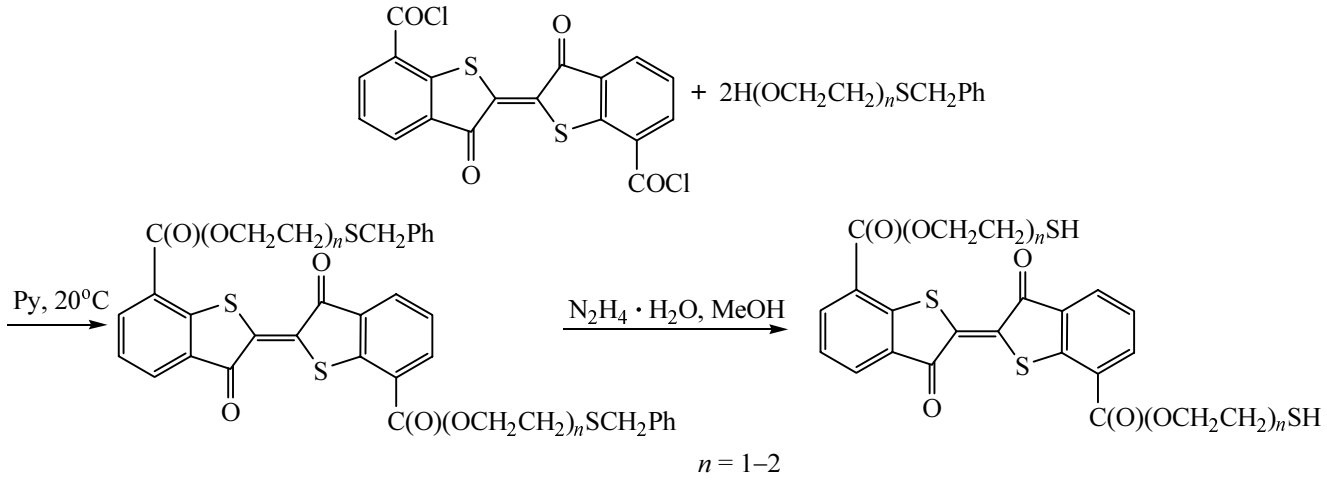
$$PhCH_2SCH(CH_2NMe_2)CH_2CH_2SCH_2Ph \xrightarrow[120\text{–}140^oC]{Na,\ BuOH,} HSCH(CH_2NMe_2)CH_2CH_2SH$$

The sodium in the liquid ammonia was also used for the cleavage of divinyl sulfide [95] to obtain ethenethiol

**Scheme 1.**



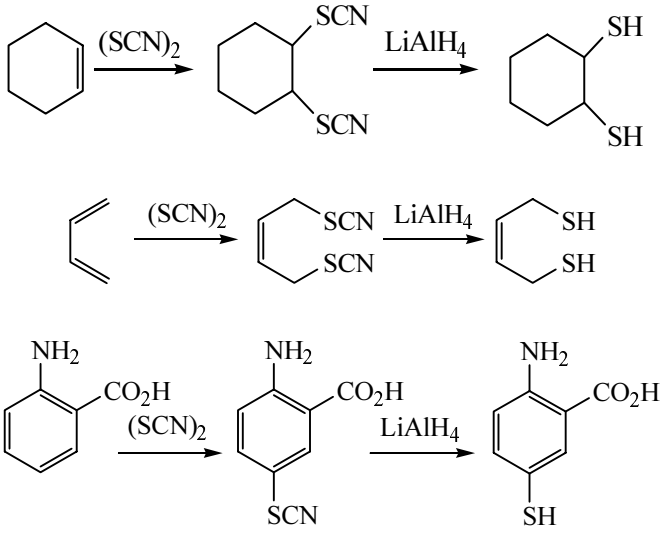
**Scheme 2.**



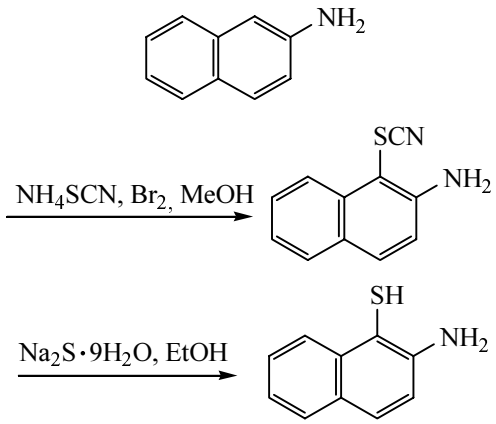

$n$ = 1–2

sodium salt. As other reagents for reductive cleavage of the C–S bond were applied hydrogen bromide in the trifluoroacetic acid [96], lithium aluminum hydride in THF [97], and sodium 2-methyl-2-butanethiolate in DMF [98].

