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The Thiohydroxamate System

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ABSTRACT: *The natural occurrence of thiohydroxamates, their methods of preparation, reactivity, properties of their derivatives including Barton's esters and complexes during the last 25 years, as well as a survey of their biological properties are reported in this review.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:169–194, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10017

INTRODUCTION

Thiohydroxamic acids (*N*-hydroxythioamides) are a class of compounds containing a group of four significantly different atoms: C_{sp^2}, S, N, and O. Unexpectedly, this unique class of bonds is relatively widespread in nature, and has been known to man as the bitter component in spices for as long as sweetening additives.

The specific system of bonds sulfur–carbon–nitrogen–oxygen results in a higher acidity of the thiohydroxyamide hydrogen atom that creates good conditions for formation of the intermolecular hydrogen bond, while the large van der Waals radius of the sulfur atom limits the conformational freedom. The free activation energy during rotation about the C—N bond is higher by 4.3 kcal/mol than in hydroxamic acids [1]. Simple thiohydroxamic acids have pK_a values from 4.2 to 5.6 compared to a pK_a of the order of 9 for the corresponding hydroxamic acids [1]. Thus, thiohydroxamic acids form metal complexes at lower pH values than the corresponding hydroxamic acids. The specific bond system causes thiohydroxamic acids to be excellent double dentate ligands capable of complexing cations of different metals. These bioligands are being used in nature for transport of many cations. They are also used in analytical chemistry for the quantitative determination of many metals. In the past 25 years, by using the specific reactivity of the thiohydroxamic system, *O*-acyl derivatives of thiohydroxamic acids have found wide application in organic chemistry as a source of efficiently generated carbon, sulfur, nitrogen, or phosphorus radicals.

In the case of thiohydroxamic acids, similarly as in the case of thioamides, we are faced with a tautomeric equilibrium, where the structure of the *N*-hydroxythioamide **1** remains in equilibrium with the structure of the *N*-hydroxythioimide **2**. In other words, thiohydroxamic acid is in equilibrium with thiohydroximic acid (Scheme 1).

However, results of recent studies indicate that the thiohydroximic form in the liquid state or in solution is not present in significant concentrations. Only the thiohydroxamic acid form is present in the solid state [2]. On the contrary, *S*-alkyl derivatives of thiohydroximic acids exist in nature as they form relatively strong bonds and are relatively easy to synthesize.

NATURALLY OCCURRING THIOHYDROXIMATES AND THIOHYDROXAMATES

Sulfated *S*-glucosyl thiohydroximates occurring in plants are a specific group of compounds

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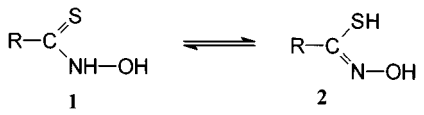


SCHEME 1

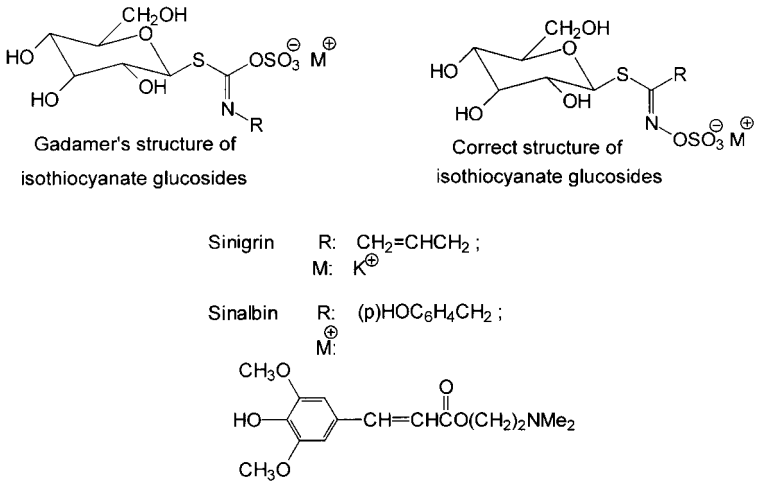
among the many naturally occurring sulfur-organic compounds. They are *S*-glucosides, derivatives of thiohydroximic acids, where the *N*-hydroxyl group is additionally acylated with a sulfuric acid residue. Unfortunately, their nomenclature is not systematized, for example, in food product chemistry they are called *glucosinolates* and this name does not reflect their structure (Scheme 2).

Sulfonated *S*-glucosyl thiohydroximates are mainly biosynthesized by plants belonging to the families Cruciferae (mustard), Capparideaceae, and Resedaceae (mignonette); also their presence has been noted in plants belonging to the families Tropaeolaceae (nasturtium), Salvadoraceae, Caricaceae, Limnanthaceae (false mermaid), Moringaceae, Plantaginaceae (plantain), and Euphorbiaceae (spurge) [3]. Therefore, they are present in such agriculturally important vegetables as cabbage, brussel sprouts, colgards, kale, and cauliflower. They have been detected in all fragments of these plants; however, the roots and seeds seem to be especially rich in these compounds and this biological material is the main source for the isolation of these compounds.

Already in the nineteenth century many chemists were able to demonstrate that formation of volatile isothiocyanates (at that time called mustard oil) from seeds of many plants requires the presence of water; later it was proven that it is an enzymatic process. Furthermore, it was proven that sulfates of O-sulfated *S*-glucosyl thiohydroximates are precursors of isothiocyanates isolated from the plant product. As the result of enzymatic hydrolysis they form glucose, the sulfate anion, and isothiocyanates, and the latter were originally isolated from natural products. In 1831 Robiquet and Boutron [4] isolated from white mustard seeds (*Sinapis alba* L.) a crystalline substance, then given the name *sinalbin,* and a little later it was stated that it is an *S*-glucoside isothiocyanate substrate (a mustard-oil producing glucoside). In 1840 Bussy [5] isolated from black mustard (*Brassica nigra*) seeds a potassium salt of an acid, which is known today under the name *sinigrin,* and demonstrated that it is a substrate in the enzymatic process of formation of allyl isothiocyanate.

On the basis of elementary analysis of sinigrin and sinalbin and their degradation products, Gadamer [6] in 1897 proposed, unfortunately, an incorrect structure of this class of compounds as isothiourethane derivatives (Scheme 2).

This incorrect structure was generally accepted for approximately 60 years, in spite of the fact that many experimental data were difficult to be rationally explained on its basis. Only Ettlinger and Lundeen [7] had noticed that sinigrin and its analogues yield the respective amines as the result of chemical degradation, while they mainly yield RCN with the same number of carbon atoms as the isothiocyanates RCNS formed as the result of the enzymatic degradation process of sinigrin and its analogues. It is important that hydrogenolysis of sinigrin on Raney nickel yields *n*-butylamine with desulfurization. Acidic hydrolysis of sinigrin gives vinylacetic



SCHEME 2

acid, while subjecting sinalbin to the same process gives 4-hydroxyphenylacetic acid; in both cases, hydroxylamine is also isolated, apart from the respective acids. The results of all presented experiments are rationally explained by the structure of the isothiohydroximic acid shown in Scheme 2, while, on the other hand, it was difficult to explain them on the basis of Gadamer's incorrect structure. Evidence was also presented relating to the sugar fragment, a β-D-thioglucopyranoside. There is no unequivocal proof concerning the stereochemistry of the C=N bond; however, taking into account the enzymatic rearrangement of sinigrin to the respective isothiocyanate, it seems very probable that in analogy to products of Hoffmann, Curtius, Beckmann, or Lossen rearrangements, the sulfate group is in the *anti* position to the substituent R. Hence, the *E* configuration is assigned to these compounds.

By the end of 1959, the structures of approximately 30 described *S*-β-D-thioglucopyranosides were determined and verified. The results of the work of this early period are sufficiently described in Kjaer's review article [3].

Unfortunately, the important matter of the nomenclature of the described class of compounds has not been rationalized up until now. It will be noted that apart from the long-established trivial names, sinigrin and sinalbin, the *S*-glucosides have been consistently named by adding the prefix "gluco" to an appropriate part of the Latin name of the botanical species in which the compound was first recognized. Also, the popular name "glucosylanes" does not reflect well the structure of these class of compounds. This arbitrary nomenclature often leads to rather unwieldy designations, which might conceivably be rationalized by an alternative nomenclature based on a generic trivial name for the molecular entity common to all glucosides, preceded by the systematic chemical name of the side chain of the individual compound. Thus the systematic nomenclature dominates in this review.

All sulfates of *S*-glucosyl thiohydroximates isolated from natural products (Scheme 2) can be divided into five basic groups, differing in structure by the R substituent on the nitrogen atom. The structure of these substituents has been determined on the basis of the structure of isothiocyanates isolated from natural compounds, formed as the result of enzymatic hydrolysis and rearrangement of natural thiohydroximates. These five groups are made up of compounds with the following substituents:

1. Saturated alkyl
2. Unsaturated alkyl
3. *O*-Methylthioalkyl and related sulfoxides and sulfones
4. Aryl
5. Oxygen-containing functional alkyl groups (hydroxy, carbonyl, carboxylic acid ester).

Examples of compounds of established structures are given in Table 1.

Glucosylanes in nature play the role of repellents, as well as food attractants of insects. Also, they belong to a group of postinhibitins, a nonactive form of toxins gathered in plant tissues, essential for protection of plants from pathogens. It has been shown that glucosylanes found in the Cruciferae (mustard)

TABLE 1 Presentation of Glucosylanes of Natural Origin with Established Structure

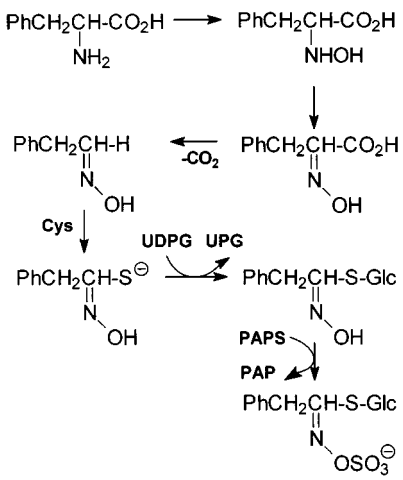
Glucoside	*R*	*Botanical Source*	*Refs.*
Glucocapparin	CH_3	Spiny spiderflower (*Cleome spinosa* Jacq.)	[8]
Glucolepidiin	CH_3CH_2	Pepperweed (*Lepidium Menziesii* DC.)	[9]
Glucoputranjivin	$(CH_3)_2CH$	*Putranjiva Roxburghii* Wall.	[10]
Glucocochlearin	$CH_3CH_2(CH_3)CH$	Common scurvy-grass (*Cochlearin officinalis* L.)	[11,12]
Sinigrin	$CH_2{=}CHCH_2$	Black mustard (*Brassica nigra* Koch.)	[11,13]
Gluconapin	$CH_2{=}CH(CH_2)_2$	Rape (*Brassica napus* L.)	[14,15]
Glucoibervirin	$CH_3S(CH_2)_3$	Candytuft (*Iberis sempervirens* L.)	[16]
Glucobeteroin	$CH_3S(CH_2)_5$	Hoary alyssum (*Beteroa incana* DC.)	[17]
Glucoiberin	$CH_3S(O)(CH_2)_3$	Bitter candytuft (*Iberis amara* L.)	[18,19]
Glucocheirolin	$CH_3S(O)_2(CH_2)_3$	English wallflower (*Cheiranthus cheiri* L.)	[10]
Glucoraphenin	$CH_3S(O)CH{=}CH(CH_2)_2$	Radish (*Raphanus sativus* L.)	[10–12]
Glucotropaeolin	$C_6H_5CH_2$	Nasturtium (*Tropaeolum majus* L.).	[11,12,20]
Sinalbin	p-$HOC_6H_4CH_2$	White mustard (*Sinapis alba* L.)	[21,22]
Glucoconringiin	$(CH_3)_2C(OH)CH_2$	Hare's ear mustard (*Conringia orientalis* L.)	[13,23]
Progoitrin	$CH_2{=}CHCH(OH)CH_2$	Field mustard (*Brassica rapa* L.).	[11,12,23]
Glucosisymbrin	$HOCH_2CH(CH_3)$	Hedge mustard (*Sisymbrium austriaceum*)	[24]
Glucopangulin	$C_3H_7C(O)(CH_2)_3$	*Capparis angulata*	[25]
Glucoerypestrin	$CH_3OOC(CH_2)_3$	Wallflower (*Erysimum rupestre* DC.)	[26]

species are an immunity factor to *Pernospora parasitica* (powdery mildew) of cultivable *Brassica* species. Damage to tissues of these plants leads to release of significant quantities of volatile isothiocyanates, including allyl isocyanate, formed as the result of hydrolysis of sinigrin by *myrosinase*. Allyl isocyanate is one of the four main taste–aroma components of cabbage and a number of other intercrossed vegetables and exhibits high toxicity in relation to powdery mildew. It has been stated that many isothiocyanates released from glucosinolates exhibit strong bacteriostatic activity to gram-positive and gram-negative bacteria, this being used in many herbal preparations used in medicine (e.g. glucotropeoline, glucoerisoline). It should be noted that isocyanates are also pheromones of such insects as *Pieris brassicae* or *Brevicoryne brassicae*. These insects during feeding effectively detoxicate sinigrin found in cabbage [27]. The presence of sulfates of *S*-glucosides of thiohydroximic acids in rapeseed presents an essential problem. Discards after production of rapeseed oil are utilized as fodder for animals, but, at high contents of *S*-glucosides, they are toxic for bred mammals. This was the cause of starting programs to obtain rapeseed modifications of low contents of thiohydroximates in the plant.

