PhD Dissertation

SYNTHESIS, PROPERTIES AND SELECTED APPLICATIONS OF SOME SULFUR CONTAINING ORGANIC COMPOUNDS

Truong Ngoc Hung

Supervisor: Prof. István Pálinkó

Co-supervisor: Prof. Pál Sipos

Doctoral School of Chemistry

Faculty of Science and Informatics

University of Szeged

Szeged

2022

Dedicated to the memory of István Pálinkó (1959 - 2021)
Professor of Chemistry
University of Szeged, Hungary
A true teacher and supervisor

ABBREVIATIONS

AFM: Atomic Force Microscopy
$BF_3.Et_2O$: Boron Trifloride Diethyl Etherate
CCl_4: Carbon Tetrachloride
$CDCl_3$: Deuterated Chloroform
CD_3COCD_3: Deuterated Acetone
CH_2Cl_2: Dicholomethane
C_6H_6: Benzene
DMSO: Dimethyl Sulfoxide
DMSO-d6: Deuterated Dimethylsulfoxide or Dimethylsulfoxide-d6
D_2O: Deuterium Oxide
EDX Spectroscopy: Energy-Dispersive X-ray Spectroscopy
ESI-MS: ElectroSpray Ionization – Mass Spectrometry
EtOAc: Ethylacetate
FT-IR: Fourier-Transform Infrared Spectroscopy
HMDO: Hexamethyldisiloxane
HMPT: Hexamethylphosphoramide
HIV: Human Immunodeficiency Virus
In vacuo: in a vacuum
IRM: Infrared Microspectroscopy
JCPDS: Joint Committee on Powder Diffraction Standards
LbL: Layer by layer
LCAO-MO: Linear Combination of Atomic Orbitals – Molecular Orbital
LDH: Layered Double Hydroxide
LH: Ligand
LR: Lawesson's Reagent
MS: Mass Spectrometry
NMR: Nuclear Magnetic Resonance Spectroscopy
NT-MDT SI: NT-MDT Spectrum Instruments Company
PABA: Para-Amino Benzoic Acid
Ph_3SbO: Triphenylstibine Oxide
PLD: Pulse Laser Deposition
$[PPh_4][W(CO)_5SH]$: Triphenylphosphine pentacarbonyl tungsten (0) thiol
PT catalysts: Phase Transfer Catalysts

Q-TOF: Quad Time of Flight
RT: Room Temperature
SAM: Self-Assembly Monolayer
SEM: Scanning Electron Microscopy
SSS-NCH type: Super Sharp Silicon – Non Contact High Resonance
TLC: Thin Layer Chromatography
TMS: Tetramethylsilane
UV: Ultraviolet Spectroscopy
XRD: X-ray Diffraction
XPS: X-ray Photoelectron Spectroscopy

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ABSTRACT

This work involves sulfur-containing compounds and consists of three studies: 1) Preparation of a sulfur-containing compound, 2-cyano-2-(hydroxyimino)-dithioacetic acid, by a thionation reaction; 2) The secondary interactions (hydrogen bonding) of three imidazole-2-thione derivatives and their aggregation behaviour in solution, the solid state and over polycrystalline gold surface; 3) Synthesis of L-cysteinate-intercalated CaAl-layered double hydroxide (LDH) and study on the interlamellar selective oxidation process of the intercalated L-cysteinate.

Chapter 1 contains a few personal reflections as well as a brief statement of the research and aims of the thesis.

Chapter 2 of the thesis deals with an entire overview on organosulfur compounds from basic concepts, properties, applications to synthetic methodologies. Contents on thiocarbonyl compounds are also specially emphasized. Next, a brief introduction on imidazole-2-thione derivatives as well as the secondary interactions between these molecules and their self-assembly capacities is described. A concise description on LDHs is also found at the end of chapter.

Results of the work including synthesis of 2-cyano-2-(hydroxyimino)-dithioacetic acid; analysis of the secondary interactions (hydrogen bonding) as well as the aggregation behavior of three imidazole-2-thione derivatives in solution, the solid state and over polycrystalline gold surface are reported and discussed in chapter 3. Chapter 3 also includes results on preparation of L-cysteinate-intercalated LDH and examination of selective oxidation of the intercalated cysteinate anions.

The first work is an attempt to develop a convenient three-step process for preparation of a ligand in which a thionation reaction is the key step. In the next step, complexation of the resultant ligand with Co(II), Ni(II), Cu(II) ions is scouted. Structural characterization of the intermediates and the ligand were accomplished. In addition, an independent study on the secondary interactions (hydrogen bonding) and self-assembly capacities of three imidazole-2-thione derivatives is also carried out and reported. The work is proceeded with results on the synthesis of L-cysteinate-intercalated CaAl-LDH, its structural elucidation and evaluation of selectivity of interlamellar oxidation of the intercalated cysteinate anion to cystinate in aqueous and cysteinate sulfenic acid in acetone.

In chapter 4, concluding remarks of the research are summarized.

Finally, entire details about experimental work of the thesis including materials, instruments and analytical techniques employed, recipes for preparation of intermediates, ligand and complexes, procedures for synthesis of LDH, the intercalation and oxidation reactions are represented in chapter 5.

***Keywords*:** *organosulfur compounds, thiocarbonyl, thionation, hydrogen bonding, aggregation, self-assembled monolayers, imidazole-2-thiones; layered double hydroxides, L-cysteinate, intercalation, selective oxidation.*

CHAPTER 1: INTRODUCTION

1.1. Statement of the research

When I started my PhD program in the Department of Organic Chemistry, University of Szeged in 2015, my supervisor Professor Istvan Palinko kindly gave me a great opportunity to access as well as challenge myself with a totally new research: *"The chemistry of sulfur-containing compounds"*. Honestly, it has been a very challenging task for me. Before then, although having at least six-year experience in the field of synthetic organic chemistry, my works mainly dealt with semi-synthesis and synthesis of generic drugs and biologically active compounds such as chalcones, aurones, murrayafoline A, zerumbone derivatives, *etc*. Thus, a research on sulfur-containing organic compounds such as the preparation of thiocarbonyl compounds and their complexation with metal ions, the investigation of self-assembly capacities or aggregation behavior of some imidazole-3-thione derivatives as well as intercalation of L-cysteinate anions among layers of LDHs and examination the selective oxidation of these intercalated anions sounded greatly unfamiliar to me. Yet, another side inside me feels a sense of curiosity and excitement to be involved in such a kind of research. A new and challenging project also means that I would be confronted with new types of reaction, new synthetic methods, new topics and given a chance to learn new knowledge as well as many techniques and manipulations.

Organosulfur compounds can be briefly defined as any molecules carrying one or more sulfur-carbon bonds in the structure. When it comes to the organosulfur compounds, our first thought might be their similarity to the oxygen analogs. In reality, stunning differences that are observed bring them interesting and special properties compared to oxygen analogs. Along with abundant applications of organosulfur compounds witnessed in the tremendous fields such as biology, medicine, industry and organic synthesis, chemistry of organosulfur compounds, although has been extensively explored, is still an appropriate research area for chemists.

1.2. Aims of the thesis

It is easily realized that despite all subjects are focused on sulfur-containing compounds, the thesis is composed of three separate studies:

+) The first study on a route for preparation of 2-cyano-2-(hydroxyimino)dithioacetic acid and its complexation with metal ions such Ni^{2+}, Co^{2+} and Cu^{2+}. In this study, the goals are:

- To design and establish a convenient three-step pathway for synthesis of 2-cyano-2-(hydroxyimino)dithioacetic acid as ligand for coordination chemistry, then to determine the structures of intermediates and products by spectroscopic methods such as MS, IR and NMR spectroscopies.
- To scout the complexation of the resulting ligand with Ni^{2+}, Co^{2+} and Cu^{2+} ions: optimize complexation conditions; characterize the formation of complexes by spectral analysis of their IR, Raman and NMR spectra.

+) The second study on the hydrogen bonding interaction of three imidazole-2-thione derivatives as well as their aggregation behavior in solution, the solid state and over polycrystalline gold surface.

The aims of this second study consist of:

- To investigate the hydrogen bonding interactions including mechanism, types of interaction that is responsible for short-range and long-range ordering by using the IR, Raman spectroscopies and the molecular modelling method.
- To explore the mechanism of formation of self-assembly monolayers of three imidazole-2-thione derivatives and to determine the major interactions that govern the long-range ordering over polycrystalline gold surface by using the IR, Raman spectroscopies and SEM-EDX, AFM techniques.

+) The last research on the selective oxidation of L-cysteinate which was intercalated into the CaAl-LDH.

This research was designed and performed with the following purpose:

- To establish a well-characterized, fully selective, non-toxic, environmentally friendly and inexpensive cysteine-oxidation process by fixing the anionic form of cysteine among the layers of CaAl-LDH (hydrocalumite) and examine different oxidizing agents in various solvents.

CHAPTER 2: LITERATURE REVIEW

2.1. Organosulfur compounds

2.1.1. Introduction

Two discoveries of xanthates in 1922 and mercaptan in 1931 by W. C. Zeise marked the first milestone in the history of the organic chemistry of sulfur[1]. Basically an organosulfur compound might be recognized as any molecule containing one or more sulfur-carbon bonds. Sulfur belongs to the group VIA of the periodic table, it should have been expected that behavior of organosulfur compounds is similar to that of oxygen analogue. In fact, there are similarities, for instance, between thiols and alcohols; sulfides and ethers. Yet, this prediction is not fully realized since many factors serve to differentiate sulfur from oxygen. The remarkable differences can be listed as:

(i) reduction of importance of hydrogen bond as a result of pronounced less electronegativity of sulfur than that of oxygen;

(ii) unlike carbonyl compounds, thiocarbonyl ones are relatively rare and generally unstable with a tendency to polymerize due to reluctance of sulfur to form π-double bonds;

(iii) unlike oxygen again, sulfur has not only valence of two but also higher ones that makes it easily produce a plenty of hypervalent compounds[2].

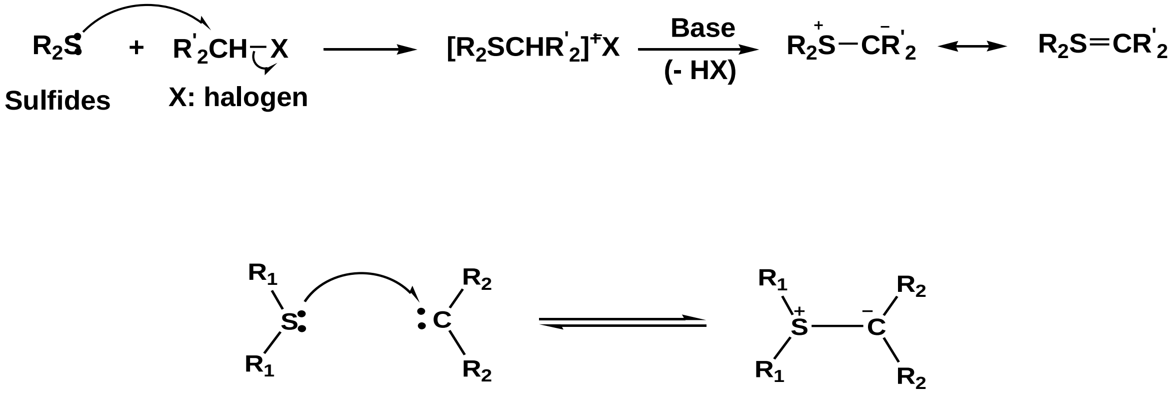
2.1.2. Applications of organosulfur compounds

Chemistry of sulfur and organosulfur has been an important and sufficiently explored area for chemists for a long period of time. However, due to their special properties and applications as well as sulfur's capacity of forming a diverse range of compounds, they still draw a lot of attention. Abundant organosulfur compounds' applications may be found in industrial, agricultural and medicinal sections. For example, carbon disulfide and DMSO are important commercial solvents; dithiocarbamates are used in the rubber industry as vulcanisation accelerators; long chain alkanesulfonic or arenesulfonic acids are important synthetic detergents. Meanwhile, xanthates are used in the manufacture of rayon and cellophane, and many commercial dyes derived from compounds containing sulfonic acid group. Sulfamic acid derivatives such as saccharin acesulfame potassium and cyclamates are valuable artificial sweeteners[2].

In addition, a large number of organosulfur compounds were reported to possess precious biological and pharmaceutical activities and many of them have been used as drugs. The discovery of sulfa antibacterial drugs that were derived from sulfonic acid dyes in 1931 was a crucial milestone in the development of medicinal chemistry. A variety of other compounds including sulfonamides, sulfapyridine, sulfadiazine, sulfathiazole, sulfamethoxazole were demonstrated to have antibacterial activity. Many antibiotics such as penicilins, cephalosporins, monobactams were found to contain β-lactam ring. The most well-known antibiotic, penicillins, are products of the β-lactam ring fused to five-membered thiazolidine ring while the cephalosporins, the β-lactam ring is fused to six-membered dihydrothiazine ring, display a wider spectrum of antibacterial activity than penicillins, especially some of them are active against organisms that are resistant to penicillins[3].

Numerous organosulfur compounds have been used in agriculture as pesticides. Methyl malathion, parathion and their derivatives as well as carbosulfan are important insecticides whilst N-sulfenylcarbamate asulam, sulfonamide oryzalin, thiolocarbamate butylate, *etc.* are employed as herbicides. Many compounds such as dithiocarbamates, N-trichloromethanesulfenyl and inorganic sulfur compounds are practically effective fungicides[2].

One of the valuable applications of organosulfur compounds is witnessed in organic synthesis chemistry. In the list of organosulfur compounds used as reagents, the sulfur ylides are on the top. Similar to phosphorus ylides, sulfur ylides are dipolar compounds carrying the negative charge on the carbon atom. Sulfonium ylides are one of the most typical groups of sulfur ylides.



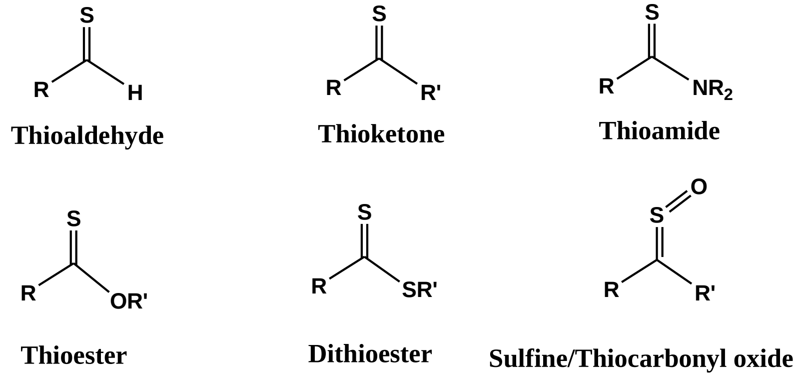
Scheme 1: A few common routes for preparation of sulfonium ylides

Besides sulfur ylides, sulfones are also among most common reagents in organic synthesis. The advantages such as very good leaving group, effortless synthetic pathway and the inertness to nucleophiles make sulfonyl group, particularly sulfonyl carbanion, a versatile tool in synthetic transformations. Various functional groups may be achieved by transformations of sulfonyl group namely cycloaddition of sulfones bearing alkenyl or alkynyl groups; the Michael reaction of sulfonyl carbanion with *α,β*-saturated esters or metalation of aromatic sulfones or the electrophilic fragmentation cyclization of mono- and diallenic sulfones that are considered useful tools in organic synthesis[2, 4].

2.2. Thiocarbonyl compounds

2.2.1. Introduction and comparison with the carbonyl counterparts

Based on valence of sulfur, organosulfur compounds are classified into two groups: divalent sulfur compounds (thiol, sulfide, disulfide, sulfenic acid) and sulfur compounds of higher valences (sulfoxide, sulfonic acid and esters, sulfone, thiocarbonyl derivatives, *etc*). Among sulfur compounds of higher valences, thiocarbonyl compounds attract special attention with interesting characteristics and applications. Simply, thiocarbonyl compounds (or thiocarboxylic acids and their derivatives) are defined as any compounds that contain a carbon-sulfur double bond bound to at least one organic group in their structures. Indeed, they are products of replacement the carbon-oxygen double bond in carbonyl compounds by carbon-sulfur one. Nevertheless, the transition from a carbonyl to thiocarbonyl group does not just imply a small step in periodic table but leads to another world of chemistry[4]. Thus, it is essential to give a systematic comparison of important properties between carbonyl and thiocarbonyl compounds. Typical examples of thiocarbonyl compounds and their nomenclature are depicted in Figure 1.



Thioaldehyde **Thioketone** **Thioamide**

Thioester **Dithioester** **Sulfine/Thiocarbonyl oxide**

Figure 1: Representatives of thiocarbonyl compounds

The primary reason making the difference between thiocarbonyl and carbonyl analogs is probably due to the sulfur, an element employing *3s*, *3p*. These orbitals are remarkably larger than *2s*, *2p* orbitals of oxygen that means the outer valence electrons are more loosely held, being further eliminated from the influence of the positive nuclear charge. This also leads to the higher polarisability of sulfur relative to oxygen. According to S. Patai[4], based on an approach of electronegativity and polarizability, it was seen that substitutions on the thiocarbonyl group will cause strong impacts on physical and chemical properties of the derivatives. For instance, substituents on the thioformaldehyde might cause a decrease in charge density on sulfur atom resulting in a polarization that is invert of charge distribution in carbonyl compounds or substituents may have opposite effect. The Figure 2 below represents the order of increasing nucleophilicity and accordingly decreasing electrophilicity of sulfur for a few thioformaldehyde derivatives[4].