With minor reservations among these thiol preparation methods a procedure can be cited consisting in introduction of a thiocycnate group into a organic compound followed by reductive cleavage of the thiocyanate group. The dithiocyanogen is the reagent of choice for these syntheses since it relatively readily adds to the C=C bond or substitutes a hydrogen atom by an electrophilic mechanism in a benzene ring activated by the presence of electron-donor substituents [12].

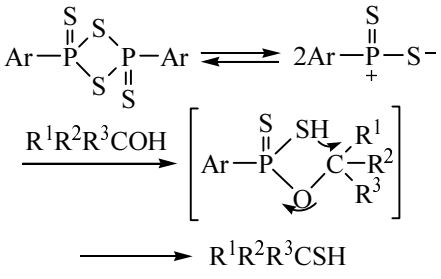



In the synthesis of 2-aminonaphthalene-1-thiol the thiocyanate group was introduced via dithiocyanogen obtained *in situ* from $Br_2$ and $NH_4SCN$, and the reductive cleavage was effected with sodium sulfide [99].




*Syntheses Involving Lawessons' Reagent*

For the replacement of the hydroxy group in alcohols by a thiol one under relatively mild conditions the cyclic anhydrides of dithiophosphonic acids (Lawessons' reagent) recently found application. For instance, the conversion of a series of alcohols into the corresponding thiols with the use of this reagent was reported [100, 101]. The reaction was carried out by heating the initial reactants in toluene or 1,2-dimethoxyethane. The corresponding thiol yields amounted to 39–100%.

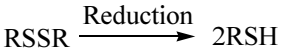



$R^1$ = Ph; $R^2$ = H, Me, Ph; $R^3$ = H, Me, Ph; Ar = Ph, 4-$MeC_6H_4$

The Lawessons' reagent was reported [102] to be used in the stereoselective synthesis of cyclosporine A analog.

### *Thiol Synthesis by Reduction of Organosulfur Compounds*

The reduction of aliphatic, aromatic, and heterocyclic disulfides is one of traditional widely used methods of thiol syntheses [103].



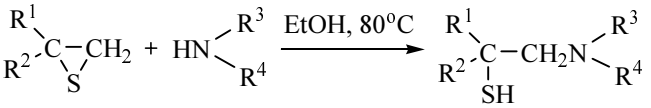
R = Alk, Ar, Ht.

Depending on the disulfide character the reductants used are zinc in acetic, hydrochloric, or sulfuric acid [103, 104], sodium in xylenes [103], lithium aluminum hydride in ether or THF[103], activated copper powder in DMF [105] or acetonitrile [106], selenophenol [107], dithiothreitol [108], systems $BF_3$–$H_2O$–$Et_3SiH$ [109], $ZrCl_4$–$NaBH_4$ [110], $Cp^2$–$TiCl_2$–*i*-BuMgBr [111], and hydrazine hydrate [112]. Apart from the chemical reduction the electrochemical reduction is frequently used [113].

Besides sulfide in the synthesis of aromatic thiols the reduction of sulfonyl chlorides [103] or sulfonic acids esters [114] is often performed. The most common reductants in this case are zinc in sulfuric acid [115] or lithium aluminum hydride in anhydrous THF [114]. The reduction of *p*-iodobenzenesulfonyl chloride was carried out using a system Zn–$Me_2SiCl_2$–DMA. The yield of the *p*-iodothiophenol was here 90% [115].