It was important to find details of the route of biosynthesis of thiohydroximic acid derivatives. The substrate during formation of sinigrin is phenylalanine, which is oxidized to the *N*-hydroxy derivative. This *N*-hydroxyaminoacid in a disproportionation reaction gives phenylalanine and the oxime of phenylglyoxalic acid. The oxime, after decarboxylation, is transformed into phenylacetaldoxime, which, after sulfurization with the participation of cysteine, forms the phenylacetohydroximate system. The anion of this acid in a process catalyzed by *UDPG glucotransferase* (thiohydroximate glucosyltransferase EC 2.4.1) forms an *S*-thioglucoside. The last step in the biosynthesis is introduction of the sulfate anion on the oxygen atom of the thiohydroximate group with the participation of sulfotransferase of the PAPS enzyme (3′-phosphonoadenozyno-5′-phosphonosulfate EC 2.8.2) (Scheme 3) [28].

Natural thiohydroxamates comprise a small group. In the early 1970s it was discovered that *Pseudomonas fluorescens* produces two antibiotics: fluopsin C and fluopsin F [29,30]. Both antibiotics are complex compounds of Cu(II) and Fe(III), wherein *N*-methyl-*N*-thioformylohydroxylamine, customarily called *thioformin,* is the ligand (Scheme 4). These antibiotics exhibit high biological activity in relation to gram-positive as well as gram-negative bacteria.

Thioformin itself should be classified as a siderophore. It is a quite recently discovered bioligand,

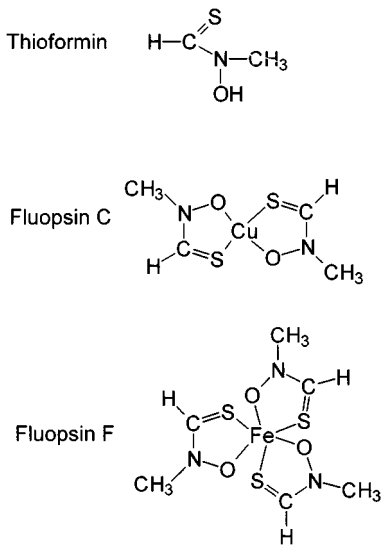


SCHEME 3

playing an important role in the processes of transport of Fe(III) ions through the cell membrane to cells of algae, fungi, and bacteria [31]. Hydroxamic acids frequently occur in the group of siderophores. It should be emphasized that thioformin is the only siderophore up until now with the thiohydroxamic group.

The mechanism of action of fluopsin C is not clear. Based on well-investigated matter of siderophores, one may presume that fluopsin ligands—thioformin—act as a cuprophore, i.e., a specific ligand transporting copper ions into cells through the bacterial membrane.

Syntheses of many analogues of thioformin have been performed [32] by changing the substituent on the nitrogen atom. The multiple regression analysis



SCHEME 4

showed that antibacterial activity of N-substituted *N*-thioformylhydroxylamines was greatly influenced by a lipophilic nature of these compounds, but not by an electronic effect. All these derivatives exhibited high biological activity in relation to gram-positive as well as gram-negative bacteria. These antibiotics, because of their high toxicity, have not found clinical application up until now.

THE SYNTHESIS OF THIOHYDROXAMIC ACIDS

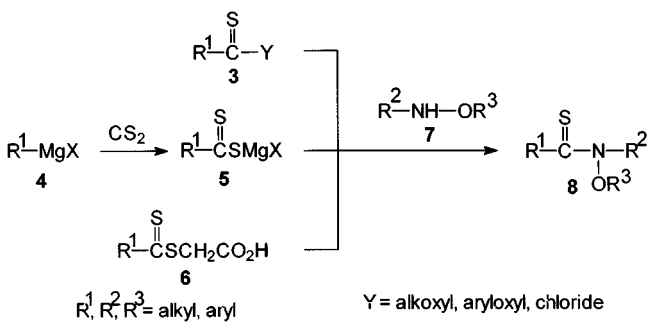
The methods of synthesis of thiohydroxamic acids were the subjects of two comprehensive review articles by Walter [33] and Bauer and Kuhlein [34].

The synthesis of the cyclic aromatic *N*-hydroxypyridine-2-thione, which is at present produced on a large scale because of its high industrial significance, is still based on the nucleophilic substitution reaction of 2-chloropyridine *N*-oxide with a mixture of sodium sulfide and hydrogen sulfide [35]. Other possibilities are presented by the Abramovitch method based on sulfurization with elementary sulfur of lithium salts of pyridine *N*-oxides [36]. The yields of both of these methods are moderate.

The noted low yields of the syntheses of unsubstituted thiohydroxamic acids are caused mainly by their small stability and tendency to decompose during isolation.

Thioacylation of Hydroxylamine and its Derivatives

A wide range of methods of synthesis of thiohydroxamic acids are based on the reaction of thioacylation of hydroxylamine and its N- and O-derivatives (Scheme 5). The following were used as thioacylating agents: dithiocarboxylic acids **3** (Y = SH), their esters (Y = *S*-alkyl, *S*-aryl), thionocarboxylic acid esters (Y = alkoxyl, aryloxyl), and chlorides of these acids **3** (Y = Cl).



SCHEME 5

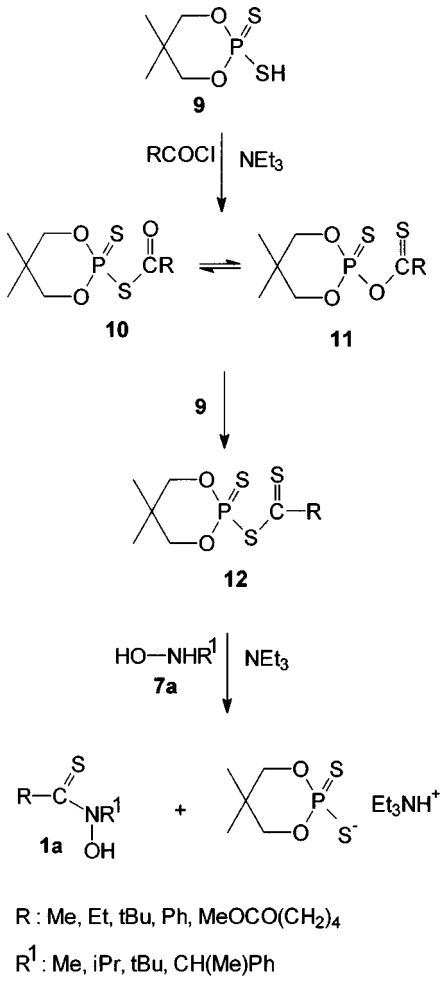
Salts of dithiocarboxylic acids **5** react with hydroxylamine and its N- as well as O-derivatives giving the respective thiohydroxamic acids **8**. This reaction is historically the oldest method of synthesis of these compounds [37]. In this group of methods, the so-called *one pot procedure* is especially attractive based on the reaction of a magnesium salt of a dithiocarboxylic acid **5**, obtained by the reaction of a Grignard reagent and carbon disulfide, with hydroxylamine. Based on this reaction, the first synthesis of sinigrin, the naturally occurring *S*-ester of thiohydroximic acid, was performed [38]. Also according to this procedure, a number of aromatic and heteroaromatic thiohydroxamic acids were obtained with yields of 26–72% (Scheme 5) [39].

Esters of dithiocarboxylic acids **3** (Y = *S*-alkyl, *S*-aryl) are the most frequently used thioacylating agents in the syntheses of *N*-thioacylhydroxylamines, although the syntheses of dithioacids, as well as their methyl or ethyl esters [40], proceed in small yields. An *S*-thioacylthioglycolic acid (**6**) is an especially useful thioacylating agent [41]. In spite of the fact that **6** is often obtained with different, and frequently very low yields [40], in the reaction with hydroxylamine, as well as its N- and O-derivatives, it gives respective thiohydroxamic acids with very good yields (70–80%) (Scheme 5) [1,42]. By this route, i.e., in the reaction of *O*-alkyl *S*-carboxymethyl dithiocarbonates with hydroxylamine [43], *N*-hydroxy-thionocarbamic acid esters were also obtained in very high yields (87–98%).

Thionocarboxylic acid esters (mainly methyl and ethyl **3**, Y = OMe, OEt) also are convenient thioacylating agents. These compounds in the reaction with hydroxylamine, as well as its N- and/or O-derivatives, give the respective thiohydroxamic acids; however, the yields in these reactions are lower than those obtained for the same products obtained in the reaction with the use of dithiocarboxylic acid esters (Scheme 5) [1,42,44,45].

Thiocarboxylic acid chlorides **3** (Y = Cl) are not easily accessible and are relatively labile compounds [46], and, because of this, practically are not used in the synthesis of thiohydroxamic acids. In the chemical literature, there are few papers on application of only thiobenzoyl chloride in the synthesis of thiobenzohydroxamic and thiobenzohydroximic acids [33].

Recently, Rachon et al. [47] discovered that *S*-acyldithiophosphates **10** isomerize to *O*-thioacylmonothiophosphates **11**. The equilibrium mixture of *S*-acyldithiophosphate and *O*-thioacylmonothiophosphate, treated with an excess of dithiophosphoric acid **9**, gives *S*-thioacyldithiophosphate **12**, which was found to be a selective thioacylating agent. The authors demonstrated that this compound gives,



SCHEME 6

on reaction with *N*-alkylhydroxylamine, the respective thiohydroxamic acids **1a** in high yields (Scheme 6).

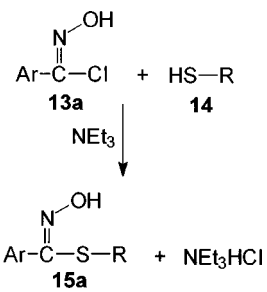
By observing the tendencies for introduction of new thioacylating reagents in the synthesis of thioamides [48], one may expect that they will replace the above-mentioned archaic derivatives of thiocarboxylic acids in the synthesis of thiohydroxamic acids.

Reactions of Sulfur Nucleophilic Reagents with Hydroximic Acid Chlorides and N-Oxides of Nitriles

Hydroximic acid chlorides, especially those with aromatic residues, are easily accessible compounds obtained by chlorination of the respective aldoximes [49], as well as by the reaction of nitroalkane salts with dry hydrogen chloride [49,50]. Thiohydroxamic acid is formed as the result of the addition of the hydrosulfide anion to hydroximic acid chlorides, however only in very small yields [33]. On the other hand, Eckstein [51] demonstrated that aromatic hydroximic acid chlorides **13a** with thiols and thiophenols in the presence of triethylamine give the respective *S*-esters of thiohydroximic acids **15a** in very high yields (70–99%) (Scheme 7). In this way, i.e., by the reaction of 2-dimethylaminoethanethiol with hydroxyimoyl chlorides, a number of 2-(diethylamino)ethyl thiohydroximates have been obtained in yields of the order of 47–84% [52].