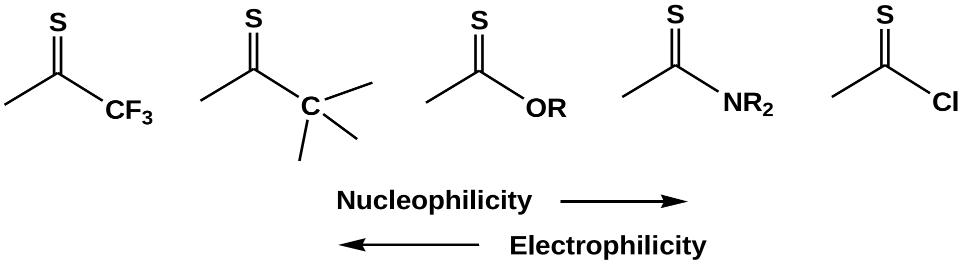
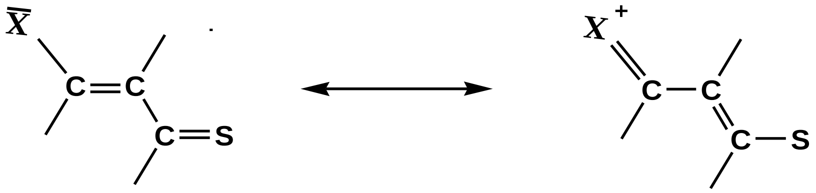


Figure 2: Effects of substituents on properties of some thioformaldehyde derivatives

In the regard to charge distribution, by using a simple LCAO-MO method, M. J. Janssen and J. Sandstrom showed that the thiocarbonyl group has a tendency to give a stronger mesomeric interaction than the carbonyl one[5]. As a result, their proposed model was applied for evaluation of transition energies of both $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition in thiocarbonyl compounds with wildly different structures[5-6]. Simultaneously, chemical properties including basicity of thioamides and thioureas and the acidity of carboxylic acid bearing substituents with the thiocarbonyl function were in the agreement with the model in which the mesomeric electron displacement was reflected in the observed properties. In addition, in the comparison with the carbonyl group, Luttringhaus *et al.* noticed that the thiocarbonyl was surprisingly the stronger electron accepting substituent. They also found that the dipole moments of thiocarbonyl exceed those of the corresponding carbonyl compounds if, and only if, substituents capable of strong mesomeric electron release were present in the molecule[7].

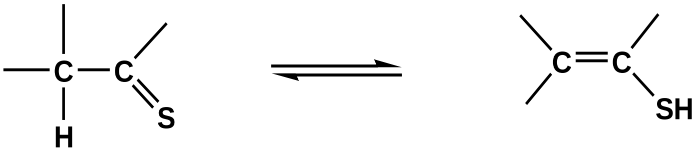
Indeed, the fact that bivalent sulfur is multiply-bonded to carbon is a comparatively rare situation in organic compounds because of its inherent instability. The most stable compound containing the C=S linkage tends to be those in which the carbon atom of the C=S group is directly bound to an atom possessing available lone electron pair, for example nitrogen atom in case of thioamides. Interaction of the lone electron pair with the C=S group leads to a polarization towards a more stable singly-bonded form, for instance C^{+}—S^{-}, the dipole being stabilized by delocalization of the positive charge within the remainder of the molecule. For thials and thiones without such stabilizing influence, the stability of system is guaranteed by either enolisation for thials or oligomerization[8]. However, the exceptions of quite stable thiocarbonyl derivatives with bulky substituents such as thiopivaldehyde, tri-t-butylthioaldehyde, di-t-butylthioketene, bis(triflouromethyl)-thioketene, were observed[9]. Aside from the kinetic stabilization by bulky substituents, thermodynamic stabilization of thiocarbonyl group in thials, thiones, thioketenes was also achieved by the resonance effects, for example, for *α,β*-unsaturated thioaldehydes and thioketones with an electron-donating substituent at beta-carbon given in the Scheme 2 below (X = OR, SR, NR_2) or thioketones containing aromatic rings as substituents:



Scheme 2: An example of the resonance effects of α,β-unsaturated thioaldehydes

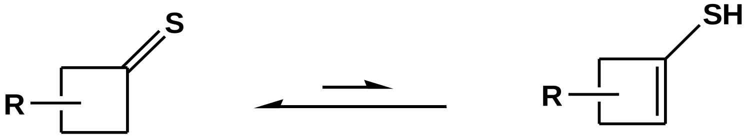
In contrasting of basicity between the thiocarbonyl and carbonyl analogs, Abboud *et al.*[10] concluded that a thioformaldehyde series is generally more basic than their carbonyl counterparts (formaldehyde series), although the latter are slightly more sensitive to substituent effects than the former. Accordingly, this is explained because, on one hand, sulfur is less electronegative than oxygen and, on the other hand, it is much more polarizable.

There is an existence of tautomerism in thiocarbonyl compounds where thiol – thione tautomerism has received the most deal of attention. In thials and thiones with *α*-hydrogen(s), the existence of the corresponding enethiol is possible and is much more favored than enolization for carbonyl analogs to avoid the inefficient p_π - p_π C=S bond. Therefore, on generating a thioketone, quite often a rapid transition of the thiocarbonyl tautomer into enethiol form occurs.



Scheme 3: A tautomerism system of thials and thiones with a-hydrogen(s)

When examining the tautomerism of thioformic acid, the simplest thiol/thione tautomerism system, M. Alcami *et al.*[11] discovered that the thiol form is more stable than the thione one, about 3 kcal/mol based on *ab initio* calculations as well as high-level calculations. Crucially, most of this energy difference has its origin in the much smaller zero-point vibrational energy of the thiol form. This is a direct consequence of replacing an O-H bond by a S-H one. It was concluded that this finding shall be common to all the thiol/thione tautomerism[12]. Nevertheless, in case of cyclobutanethiones, formation of the enethiol is not favored due to ring strain[13]. Interestingly, it has been also reported that separation of the thiol/thione tautomers might be achieved by vapor–phase chromatography method[14].



Scheme 4: The tautomerism system of cyclobutanethiones

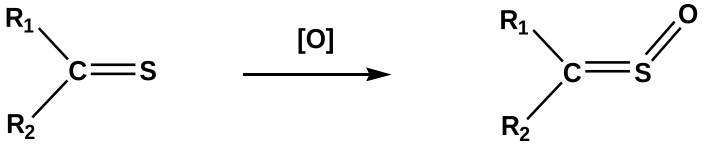
The IR spectroscopic characteristics of the thiocarbonyl compounds are not plentiful and are often stemmed from theoretical studies due to their instability. Indeed, the C=S stretching vibration of the thiocarbonyl group often shows a medium intensity and the position in the fingerprint region of the spectra makes identification not easy. A range of 1244 – 1270 cm^{-1} for aliphatic thiones and a region at slightly lower wavenumber for aromatic thiones has been reported[15]. Generally, for the IR spectroscopy of thiocarbonyl compounds, a very prominent feature can be seen: the C=S stretching mode usually appears coupled with other vibrational modes. Thus, in some cases it is quite hard to make an unambiguous assignment of the C=S stretching absorption, especially for cyclic compounds in which the C=S stretching vibration is often coupled with ring in-plane bending motions[12]. For thioketenes, an isolated C=S vibration is also not observed, but a coupling of the CCS system takes place and give a strong shift to 1750 cm^{-1} value[4].

NMR spectroscopy is especially useful for structural characterization of thiocarbonyl compounds. While ^{13}C-NMR spectroscopy is utilized to take insights into the nature of the thiocarbonyl carbon because of its characteristic of the extreme low-field position, ^{1}H-NMR spectroscopy helps to identify the substituents on the thiocarbonyl group and assess quantitatively the thione/enethiol ratio[14]. Actually, compared to carbonyl carbon analogs, the chemical shift of C=S carbon is usually shifted to a lower field by 35-63 ppm that might be very helpful in following as well as controlling the conversion of a carbonyl group into thiocarbonyl one[16]. A reasonable explanation for this shift was proposed that the high value of $\delta_{C=S}$ carbon is due to the paramagnetic term of the chemical shift[17].

2.2.2. Reactions of thiocarbonyl compounds

As mentioned previously, thiocarbonyl compounds are often more reactive than carbonyl analogs[4]. As a result, they are considered to be more nucleophilic and more electrophilic than carbonyl compounds. Still, this leads to a tendency to dimerize or polymerize that should be pondered along with others reaction at the same time. What's more, thiocarbonyl compounds show the participation in various reactions including cycloadditions as well as the reactions intervening in sulfur atom such as formation of S-oxides or thiophilic attack of organometallics.

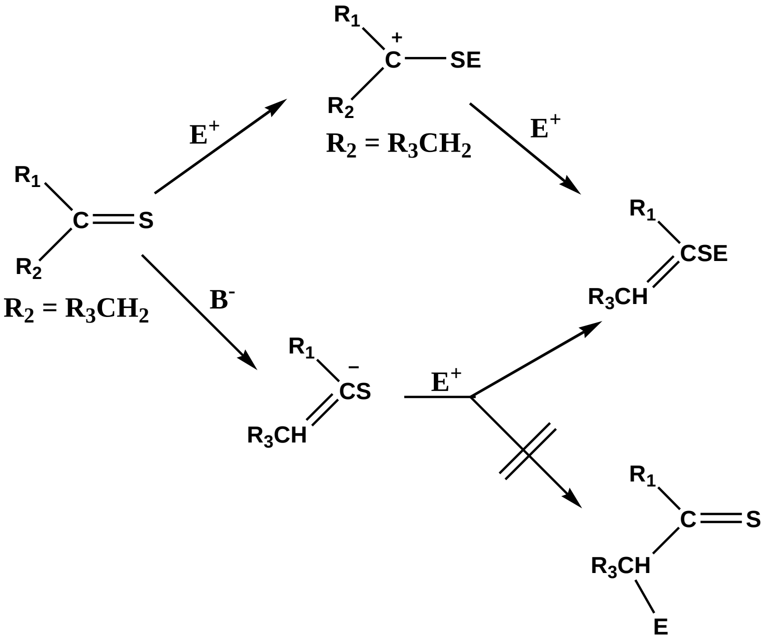
Firstly, oxidation to yield thiocarbonyl *S*-oxides (sulfines) is arguably one of the most striking reactions of thiocarbonyl compounds.



Scheme 5: Conversion of thiocarbonyl group into sulfine by an oxidation

The oxidation is usually accomplished by using a wide range of the oxidizing reagents such as peracids, hydrogen peroxide[18], ozone[19], *etc.* However, the peracids, particularly 3-chloroperbenzoic acid are found to be the most typical and efficient reagent[20]. It is noteworthy that isolation of *S*-oxides products from the oxidation of thiocarbonyl compounds is often difficult because they are less stable than thiocarbonyl precursors. Consequently, they are frequently trapped in 1,3-dipoles or dienes[21].

Nucleophilicity of thiocarbonyl compounds is expressed in the reactions with different electrophiles *E*+, especially for thioketones. The primary product of the reaction for thioketones is a salt as given in Scheme 6, while for enethionizable thioketones, the electrophilic attack is regiospecific on the thiocarbonyl sulfur, leading to formation of C-S single bonds[21]. For thioaldehydes and thioketenes, this reaction has not been thoroughly investigated[4].



Scheme 6: Electrophilic attacking patterns to thioketones

Actually, alkylation is the most popular electrophilic addition reaction of thiocarbonyl compounds. Many methylation as well as alkylation of thiones were explored[22] [22b] [22c]. In addition to alkylation, formation of a C-S single bond may be achieved by using S-arylation or S-acylation[23]. Not only C-S bond, but S-hetero bonds might be formed by different ways, for instance the addition of SCl_2[24], chlorination[25] and silylation[26].

Although thiocarbonyl compounds are much more reactive than carbonyl analogs, they are also less selective in most reactions owing to the poor polarity of C-S unit. This leads to a sharp contrast between them and carbonyl compounds. For instance, in nucleophilic addition, whilst the carbonyl compounds only sustain an attack on the electron deficient carbonyl atom, this addition might take place either at the carbon or sulfur atom of thiocarbonyl compounds. Two types of nucleophilic attack on carbon (carbophilic addition) and sulfur center (thiophilic addition) for thiocarbonyl compounds are illustrated in Figure 3[27].

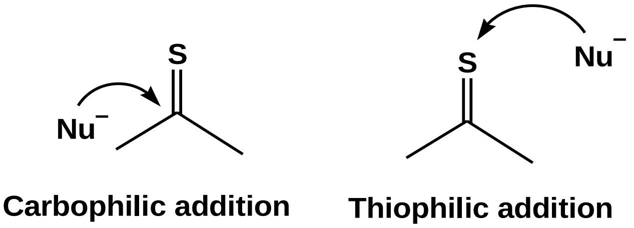
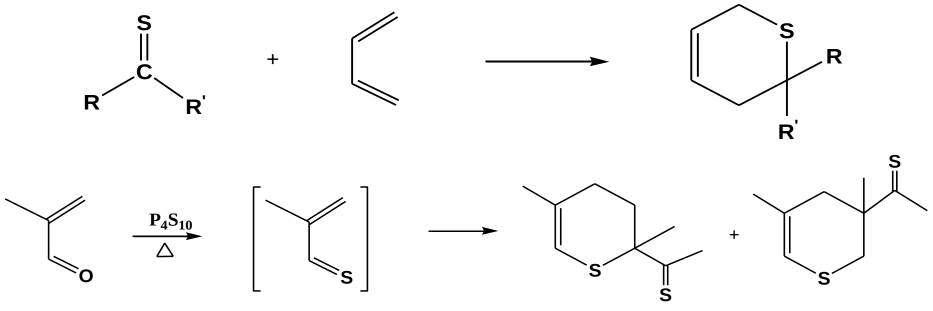


Figure 3: Two nucleophilic attacking patterns to thiocarbonyl compounds

The typical examples of carbophilic addition are reactions of thioaldehydes with the organometallic reagents such as MeMgI, BuLi[28], with furans[29] or amines[30]. In general, carbophilic addition is characteristic of stabilized carbanions such as cyanide deprotonated *α*-isocyanopropionate[18]. However, for thiones, the attack by carbanions is likely to occur on the sulfur rather than on the carbon with an exception of the reaction of thiones with allylic Grignard reagents to yield homoallyl thiols and then thiolanes[31].

Cycloaddition is a characteristic and important reaction of thiocarbonyl compounds, in particular 1,3-dipolar and Diels – Alder reactions. These reactions are especially useful for trapping unstable thiocarbonyl derivatives[12]. In the Diels – Alder reaction (2+4 cycloaddition), thiocarbonyl compound plays the role of both dienophiles and dienes[22c] [21].

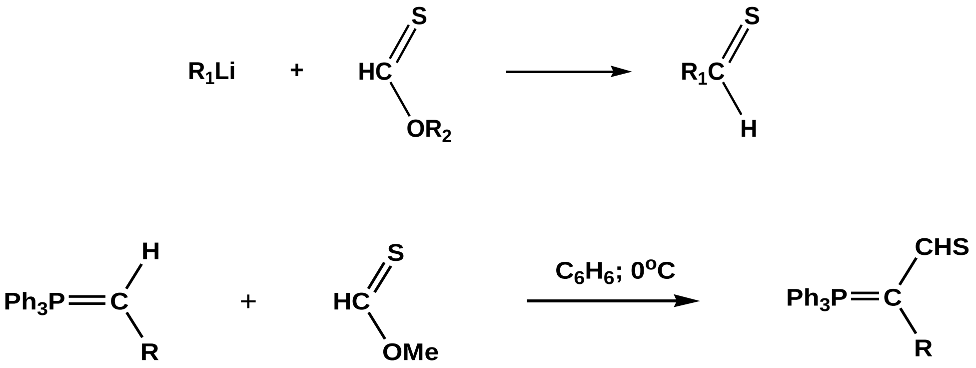


Scheme 7: Examples of Diels – Alder reaction of thiocarbonyl compounds as a dienophile

2.2.3. Syntheses of thiocarbonyl compounds

2.2.3.1. Formation of the α-Carbon-Thiocarbonyl bond

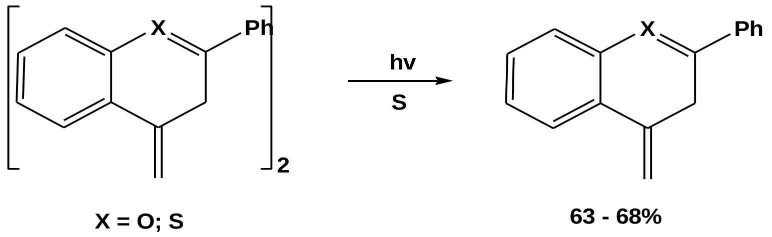
Formation of the *α*-carbon-thiocarbonyl bond is a simple method to prepare stabilized thiocarbonyl compounds from available thiocarbonyl derivatives. For instance, using the reaction of organolithium compounds with *O*-alkyl thioformate, thioaldehydes might be achieved[9b]. Similarly, a thioformyl group may be also formed by conversion of a vinylic hydrogen in methylene or ethylene phosphorene[32]:



Scheme 8: Some examples of formation of the α-Carbon-Thiocarbonyl bond for preparation of thiocarbonyl compounds

2.2.3.2. Addition of Sulfur to Carbenes

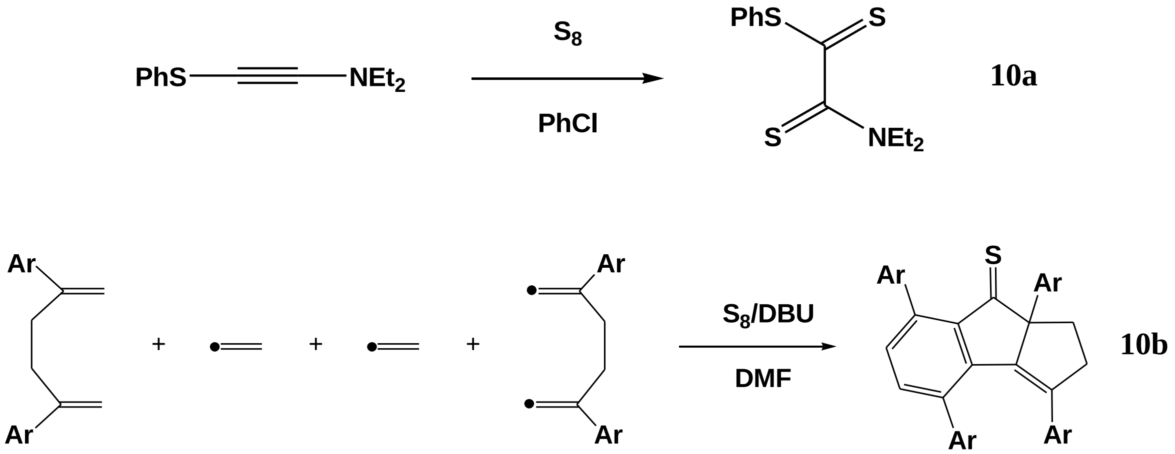
The most important example of this method is cleavage of the ethylene bond in dithioflavylene in high yields by either sulfur in a harsh condition (280⁰C) or a photolytical process under reflux in toluene[33].