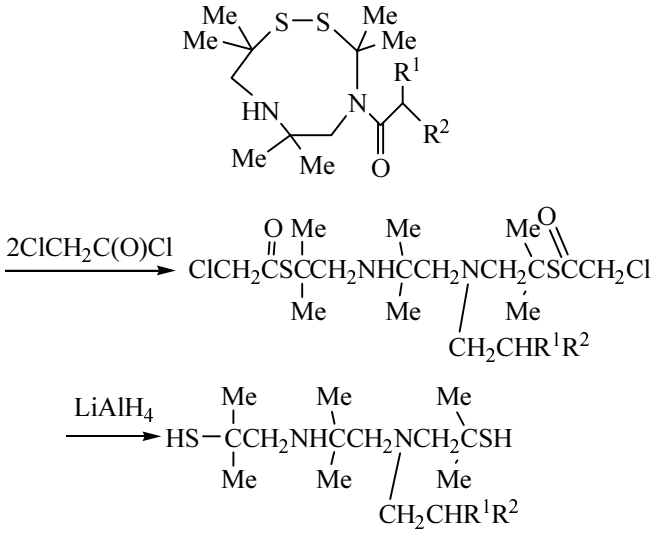
### *Thiol Formation Resulting from the Opening of Sulfur-Containing Rings*

The opening of sulfur-containing rings effected by various reagents is often used for preparation of bifunctional thiols. For instance, in the synthesis of β-aminothiols was successfully used the opening of the thiirane ring under treatment with primary [116] and secondary [117, 118] amines. The process was performed by heating the initial reagents in ethanol, and the β-aminothiols were obtained in a quantitative yield.



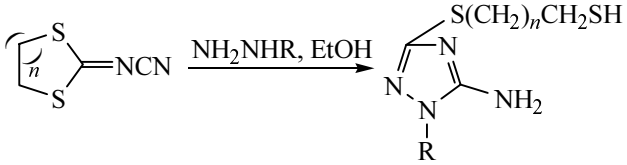
$R^1$ = Me, $BuOCH_2$; $R^2$ = H, Me; $R^3$ = H, Et; $R^4$ = Et, $(CH_2)_5Me$, $(CH_2)_2Me$, 2-$NH_2C_6H_4$.

The events of cleavage of other sulfur-containing rings are known. For instance [119], the alkaline hydrolysis of 2-amino-5-methyl-4-nitrobenzothiazole afforded 2-amino-5-methyl-3-nitrophenol. The ring opening of 3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodecane under the action of monochloroacetic anhydride was described [120]. The arising intermediate product was reduced into a dithiol by $LiAlH_4$.



$R^1$ = H, Me; $R^2$ is the fragment of heterocyclic amine

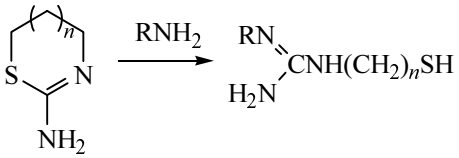
The ring opening in 2-cyanimino-1,3-dithianes effected by R-hydrazines is followed by a new cyclization into 3-amino-1-R-1,2,4-triazoles with a thiol group in a side chain [121].



*n* = 1, 2; R = Alk, Ar

In the synthesis of enthiols $R^1R^2C{=}CH(SH)$ ($R^1$ = $R^2$ =H; $R^1$ = H, $R^2$ = Me) a Diels–Alder retro reaction was performed with the use of 12-$R^1$-12-$R^2$-11-mercapto-9,10-dihydro-9,10-ethyleneanthracenes occurring at 625°C [122]. It was reported [123] that the reaction of 2-amino-9*H*-1,3-thiazino[6,5-*b*]indole with alkyl halides in the alkaline medium was accompanied by recyclization of the thiazine ring into a pyrimidine one, and also by its cleavage with water molecules addition and cyanamide elimination resulting finally in formation of 2-mercapto-pyrimido[4,5-*b*]indole and 2-mercapto-3-formylindole derivatives.

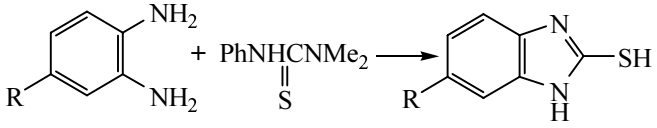
A new synthetic procedure was developed [124] for N-monoderivatives of 2(3)-mercaptoalkylguanidines involving aminolysis of the corresponding sulfur and nitrogen containing heterocycles affording thiol yields of 47–90%.



R = Me, Et; $n$ = 0, 1.