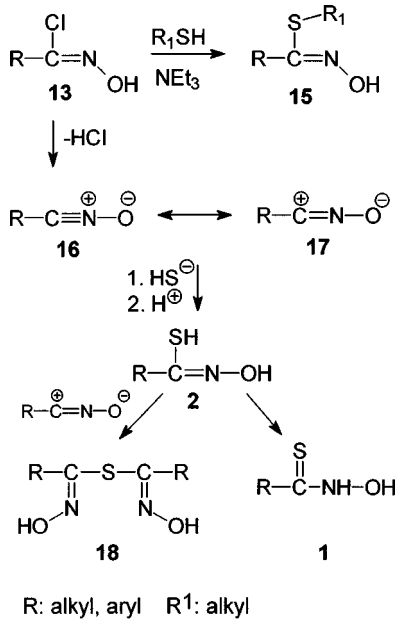
The mechanism of the reaction presented in Scheme 7 is not fully known. It is known that hydroximic acid chlorides **13** give nitrile oxides **16/17** as the result of elimination of hydrogen chloride [53], which are electrophilic reagents, and by reacting with hydrogen sulfide give the respective thiohydroxamic acids **1** or thiohydroximates **15** [54]. Also, it was stated that, in the $2 < pH < 8$ range, thiohydroxamic acids can undergo addition to nitrile oxides, giving the respective thiohydroximic acid anhydrides **18** [55] (Scheme 8). On the other hand, it is known that the reaction of a dilute aqueous-alcoholic solution of sodium hydrogen sulfide with a nitrile oxide (generated in situ from the respective hydroximic acid chloride) gives the respective thiohydroxamic acids in high yields [33].

Additionally, Nagata [44] showed that *O*-methylbenzohydroximic acid chloride formed, on reaction with thiourea, an isothiuronium salt, which, as the result of hydrolysis, yields the thiobenzohydroxamic acid methyl ester (Scheme 9). Similarly, in the nucleophilic substitution reaction of 2-halopyridine-1-oxides with the hydrosulfide anion, thiourea, or the thiolane anion, *N*-hydroxythiopyridone and its S-derivatives (cyclic thiohydroxamic acids and their derivatives) were obtained in good yields (Scheme 10) [56–59]. *N*-Hydroxythiopyridone is the substrate in the synthesis of Barton's esters, which are important from the synthetic point of view. It should be

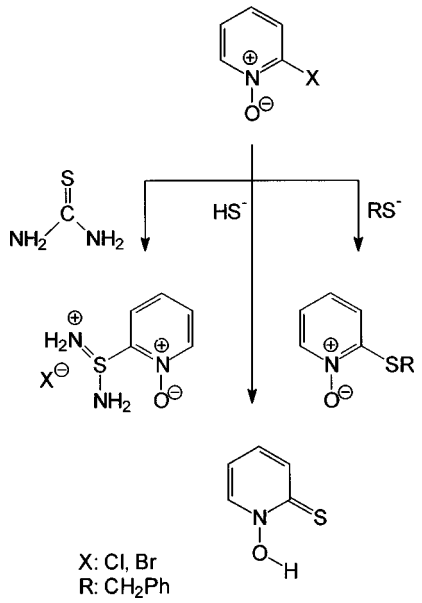


R—SH : $HSCH_2CH_2OH$; Ar–SH

SCHEME 7



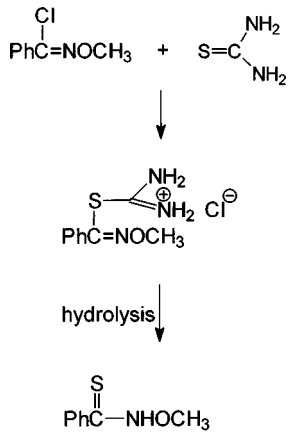
SCHEME 8



SCHEME 10

emphasized here that 2-alkylsulfanyl-1-oxo-pyridine is not available in the reaction of direct oxidation of 2-alkylsulfanylpyridine.

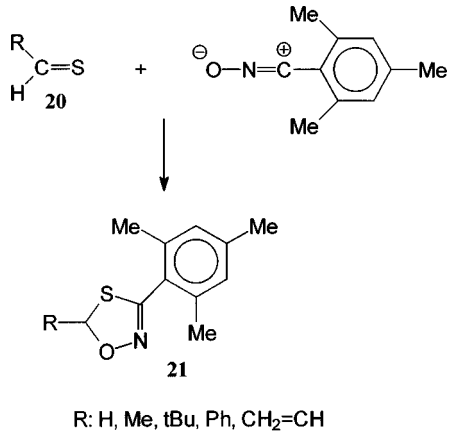
The problem of whether nitrile oxides are intermediate products in the reaction of hydroximic acid chlorides with sulfur nucleophilic reagents requires collection of additional proof and a final explanation. On the basis of experimental results presented in the chemical literature, one may state that, depending on the constitution of the substrates and reaction conditions, direct substitution of the halogen in hydroximic acid chlorides is possible, as well as addition of the sulfur nucleophilic reagent to the *N*-oxide of a respective nitrile, as the intermediate product.



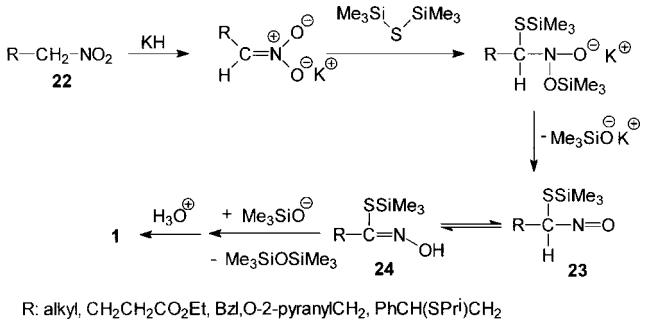
SCHEME 9

It should be emphasized here that thiocarbonyl compounds effectively undergo the reaction of 1,3-cycloaddition to nitrile *N*-oxides, giving cyclic thiohydroximic acid derivatives (Scheme 11) [60,61]. By reaction of 1-sulfanyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose with respective hydroxamoyl chlorides or nitrile oxides, syntheses have been conducted of a series of natural [49,50] and synthetic [62] glucosinolates **15** (R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) and thiohydroximate-linked pseudodisaccharides [63].

Hwu et al. [64], basing his approach on the so-called concept of counterattack reagents, presented an elegant and efficient method of conversion of primary nitroalkanes to thiohydroxamic acids **1** (Scheme 12). The nitroalkane potassium salts were treated with hexamethyldisilalthiane and gave the



SCHEME 11



SCHEME 12

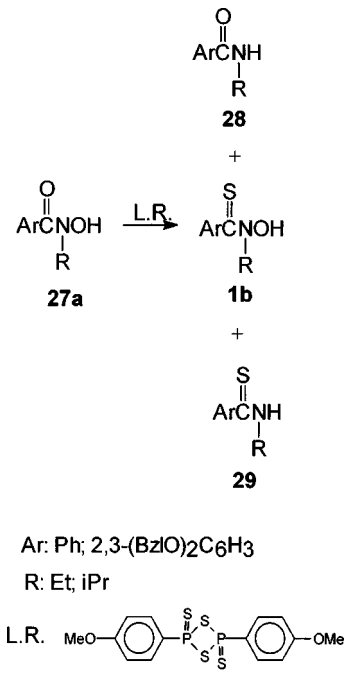
respective thiohydroxamic acids in yields of 81–87% in the case of nitroalkanes having no additional functional groups in the aliphatic chain. The authors demonstrated that this reaction is of general importance, and, in the case of nitroalkanes with additional groups in the aliphatic chain (methoxycarbonyl, acetal, or sulfide), they obtained the respective thiohydroxamic acids in yields of 56–92%. When using thiosilanes ($MeSSiMe_3$ and $PhSSiMe_3$) in the reaction, the authors obtained thiohydroximates in yields of 61–78%.

It should be noted that the method proposed by Hwu et al. [64] is based on easily accessible substrates. It is efficient and does not require isolation of intermediate products and therefore can be classified as a *one flask procedure* (Scheme 12).

Reactions of Direct Thionation of Hydroxamic Acids and Their Derivatives

Hydroxamic acids are an easily accessible group of compounds. On the other hand, today, we have a number of sulfating agents at our disposal, allowing transformation of amides to thioamides in high yields. Diphosphorus decasulfide and Lawesson's reagent are the most popular reagents used for this purpose. Taking these facts into account, it would seem that the most logical method of the synthesis of thiohydroxamic acids should be the sulfation of hydroxamic acids using reagents such as diphosphorus decasulfide and Lawesson's reagent. However, diphosphorus decasulfide with hydroxamic acids gives a complex mixture of products, among which thiohydroxamic acids are present only in small quantities. Hence, this reaction cannot be classified as a good synthetic method [65,66].

Recently, Przychodzen [67] has shown that, in the reaction of *N*-alkylarylhydroxamic acid **27a** with Lawesson's reagent, thiohydroxamic acids **1b**, amides **28**, and thioamides **29** are formed (Scheme 13). Results of performed experiments

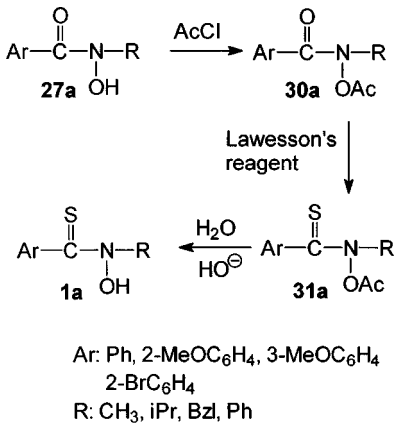


SCHEME 13

suggest that hydroxamic acids as well as *N*-hydroxythioamides are reduced by Lawesson's reagent to amides and thioamides, respectively. Also a significant solvent effect has been observed on the course of the described reaction; thus, in THF, thiohydroxamic acid is formed in yields up to 50% and no presence of amide is observed. On the contrary, in HMPA, respective amides and thioamides are the only products, and no presence of thiohydroxamic acids has been found.

It has been shown that O-protected hydroxamic acids give, on reaction with Lawesson's reagent, O-protected thiohydroxamic acids [66,68]. Rzepa et al. [68] proposed a method of transformation of hydroxamic acids **27** to thiohydroxamic acids **1a** based on O-acetylation of the hydroxamic acid, followed by thionation of the *O*-acetyl derivative with Lawesson's reagent and then deprotection of the hydroxyl group (Scheme 14). However, this multistep procedure does not guarantee high yields (10–50%) probably because of the lability of the direct precursors—*O*-acetylthiohydroxamic acids **30**.

Recently, Kim et al. [69] have shown that 2-benzyl-5-phenylisoxazolidin-3-ones (**32**) give, on reaction with diphosphorus decasulfide, 2-benzyl-5-phenylisoxazolidin-3-thiones (**33**) in very high yields (85–92%). These compounds, in the presence of aluminium chloride, react with aromatic systems in the Friedel–Crafts reaction, with splitting of the carbon—oxygen bond, giving respective thiohydroxamic acids **1c** in yields of 63–86% (Scheme 15).



SCHEME 14

REACTIVITY OF THIOHYDROXAMIC AND THIOHYDROXIMIC ACIDS

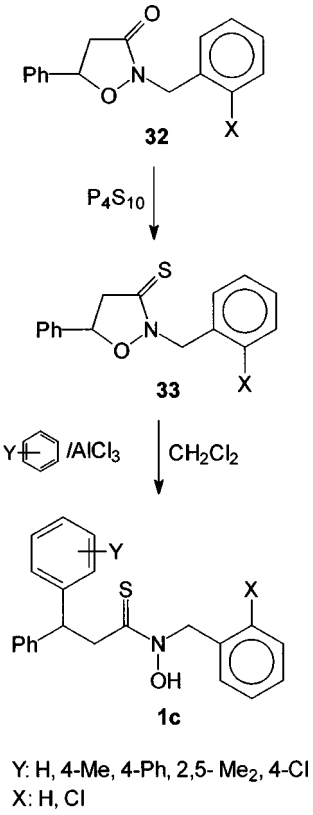
Decomposition and Rearrangements

Unsubstituted thiohydroxamic acids decompose into nitriles, elemental sulfur, and water [33]. Among aceto-, phenylaceto-, and benzothiohydroxamic acids, only *ortho*-alkoxybenzothiohydroxamic acids are reasonably stable compounds. The mechanism of this decomposition reaction is still unknown. On the basis of thiobenzohydroxamic acid MS fragmentations, Florêncio [70] suggests the influence of the ortho hydrogen atom on its decomposition.