Scheme 9: An example of the addition of sulfur to carbene to give thiocarbonyl compound

2.2.3.3. Addition reactions to alkenes and alkynes

Several addition reactions to alkenes as well as alkynes have been described. In case of alkynes it is the addition of lithium hydrosulfide to acetylene to give enethiol systems[34] and the addition of elemental sulfur to diethylaminoacetylenes to generate *α*-dithiocarbonyl compounds[35] (Scheme 10a). Meanwhile, syntheses of mercaptol annulenone by heating annulenone with sodium sulfide and elemental sulfur and of the tricyclic thiones by the addition of sulfur to cyclic cumulenes followed a few steps of cyclizations are highlight examples of the addition reactions to alkenes[36] (Scheme 10b).

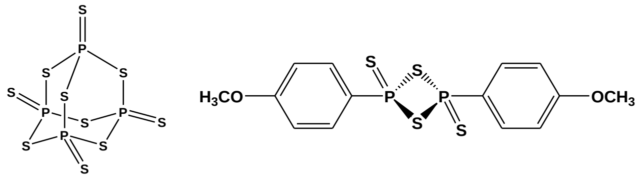


Scheme 10: Examples of addition to alkenes, alkynes to give thiocarbonyl compounds

Aside from the principal routes listed above, other methods might be considered to produce thiocarbonyl compounds, namely cleavages of S-X bonds (X = C, N, O, S, CN, halogens)[37], reduction of sulfines[38] or using chemical transformations of available thiocarbonyl compounds[39].

2.2.4. Thionation reaction for synthesis of thiocarbonyl compounds

As stressed in the previous section, the chemical transformation of carbonyl to thiocarbonyl compound has been a field of interest to synthetic organic groups for hundreds of years. Despite a dozen of available methods, thionation is generally the most commonly used and efficient route to obtain thiocarbonyl compounds from carbonyl analogs. A huge number of systematic studies on thionation reaction including types of carbonyl precursors, reaction conditions, mechanism of reaction, in particular, thionating reagents have been documented.



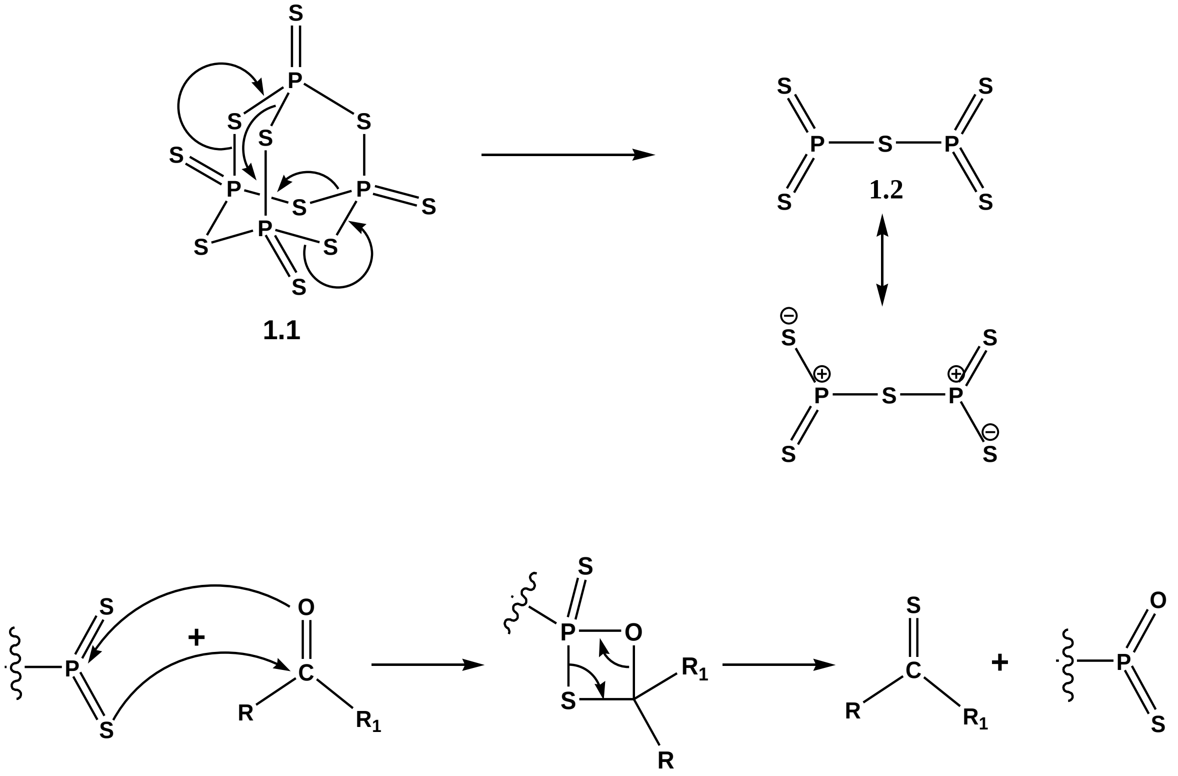
1.1

1.3

Figure 4: Structure of phosphorus pentasulfide and Lawesson's reagent

2.2.4.1. Phosphorus pentasulfide (P_4S_{10}) as thionating reagent

Phosphorus pentasulfide is recognized as the oldest reagent to convert a carbonyl functional group into thiocarbonyl group. So far, along with Lawesson's reagent, they are the two most widely employed reagents for thionation reactions. The first reports on synthesis of P_4S_{10} might be dated from the 1840s by J. Berzelius[40]. J. Berzelius prepared P_4S_{10} by a violent reaction of white phosphorus and sulfur which was improved later by using red phosphorus. The use of P_4S_{10} for this purpose was first reported by Henry and Wislycenus in 1869[41]. When it comes to the mechanism of thionation reaction using P_4S_{10} as reagent, it has been proposed that structure 1.1 of phosphorus pentasulfide (P_4S_{10}) as given in the Figure 4 is first dissociated to form intermediate 1.2 that directly involves in the conversion of a carbonyl group into thiocarbonyl (Scheme 11)[40, 42]. On the basis of the proposed mechanism, some *in situ* derivatives achieved by combination of P_4S_{10} with sodium bicarbonate or sodium carbonate have been introduced[43].



Scheme 11: Mechanism of thionation using P_4S_{10} as thionating reagent

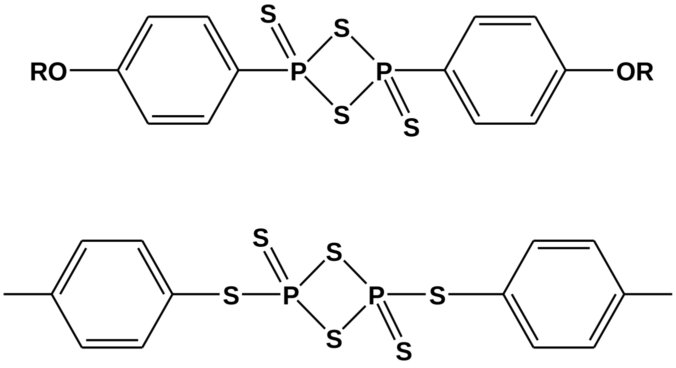
Because the major challenge accompanied with P_4S_{10} is its poor solubility in organic solvents at room temperature, the usual procedure are carried out at reflux condition in different solvents such as toluene, xylene, pyridine, HMPT, *o*-dichlorobenzene[12, 41]. Normally, procedure requires a large excess of reagent and long reaction time to give varying yields[44] . Recently, a reaction of a carbonyl compound with P_4S_{10} that may be performed advantageously at 30^{0}C in polar solvent, for instance, acetonitrile, tetrahydrofuran, diglyme in the presence of basic catalysts has been investigated[45].

Phosphorus pentasulfide has been utilized in thionation reaction for a wide range of carbonyl compounds such as ketones[46], esters[47], amides[48] to peptides, nucleosides[49].

Besides, several thionation of carboxylic acids have been reported. R. Nomura *et al.* described a facile catalytic conversion of carboxylic acids into thiocarboxylic S-acids using P_4S_{10} with Ph_3SbO as catalyst in great yields[50]. A thionation between benzoic acid and P_4S_{10} to prepare dithiobenzoic acid as an intermediate for esterification, polymerization reactions was also studied[51].

2.2.4.2. Lawesson's reagent

It is readily inferred from above discussion about using phosphorus pentasulfide as thionating reagent that there exists a few disadvantages such as low yields and harsh conditions (high reaction temperature, requirement of excess of reagent, long reaction time). Thus, in 1978, Lawesson and co-workers developed a new reagent, commonly named Lawesson reagent 1.3 (LR), and systematically studied its use in organic syntheses[40]. Lawesson reagent that is commercially available can be readily synthesized by a reaction of anisole with P_4S_{10}[52]. Besides, other analogs of LR with increased solubility in organic solvents such as Belleau's reagent 1.4[53], Yokoyama's reagent 1.5, 1.6[54] have been also prepared and investigated.



(1.3) R= CH_3

(1.4) R= Ph

(1.5) R= H

(1.6) R= OCH_3

Figure 5: Some common analogues of LR

Since then, LR has become the thionating reagent of choice and method of thionation using LR has been the most important and popular for synthesis of thiocarbonyl compounds from carbonyl precursors. With using LR as reagent, thionation might be achieved for a diversity of carbonyl compounds from ketones, aldehydes, esters, amides, lactones, alcohols, steroids[55]. For thionation of carboxylic acids, a simple one-step protocol for conversion of carboxylic acids into corresponding thioacids and thioester using LR was developed[56]. For thionation of oxime, using LR as reagent holds a great interest for chemists. Unlike P_4S_{10}, using LR brings many improvements in reaction conditions and yields. Various successful routes for thionation of different oximes using LR have been examined and reported[57].

2.2.4.3. Other P_4S_{10}-based thionating reagents

It has been concluded from the two previous sections that LR is the most important and efficient reagent for thionation processes and followed by P_4S_{10}. Apparently, LR overcomes major drawbacks of P_4S_{10}, particularly in term of yield that was discussed in the *2.2.4.2* subsection. However, it is impossible to not spot disadvantages of LR such as its high cost and the fact that side products originated from the reagent itself is hard to be removed out of reaction mixture and usually isolated by only column chromatography method that is clearly not suitable for large scale procedure due to high equivalent weight of LR. Hence, an improved reagent has been developed by Curphey where a combination of P_4S_{10} and hexamethyldisiloxane (HMDO) is employed. This new reagent is so called Curphey reagent (P_4S_{10}/HMDO).

This reagent is widely applied to synthesize a variety of thioketones, thioesters, thioamides, thiolactams, etc. from corresponding carbonyl precursors. Some important examples are represented in Figure 6[58].

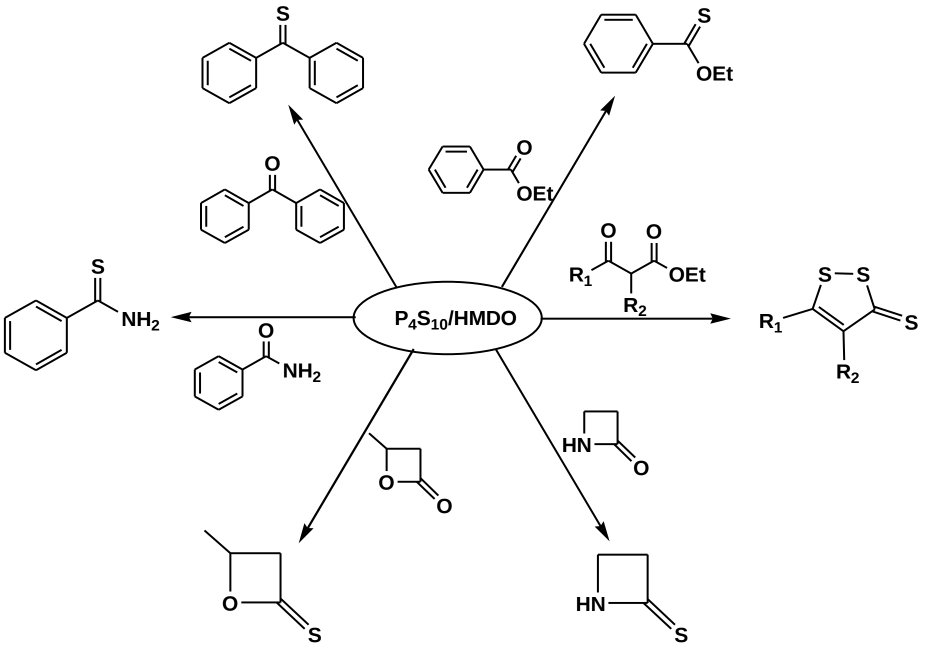


Figure 6: Important applications of using the Curphey reagent for thionation

2.2.4.4. Inorganic thionating reagents

Using inorganic reagents containing sulfur, for instance, hydrogen sulfide, carbon disulfide are traditional methods to accomplish the thionation process. A striking example of thionation reaction employing CS_2 is the thermal reaction of this reagent with N-methyl-2-pyrrolidinone, formamide, acetamide and DMF in very good yields as depicted in Figure 7[59].

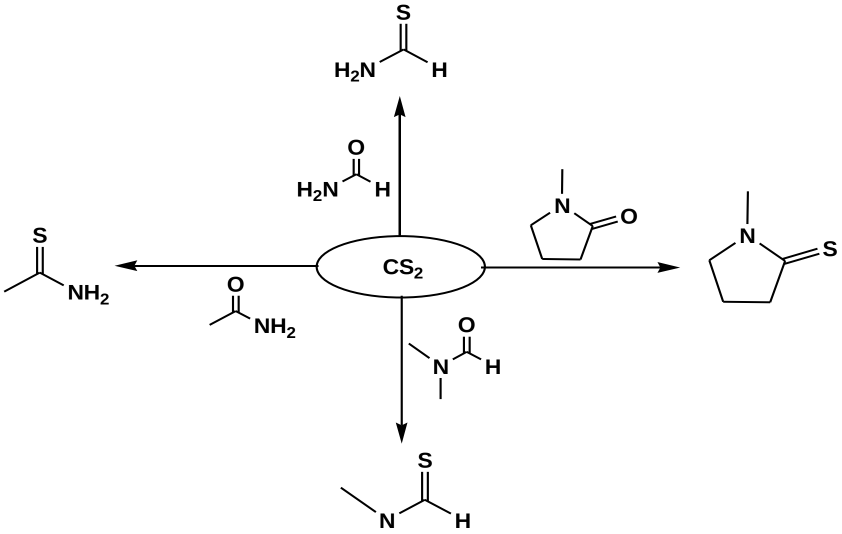
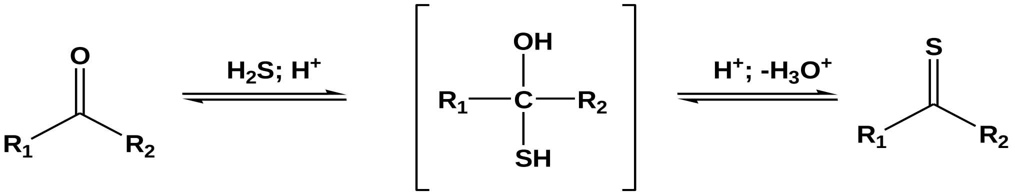


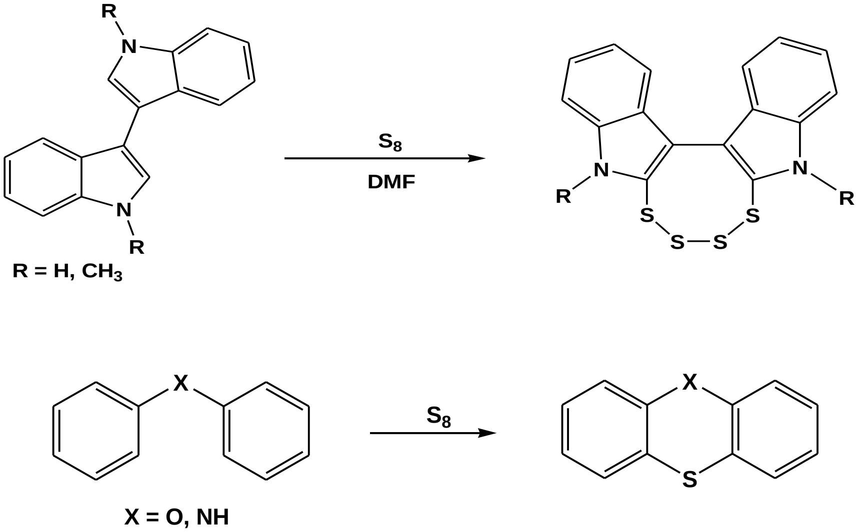
Figure 7: CS_2 may be used for many thionation reactions

Thionation reaction may be succeeded by using hydrogen sulfide as reagent in the presence of an acidic catalyst, frequently hydrogen chloride. The mechanism of this type of reaction is displayed in Scheme 12[60].



Scheme 12: An example of conversion ketones into thioketones using H_2S

Notably, thionation reaction might be also obtained by using elemental sulfur alone (S_8 form). Thionation of 3,3'-biindolyl derivatives[61], anthrone[62] are a few typical examples of this kind of reaction.