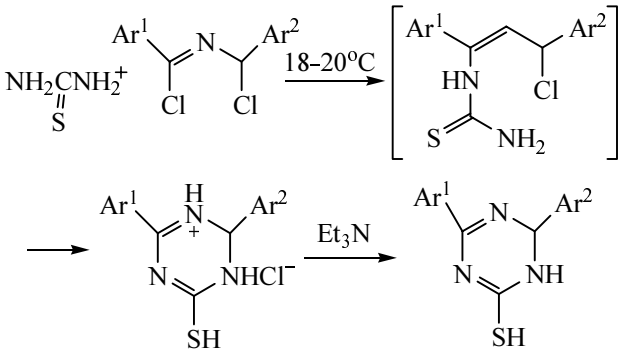
*Thiol Formation as a Result of Heterocyclizations*

The thiourea and its derivatives are the most frequently used reagents in these reactions. For instance, the synthesis of 2-mercaptobenzimidazoles was possible by heterocyclization of *N,N*-dimethyl-*N'*-phenylthiourea with *o*-phenylenediamines [125].



R = H, Me, Br, Cl.

The thiourea selectively reacted with *N*-(1-chlorobenzyl)benzimidoyl chlorides giving 2,4-diaryl-1,2-dihydro-6-mercapto-1,3,5-triazines hydrochlorides that by treating with triethylamine were converted into the corresponding bases which were isolated [126].

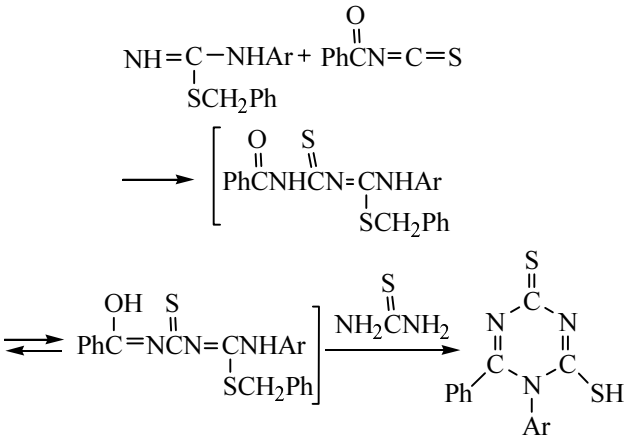


$Ar^1$ = Ph, 4-$FC_6H_4$; $Ar^2$ = Ph, 4-$FC_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$.

However the reaction of the thiourea with the *N*-(prechloroethenyl)benzimidoyl chloride and its analogs did not afford the corresponding mercaptotriazines [127]. It was presumed [127] that in this case the primary attack of the imidoyl chloride occurs at the sulfur and not at the nitrogen atom.

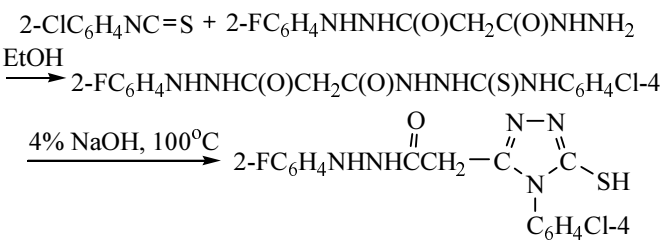
The thiourea was used alongside chloroacetic acid, furfural, and thiosemicarbazide in the four-stage synthesis of 3-mercapto-6-furfuryl-1,2,4-triazin-5-one [128]. This synthesis involves a condensation of monochloroacetic acid with thiourea, a hydrolysis of the arising 2-aminothiazolidin-4-one followed by a condensation of the intermediate thiazolidine-2,4-dione with the furfural, and a reaction of 5-(2-thienylmethylene)thiazolidine-2,4-dione with the thiosemicarbazide.

A series of heterocyclic thiols was prepared based on isothiocycnates. For instance, it was reported [129] that the reaction between benzoyl isothiocyanate and S-benzyl-*N*-arylisothiourea followed by heating of the addition products resulted in 1,6-diaryl-2-mercapto-1*H*-1,3,5-triazine-4-thiones.

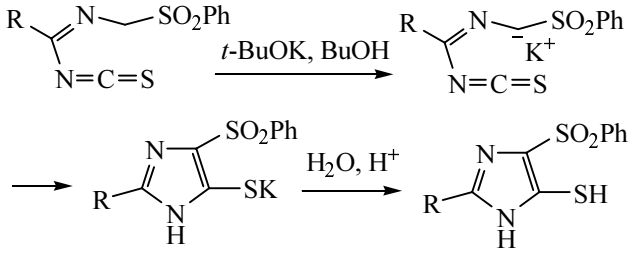


Ar = Ph, 2-$MeOC_6H_4$, 4-$MeC_6H_4$, 4-$ClC_6H_4$, 4-$MeOC_6H_4$, 4-$BrC_6H_4$.