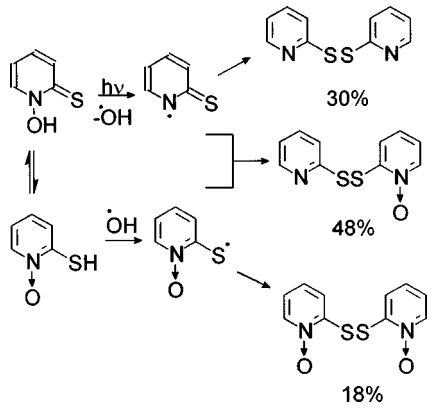
Another common reaction, generally proceeding during fragmentation in a mass spectrometer, is hydroxyl abstraction. Also, Zard [71] found that 1-hydroxy-2-pyridinethione is a good source of hydroxyl radicals when irradiated and it can be a useful reagent in radical chain processes involving hydrogen abstraction. Its 3-h irradiation yielded products formed from initial N—OH bond scission (Scheme 16). However, strong dependence of the photochemistry of this compound on the solvent and pH and also the occurrence of a number of secondary reactions connected with formation of reactive 2-pyridylthiyl radicals ruled out its potential application as a photoactive agent for investigations of oxidative damage in vivo [72].

Recently, some interesting mechanistic considerations of thiohydroximic *S*-esters fragmentations were given by Sikder [73]. According to him, elimination of N-substituted hydroxylamine, is attributed probably to the migration of the alkyl or phenyl substituent from sulfur to the nitrogen atom (Scheme 17). Protic solvents increase the instability of unsubstituted thiohydroxamic acids, and also their thermal instability may lie in autoprotolysis. Alkali salts of thiohydroxamic acids are very stable, but their solutions are less stable [33].

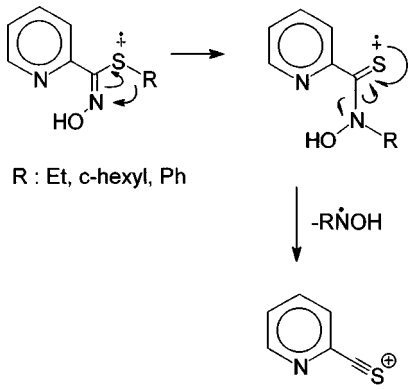
Thioformhydroxamic acid *O*-esters may decompose in a different manner, with elimination of alcohol and with isothiocyanate formation. The Lossen rearrangement is a typical reaction for unsubstituted thiohydroxamic acids, and it often occurs even during their storage (Scheme 18). As expected, benzothiohydroxamic acids with electron-donor groups



SCHEME 15



SCHEME 16



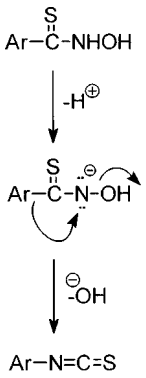
SCHEME 17

rearrange more readily and those with electron-withdrawing groups are more stable [33]. Thiohydroximic acid *S*-esters **15**, undergo Beckmann rearrangement, as with typical oximes to form *S*-esters of thiocarbamic acids **34** (Scheme 19). In this way, myrosinase decomposes sinigrin enzymatically to isothiocyanates.

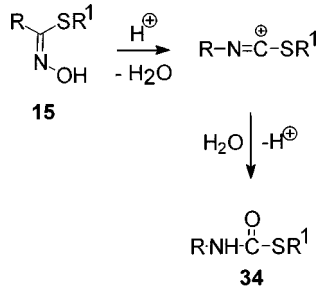
Oxidation and Reduction

As with other derivatives of hydroxylamine, thiohydroxamic acids (formally thioacyl hydroxylamines) are prone to redox reactions. Hydrogen peroxide effectively desulfurized *N*-phenyl thiobenzohydroxamic acid to the corresponding hydroxamic acid, while unsubstituted thiohydroxamic acids **1** gave hydroximic acid disulfides **35** under these conditions (Scheme 20) [33].

A total reduction of thiohydroxamic acids leads to amines, but it is possible to stop the reaction at the thioamide stage. Legrand [74] reduced thiohydroxamic acids to the thioamides with the P/I_2 system. Also, Przychodzen [67] found that Lawesson's reagent is able to reduce *N*-isopropyl thiobenzo-



SCHEME 18



SCHEME 19

hydroxamic acids to the corresponding thioamides (Scheme 21).

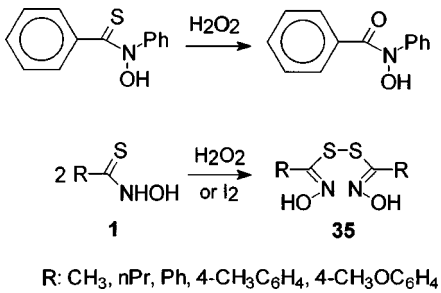
Reactions with Electrophiles

Thiohydroxamic acids are about 10^4 times more acidic than hydroxamic acids. Mizukami [75] found a correlation of pK_a values with Hammett's constants for para-substituted benzothiohydroxamic acids.

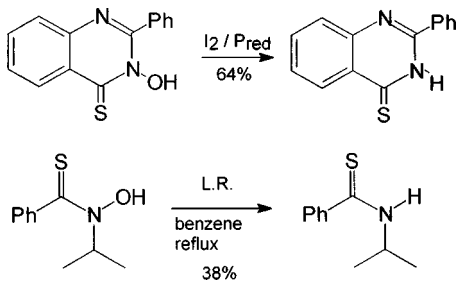
Thiohydroxamates are ambident *S*- and *O*-nucleophiles (Scheme 22). S-Alkylation of thiohydroxamate salts or their nickel complexes competes with O-alkylation. *S*-Alkyl derivatives of thiohydroxamic acids are thermodynamically favored, but their intramolecular rearrangement to *O*-alkyl derivatives is not possible.

^{13}C NMR investigations of different 2-sulfanylpyridine *N*-oxide salts have shown [76] that they occur in thionic form with the highest electron density on the oxygen atom (especially in the case of tetra-n-butyloammonium salts). On the basis of these spectroscopic studies one may predict that elaboration of a selective alkylation method (O- or S-) should be based on Pearson's HSAB theory.

Selectivity of the alkylation process therefore depends on reaction conditions. Methylation with diazomethane gives only O-methylated derivatives [33]. On the other hand, methylation or ethylation of N-substituted thiohydroxamic acids **27b** with alkyl iodides in acetone in the absence of base gave only the



SCHEME 20

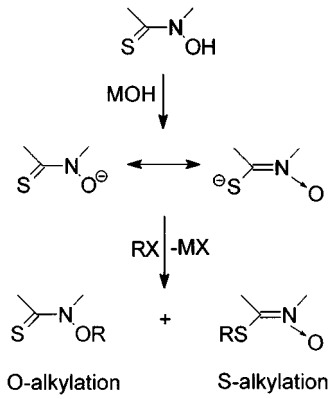


SCHEME 21

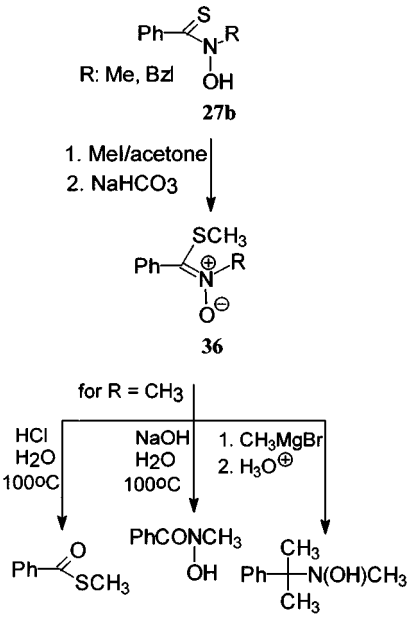
S-alkylated products **36** as a mixture of Z and E isomers [42]. Coates studied the reactivity of the nitrone **36** ($R = CH_3$) toward methylmagnesium bromide as well as its hydrolysis under basic and acidic conditions. He found that acidic hydrolysis occurred with C—N bond scission, while alkaline hydrolysis led to C—S bond cleavage. The reaction with a Grignard reagent takes place by a sequence of nucleophilic addition and substitution leading to *N*-methyl-*N*-(1-methyl-1-phenylethyl)-hydroxylamine (Scheme 23).

Development of an efficient method for the synthesis of thiohydroxamic acid *O*-esters is of great significance in view of their application for alkoxyl radicals generation. Recently, Hartung [76] was able to demonstrate that when a thiohydroxamic acid salt with a large counterion (e.g. NBu_4^+), a hard alkylating agent (e.g. a secondary alkyl tosylate), and a polar protic solvent (e.g. DMPU) are used, a thiohydroxamic acid *O*-alkyl derivative will be obtained with a reasonable yield (Scheme 24). The same results were achieved under phase-transfer catalysis conditions. In accordance with the predictions of Hartung, lithium, Pd(II), Ni(II), and Cu(II) salts did not react with tosylates at all.

In another article, Hartung [77] dealt with the synthesis of *N*-ω-alkenyloxypyridinethions, wherein the expected reaction selectivity was not achieved by



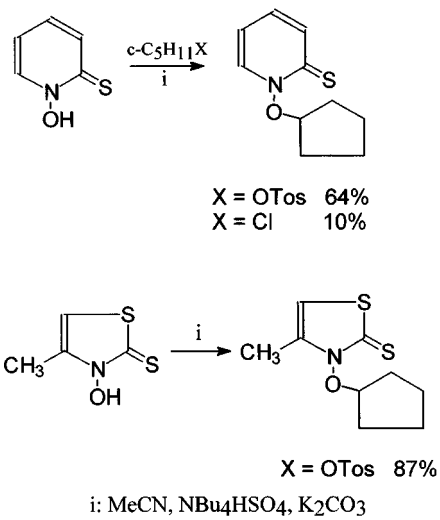
SCHEME 22



SCHEME 23

use of the above-mentioned conditions. He obtained a mixture of O- as well as S-derivatives. Probably this was caused by the noticed ability of *O*-ω-alkenyl derivatives to spontaneously undergo intramolecular rearrangement to the respective S-derivatives, even in the dark.

It was found that a high light sensitivity for storage of the respective *N*-alkoxypyridinethiones represents a disadvantage for the use of this class of compounds as precursors in alkoxy radical generation. However, recently, other compounds having the *O*-alkyl thiohydroxamic acid moiety [*N*-(alkoxy)thiazole-2(3*H*)-thiones] are of smaller



SCHEME 24

susceptibility to photochemical degradation, and were selected as more suitable starting materials for alkoxy radical generation [76].

In contrast to alkylation, acylation of unsubstituted thiohydroxamic acids is a more complex reaction. Acetylation of sodium 4-methoxybenzothiohydroxamate yields products typical of decomposition, i.e., sulfur and the corresponding nitriles. On the other hand, it was reported [2] that sodium thiohydroxamates **2a**, treated with benzoyl chloride, produce dibenzoyl disulfide as the major product besides *S*,*O*-dibenzoyl derivatives **37** (Scheme 25).

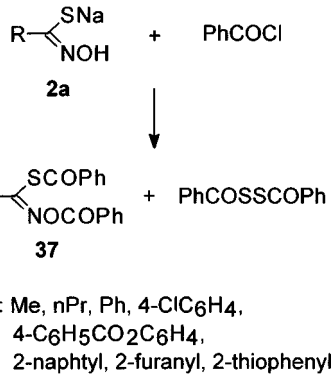
In contrast to alkylation, typical acylation of an N-substituted thiohydroxamic acid leads to only one product, viz. an *O*-acyl derivative [78]. It is believed that, at the first stage of the reaction, kinetically controlled S-acylation occurs and next the *S*-acyl derivative rearranges into the thermodynamically favored *O*-acyl derivative (Scheme 26).

All spectroscopic data confirm the structures of *O*-acyl thiohydroxamic acids. However, Garner [79] proved that the reaction between 1-hydroxypyridine-2-thione and 1,1,3,3-tetramethylchlorouronium salt gave only the S-acylated product. Very recently, the application of this product in the peptide synthesis as a relatively inexpensive and very efficient new coupling reagent has been reported (Scheme 27) [80].