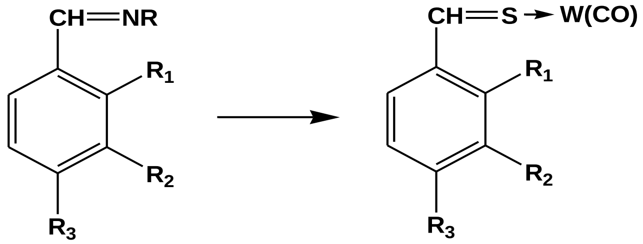


Scheme 13: Elemental sulfur is utilized in some thionation reactions

2.2.5. Coordination chemistry of thiocarbonyl compounds

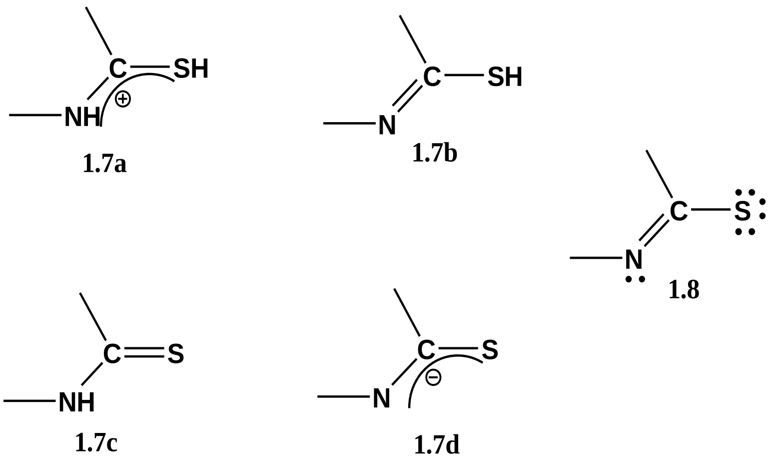
With goals to stabilize labile derivatives and modify thiocarbonyl reactivity along with versatility of sulfur as heteroatom in hetero–organic compounds, the coordination chemistry of thiocarbonyl compounds with metal ions has been attracted great interest to chemists. Among thiocarbonyl ligand's complexes, coordination complexes of thioketenes and thioaldehydes have been extensively investigated. Whilst thioketenes might form complexes with numerous metal ions such as Mo[63], Os[64], Co, Fe[65], *etc.*, complexes of thioaldehydes with Mo[63], Ti[66], W[67] has been also documented. For example, aromatic pentacarbonyltungsten (0) complexes were reported in which N-phenyl or N-cyclohexyl imines of aryl aldehydes were treated with $[PPh_4][W(CO)_5SH]$ in solvents CH_2Cl_2 or C_6H_6

in the presence of $BF_3.Et_2O$ in acetic acid as catalyst[67] (Scheme 14). The similar procedure was also applied to pentacarbonyltungsteng (0) complexes with a few other heteroaromatic thioaldehydes.



Scheme 14: Complexation of W(CO)⁰ with heteroaromatic thioaldehydes

It is fascinating to discuss the coordination chemistry of thiones. Basically, all the ligands possessing thione and, sometimes, thiol group which is directly bound to the heterocyclic skeletons. Therefore, the combination of an exocyclic thione group and a heterocyclic skeleton bearing oxygen, nitrogen or sulfur makes them a system with significant coordination characteristic where the prototropic tautomerism also plays an important role[68]. Take nitrogen – containing heterocyclic thiones as an example, as far as we have known that this type of thiones all shares a common property: the thione – thiol tautomerism (1.7c and 1.7b). In fact, these thiones can be deprotonated to afford thionate ions (1.7d) where an electron pair on heterocyclic nitrogen and three electron pairs on the thionate sulfur may be potential coordination centers 1.8[12].



1.7a

1.7b

1.8

1.7c

1.7d

Figure 8: A prototropic tautomerism of the nitrogen-containing thione (resonance structures of thione and thionate ion)

2.3. An outline of the imidazole-2-thione derivatives

2.3.1. Introduction

The chemistry of imidazole-2-thiones has been initiated and grown for more than a hundred years since imidazolylmercaptan and its derivatives were first synthesized by Marchwald *et al.*[69]. Imidazole-2-thiones are an interesting class of sulfur-containing five membered heterocyclic compounds. It is noteworthy that the S atom in structure of these thiones is essential for their well-known biological activities[70]. Imidazole-2-thione 1.9 and benzimidazole-2-thione 1.10 are described as the most simple but important in this class of compounds (Figure 9).

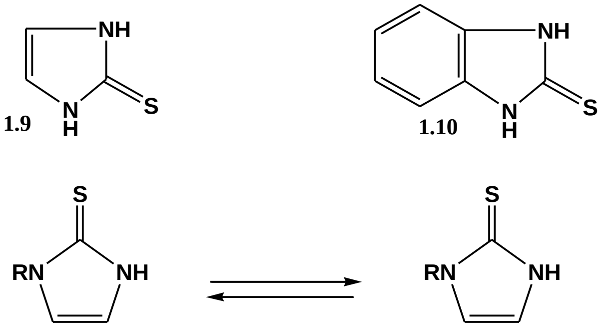


Figure 9: Structure of two most important sulfur-containing five membered heterocyclic compounds

These two compounds are convenient representatives to examine thione–thiol tautomerism (Figure 10), hydrogen bonding, acid-base properties as well as spectral characteristics. Practical data of dipole moments, IR, UV, ^{1}H-NMR, ^{13}C-NMR, ^{15}N-NMR spectroscopies and X-ray diffraction confirmed existence of imidazole-2-thiones in the thione form both in the crystalline state and in solution[71]. Especially, the ^{15}N-NMR data proved that 1-methylimidazole-2-thione in DMSO exists exclusively as the thione tautomer, whereas for benzimidazole-2-thione the equilibrium concentration of the latter is 92%[72]. More deeply, according to the various calculations of C-S bond order and its length, imidazole-2-thiones are justified to exist in the resonance hybrid A and the dipolar B form (anionic form)[73].

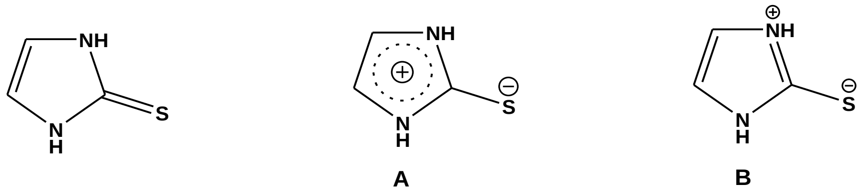


Figure 10: The thione-thiol tautomerism of imidazole-2-thione

Structurally, the most striking feature of imidazole-2-thiones is the presence of a thiourea moiety. In particular, imidazole-2-thiones are associated through intermolecular hydrogen bond of N-H…S[74]. This type of interaction was also comprehensively proved by thorough studies using the IR spectroscopic method[74] or X-ray diffraction[75].

In addition, one of the most important things to describe imidazole-2-thione and its derivatives is their valuable applications in medicine, industry as well as in organic synthetic chemistry. These compounds have been reported to display various remarkable biological activities such as antimicrobial, antifungal, antihypertensive, tuberculostatic activity or anti-HIV[76]. In industry, many imidazole-2-thiones have been used as accelerators of rubber vulcanization or as rubber antioxidants[77]. Thanks to their striking chemical properties, imidazole-2-thiones become potential and convenient synthons in synthesis of other important compounds[78] as well as ligands for coordination chemistry[79].

Due to their great importance, synthesis of imidazole-2-thione and its derivatives has received immense interest. A variety of methods for preparation of these compounds have been developed. A full review by B. V. Trzhtsinskaya and N. D. Abramova summarized the most common methods including cyclization, reaction of halo- and oxoimidazole derivatives with sulfur-containing nucleophiles and direct insertion of sulfur into position 2 of the imidazole ring[71].

2.3.2. Intermolecular interactions of imidazole-2-thione derivatives

Along with features of the atoms and molecules, the interactions between them determine the characteristic properties of any matters. There are two main types of interactions between the atoms and molecules: intramolecular (primary) forces and intermolecular (secondary) forces. Whilst intramolecular interactions including covalent bond, ion bond or metallic bond are the forces that hold atoms together within a molecule, intermolecular interactions exist between molecules. The secondary interactions are not important in considering the chemical reactivity and thermal stability of compounds in that the primary interactions are of the greatest importance[80]. Yet, these secondary forces are responsible for the aggregation of molecules into solid and liquid phases and are still strong enough to determine the orientation of groups of atoms and molecules in the solids. Basically, intermolecular interactions consist of major types namely: dipole forces, ion–dipole and ion-induced dipole forces, hydrogen bonding and van der Waals forces[80].

Among the secondary interactions, hydrogen bond is undoubtedly the most important due to its notable characteristics as well as application to explain a lot of special physical properties of compounds. Actually, the hydrogen bond is usually considered as a quite strong electrostatic dipole–dipole interaction and is almost non-covalent. Nonetheless, it also has a few features of a covalent bond such as it is directional, stronger than van der Waals forces, form interatomic distances shorter than the sum of van der Waals radii and often concerned to a limited number of interaction partners[80].

As depicted in 2.3.1 subsection, imidazole-2-thione molecules are also linked together by hydrogen bonds of N-H…S. This is manifested by the substantially higher melting points of imidazole-2-thiones in comparison of those N- and S-substituted derivatives. The IR spectra of imidazole-2-thiones in CCl_4 display two absorption bands: a narrow one at 3470cm^{-1} corresponds to the vibrations of free NH groups, whereas a broad band at 3200-2900cm^{-1} is assigned for H-bonded NH group vibration[74]. As established by X-ray diffraction, each sulfur atom in benzimidazole-2-thione is bound by a hydrogen bond to two NH groups of neighboring molecules in which length of N…S contact is 3.336Å and that of S…H contact is 2.420Å that is markedly shorter than the corresponding van der Waals radius sum (2.85 ± 0.2Å). The HN…S angle (22^0) indicates a slight deviation from linearity[75].

In a study on molecular and crystal structure of 2-mercaptobenzothiazole, J. P. Chesick and J. Donohue estimated the shortest intermolecular nitrogen–sulfur distance, 3,347Å[81]. It is characteristic of the N-H…S system, hence no unusually short hydrogen bond exists. These molecules form centrosysmetric hydrogen-bonded dimers in crystal[82].

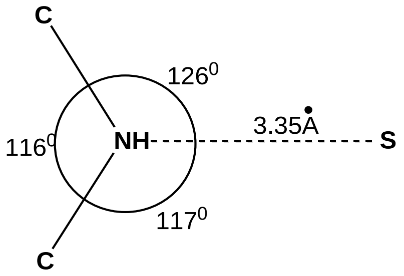
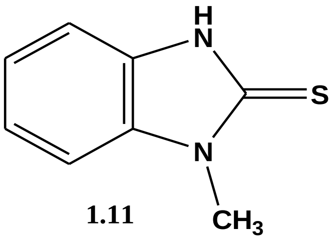


Figure 11: Some details of the NH…S hydrogen-bond system

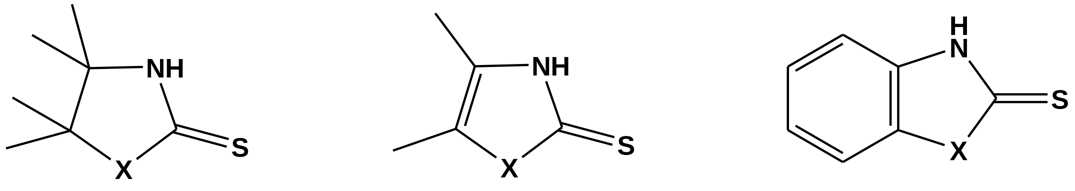
Intermolecular N-H...S interactions in 1-methyl-*1H*-benzimidazole-2(3H)-thione 1.11 was also interpreted by H. Khan *et al.*[83]. Accordingly, the crystal structure of this compound is stabilized by N-H...S hydrogen bond along with a C-H...**π** interaction between a benzene hydrogen atom and the benzene ring of a neighbouring molecule that might be observed in aromatic ring–substituted imidazole-2-thiones.



1.11

Figure 12: Structure of 1-methyl-1H-benzimidazole-2(3H)-thione

Notably, hydrogen bonding abilities of 2-mercaptoazoles including some imidazole-2-thione derivatives towards DMSO or 4-chlorophenol have been investigated quantitatively in chloroform by IR spectroscopy at 25^0C[84]. It has been reported that NH protons of the molecules studied exhibit a high tendency to hydrogen bonding which is correlated with the basicity of the 2-alkylazole analogues. Meanwhile, the C=S sulfur atom indicates great hydrogen bonding capacity which approximately parallels its nucleophilic reactivity towards methyl iodide.



1.12 **1.13** **1.14**

1.12: X = O

1.13: X = S

1.14 X = NMe

Figure 13: A series of 2-mecaptoazoles[84]

2.3.3. Self-assembly properties of imidazole-2-thiones

It is well known that most of aggregation structures such as micelles, microemulsions, bilayers, vesicles, biological membranes or proteins might form steadily in aqueous solution by spontaneous self-assembly of amphiphilic molecules. Self-assembly is an autonomous and spontaneous organization of different components into patterns or structures (aggregates) without human intervention[85]. Self-assembly is a ubiquitous process in nature and may be categorized into two types: static and dynamic self-assembly. Self-assembly, at molecular and nanoscale, might be further divided into intramolecular and intermolecular self-assembly[86]. Whitesides *et al.*[87] studied and summarized five determining factors to this achievement including components in the system; interactions between molecules in the system; reversibility of association of components in the system; environment of the system and mass transport and agitation processes that occur in the system. It is notable that the interactions that hold molecules together in these structural systems are not due to strong covalent or ionic bonds but arises from the weaker interactions[88].

Among self-assembly forms, self-assembled monolayers (SAMs) are characteristic and popular for sulfur-containing compounds such as thiols, disulfides when they are chemisorbed on gold, sometimes silver, surfaces[89]. SAMs are highly ordered thin surface films that spontaneously form on a few substrates[90]. The majority of molecules that form SAMs (Figure 14) include a chemical "head" group bound moderately strongly to the underlying substrate as well as attached tail group bearing a terminal group that might be further chemically transformed[91]. It is expected that for substrates such as thiols, thiones, the first formation of a SAM is the chemisorption of the thiol or thione groups to gold surface through the generation of sulfur-gold bond. The second step of this highly ordered SAM formation concerns to van der Waals forces between hydrocarbon chains in substrate structures[92]. Areas of application of SAMs are found in a lot of fields from biology, medicine, dentistry, electrochemistry to household items[86, 92].

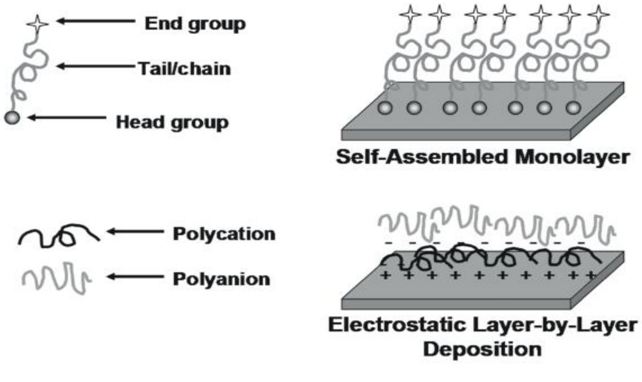


Figure 14: Electrostatic LbL deposition[91]

The self-assembly of hydrocarbon thiol, sulfide and disulfide monolayers on metallic films has been vastly explored as a route to the fabrication on surfaces with rationally designed interfacial structure and features[93]. Without doubt, thiol SAMs on gold are the most popular films because obtained oxide-free, clean and flat surfaces may be effortlessly modified both in solution media and gas phase under conventional conditions[94]. The reason that gold surfaces offer a convenient substrate for SAM formation is because they are easy to prepare and clean, owing to the chemical inertness of gold under ambient condition. In this field, for a long time, the nature of gold-sulfur bond at interface had been covered and detailed information on the atomic structure of that interface has largely been missing. Until recently, according to a review by H. Hakkinen[95], the covalent interaction at the gold–sulfur interface requires formation of gold–thiolate bond. The thiolate–gold (RS–Au) bond has strength close to that of the gold–gold bond, so it can significantly modify the gold–gold bonding at the gold–sulfur interface.

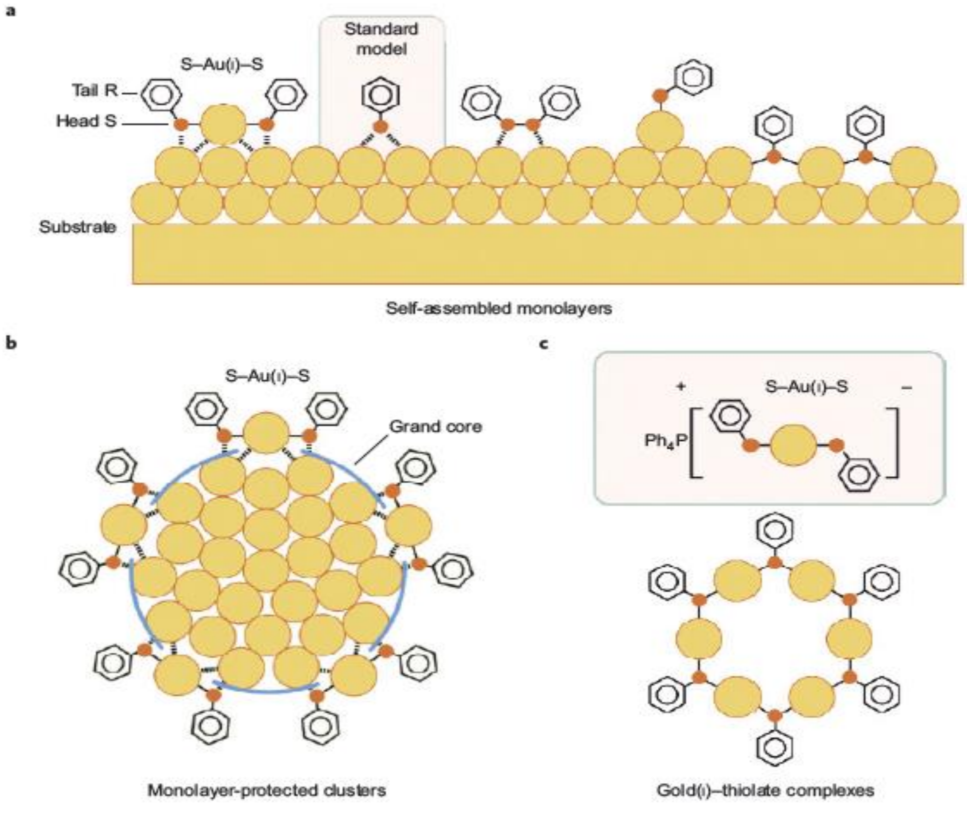


Figure 15: The bonding motif between thiolates and gold[95]

As a sequence, it has been surely expected appearance of tremendous similar studies on thione SAMs over metallic surfaces. Surprisingly, chemistry and interactions of thiones, especially imidazole-2-thiones, towards passivation and self-assembly of metal nanoparticles is nascent and poor understood[96]. Rao *et al.* represented a sensitive and rapid thiourea-based self-assembly of citrate stabilized gold nanoparticles into 1D arrays through a non-crosslinking mechanism[96]. Moreover, soft-soft interactions of gold-thione pair and the kinetics of ligand exchange were also examined and found to be influenced the manner in which the substituents stuck to thiourea moiety alter the electron density around the thione sulfur. Notably, the formation of monolayers of a series of imidazole-2-thiones on gold films was described. Because up to four different substituents might be attached on the imidazole ring, these derivatives provide for monolayers with diverse functionality in molecularly controlled proportions[97]. According to the molecular structure of low valent metal-thione complexes, the imidazole ring can be probably oriented nearly parallel to the gold surface. In this orientation, the imidazole dictates the molecular packing on the surface. It was also discovered the presence of void between the alkyl chains in the monolayers that suggested that monolayers generated from these imidazole-2-thiones may possess a capacity of incorporating fluorocarbon chains via intercalation[98].