The addition of *N*-(2-fluorophenyl)malonic acid hydrazide to the 4-chlorophenyl isothiocyanate followed by the addition product treatment with a water solution of NaOH resulted in a thiol with a thiol group attached to the triazole ring [130].



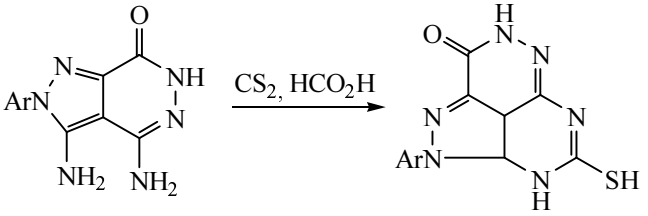
The hetrocyclization of imidoyl isothiocyanates in the presence of potassium *tert*-butylate was reported [131] to yield 2-R-4-arylsulfonyl-5-mercaptoimidazoles.



R = Me, Ph.

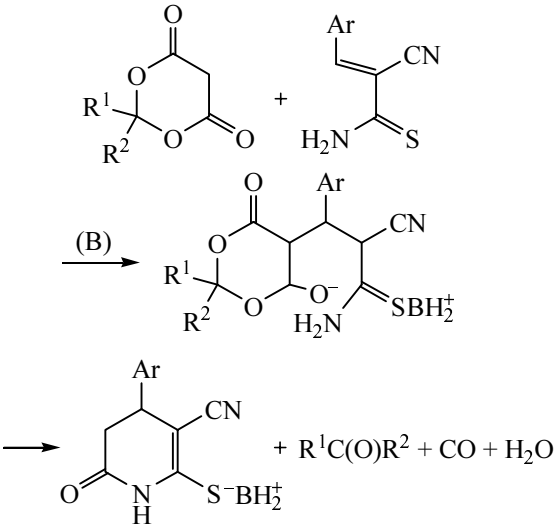
In some cases heterocyclic thiols were known to be obtained with the use of carbon disulfide. For instance, 1-sulfomethyltetrazole was synthesized from carbon disulfide, aminomethanesulfonic acid, ethyl bromide, and sodium azide [132]. The synthesis involved a reaction of carbon disulfide with aminomethanesulfonic acid in the presence of KOH, then ethylation of the dithiocarbamic acid derivative with ethyl bromide, and condensation of the arising ethyl ester with the sodium azide. The reaction of carbon disulfide with methyl S-methoxycarbonylthioglycolate follows the Scheme 3 [133].

The carbon disulfide was used also in the synthesis of fused pyrimidines containing a thiol group [134].



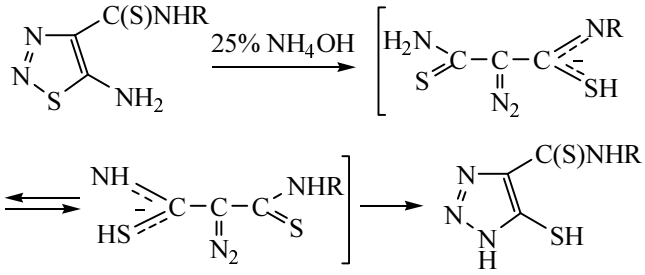
Ar = Ph, 4-$MeC_6H_4$

Among other reagents thioamides find application with increasing frequency to the synthesis of heterocyclic thiols. For instance, a reaction was described [135] of arylmethylenecyanothioacetamide with Meldrum's acid leading to Michael adducts in the form of ammonium salts that underwent cyclization on heating into 4-ammonium aryl-2-oxo-5-cyano-1,2,3,4-tetrahydropyridine-6-thiolates [135].