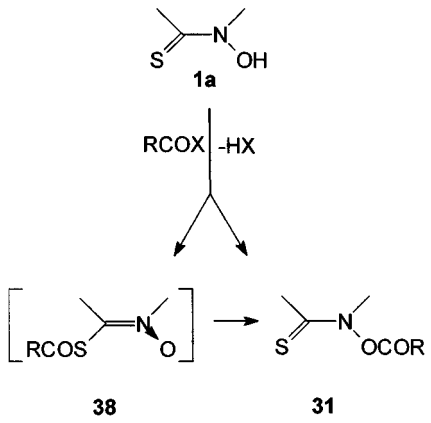
Thiohydroxamic acid *O*-esters **31** (also Barton esters) are obtained by three main routes [78]: (a) By acylation of thiohydroxamic acids with an acyl chloride, (b) by reaction of carboxylic acid with oxathiazolone derivative **39** (obtained in situ from hydroxamic acid and phosgene), and (c) by thionation of *O*-acylhydroxamic acids with Lawesson's reagent [68] (Scheme 28). In the last described method, *O*-acyl thiohydroxamic acids were not isolated from the reaction mixture but were formed only as intermediates.

Unsubstituted thiohydroxamic acids in the reaction with reagents capable of undergoing nucleophilic attack twice at the same carbon atom can cyclize, giving 1,3,4-oxathiazole derivatives **40** [33,81] (Scheme 29).

An analogous heterocyclic system, namely 2-(4-methoxy-phenyl)-4-phenyl-[1,3,5,2]oxathiazaphosphole-2-sulfide was obtained by the reaction of *N*-hydroxybenzimidoyl chloride with Lawesson's reagent [82] (**40**) (Y = P, X^1 = S, X^2 = *p*-$C_6H_4OCH_3$).



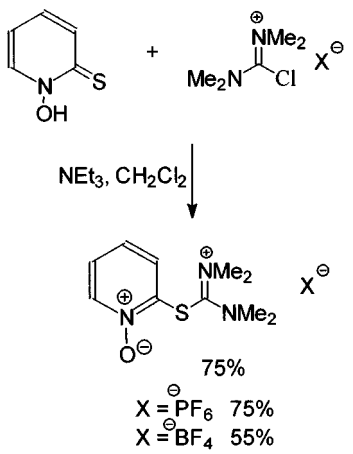
SCHEME 25



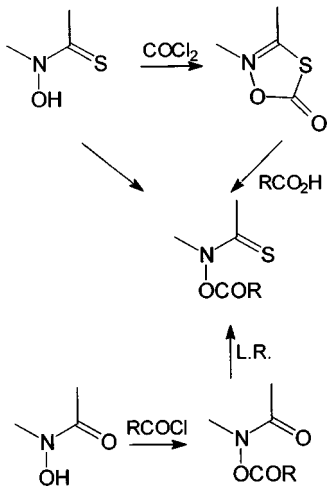
SCHEME 26

BARTON'S ESTERS

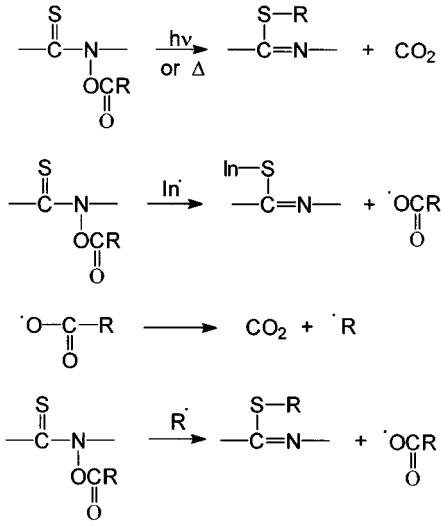
In recent years, we have been witnessing a rapid development of the chemistry of radicals, including application of radical reactions in organic synthesis [83]. *O*-Acyl thiohydroxamates have found wide application in recent years in processes of rational generation of carbon [84], oxygen [71,85], nitrogen [86], and phosphorus radicals [87] and also as substrates for obtaining carboxyamides [88], including peptides [89].



SCHEME 27



SCHEME 28

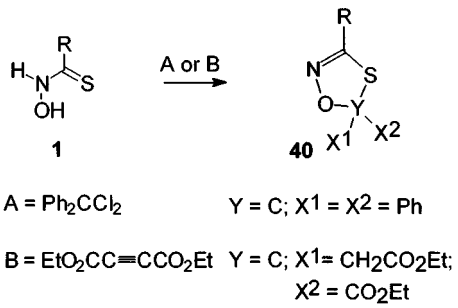


SCHEME 30

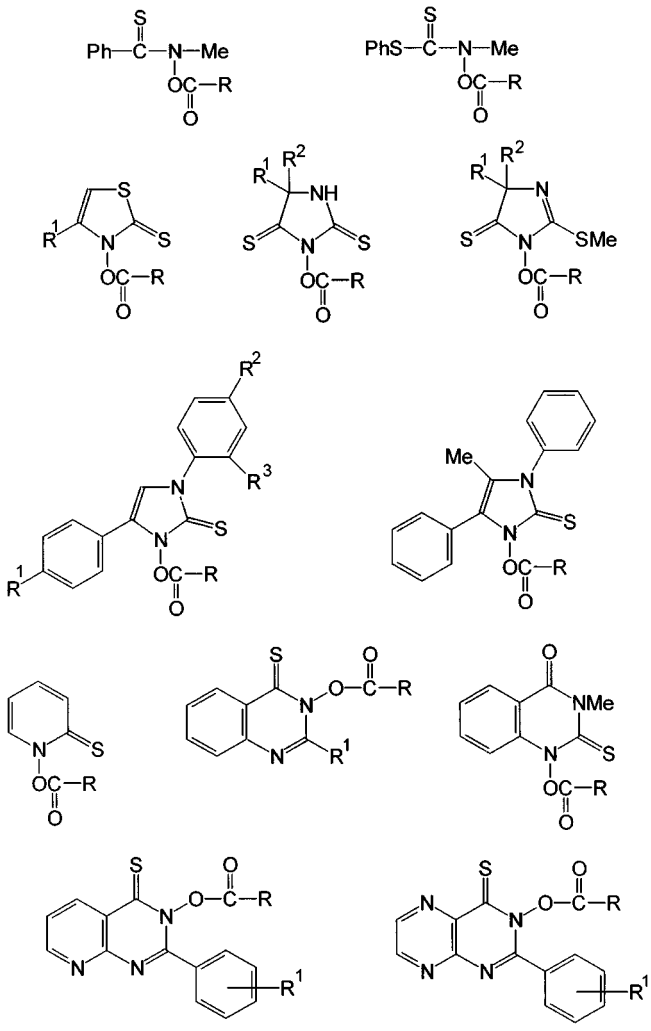
D. H. R. Barton in his famous research program "The Invention of Radical Reactions," while pursuing a convenient source of carbon radicals, gave prominence to the *O*-acylthiohydroxamate system, containing the labile N—O bond and the thiocarbonyl function. Compounds of this type, by heating, irradiation, ultrasound irradiation, as well as by use of radical reaction initiators, undergo (mainly in a chain process) the so-called reaction of decarboxylative rearrangement (Scheme 30).

Introduction into the reaction environment of an appropriate radical trap makes possible the exchange of a carboxylic group by another group, hence giving rise to syntheses of a series of different classes of new compounds in high yields. Methods of synthesis of a significant class of compounds having an *O*-acylthiohydroxamic acid moiety as precursors of carbon radicals have been designed and elaborated (Scheme 31) [90].

Compounds presented in Scheme 31 undergo decarboxylative rearrangement (Scheme 30) with varying effectiveness, and the process of radical



SCHEME 29



SCHEME 31

decomposition can be initiated, depending on the substrate structure, by heating, irradiation with UV, visible light, and by sonication. Rearrangement reactions (as well as radical chain reactions), presented in Scheme 30, are thermodynamically privileged. As the result of the described reactions, a strong carbonyl bond (CO_2) is formed in place of a weak thiocarbonyl bond and aromatization can be an additional driving force (reactivity of *O*-acyl derivatives of 1-hydroxypyridine-2(1*H*)-thione (**31a**) is a classic example). Finally, the reaction is favored from an entropy point of view, two product molecules being formed from one molecule of substrate.

From the compounds presented in Scheme 31, *O*-acyl derivatives of **31a** (called customarily Barton's esters, PTOC [91]) have found the widest application in methods of rational generation of carbon, oxygen, and nitrogen radicals, as well as in a number of synthetically useful radical processes. 1-Hydroxypyridine-2(1*H*)-thione is a commercially available and relatively inexpensive substrate, for which many methods of O-acylation have been elaborated [79,92].

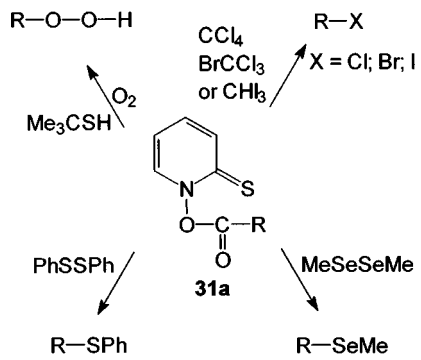
The chemistry of the *O*-acyl derivatives of **31a** has been extensively and comprehensively reviewed by Crich et al. [84c] and by Barton et al. [93]; in this review only highlights of their applications in organic synthesis are presented.

O-Acyl derivatives of **31a** can be used in a chain radical process for C—C bond formation, for the transformation of carboxylic acids into the respective alkanes (in the presence of appropiate hydrogen atom donors, e.g. *n*-BuSnH, Me_3CSH), and also for the selective conversion of the carboxyl group into a number of other functional groups, such as halogen, arylthio, arylseleno, hydroperoxide, hydroxy, and phosphono (Scheme 32).

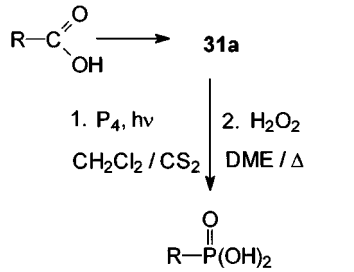
Particularly, the last transformation is of special interest. Recently, it was demonstrated [87] that white phosphorus (P_4) readily traps carbon-centered radicals generated from carboxylic acids via photolysis of the corresponding Barton's PTOC esters in a CH_2Cl_2/CS_2 binary mixture. Oxidation of the products of this reaction with aqueous hydrogen peroxide afforded phosphonic acids in yields ranging from 71 to 86% (Scheme 33).

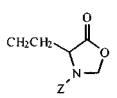
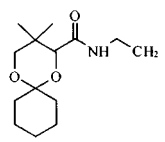
The importance of such a simple procedure for the introduction of a phosphonic acid moiety is significant, since many such derivatives have important biological activity [94]. This procedure was also applied for the modification of natural products and, according to this method, 3,3-Dimethylbutyl-1-phosphonic acid (from 4,4- dimethylpentanoic acid), (*S*)-*N*-benzoyloxycarbonyl-2-amino-4-phosphonobutyric acid (from L-glutamic acid), and the phosphonic analogue of pantothenic acid cyclohexyl ketal (from panthothenic acid) were synthesized (among others).