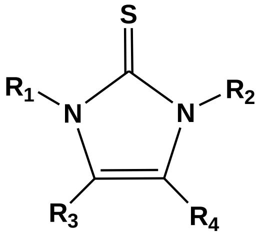


Figure 16: Four different substituents on the imidazole ring of imidazole-2-thiones[98]

2.4. A concise introduction on layered double hydroxides (LDHs)

Layered double hydroxides (LDHs) are a class of layered materials with a general formula of $[[(M^{II})_{1-x}(M^{III})_x (OH)_2]^{x+} (A^{m-}{}_{x/m}). nH_2O]$, where M^{II} = divalent cation; M^{III} = trivalent cation; A = interlayer anion; n = charge on interlayer; x and y are fraction constants. The general structure of LDHs was shown in Figure 17[99]. The layers contain M^{II} (Ca^{2+}, Mg^{2+}, Fe^{2+}, Co^{2+}, Mn^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) and M^{III} (commonly Al^{3+}, Fe^{3+}, Co^{3+}) while the interlayer region is occupied with charge-balancing anions. The anions, such as $CO_3{}^{2-}$, $NO_3{}^{-}$, and Cl^{-}, in the interlayer galleries might be readily replaced[100].

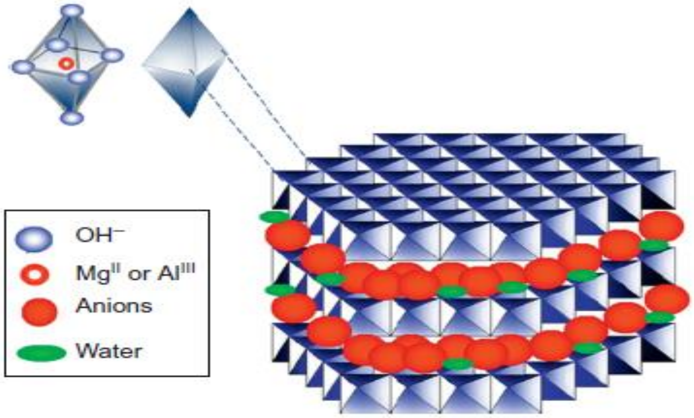


Figure 17: General structure of LDHs[99]

The interlayer region is hydrated, and the amount of water in the interlayer region depends on the nature of the interlayer anions, the water vapor pressure, and temperature[101]. The water molecules which are hydrogen bonded to both the metal hydroxide layers and interlayer anions stabilizing structure of the LDHs. Along with the chemical composition and degree of crystallinity, the crystallite size and its distribution are also important for certain applications of LDHs[102].

The thermal behavior of LDHs is a multistep thermal degradation concerning (1) removal of water physically adsorbed on the external surface of the crystallites; (2) removal of interlayer water; (3) removal of hydroxyl groups from the layers as water vapor; and (4) removal of the interlayer anion in some cases. The first step occurs below 100^0C while step (2) takes place between 100 and 200^0C. Steps (3) and (4) usually occur between 200 and 400^0C[103].

LDHs have emerged as potential layered materials and attracted a great deal of interest because of many their unique features, namely ease of synthesis, being low–cost and non-toxic, highly porous structure, uniform distribution of different metal cations in the brucite layer, swelling properties, oxo-bridged linkage, high chemical as well as thermal stability, ability to intercalate different type of anions (inorganic, organic, biomolecules, and even genes)[104]. Therefore, LDHs have been broadly used in catalysis, flame retardants, fuel cells, drug delivery, adsorption, analytical extractions waste water treatment, *etc*. All applications were thoroughly summarized in the review by N. Baig *et al.*[105].

The most common methods for synthesis of LDHs were represented in Figure 18[104]. Generally, it may be divided into two types of methods: direct methods and indirect methods for the synthesis of LDHs.

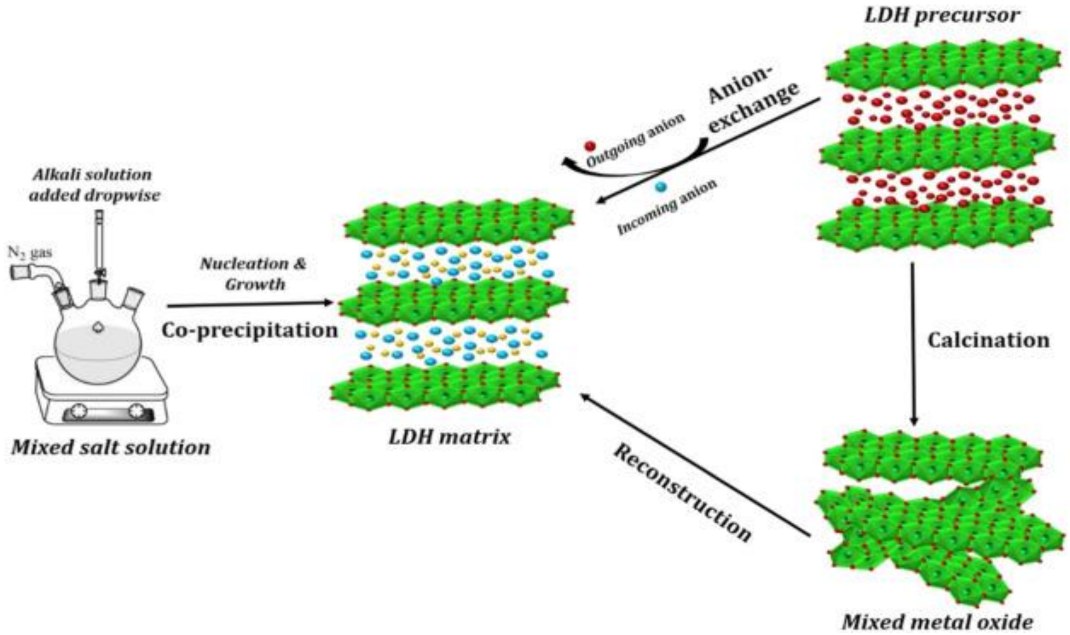


Figure 18: Three popular methods of development and modification of LDHs[104].

The direct methods include co-precipitation, urea hydrolysis and sol-gel method in which co-precipitation is the most frequently used method. Co-precipitation might be conducted at constant or variable pH values. In reality, the pH value of the reaction mixture in co-precipitation method has a pivotal effect on the chemical, structural, and textural features of the obtained materials[102]. Notably, the prepared LDHs by co-precipitation possess a number of interesting properties such as high crystallinity, small particle size, high specific surface area, and high average pore diameter[106] which found them in high technology applications. In case of urea based co-precipitation, the final products provide better crystallinity and better control of the particle size because the hydrolysis of urea proceeds very slowly[107]. For the sol-gel approach, it is similar to the procedure for preparation of silica gel and other inorganic particles. The synthesized materials by sol-gel route were reported to show a higher specific surface area in comparison to those by the co-precipitation method[108].

In terms of preparation of LDH composites or hybrid materials, anion-exchange was found to be more beneficial over the co-precipitation owing to the large size of anions causing the difficulty in co-precipitation[109].

Anion-exchange is an indirect method for synthesis of LDHs and particularly effective for intercalation of various sorts of anions[110]. Accordingly, firstly LDH was afforded by co-precipitation with host anions, usually NO_3^-, CO_3^{2-}, and Cl^-. In the next steps, anions present in the interlayer region are exchanged with the desired anions by stirring the resulting LDH in a solution of the anion to be intercalated in the excess. The anion exchange basically depends on the electrostatic forces between positively charged LDH layers and the exchanging anions. Anions might be readily replaced by anions or organic molecules with higher electrostatic interaction with layers due to weak electrostatic interaction with layers[111]. An illustration of anion-exchange route is depicted in Figure 19[112]:

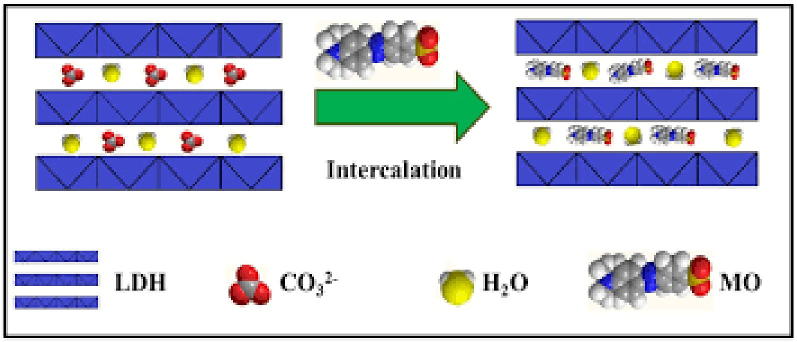


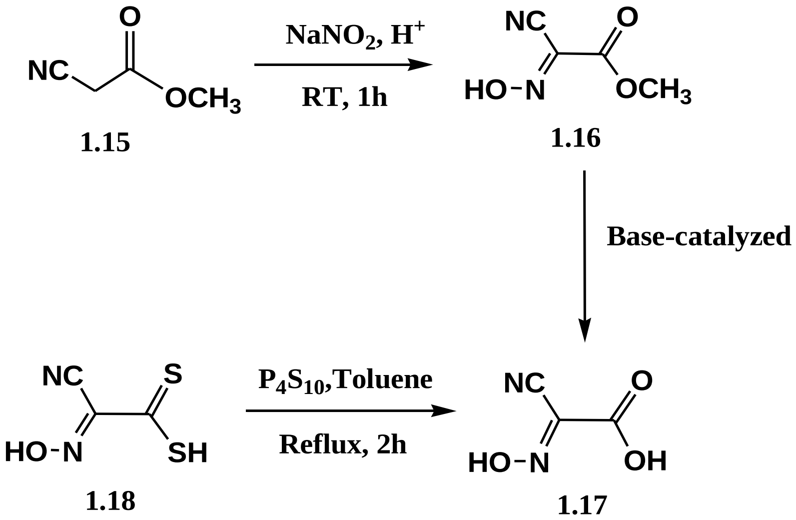
Figure 19: The illustration of an anion-exchange route

Some crucial factors influenced formation of desired materials by anion-exchange method can be listed as solvent, chemical composition of layers, temperature and pH. The high temperature and pH from 4 or above 4 were shown to be favorable[104]

CHAPTER 3: RESULTS AND DISCUSSION

3.1. Results of synthesis of the ligand 2-cyano-2-(hydroxyimino)dithioacetic acid and its complexes

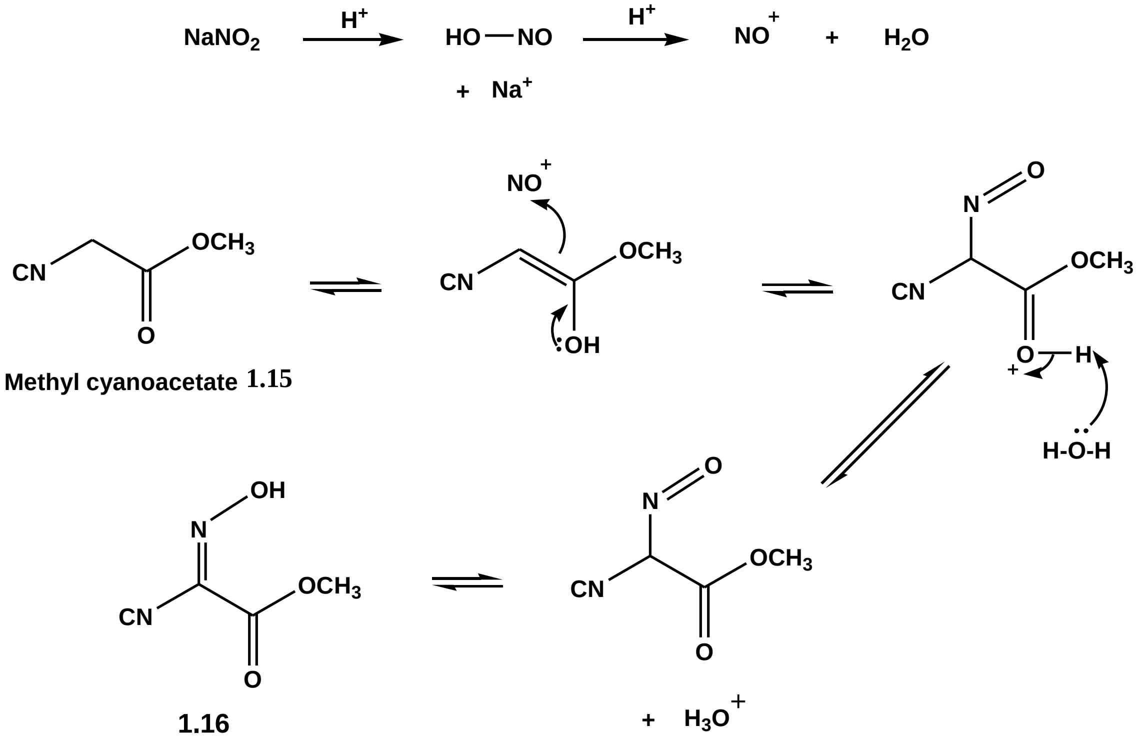
3.1.1. Synthesis of the ligand



Scheme 15: The three-step route for synthesis of the target product 1.18

Scheme 15 illustrates the three-step pathway to synthesize product 1.18 starting from available cyanoacetic acid methylester. The first step deals with a well-known reaction to produce oxime functional group, the Meyer reaction. At this point, it is appropriate to recall the Meyer reaction, undoubtedly, the most common and efficient method for preparation of oximes. Generally, the Meyer reaction infers a synthetic route that was developed by V. Meyer, a German chemist, using a condensation between either a methylene group activated by electron-withdrawing groups in substituted acetonitriles with nitrous acid in acidic conditions or alkylnitrites with anionic acetonitriles in basic media. Because nature of Meyer reaction for synthesis of oximes is a nitrosation, the reaction has been obviously performed by using common nitrosation reagents, for instance nitrous acid, alkyl nitrites, nitrosyl chloride, nitrosylsylfuric acid, nitrous fumes. In some cases, acid or base is often added as a catalyst[113]. The mechanism of reaction in acidic conditions might be assumed to involve the formation of NO^+ cation that then attacked to reactive methylene center in acetonitrile component to give an oxime via a nitroso intermediate.

It is noticeable that the principal governing factor in the Meyer reaction is the nature of the compound to be nitrosated rather than a particular reagent used. The choice of the nitrosating reagent, hence, depends on the nature of the substrate selected for the synthesis of cyanoximes.



Scheme 16: Proposed mechanism of the Meyer reaction in acidic media

For starting material cyanoacetic acid methylester, the Meyer reaction is simply performed at ambient temperature within 1-2 hours with the acidic catalyst. When the reaction is performed in acidic conditions, nitrous acid was chosen as reagent. In fact, nitrous acid was released *in situ* by an instant reaction of nitrite salt with acid. When glacial acetic acid was used, a 4h reaction time was needed to gain acceptable yield of the product, and care had to be taken of avoiding excess acid. Using a mixture of concentrated H_3PO_4 and HCl afforded high yield in 2h at somewhat higher reaction temperature (35°C). The reaction gives an excellent yield 91% after a purification step by recrystallization in toluene to yield intermediate 1.16 which is then structurally verified by IR (not shown) and NMR spectroscopies (Figure 20, 21).

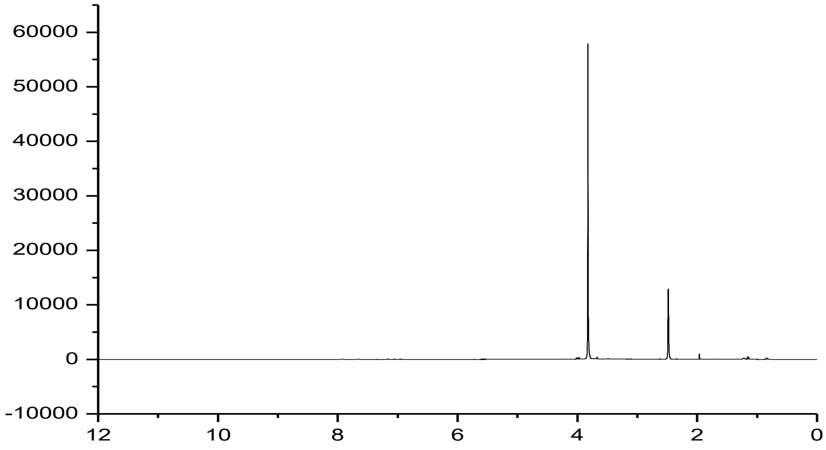


Figure 20: ^{1}H-NMR spectrum of intermediate 1.16 (in DMSO-d6)

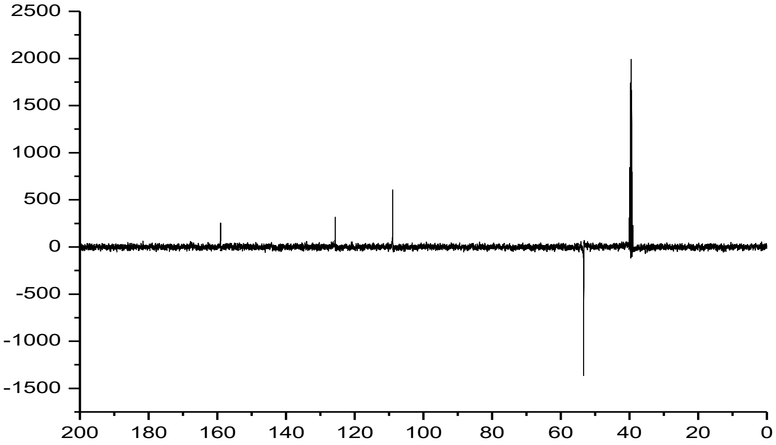


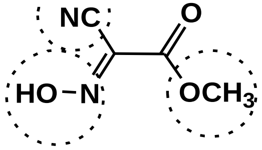
Figure 21: ^{13}C-NMR spectrum of intermediate 1.16 (in DMSO-d6)

All lines in the spectra could be assigned to the functional groups of the cyanoxime. The C=O carbon, as it is expected, appears at the deshielded end (158,5 ppm), while the methoxy carbon, being the most shielded, is seen at 53,1 ppm. As it is seen in the Figure 21, the oxime carbon (C=N) and the cyanide carbon (C≡N) appearing at 127,2 ppm are well separated from each other in the ^{13}C-NMR spectrum. Due to fast exchange, the oxime proton is not observed in the ^{1}H-NMR spectrum; however, the methoxy protons are readily identified at 3,79 ppm.