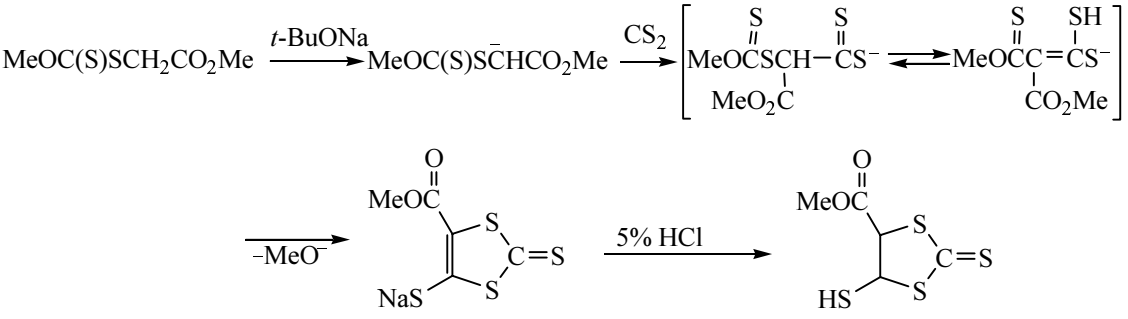
$R^1 = R^2 = Me$; Ar = 2-$ClC_6H_4$, 4-$BrC_6H_4$; B:piperidine, *N*-methylmorpholine.

Diazoalkanes with a thioamide group in the α-position due to their high reactivity transform into thiazoles with an SH group in the side chain already under conditions of their generation [136]. For instance, 5-amino-1,2,3-thiadiazole-4-carbothioamides are converted finally into 5-mercapto-1,2,3-triazole-4-carbothioamides.



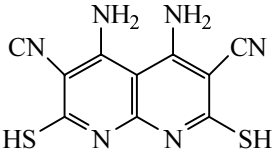
The cyanothioacetamide together with 1,1-dicyano-2,2-di(methylthio)ethylene was used in the synthesis of

**Scheme 3.**

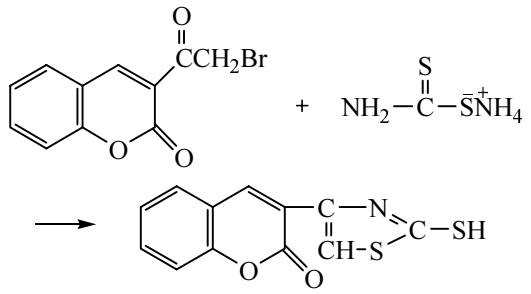


4,5-diamino-2,7-dimercapto-3,6-dicyano-1,8-naphthiridines [137]. In this case the heterocyclization was performed in dioxane under conditions of the phase-transfer catalysis at the ratio of the initial reagents 2:1, and the yield of the reaction product was 77%.

$$2NH_2C(S)CH_2CN + (NC)_2C{=}C(SMe)_2 \xrightarrow{K_2CO_3,\ Bu_4^+N^-Br}$$

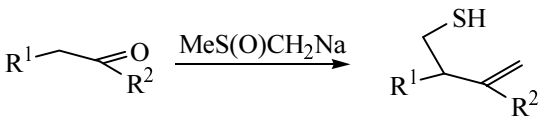


The heterocyclization of ammonium dithiocarbamate with 3-bromoacetylcoumarine was reported in [138] affording in a 70% yield 3-(2-mercaptothiazol-4-yl)-2*H*-1-benzopyran-2-one.



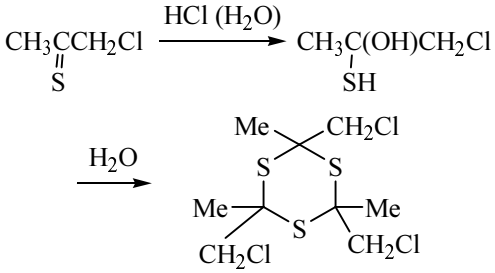
*Other Methods of Thiols Synthesis*

A special preparative method was developed for the synthesis of homoallyl thiols affording various aliphatic and cage-like homoallyl thiols in a high yield [139]. This method consists in treating ketones with sodium dimsyl in DMSO.



$R^1$ = H, Et; $R^2$ = Pr, *t*-Bu, Hex.

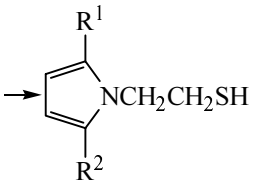
In reaction of 1-chloropropanethione with the hydrochloric acid formed 2-mercapto-1-chloro-2-propanol that



under the conditions of the process transformed into 2,4,6-tri(chloromethyl)-1,3,5-trithiane [140].