Conversion of the hydroxyl group into a hydrogen atom is a major problem in organic synthesis, especially in the synthesis of natural products. Most ionic reactions warranting this type of transformation are not selective and have appropriate stereochemical requirements. In the case of tertiary alcohols, yields obtainable by these types of reactions are minimal and are accompanied by side reactions,



SCHEME 32

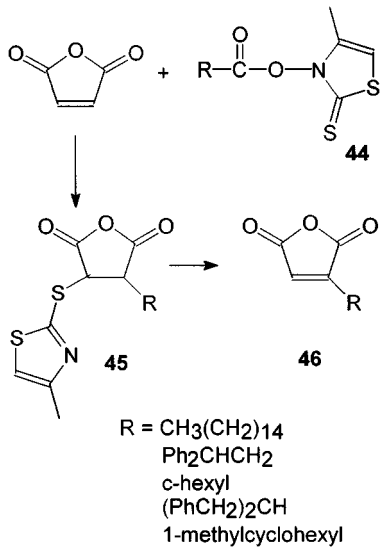


	R
a	CH_2CH_2Ph
b	cyclohexyl
c	1-adamantyl
d	$CH_2CH_2C(CH_3)_3$
e	$CH_2(CH_2)_6CH{=}CH(CH_2)_7CH_3$
f	$CH_2(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_4CH_3$
g	
h	

SCHEME 33

such as elimination or rearrangement. Radical reactions involving conversion of an alcohol derivative (including tertiary alcohols) into the corresponding hydrogen derivative have been found to be very effective processes, especially in cases of the use of polyfunctional compounds where selective exchange is required for the change of a hydroxyl group to a hydrogen derivative. The Barton–McCombie reaction is an example of this type of chemo- and regioselective transformation [95]. Intensive investigations of the reactivity of thiohydroxamic acid *O*-acyl derivatives have led to a new, effective strategy for conversion of the hydroxyl group of tertiary alcohols into the hydrogen derivative [96]. This strategy is based on the thermal homolytic decomposition of the oxalate alcohol derivative **41** and *N*-hydroxy-2-thiopyridone (oxalyl thiohydroxamates **42**), generated in situ, in the presence of *tert*-butyl thiol. The oxalyl derivative undergoes fragmentation under these conditions, liberating carbon dioxide and the respective carbon radical. The carbon radical formed by the transfer reaction of the hydrogen atom gives the expected product **43** (in high yield), also liberating the chain carrying thiyl radical to ensure the chain character of the whole process (Scheme 34).

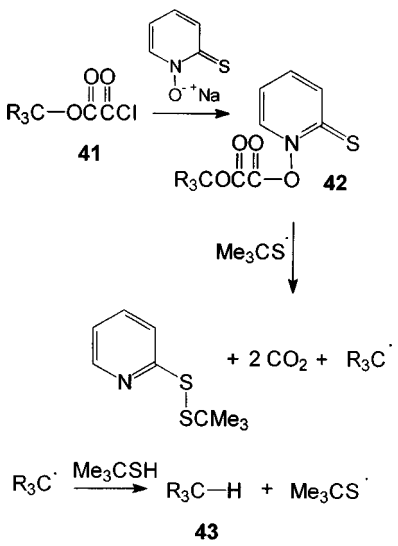
Maleic anhydride, used as a radical trap in the chain process of the homolytic decomposition of *O*-acyl thiohydroxamic acid derivatives **44**, gives the respective adducts **45** in very high yields. However, under the reaction conditions, elimination of the heterocyclic sulfide occurs and thus provides an extremely simple entry into substituted maleic anhydrides **46** [96–98] (Scheme 35). A similar reaction is observed with *p*-quinones. Based on the alkylation



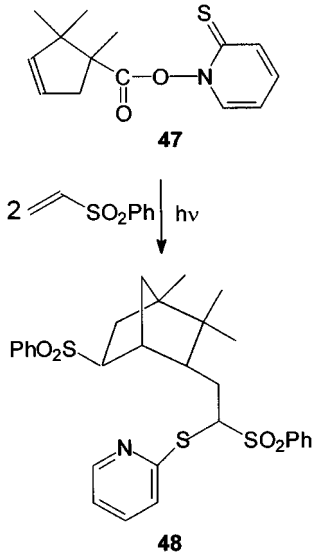
SCHEME 35

method of maleic anhydride, Samadi et al. [99] recently performed syntheses of chaetomellic anhydrides A and B.

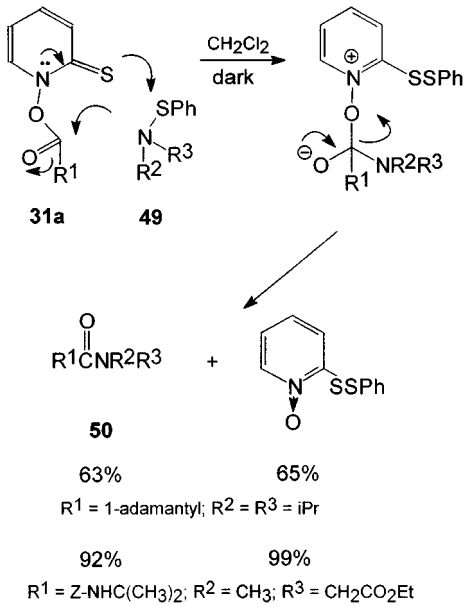
O-Acyl thiohydroxamic acid derivatives with multiple C=C bonds in the acyl residue have found application in the synthesis of cyclic systems [90c,100]. Also, Zard [101] presented an elegant cascade of consecutive addition/cyclization/addition reactions of radicals generated from *O*-acylhydroxamic acids. This cascade reaction allowed synthesis of a complex bicyclic system **48** from a simple system of γ, δ-unsaturated acids **47** and two equivalents of an electron-deficient alkene (Scheme 36).



SCHEME 34



SCHEME 36



SCHEME 37

Barton's PTOC esters have also been used with success in typical ionic reactions as active acid derivatives. The closely investigated reaction of these esters **31a** with sulfeneimides **49** (Scheme 37) is of special importance. It is a convenient method of synthesis of crowded tertiary carboxyamides, and α-alkyl and α, α-dialkyldipeptides **50** easily isolated from the reaction mixture [89].

METAL COMPLEXES OF THIOHYDROXAMATE LIGANDS

Thiohydroxamates well fulfill conditions for construction of a chelate ligand. Coordination proceeds with participation of electron pairs of a soft sulfur atom and a hard oxygen atom, allowing formation of complexes not only with Fe(II), Cu(II), or Ni(II) ions but also with a significant number of other metal ions. The metal ion is bonded directly to the sulfur and oxygen atoms, with loss of the proton. High versatility of coordinating atoms in the ligand, i.e. nitrogen, oxygen, and sulfur, makes possible the occurrence of different ligand systems around the central atom and formation of coordination geometric isomers. A higher acidity of the thiohydroxyamide hydrogen atom creates good conditions for formation of the intermolecular hydrogen bond, while the large van der Waals radius of the sulfur atom limits the conformational freedom.

Walter's review [33] describes several thiohydroxamic acid complexes only. Nagata's review [75] widely describes tautomerisms, dissociation constants, reactivities, and structures of thiohydroxamic and thiohydroximic ligands up to 1968 and offers a comparative study of metal complexes of these sulfur hydroxamic acid analogues.

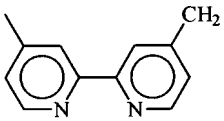
Color complexes of thiohydroxamic acids have found application in analytical chemistry for spectrophotometric and gravimetric determination of metals [102]. *N*-Hydroxypyridine-2-thione complexes with Mn(II), Ni(II), Fe(III), and Co(III) can be used for simulation of the action of cysteinyl metalloenzymes [103], while with vanadyl VO^{2+}, as effective insulin enhancing agents [104], *N*-methylbenzothiohydroxamic acid complexes with dioxomolybdenum(VI) can be used for investigations of active redox enzymes such as xanthine oxidase and sulfide oxidase [105]. Ferric and lead complexes have been used in the chelation therapy of iron overload [106] and lead poisoning [107] in humans and animals. The specifications of investigated metal ions and ligands in complexes are given in Tables 2 and 3, respectively.

There is only one paper of each, that describe complexes with metal ions of O-derivatives of thiohydroxamic acids and S-derivatives of thiohydroximic acids [141,142].

TABLE 2 Metal Ions from Thiohydroxamato Complexes

Cation	*References*
VO^{2+}	[104,108]
Cr^{3+}	[109–112]
Mn^{2+}	[103,111,113,114]
Fe^{2+}	[103,115,116]
Fe^{3+}	[103,107,109,111,113,117–123]
Co^{2+}	[102,103,113,117]
Co^{3+}	[103,111,120]
Ni^{2+}	[103,111,117,124]
Cu^{2+}	[111,113,117,125,126]
Zn^{2+}	[113,117]
Y^{3+}	[127,128]
Zr^{4+}	[111]
Mo^{6+}	[117,129,130]
MoO_2^{2+}	[131]
Ru^{3+}	[112,132]
Ru^{4+}	[133]
Rh^{3+}	[112,132]
Pd^{2+}	[124]
Ag^{+}	[117]
Cd^{2+}	[111,113]
Sn^{4+}	[134]
La^{3+}	[127,128]
Pr^{3+}	[127,128]
Nd^{3+}	[127,128]
Sm^{3+}	[127,128]
Gd^{3+}	[127,128]
Hf^{4+}	[135]
Pt^{2+}	[112,124]
Hg^{2+}	[111,117]
Pb^{2+}	[107,113,117,136–138]
U^{6+}	[117]

TABLE 3 Thiohydroxamato/ Thiohydroximato Ligands

R	*R′*	*X.*	*Refs.*
Monodentate R—C(=S)NR′OH			
H	Me		[112,115,121]
H	C_6H_{11}		[115]
H	Ph		[115,127]
Alkyl	Me		[107]
Me	H		[116]
Alkyl, aryl	H, Me, Ph		[123]
Me	Ph		[128]
Ph	H		[109,110,113, 116,119,120,123]
Ph	Me		[107,109,129,130]
3-OHC_6H_4	Me		[107]
4-$MeOC_6H_4$	H		[119]
4-$MeOC_6H_4$	Me		[132]
4-MeC_6H_4	H		[115]
4-MeC_6H_4	Me		[131,135]
Ph	Ph		[115]
C_2H_5	Me		[138]
$PhCH_2$	H		[115]
$PhCH_2$	Me		[138]
$PhCH_2$	*c*-C_6H_{11}		[138]
$PhCH_2$	Ph		[138]
3-Pyridyl	Me		[138]
3-(3-Methyl phenyl)$C_6H_4CH_2$	Me, *c*-C_6H_{11}		[138]
	Me		[138]
N-Hydroxypyridine-2-thione			[102,103,111,139,140]
6-Carbamoyl-*N*-hydroxypyridine-2-thione			[122,137]
Bidentate HON(R′)CS—X—CSN(R′)OH			
	H	4,4′-biphenyl	[136]
	Me	3,3′-biphenyldimethyl	[136]
	Me	$(CH_2)_7$, $(CH_2)_8$, $(CH_2)_9$	[136]
	c-C_6H_{11}	$(CH_2)_8$	[136]
	Me	2,2′-bipyridyl-4,4′-dimethyl	[136]
	Me	$CH_2CH_2OCH_2CH_2OCH_2CH_2$	[136]
Bidentate $[C(SR')=NOH]_2$			
	CH_2CH_2OH, CH_2CO_2Et, $PhCH_2$, Ph, 3-Tolyl		[141]

Stability of Complexes

Stability constants of complexes were usually determined potentiometrically by the Bjerrum–Calvin titration technique. The stability sequence for 1:1 complexes of *N*-phenyl-*N*-thioformylhydroxylamine is Sm > Nd > Gd > Pr > La > Y [127]. The formation constants of Amberlite IRC-50 containing thiohydroxamate group complexes (log KHL) for Fe(III), U(VI), Ag(I), Cu(II), Hg(II), V(V), and Mo(VI) are 9.17, 8.07, 7.39, 6.63, 5.81, and 2.47, respectively [117]. Stability constants were also measured for Pb(II), Zn(II), Cd(II), and Mn(II) complexes with phenylthiohydroxamic acid (log KHL: 11, 10, 9, and 6, respectively) [113].

Several papers describe voltammetric studies of thiohydroxamic acid complexes. They are connected with formation of the antibiotic thioformin, which is a Cu(II) complex with *N*-methylthioformohydroxamic acid. Thioformin probably acts as a siderophore, but one can presume that it transports copper ions to the cell. Taking into account the fact that siderophores transport the ferric ion to cells [108], cyclic voltammetric studies of complexes of tris(*N*-methylthioformohydroxamato) Fe(III) were carried out by Murray. Direct-current polarographic, cyclic voltammetric, and constant-potential coulometric measurements have been made on tris(thiohydroxamato) and tris(hydroxamato)-complexes of

Fe(III). Rapid one-electron reductions to Fe(II) are observed with the reduction potential for the thiohydroxamate being less cathodic than that of the hydroxamates. The softer S-donor ligand better stabilizes the Fe(II) state [115]. The biological release of iron by reduction seems easier for thiohydroxamate than for hydroxamate siderophores [116]. Comparison of the data reveals that substitution of sulfur (in thiohydroxamic system) for carbonyl oxygen raises the reduction potential by 400 mV, consistent with the greater basicity of oxygen (in hydroxamic acid) relative to sulfur partly because of the greater affinity of a soft acid such as Fe(II) for a soft base ligand such as sulfur in contrast to a hard base such as oxygen [116]. Fish [118] described a direct comparison between the Fe(III) chelation of hydroxamic and thiohydroxamic acids. The kinetics and thermodynamics of aq. Fe(III) complexation by 4-methoxybenzohydroxamic acid and its thio analogue are reported. Equilibrium quotients and rate constants for the complexation path were obtained, together with corresponding ΔH^0, $H^{\#}$, ΔS^0, and $S^{\#}$ values. The thiohydroxamic acids form more stable complexes at physiological pH, and aquation by the acid-dependent and acid-independent path is 50 times slower than that for the hydroxamic acid complex. This increased kinetic stability is consistent with enhanced delocalization of the lone N pair into the C—N bond in the thiohydroxamic complex [118].