After discussing about the first step of the pathway (Scheme 15), it could be easily supposed that the key intermediate 1.17 should be obtained from cyanoacetic acid, an easily accessible material too, through only one Meyer reaction instead of two steps. As a result, this would cut down one step reaction and hopefully improve the total yields of the whole route. In reality, it was the first thought arisen from our mind before we started these experimental works. A few experiments on the Meyer reaction of cyanoacetic acid were attempted to directly give the intermediate 1.17. However, it was observed that the substrate cyanoacetic acid immediately reacts with sodium nitrite salt to form *in situ* nitrous acid, even without an addition of the mixture of concentrated H_3PO_4 and HCl. Consequently, no the Meyer reaction was then proceeded. This might be explained by formation of sodium cyanoacetate salt that is no longer reactive for the Meyer reaction. Therefore, the preparation of the compound 1.17 *via* the intermediate methylester form of cyanoacetic acid was proved as the optimal option.

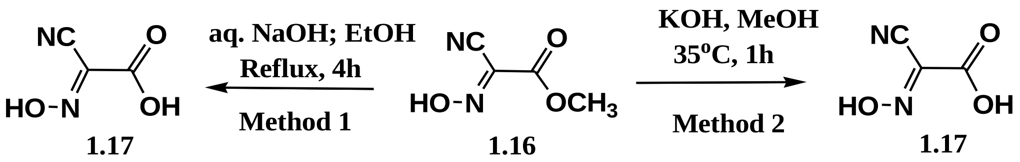
After the Meyer reaction of cyanoacetic acid, a hydrolysis of resultant ester was required to achieve 1.17 intermediate which is the second step of the synthetic pathway of ligand 1.18. Apparently, the hydrolysis of ester to produce carboxylic acid is ubiquitous in organic chemistry in which a dozen of different hydrolysis methods are available. In general, this procedure may be accomplished by using both acidic and basic catalysts. The selection of catalyst highly depends on nature of substrates such as functional groups on their structures and their thermal stability. In case of intermediate ester 1.16, it is not difficult to realize that structure 1.16 contains three functional groups including methylester, cyanide and oxime groups which are sensitive to hydrolytic conditions, especially more vulnerable to acidic media. On the basis of that consideration, a base-catalyzed hydrolysis was the method of choice for 1.16.

(1.16)



Cyanoacetic acid methylester

Figure 22: Structure of 1.16 with three reactive centers



Scheme 17: Two different methods for hydrolysis of 1.16

The procedure was performed by using two methods. Method 2, hydrolysis in methanolic KOH at 35°C in 2h, was proved to be better since there was no by-product formation. To achieve similar yield (73-74%), the reaction with ethanolic NaOH in method 1 required higher temperature (100°C) and longer reaction time (4h). Structural identification was performed by IR as well as ^{13}C-NMR spectroscopies (Figure 23, 24). Again, the functional groups could be readily identified. The hydrogen-bonded OH groups gave the typical wide absorption band in the 3400–2400 cm^{-1} region. Concomitantly, disappearance of the signal around 52-53 ppm of methoxy group is a sign of the successful conversion into hydroxy group.

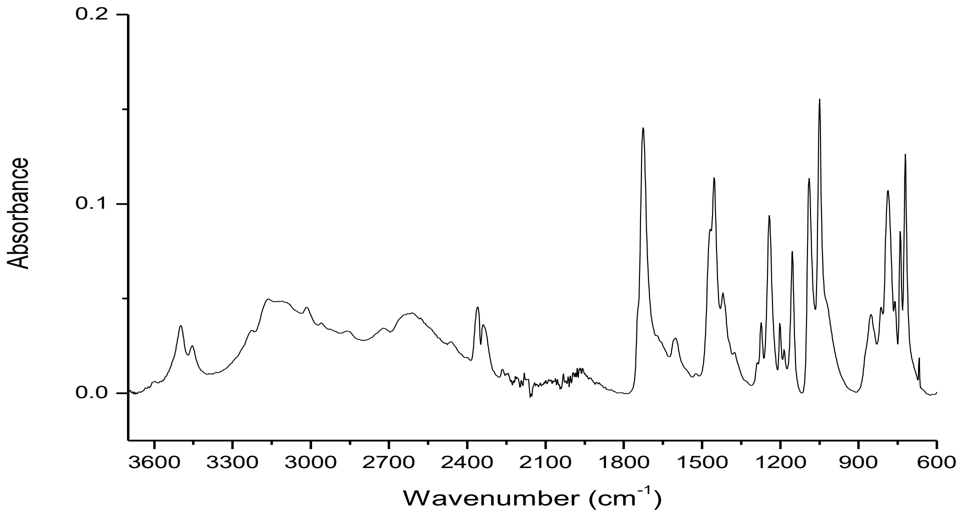


Figure 23: IR spectrum of intermediate 1.17

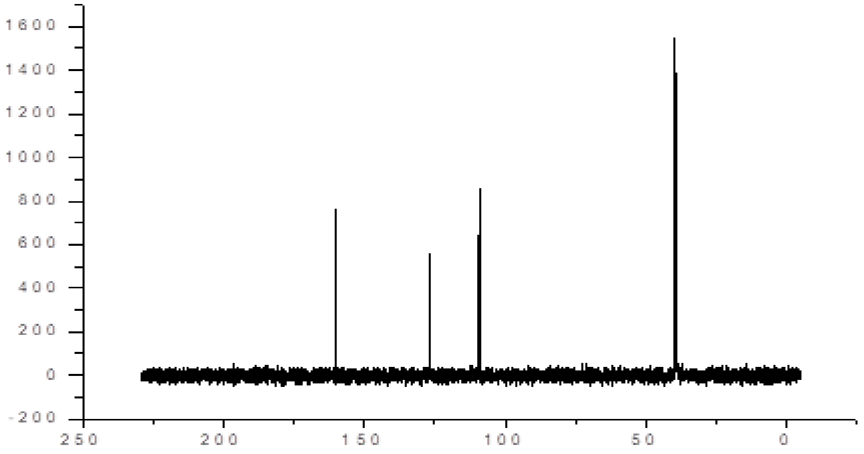
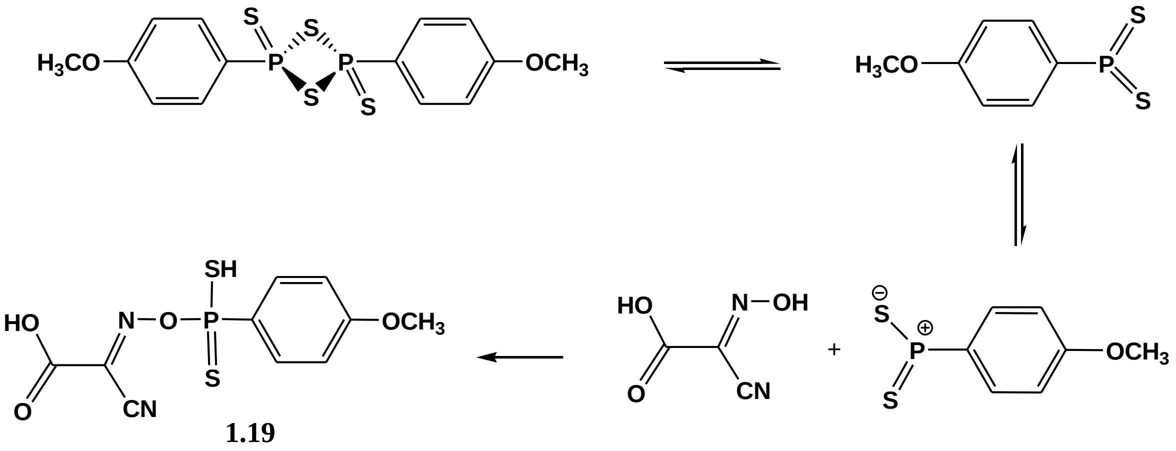


Figure 24: ^{13}C-NMR spectrum of intermediate 1.17 (in DMSO-d6)

In the final step, the target product 1.18 was obtained by a thionation of the key intermediate 1.17. As previously mentioned, thionation is the most efficient to directly convert a C=O group into a C=S group with phosphorus pentasulfide and LR as the most common thionating reagents. The first effort in order to achieve 1.18 was conducting thionation reaction using LR as reagent in toluene, acetonitrile solvent, respectively. Unfortunately, a product 1.19 in moderate yield was then confirmed not to be the desired product by spectroscopic tools. Based on NMR spectral data (Figure 25, 26), this undesired product was suggested as 1.19 in Scheme 18, a by-product of substitution reaction between 1.17 and LR[57b].



Scheme 18: The proposed mechanism for formation of the by-product 1.19

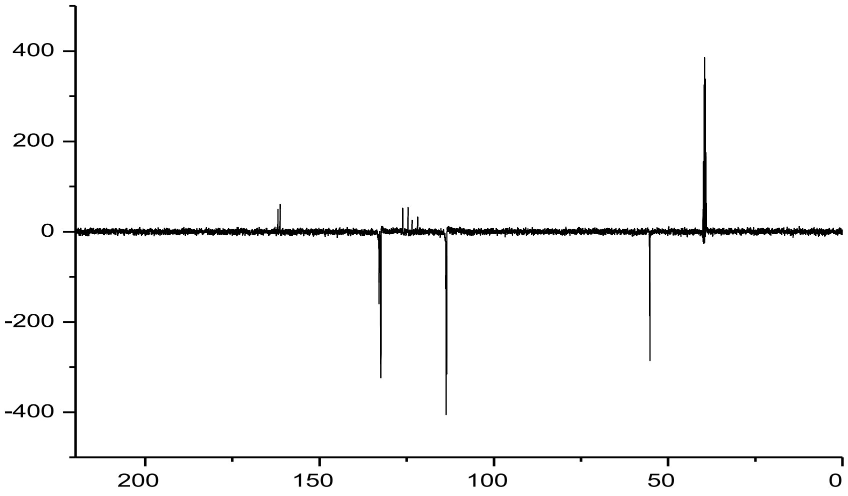


Figure 25: ^{13}C-NMR spectrum of by-product 1.19 (in DMSO-d6)

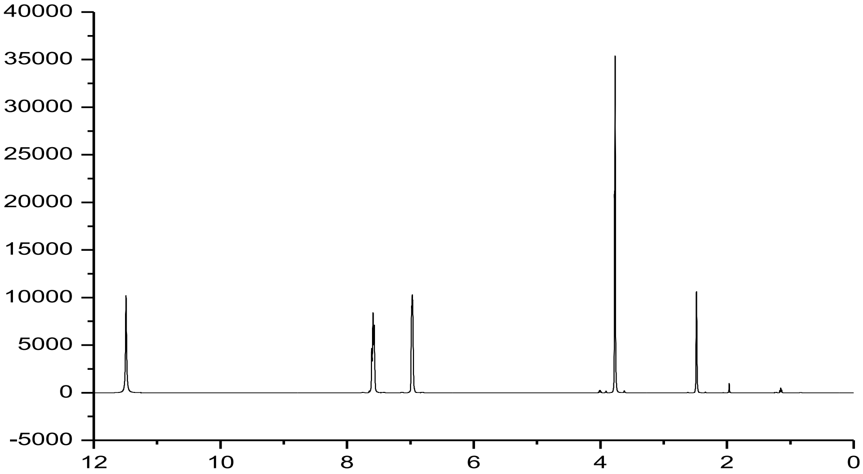


Figure 26: ^{1}H-NMR spectrum of by-product 1.19 (in DMSO-d6)

After failed attempts in using LR as reagent to yield the desired product, phosphorus pentasulfide emerged as an excellent alternative. At that time, the first priority was to check whether the obtained product is the target product. The formation of the target product was confirmed by IR and NMR spectral data. The IR spectra (Figure 27) of the crude product indicated the presence of diminished C=O vibration at 1750 cm^{-1}, increased C=S vibration at 863 cm^{-1}, an S–H vibration at 2613 cm^{-1} and a broad band in the 3500–2500 cm^{-1} range indicating H-bonded OH groups from the residual acid reactant and the unchanged =N–OH. The ^{1}H-NMR spectrum of the recrystallized product verified the presence of the –SH (at 2,82ppm) and the unchanged =N–OH (at 9,60ppm) functional groups (Figure 28).

Figure 27: IR spectrum of target product 1.18

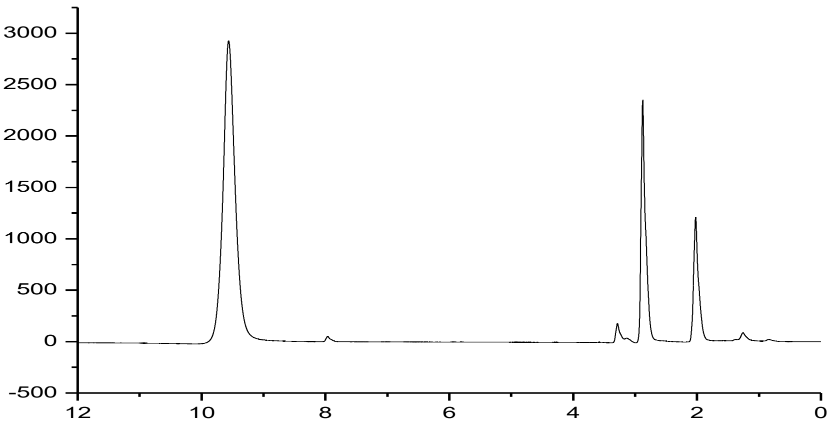


Figure 28: ^{1}H-NMR spectrum of target product 1.18 (in acetone-d6)

The structure of the target product was further confirmed by its MS spectrum. The ESI-MS result indicated that there were two sulfur atoms in the product as the molecular ion was found at M/z = 146. All these observations mean that both oxygens of the carboxylic group were replaced by sulfur atoms, while, as expected, the oxygen in the =N–OH group was not. The product is, therefore, 2-cyano-2-(hydroxyimino)-dithioacetic acid 1.18.

Aftermaths, an optimization of the reaction conditions was carried out. The results showed that the reaction should be carried out in toluene or acetonitrile under refluxed condition with ratio of substrate : P_4S_{10} = 1:0.25 and 1 hour reaction time is sufficient to give the target product in an acceptable yield (39%) after a refinement by silica gel column chromatography with a mixture of n-hexane : ethylacetate = 3:1 as eluent. Actually, no difference in reaction time as well as yield between using toluene and acetonitrile was seen during these reactions.

It is well-known that cyanoximes are characterized by the high acidity that is due to the presence of the cyano group located close to the oximic moiety. Deprotonation of the oximic proton in solution causes formation of stable anions. Hence, the deprotonated cyanoximes form various coordination compounds with different metal ions. A plenty of complexations of cyanoximes with Ag(I)[114], Co(II), Ni(II), Cu(II)[115], Pt(II) and Pd(II)[116] were reported.

If sulfur derivatives of the cyanoximes can be made, one may expect even better coordination ability and a larger variety of coordination modes being the sulfur atom larger and thus being more polarizable. In specific circumstances, sulfur ligands might form more stable complexes than oxygen analogues. Surprisingly, coordination chemistry of the ligands bearing sulfur atom has been much less thoroughly investigated. Very few studies on complexes of thioamide[117], thiooximes[118]; thioacid[119] has been described.

During our experimental work, the coordination ability of the ligand prepared by us was tested against Co(II) ion. (Preparations of complexes were also made with using Cu(II) and Ni(II), as it is described in the Experimental part, but the detailed study of them, due to lack of time, was not carried out. Therefore these results can be considered as scoping experiments without being completed.)

^{1}H-NMR and IR spectra of the Co(II) complex are shown in Figure 29 and 30. Moreover, images of the ligand and Co (II) complex in solid state are also displayed in Figure 31.

In the comparison with those of the ligand, absence of hydroxyl oxime proton in ^{1}H-NMR spectrum at 9-10 ppm in the spectrum of complex might suggest a coordination of oxygen atom attached to C=N group with the metal ion.