Sometimes with goal of preparation of new thiols various functional groups in thiols are subjected to purposeful modification (Scheme 4). The most often modified groups are amino, hydroxy, and carboxy groups. For instance, amino group of 2-aminothiophenol was acylated with complex keto-esters and ketoimidoyl bromides.

$$HSCH_2CH_2NH_2 + R^1C(O)CH_2CH_2C(O)R^2 \longrightarrow$$



$R^1$ = Me, $R^2$ = Et, Pr, *i*-Pr, Bu, Pent, $Et_2CH$

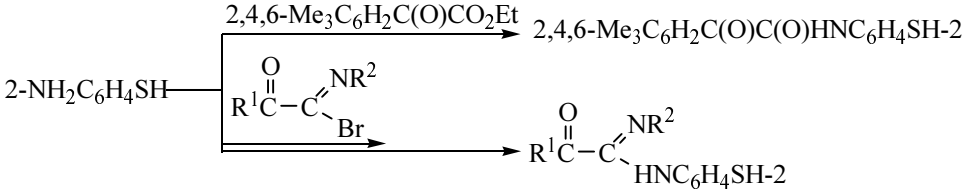
The cystamine condensation with diketones was performed [142] occurring with participation of the amino group and resulting in *N*-(2-mercaptoethyl)-2,5-dialkylpyrroles in 68–75% yields.

A series of thiols containing an ester group were prepared by transesterification of 2-mercaptoethanol with aliphatic acids ethyl esters in the presence of lipase isolated from pancreas [143].

$$Me(CH_2)_nCO_2Et + HOCH_2CH_2SH \longrightarrow Me(CH_2)_nCO_2CH_2CH_2SH$$

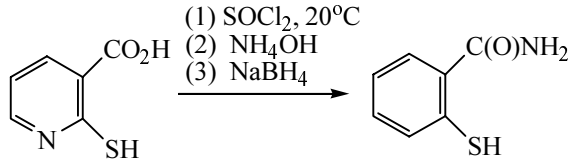
$n$ = 0, 1–4, 6, 8, 10.

**Scheme 4.**



$R^1$ = (4-oxo-$D^2$-1,3-thiazolin-2-yl)cyanomethyl; $R^2$ = PhNH, 4-$MeC_6H_4NH$, 4-$NO_2C_6H_4NH$, 4-$ClC_6H_4NH$.

A stepwise transformation of the carboxyl into an amide group in the 2-mercaptonicotinic acid was described in [144].

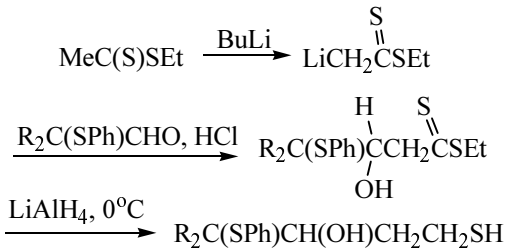



A synthesys of thiol with a phosphonate group was based on thioglycolic acid and diethyl allylphosphonate [145]. In the process of this reaction alongside the addition of one molecule of the thioglycolic acid to the C=C bond of the allyl fragment its carboxy group obviously was reduced to an alcohol with subsequent esterification with the second molecule of the thioglycolic acid.

$$CH_2{=}CHCH_2P(O)(OEt)_2 + 2HSCH_2CO_2H$$

$$\longrightarrow HSCH_2CO_2(CH_2)_2S(CH_2)_3P(O)(OEt)_2$$

A multistage synthesis of a number of mercapto-alcohols occurring along the scheme below was described in [146].




R = Me; $R_2 = (CH_2)_4, (CH_2)_5$.

## 4. CONCLUSION

Thiols are constantly attracting widespread attention of many researchers. This is due to the importance of these compounds both for the organic synthesis and industry. The role of thiols in various biochemical processes and in the chemistry of natural substances is also very significant. The recent attempts of researchers were directed on development of methods for generation of various intermediates based on thiols (thiyl radicals, thiolate anions, sulfenyl cations), and also on the comprehensive investigation of their physicochemical characteristics. Therewith a number of new methods was developed for generating these intermediates. Concerning thiol preparation alongside development of the well known procedures, like syntheses with the use of thiourea and mercaptoacetic acid, a series of new methods was introduced, in particular, with application of carbon disulfide, Thiokol reduction, ketones reaction with sodium dimsyl etc. Although these methods are not sufficiently tested and the degree of their generality is not yet clear, their development is a certain contribution to the advancement of the thiol chemistry.

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