Structure and Stereochemistry

The asymmetry center at the metal cation found in tris-thiohydroxamic complexes is a fact that should be emphasized. Taking into account the absolute configuration on the central atom (Λ or Δ, asymmetry of the ligand (S different from O), and occurrence of the ligand in the thiohydroxamic as well as thiohydroximic forms for $Me(III)L_3$, one may theoretically expect existence of eight stereoisomers (Fig. 1).

Up until now no occurrence has been observed of complexes containing simultaneously thiohydroxamic and thiohydroximic ligands. Among thiohydroxamate complexes the following are found: eight-coordinate (tetradentate) of bicapped trigonal prism (BTP) geometry, six-coordinate (tridentate) of tetragonal bipyramidal (TTBP) geometry, five-coordinate (bidentate) of square pyramidal (SPD) geometry and trigonal bipyramidal (TBP) geometry, and four-coordinate of square (SP) geometry (Fig. 2).

Surprisingly, alkali salts of tris(thiobenzohydroxamato)Fe(III), Cr(III), and Co(III) are so stable that the diastereoisomeric salts with resolving agent $Co(en)_3I_3$ were obtained and resolved, and, after decomposition of the salt, λ and δ forms of the complex were isolated. The λ-cis form has a positive CD band at 465 [119]. The above complexes are so remarkably inert that protonation of the optically active anion gives retention in the neutral complex. Thus, the neutral complexes can be

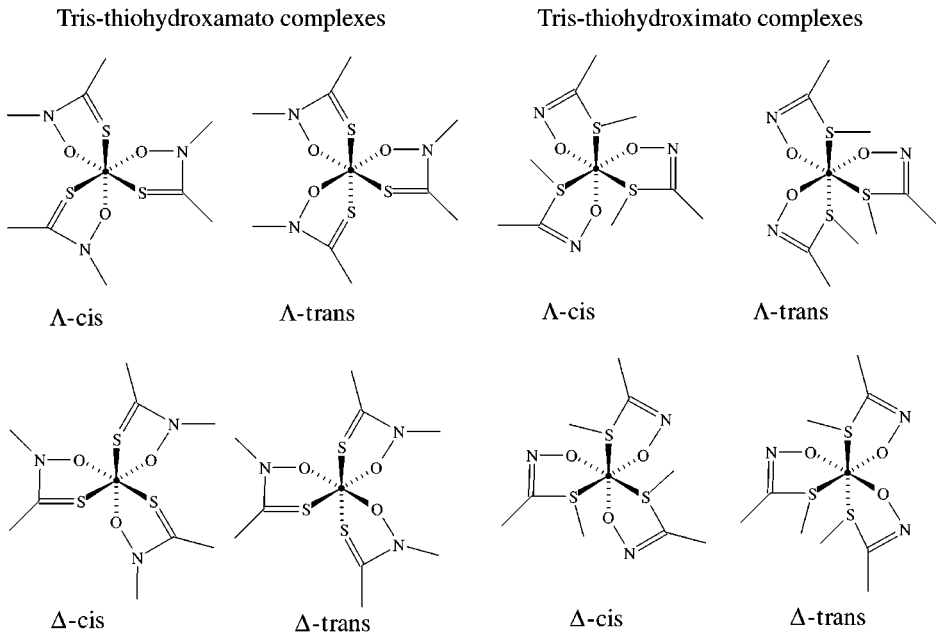


FIGURE 1 All possible stereoisomers of tris-thiohydroxamato/thiohydroximato complexes.

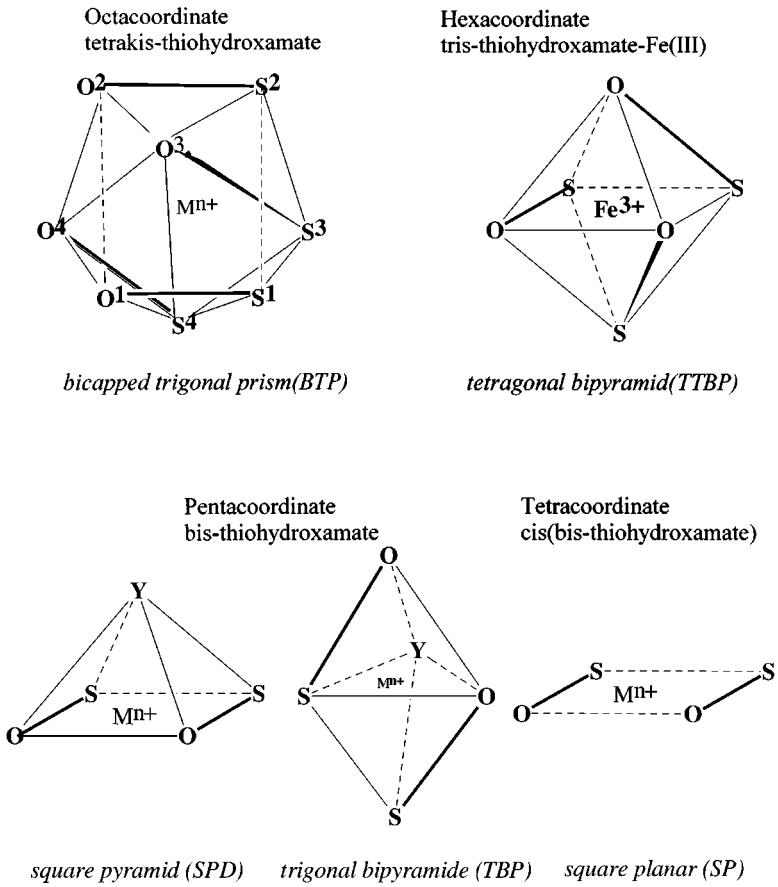


FIGURE 2 Geometries of bidentate thiohydroxamato complexes.

resolved using optically active organic cations. The half-life for racemization is 50 h and 10 h for Cr(III) and Fe(III) tris(thiohydroxamate) complexes, respectively [120]. The kinetic lability of bis(*N*-methylthioformohydroxamato)Cu(II) and Fe(III) (complexes of fluopsin C and F) precludes the isolation of cis and trans geometrical coordination isomers. However, when investigating two complexes of the same ligand with Ru(III) and Pt(II) ions possessing a large crystal field stabilization energy, Leong managed to separate by column chromatography and characterize two geometric cis and trans isomers of these complexes. Its geometric isomerism occurs with a half-life of several days [143].

The successful isolation of one of the isomers of ruthenium (*N*-methyl-*p*-methoxyphenylthiohydroxamato)(CO)(P(OCH_2O_3CMe)) enabled Basson, Leipoldt, Steynberg, and Smit to perform kinetic studies of isomerization at elevated pressures [132].

The structure of tris(*N*-methylthioformohydroxamato)Fe(III) has a cis (facial) arrangement of the two asymmetric (S, O) bidentate ligands. The absolute configuration on the central ion was Λ. Magnetic, ESR, and Mössbauer studies are compatible with the distorted octahedral (TTBP) complex of high-spin (s = 5/2) Fe(III). The C—S and N—C bond lengths both indicate substantial double bond character [121].

The five-coordinate, high-spin d^5chlorobis(*N*-methylbenzothiohydroxamato)Fe(III) has an overall ligand field strength provided by the (S_2O_2Cl) donor set similar to that in the related β-diketonate (O_4Cl) complexes but weaker than that in the dithiocarbamate (S_4Cl) species. X-ray analysis shows the iron environment as pseudo-SPD with C_2 symmetry with the halide atom at the top of the pyramid and the sulfur atoms in the trans arrangement [109].

The structure of the tris(thiohydroximato)Cr(III) anion shows relatively little changes in complex geometry from these of the thiohydroxamate complexes [144]. Small changes were observed indicating a lengthening of the Cr—O, Cr—S, C—S, and N—O bonds, and contraction of the C—N bond as the neutral complex is deprotonated. Systematic X-ray studies of four complexes,

tris(methylthiobenzohydroxamato)Co(III), Cr(III), Fe(III), and Mn(III), show that they are isostructural in the cis configuration. The coordination depends on the metal ion, i.e., it is octahedral for Co, it shows an increased trigonal distortion for Cr and Fe, and a substantial tetragonal distortion for Mn [124]. As shown by the X-ray method in the series of mononuclear Co(II) complexes with phosphine or pyridine, the cobalt ion is in an SPD environment with trans-oriented *N*-hydroxypyridine-2-thione ligands in the basal plane position [146]. *N*-Hydroxypyridine-2-thione complexes MeL_2 and MeL_3 [Me Mn(II), Ni(II), Fe(III), Co(III)] have been of interest for the simulation of cysteinyl metalloenzymes. Therefore, Co(II) complexes were investigated by cyclic voltammetry [103], showing two reversible processes following a one-electron charge. The complex of Ni(II), unstable in air, has nickel in the center of the square plane of NiS_2O_2 with two organic ligands in the cis configuration [103].

Thiohydroxamate ligands have been evaluated in the therapy of lead poisoning in both humans and animals. *N*-Methylthioaceto- and *N*-methylthiobenzohydroxamic acids typically form bis-complexes $Pb(II)L_2$ with Pb(II) that have pseudo-TBP geometry about the metal, with the fifth coordination site occupied by the lone pair of lead. Two isomers have been observed in these complexes: one isomer has both sulfurs in the equatorial plane, while the other has one sulfur and one oxygen in these positions. Additional weak outer-sphere coordination is formed by two oxygen atoms or one oxygen atom and one sulfur atom from adjacent molecules [107]. Bis-thiohydroxamic acids, with the linking group of varying lengths and rigidities, are also synthesized as potential Pb(II) chelating agents. In contrast to the predictions of molecular mechanics calculations, the most rigid ligands containing biphenyl, 2,2′-bipyridyl and 1,10-phenanthrolinyl linkers do not form discrete complexes with Pb(II), but rather polymeric polynuclear complexes are formed [136].

As part of a program devoted to the metal chelation therapy of iron overload, three hexadentate thiohydroxamate, polyamide ligands derived from *N*-hydroxy-pyridine-2-tione-6-carboxylic acid and triamines have been prepared. Structures of their Fe(III) complexes are similar to that of *N*-hydroxy-pyridine-2-thione [122].

The structure of bis(6-(diethylcarbamoyl)-1-hydroxy-2(1*H*)-2-thionato-*O*,*S*)Pb(II) has been characterized by X-ray diffraction. This complex has five-coordinate geometry in which a sulfur atom, an oxygen, and the lone pair of Pb(II) occupy the equatorial positions of a TBP. The axial positions are occupied by sulfur and oxygen atoms. The measured Pb—O and Pb—S bond lengths and the upfield shift of the NMR resonances of ring protons upon chelation may indicate that, during complexing of lead, the ligand occurs in thiol and not in thione form [137].

The single crystal structure of bis(*N*-cyclohexyl-phenylacetothiohydroxamato)Pb(II) shows that it is TBP, with the lone pair lead dominating the coordination geometry. The sulfur atoms occupy equatorial positions. The structure of bis-(*N*-methyl-3-pyridothiohydroxamato)Pb(II) shows similar geometry of the Z but not the E isomer [137].

Murray investigated the structure of crystals of a Mo(VI) complex containing, apart from two thiohydroxamic ligands, a diazenide group and an end-on-bonded hydrazido(1-) group. It was the first complex containing the NH—NH group, in which the location of hydrogen atoms was accurately determined [129]. Substituted hydrazines such as *N*,*N*-diphenylhydrazine or phenylhydrazine, and *N*-methylbenzothiohydroxamic acid have been employed for the preparation of the six-coordinate *cis*-oxohydrazido(2-)- and bis-diazenido-bis-*N*-methylbenzothiohydroxamatoMo(VI) complexes. The thiohydroxamate sulfur atoms are trans to each other in both complexes [130].