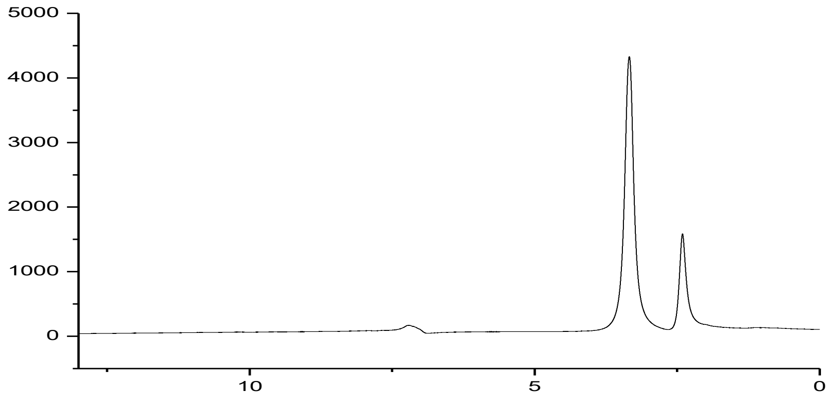


Figure 29: ¹H-NMR spectrum of the Co(II) complex (in DMSO-d6))

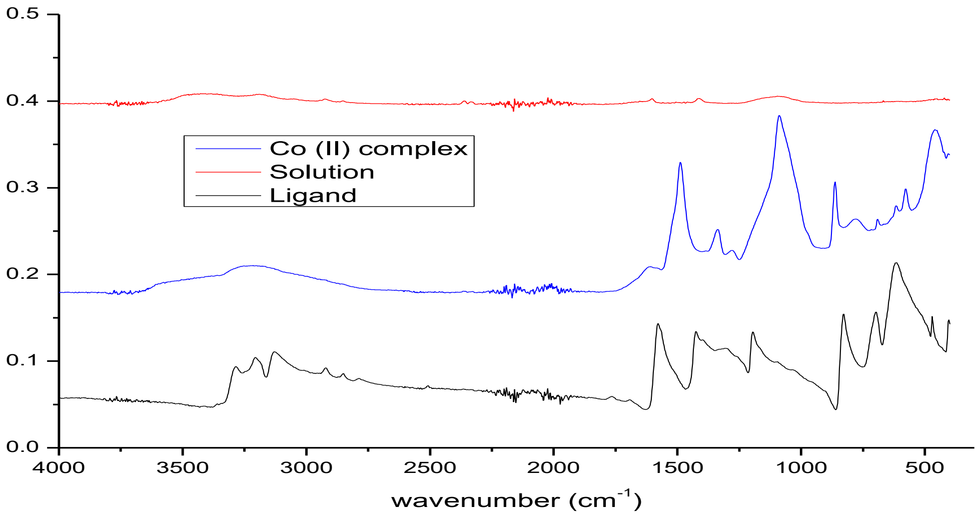
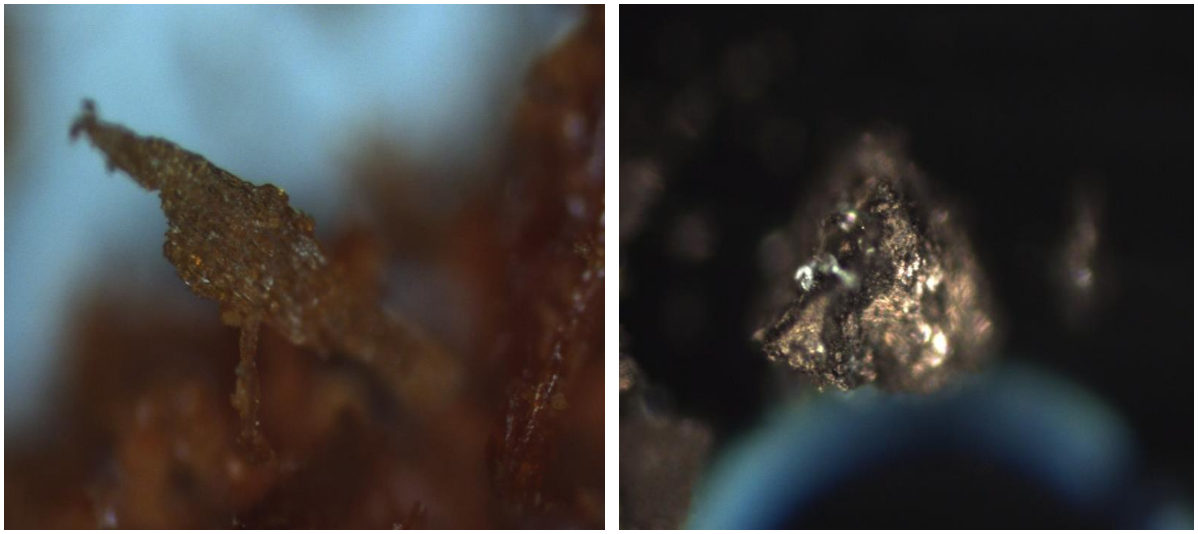


Figure 30: The IR spectrum of the Co(II) complex

Whereas, some shifts of characteristic bands seen in the IR spectrum partly indicated the formation of complex of the metal ion. The initial achieved result was potential, however, in order to interpret the binding mode as well as characterize structure of the complex, further quality experiments are needed, especially obtaining the single crystal for the XRD measurement.



Ligand Co(II) complex

Figure 31: The images of the ligand and Co(II) complex

3.2. The results of the study on hydrogen bonding interaction and aggregation behavior of 2H-imidazol-2-thione derivatives

3.2.1. Synthesis of 2H-imidazol-2-thione derivatives

The compounds studied 1.23 – 1.25 were synthesized *via* the reaction of azole N-oxides and thioketones[120].

3.2.2. Hydrogen bonding interaction and aggregation behavior of compounds 1.23 – 1.25

The IR and the Raman spectra of compounds 1.23 – 1.25 taken in solution and the solid state are displayed in Figures 32 and 33. The assignation of the bands indicated in the spectra is to be found in Tables 1-4.

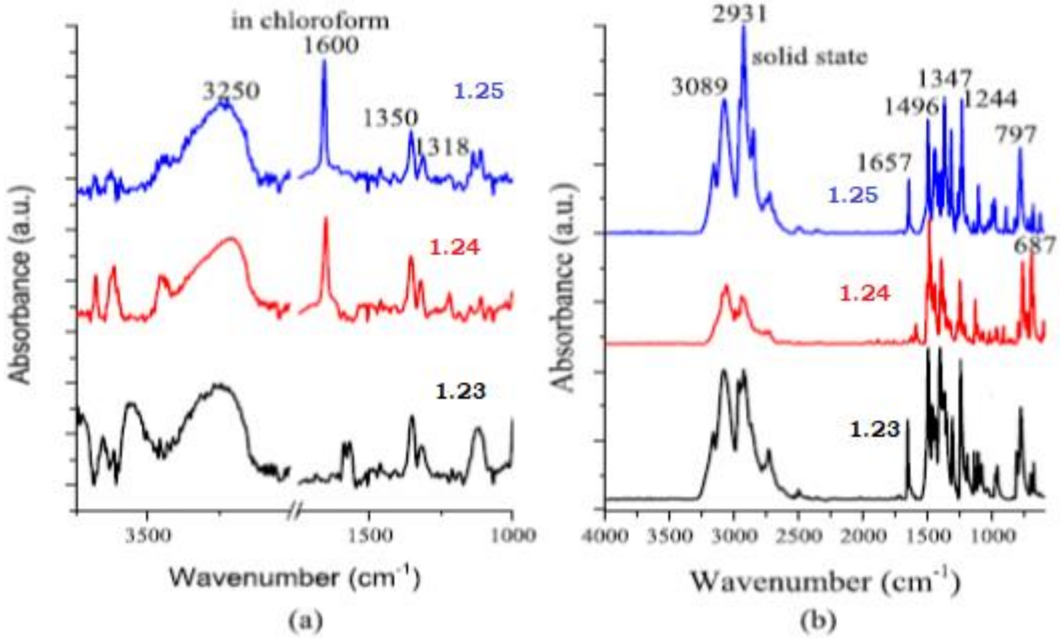


Figure 32: The FT-IR spectra of our 2H-imidazole-2-thiones dissolved in chloroform (a) and in the solid state (b). The numbers on the traces correspond to the numbers of the compounds.

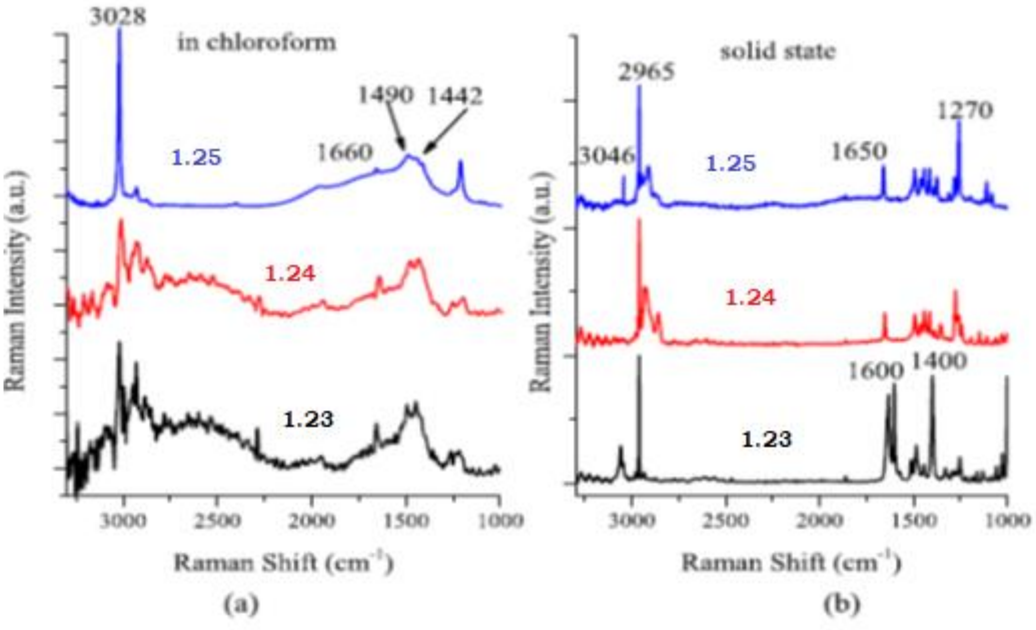


Figure 33: The FT-Raman spectra of our 2H-imidazole-2-thiones dissolved in chloroform (a) and in the solid state (b). The numbers on the traces correspond to the numbers of the compounds.

Table 1.

Vibration assignation in the IR spectra recorded in the solid phase

Vibrations	Compounds			Vibration mode	Ref.
	1.23	**1.24**	**1.25**		
3089	+	+	+	νCH (sp^2)	[121]
2931	+	+	+	νCH (sp^3)	[122]
1657	+	–	+	δN–C	[123]
1496	+	+	+	δN–H/νC=N	[124]
1347	+	+	+	νC–N	[125]
1244	+	+	+	δCH_2–S	[126]
797	+	+	+	δring(imidazole) vibration	[127]
687	–	+	–	δring vibration	[128]

Table 2.

Vibration assignation in the IR spectra recorded in solution

Vibrations	Compounds			Vibration mode	Ref.
	1.23	**1.24**	**1.25**		
~3250	+	+	+	νCH (sp^2) + νCH (sp^3)	[121-122]
~1600	+	+	+	δN–C	[123]
1350	+	+	+	νC–N	[125]
1318	+	+	+	δCH_2–S	[126]

Table 3.

Raman shift assignation in the Raman spectra recorded in the solid phase

Vibrations	Compounds			Vibration mode	Ref.
	1.23	**1.24**	**1.25**		
3046	+	+	+	νCH (sp^2)	[121]
2965	+	+	+	νCH (sp^3)	[122]
1650	+	+	+	νC=C + νC=N	[129]
1600	+	–	–	νC=C + δN–H	[129]
1400	+	–	–	νC–N	[130]
1270	+	+	+	νC=S	[131]

Table 4.

Raman shift assignation in the Raman spectra recorded in solution

Vibrations	Compounds			Vibration mode	Ref.
	1.23	**1.24**	**1.25**		
3035	+	+	+	νCH (sp^2)	[121]
1660	+	+	+	νC=C + νC=N	[129]
1490	+	+	+	νC–N	[130]
1442	+	+	+	νC=S	[131]

It is to be seen that the solid-state spectra are of significantly better quality than those recorded in solution, and they differ from each other. In the spectra recorded in solution, the broad features in the 3500-2500 cm^{-1} region indicate N-H…S hydrogen bonding interaction, in accordance with the received knowledge[120] that the tautomeric equilibrium depicted in Figure 36 is shifted towards the thioketone tautomeric form in solution.

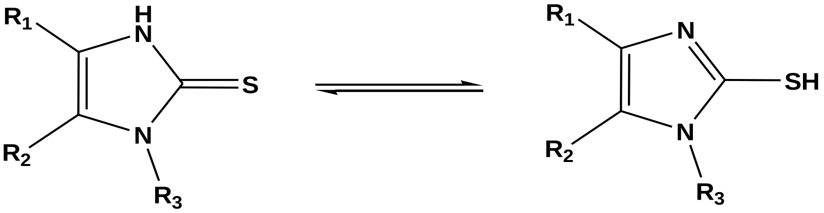


Figure 34: Tautomeric equilibrium between the thioketo and the thiol forms

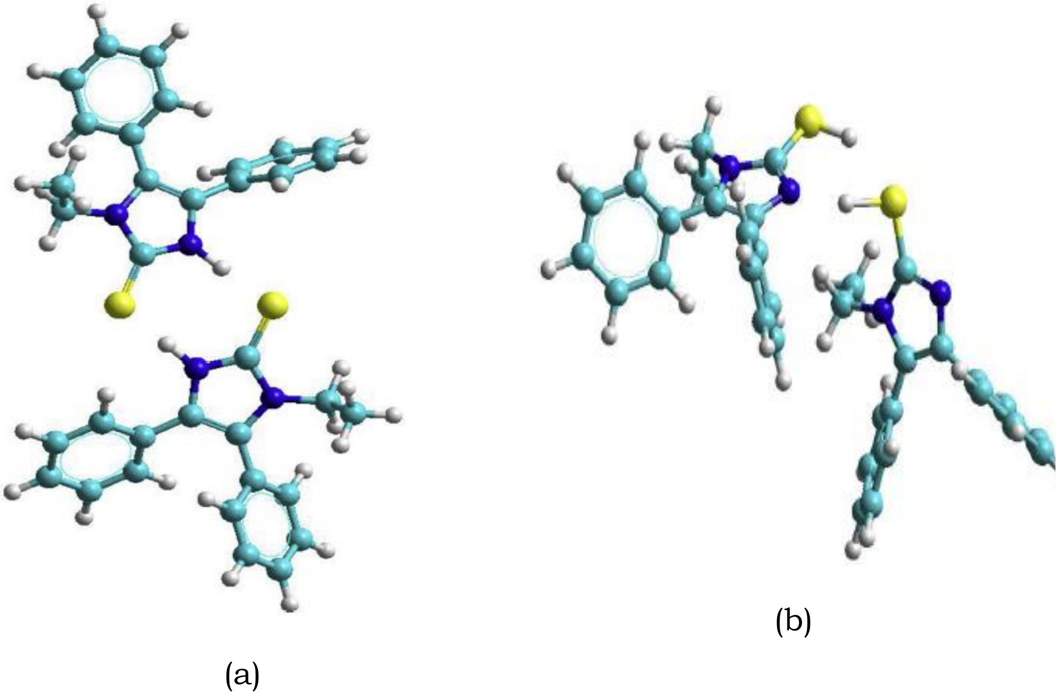


Figure 35: (a) an example of short-range ordering N-H…S in compound 1.25 (b) an example of long-range ordering N-H…S in compound 1.24

This is verified by the appearance of the C=S vibration near 1350cm^{-1} in the IR spectra. This broad non-structured feature disappeared from the solid-state spectra. However, the Raman spectra of the crystalline material of compounds 1.24 and 1.25 display an intense band at around 1240 cm^{-1} indicating CH_2 – S stretching vibration, and the Raman shifts (~3030 cm^{-1}) of the S-H bond for the solution-phase samples moved to lower frequencies in the solid-state recordings (~2960 cm^{-1}). These features indicate that the tautomeric equilibrium is shifted towards the thioenol form in the solid state, and S-H…N hydrogen bond may keep the crystal together.

3.2.3. Short- and long-range ordering motifs through calculations

The assumed short as well as long-range interactions (Figure 35a and 35b, respectively) were modelled and these interactions were found feasible. The distances between the heavy atoms were 289 pm and 234 pm, respectively, both well within the sum of their van der Waals radii (350 pm) compiled by Bondi[132]. Since it is a generally accepted strong criterium of considering an interaction to be hydrogen bond[133], therefore, the spectroscopic and the molecular results together make it quite possible that for short-range ordering found in solution and for long-range ordering in the solid state N-H…S and S-H…N close contacts are mainly responsible, respectively.

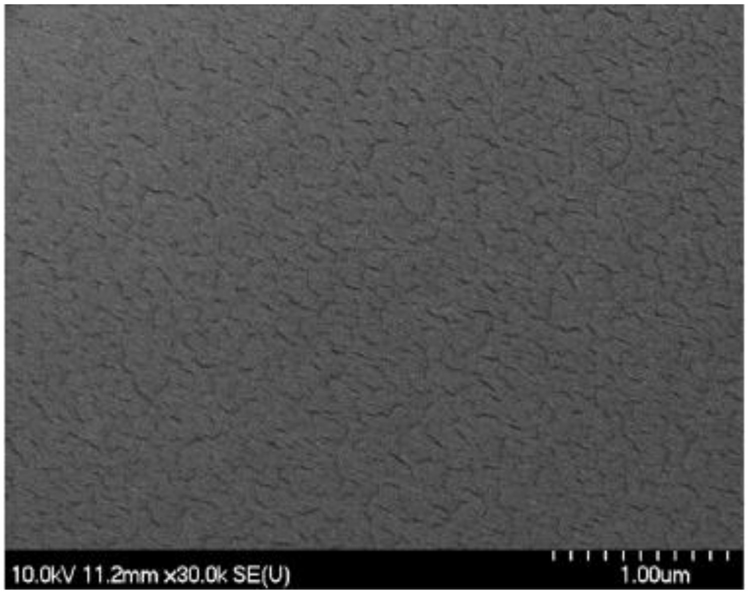


Figure 36: The SEM image of the polycrystalline gold surface

3.2.4. Structure forming properties over polycrystalline gold surface

On using the gold-coating facility of the SEM-EDX instrument the quartz slide could be continuously covered by gold; this way, polycrystalline gold surface could be obtained (Figure 36).