Complexes of molybdenum (IV, V, and VI) with sulfur-containing ligands are of particular interest to understand the molybdenum active site in redox enzymes such as xanthine oxidase and sulfide oxidase. Murray [147] described the first mononuclear $Mo(VI)O_2L_2$ chelate, which possesses a donor set $MoO_2(S_2O_2)$. The *N*-methyl-*p*-tolylthiohydroxamic acid residue was the ligand. This complex has distorted octahedral geometry. The Mo—O bonds trans to the terminal oxygens have been significantly lengthened and are similar to those in diketone chelates. The Mo—S bonds cis to terminal oxygens are similar in length to those found in other thio complexes. The cyclic voltammogram suggests either that Mo(VI) to Mo(V) electron transfer is irreversible or that the Mo(V) species is rapidly decomposing.

Lobana described a series of air and moisture stable green Cu(II)-*tert*-phosphine complexes of *N*-hydroxypyridine-2-thione, which play the role of a ligand stabilizing this complex. Based on the ESR data, square, pyramidal, and octahedral structures are suggested. Cu(II) is bonded to one halogen, one oxygen, one sulfur, and to phosphorus atoms [125]. Analogous stable complexes with triphenylphosphine of the $MeL_2(PPh_3)$ type were obtained with nickel, palladium, and platinum. In the latter two complexes, evidence of intramolecular scrambling has been adducted from NMR spectra [124].

It was shown that tetrakis(*N*-methyl-*p*-tolylthiohydroxamato)Hf(IV) has a geometry close to that of a BTP. All the sulfur atoms lie on two adjacent trigonal faces. This maximizes the polarity of the complex [135].

It should be underlined that, during X-ray analysis of the chromium salt complex prepared from the tris(thiobenzohydroximato)Cr(III) and triethylmethylammonium iodide in a solution of sodium hydroxide, the presence of monohydrated hydroxide was first reported. The bishydroxide exists as a discrete species $H_3O_2^-$ with an extremely short hydrogen bond. The O—O distance in the $H_3O_2^-$ anion is 2.29 nm [110].

Complexes with the thiohydroximic ligand are rarely formed [148]. Also *S*-alkyl derivatives of thiohydroximic acids complex metal ions. The *S,S'*-bisalkyl-oxalobis-thiohydroximic acid derivatives formed 2:1 chelates with Ni(II), Co(II), and Cu(II) at pH 8–9 [109].

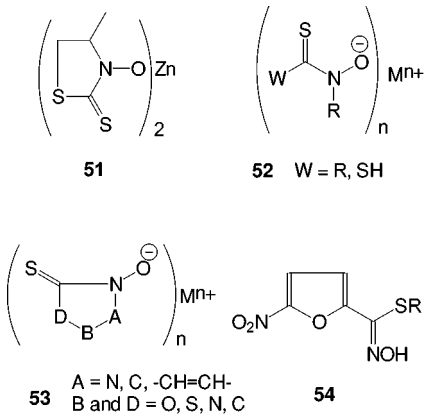
A SURVEY OF PRACTICAL APPLICATIONS OF THIOHYDROXIMATES AND THIOHYDROXAMATES

Thiohydroxamic and thiohydroximic acids were designed and synthesized with biocide properties in relation to bacteria, mites, fungi, insects, and weeds, were of specific physiological action for humans (antiperspiration, antihypertensive agents), and were used as inhibitors of enzymes or as drugs for the treatment of leukemia. Also, thiohydroximic acid derivatives have been found useful in the alleviation of paralysis caused by war toxins.

Bactericides and Fungicides

Zinc, cadmium, tin, and zirconium complexes of *N*-hydroxypyridine-2-thione were patented as active fungicide detergents of shampoo against sacharromycetes, e.g., *Malassezia furfur* (*Pityrosporum ovale*), and applied as providing effective antidandruff control [139]. *N*-Hydroxypyridine-2-thione-Cu(II) serves as a long-sought substitute for the tin reagents in antifouling paints. 3-Hydroxy-4-methylthiazol-2(3*H*)-thioneZn(II) (**51**) has been patented as one of the components of a mixture inhibiting the growth of soil bacteria and fungi [149]. Also, linear **52** and cyclic **53** metal-thiohydroxamates have been patented [114,150], including derivatives of *N*-hydroxypyrrolidine-2-thione [140], as microbiocides (Fig. 3).

Especially, derivatives of 5-nitro-2-furylthiohydroximate (**54**) showed good fungicide properties [151] and can be used in connection with the program of the withdrawal of organomercuric seed dressings in agriculture. Aliphatic *S*-alkyl and *S*-phenyl thiohydroximic acids were patented as microbiocides and acaricides [152].



51 **52** **53** **54**

FIGURE 3 Active bactericides and fungicides.

Insecticides

Six patents devoted to insecticides include compounds that are *O*-acyl derivatives of thiohydroximates-containing systems **55–58** [153–157]. Amongst them there are carbamyl derivatives **57** and **58**. It should be noted that two patents include compounds having a very labile N—S bond in weak acidic conditions (**57, 58**) and one with the phosphonic group (**56**) [158].

Only one patent [152] concerns free thiohydroximic acids **59** and another one their alkyl derivatives **60** (Fig. 4) [153]. Effective action of the above derivatives points to the probable metabolic removal of the acyl or alkyl group, the proper active ingredient containing the thiohydroximate system.

Reactivators of the Acetylcholinoesterase

Action of war toxins (tabun, sarin, and soman) is based on deactivation of the fundamental enzyme for human beings acetylcholinesterase (EC 3.1.1.7; AChE), by forming ethylmethylphosphonyl or 1,2,2-trimethylpropyl methylphosphonyl-AChE, respectively. In conventional therapy, atropine and other reactivators are used that restore activity to the enzyme. Currently, pyridinium aldoximes are the only clinically used reactivators. However, this treatment is ineffective in cases of soman intoxication. Soman-AChE transforms rapidly into a nonreactive dealkylated enzyme. The aldoximes reactivate the inhibited enzyme because they have a pK_a in the range of 7–8 and a cationic moiety at a distance from

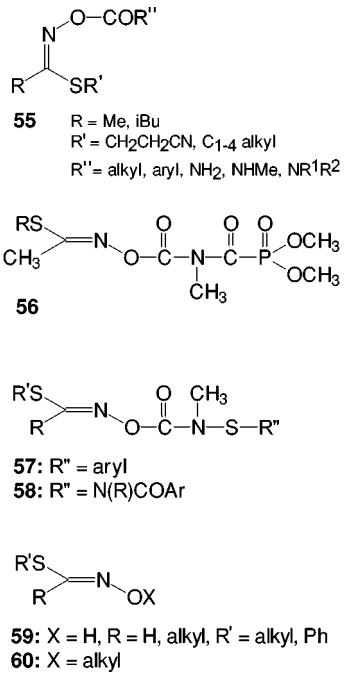


FIGURE 4 Active insecticides.

the oxime able to give the reactivator a structural similarity to the enzyme. The oximate anion displaces the organophosphorus moiety from the phosphorylated serine hydroxyl group of the AChE active site. The cationic moiety interacts electronically at the "anionic" region of the aspartic acid residue near the enzyme active site.

In the years 1975–1988, several patents [159–165] were devoted to *S*-diethylaminoethyl derivatives of various aryl thiohydroximic acids and their salts **61–65**, indicating them to be useful antidotes for poisoning from organophosphorus compounds and reactivators of AChE. Thiohydroximic acid esters were chosen because they are structurally similar to oximes; formally, they are, after all, α-thioalkyl oximes.

Bedford [166] prepared and evaluated a series of α-ketothiohydroximates **66** as reactivators of AChE. Their ease of synthesis and apparent stability in solution made this family of reactivators an attractive alternative to existing therapeutic oximes. Structure-activity studies took into account adjustment of the compound lipophilicity, which enables it to penetrate the lipophilic central nervous system tissues and the α-carbonyl group to bring an electron-withdrawing effect sufficient to bring about a near optimal pK_a value, but a quaternary pyridinium nucleus was not, as was shown, required for biological activity (Fig. 5).

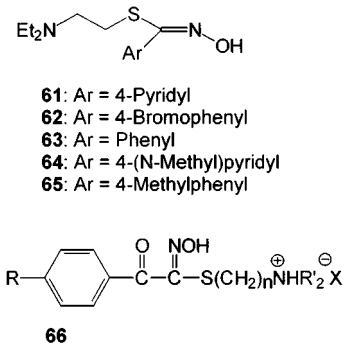


FIGURE 5 Reactivators of AchE.

Other Biological Activities

It should be noted that *S*-(2-aminoethyl)benzothiohydroximic acid hydrochloride (**67**) (Ar=Ph) was patented as an antiperspirant [167]. Thiohydroxamates were used sporadically as herbicides **68** [168]. One patent [169] claims pyrimidynylpropiothiohydroxamates, orotic acid derivatives **69**, to be antihypertensive agents (Fig. 6).

Thioarachidohydroxamic acid was found to be a strong inhibitor of arachidonate 5-lipoxygenase [45]. Four *O*-acyl derivatives of *N*-hydroxypyridine-2-thione were used in investigations in murine L1210 leukemia cells because of their ability to cause photobiological damage [170].

FINAL REMARKS

The thiohydroxamate–thiohydroximate system, investigated for over 200 years, continues to be an

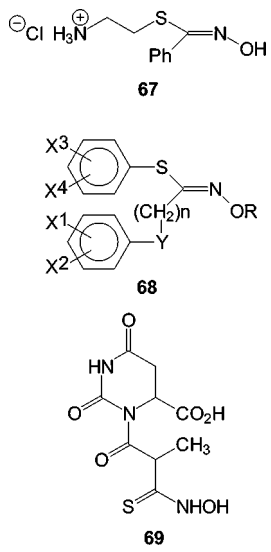


FIGURE 6 Other biological activity.

object of increasing interest in present day science. This unique system contains a directly neighboring carbon atom in an sp^2 hybridization and heteroatoms drastically differing from each other as the soft sulfur atom and the hard oxygen atom. The thiohydroximate system has been found in a wide range of *S*-glucosides formed during evolution of, and presently occurring in, plants. They are a component of food of animals and man; therefore they are metabolized. Taking this metabolism into account, their strong physiological activity is understandable. They are lethal for some types of living organisms and, in contrast, they are effective detoxicants of synthetic last generation chemical weapons. Also antibiotics are known that are metal complexes containing this atom system. It is not surprising that compounds with the thiohydroxamate system possess selective complexing properties. Their expected application in protection of the environment should be emphasized. 1-Hydroxypyridine-2(1*H*)-thioneCu(II) complex serves as a long-sought substitute for the tin reagents in antifouling paints. A large collection of synthetic complexes of almost all metal cations with thiohydroxamate ligands has been investigated. Complex chemistry of these ligands is continually being discovered because of their intricate stereochemical structures, as well as good properties in stabilizing complexes with mixed ligands. The latter, as it is known, promote current investigation trends, which are designed to provide synthetic analogues of metallo-enzyme-active centers of practical application. Also, the synthesis of compounds with the thiohydroxamate system is an almost inexhaustible field of investigation on the mechanisms of sulfurization of *N*-hydroxyamides and oxidation of thioamides. Compounds and complexes containing the thiohydroxamate–thiohydroximate system have been investigated by all available spectroscopic methods, showing rare characteristic features in relation to other atom systems. Also, it was found that cyclic thiohydroxamic acid derivatives can be widely used in chemical syntheses, being a very interesting, inexpensive, and easily available source of radicals, including carbon-, oxygen-, nitrogen-, and phosphorus-centered radicals. An increasing number of synthetic applications of these reactions has led to an unknown number of extremely complex polycyclic systems of organic compound molecules. Facile generation of radicals by photolysis of thiohydroxamic acid derivatives is connected with introduction of new techniques of kinetic investigations.

Presently, derivatives of thiohydroxamic and thiohydroximic acids have found extensive application in industry and technology, for example as a new class of polymerization regulators in the technology of polystyrene and methyl polymethacrylate [171]. All the above-mentioned data allows us to believe that this review can lead to the introduction of many new interdisciplinary investigations.

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