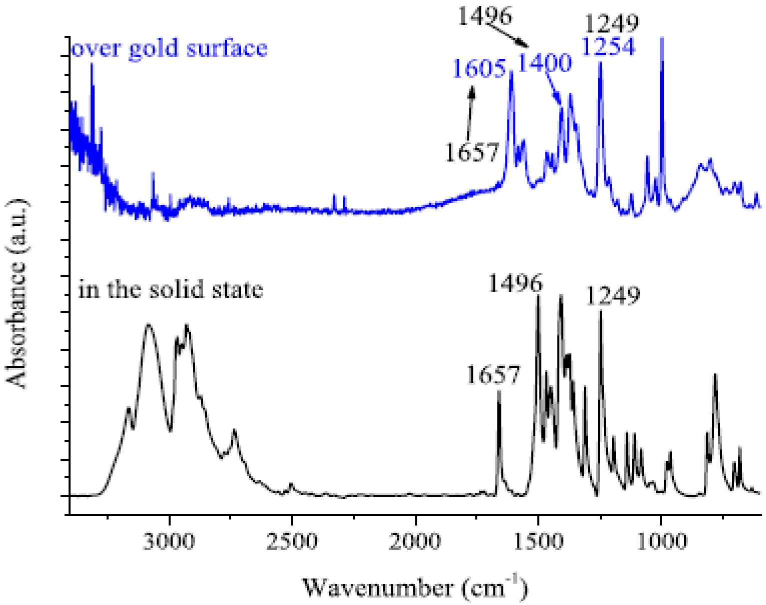
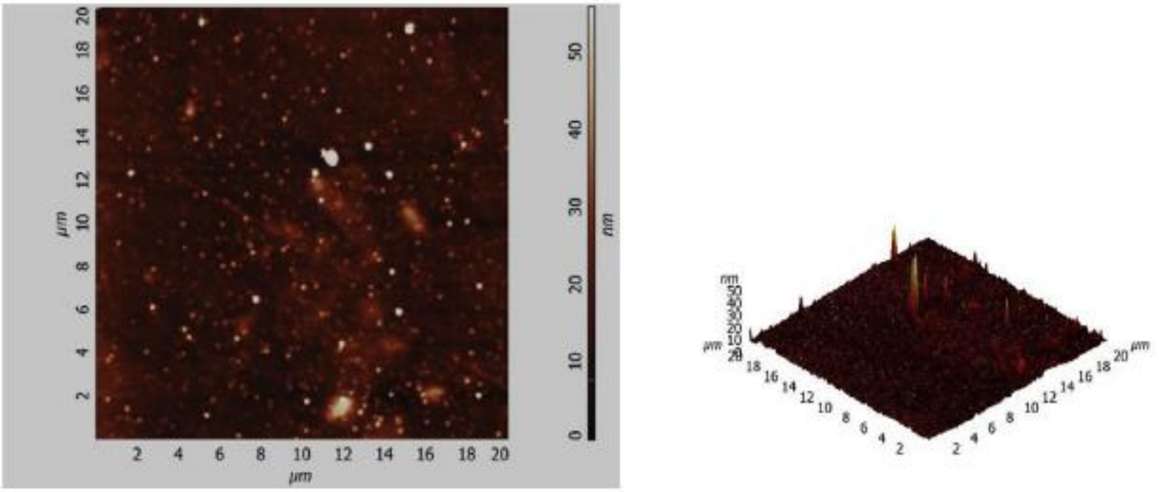


Figure 37: The FT-IR spectra of compound 1.23 adsorbed over the polycrystalline gold surface and in the crystalline form

Compound 1,3-dihydro-1-ethyl-4,5-diphenyl-2H-imidazole-2-thione 1.23 could only adsorb over the gold surface indicated by the IR spectrum obtained by infrared microscopy (Figure 37). Although the major use of the IR spectrum to prove that organic material can be found over the surface indeed, it is also seen that the intermolecular interactions at least partly differ from those in the solid state.

The AFM image (Figure 38) indicates the formation of aggregates perpendicular to the surface. Most of the pillars are small indicating limited growth of the initially adsorbed molecules; however, in a few cases lengthy (maximum length is ~50 nm) pillar-like aggregates are also seen.

The aurophilicity of sulfur is known well, thus, it is safe to state that the molecules in the first layer, the sulfur atoms are bonded to the gold surface with relatively strong coordination bonds. In the pillars, the long-range ordering may be the same as in the crystalline state, *i.e.* the molecules are probably held together with relatively weak S-H…N hydrogen bonds.



(a) (b)

Figure 38: AFM image compound 1.23 adsorbed over polycrystalline gold (a) top view, (b) side view.

3.3. Selective oxidation of L-cysteinate anions intercalated in CaAl-layered double hydroxide (CaAl-LDH)

3.3.1. Preparation of CaAl-LDH, L-cysteinate intercalated CaAl-LDH and their structural characterization

After preparing CaAl-LDH in the well-known co-precipitation synthesis route, through combining previously published intercalation methods[134], cysteinate anions were immobilized in the interlayer gallery of hydrocalumite (CaAl-LDH). The success of this operation was verified by XRD measurements (Figure 39/A). Both the as-prepared and intercalated structures exhibited diffraction patterns corresponding to lamellar monoclinic structure in $P2_1$ space group being analogous to that of a nitrate-containing CaAl-LDH (JCPDS database: PDF #89-6723). Furthermore, the (00l) and the other diffraction lines of intercalated hydrocalumite shifted to smaller angles compared to those of the as-prepared one indicating the expansion of basal spacing from 0.757 nm to 0.864 nm associated with altering the anions in the interlayer space. The extent of the expansion corresponds to single-layer insertion of the cysteinate anions, which is in good agreement with previous reports[134].

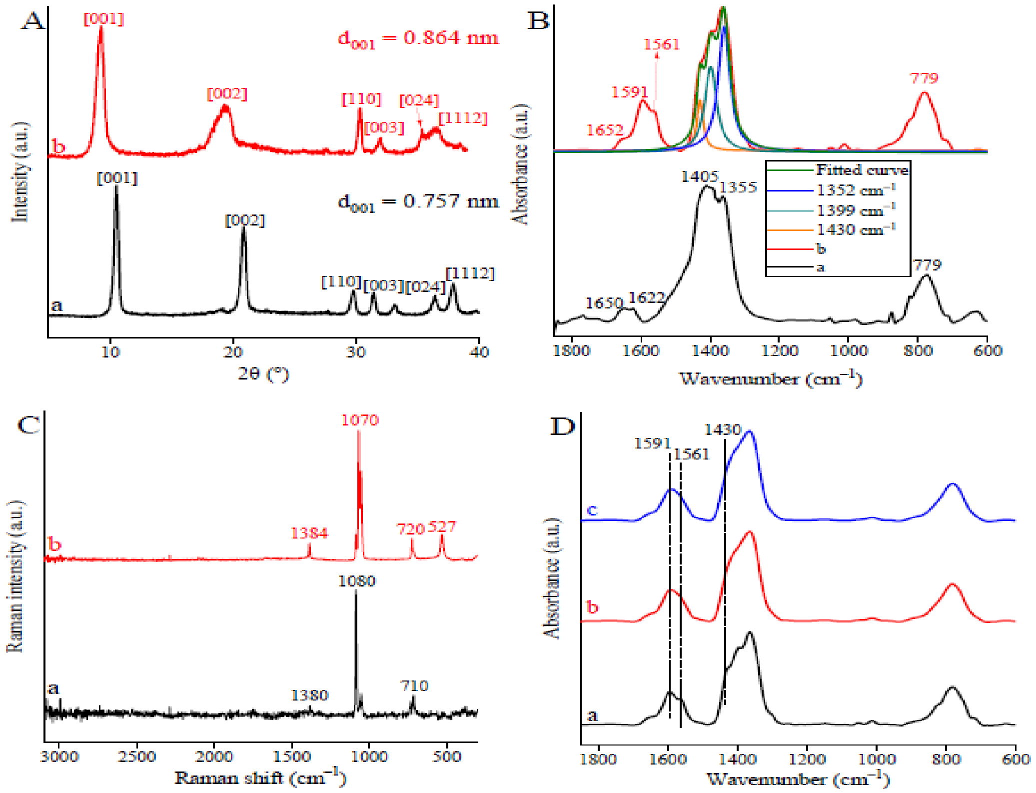


Figure 39. XRD patterns (A), IR (B) and Raman (C) spectra of CaAl–NO_3^-–LDH (a) and CaAl–cysteinate–LDH (b). IR spectra (D) of CaAl–cysteinate–LDH (0.1 g) using 6.0×10^{-3} mol (a), 1.2×10^{-2} mol (b) or 1.8×10^{-2} mol (c) intercalant

The as-prepared LDH and the intercalated composite were studied by IR as well as Raman spectroscopies (Figure 39/B, C).

The band due to the ν3 (asymmetric stretching) mode of nitrate anions at 1355 cm^{-1} could be seen in IR spectrum of the as-prepared LDH along with ν3 vibration band of surface-adsorbed carbonate (1405 cm^{-1}) and β(OH) vibration band (1650 cm^{-1}) as well as the characteristic vibration band identified as the stretching vibration mode of Al–O bond (779 cm^{-1})[135]. The IR spectrum of the composite material exhibited bands characteristic of an LDH with intercalated carboxylate anions[136]. Accordingly, fingerprint-like vibration modes of the carboxylate group appeared, the asymmetric vibrations bands at ~1600 and 1569 cm^{-1} and the symmetric one at ~1433 cm^{-1}. In accordance with literature data, doubling of νas(COO$^-$) vibration suggested that cysteinate anions were linked to the layers as syn-anti carboxylate bridges with bidentate carboxylate coordination[137]. During intercalation, partial anion exchange only occurred indicated by the “survival” of peaks attributed to carbonate and nitrate ions. In view of the absence of the significant changes in the IR spectra, the smallest amount of cysteinate (6.0×10^{-3} mol to 0.1 g of LDH) was adequate for achieving the maximum extent of ion exchange. (Figure 39/D).

On one hand, Raman spectra also indicated partial intercalation, as the characteristic Raman bands of nitrate/carbonate ions (~1380, 1070-1080, 710-720 cm^{-1}), were not eliminated. On the other hand, the appearance of a S–C stretching band (527 cm^{-1}) evidenced the presence cysteinate anions[138]. Additionally, the lack of the intense stretching vibration of sulfhydryl group (~2500 cm^{-1}) directly demonstrated that thiol groups were deprotonated during the intercalation facilitating the charge neutrality of the composite materials.

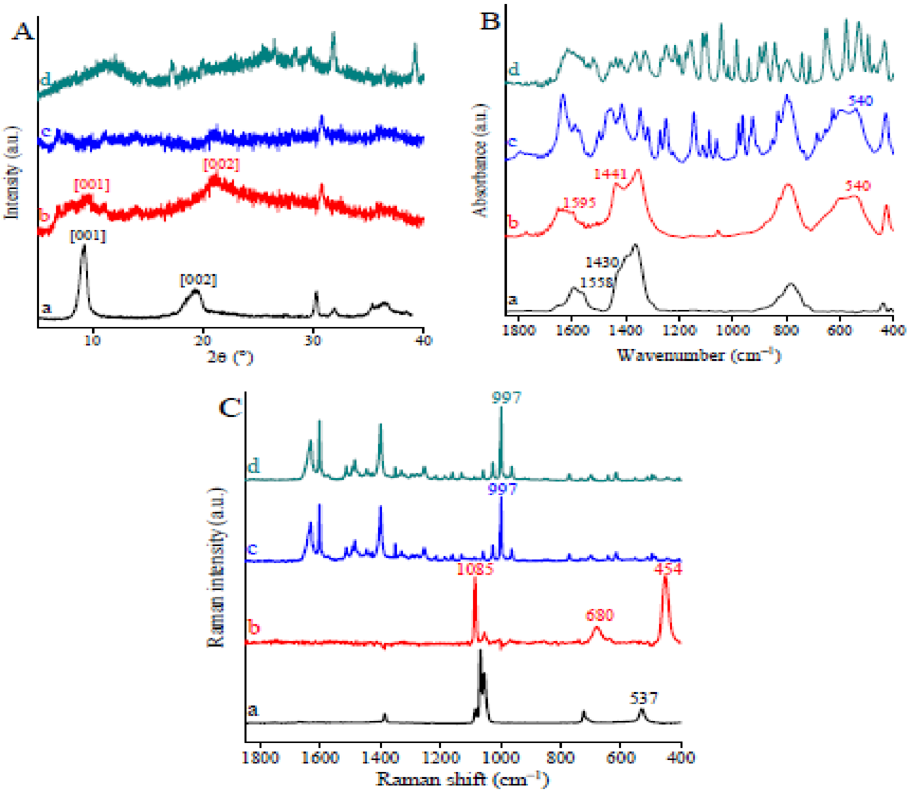
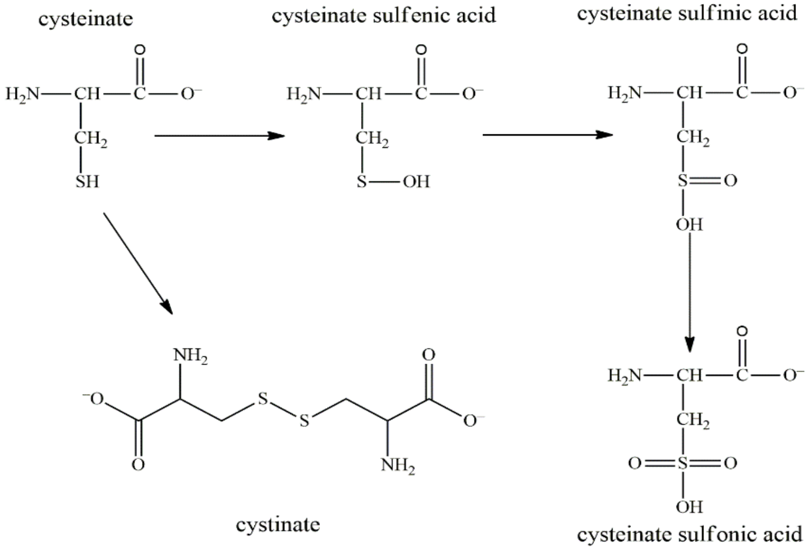


Figure 40: XRD patterns (A), IR (B) and Raman (C) spectra of CaAl–cysteinate–LDH (a) and CaAl–cysteinate–LDH (0.1 g) oxidized by 0.4 M of peracetic acid (b), bromine (c) or H_2O_2 (d) suspended in water (100 cm^3) at 298 K. The reaction time was 60 min.

3.3.2. *Oxidation process of L-cysteinate ion intercalated among CaAl-LDHs: Optimization of catalysts and solvents and structural elucidation*

In order to efficiently select a suitable reactant for the interlayer oxidation of the cysteinate ions for more detailed studies, scouting experiments were performed using peracetic acid, bromine or H_2O_2 at 298 K using water as solvent.

The possible reaction pathways are depicted in Scheme 19.



Scheme 19: The possible pathways of cysteinate oxidation

The XRD patterns (Figure 40/A) attested that both bromine and hydrogen peroxide damaged the layered structure, which resulted in uncontrollable product distribution. Many products were formed, which was indicated by the IR and Raman spectra (Figure 40/B, C) having so many bands that selecting the main products was impossible. The only exception was the case of peracetic acid, which oxidized cysteinate to cystinate selectively without losing the long-range order of the LDH. The formation of cystinate was best highlighted by the intense sharp peak at 454 cm^{-1} and the less intense at 680 cm^{-1}, assigned to the stretching vibration modes of C–S and S–S bonds, respectively[138]. Additionally, new bands at 1441 and 1595 cm^{-1} could be detected in the IR spectrum revealing changes in the local environment of the carboxylate groups[139].

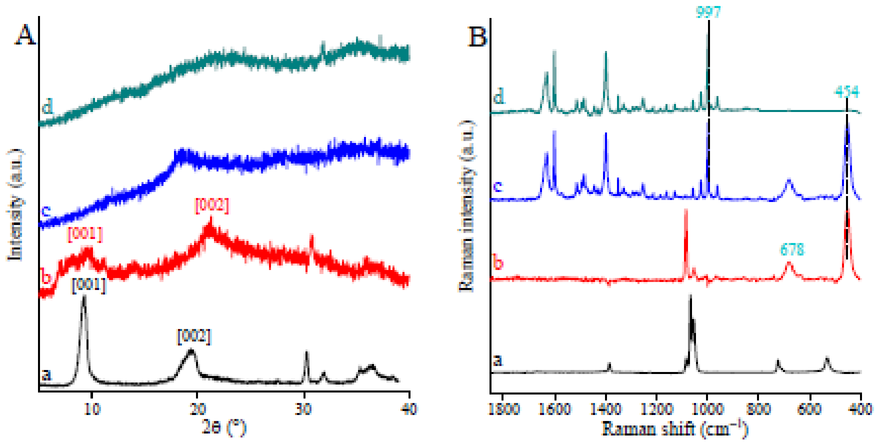


Figure 41: XRD patterns (A) and Raman (B) spectra of CaAl–cysteinate–LDH (a) and CaAl–cysteinate–LDH oxidized by peracetic acid; reaction conditions: the oxidizing agent in 0.4 M (b), 0.55 M (c) or 0.70 M (d) concentration was applied to 0.1 g of composite suspended in 100 cm^3 of water at 298 K. The reaction time was 60 min.

Upon increasing the amount of peracetic acid, the layered structure disappeared indicating the collapse of hydrocalumite structure (Figure 41/A) leading to uncontrollable product distribution once again (Figure 41/B). Clearly, the presence of the layered structure was crucial for the selective oxidation to occur[140].

On replacing water with organic solvents (acetone or methanol), notable changes in the product distribution were observed. In methanol, the oxidation resulted in significantly lower extent in the degradation of LDH structure than it was experienced in aqueous medium (Figure 42/A). On detecting relatively high shift in the characteristic (00*l*) reflections, significant decrease in the interlayer space occurred, quite the opposite of the expectations. This finding called our attention to another possible transformation pathway. The IR spectrum of the composite exhibited some strong absorptions over the whole measurement range with bands differing from those of cystinate (Figure 42/B). Intense bands in the range of 1600–1400 cm^{-1} were assigned to antisymmetric and symmetric absorption bands of cysteinate derivatives, while less intense bands centered at 1073 cm^{-1} could be assigned to the in-plane carboxylic acid COH bending mode of cysteine sulfonic acid, consistent with previous assignments[141]. Furthermore, the band position and intensity of the stretching vibration bands of C–S band were changed substantially indicating the formation of one or more cysteine oxo acid forms. On the basis of the observations described above, the formation of oxo acid anion mixture is suggested, the main product being cysteine sulfonate along with cysteine sulfenate or, as it was intuitively rather expected, cysteine sulfinate. Too much of our surprise, the Raman spectra of the composite suggested the formation of cysteine sulfenate without any doubt (Figure 42/C). The absorption band at 958 cm^{-1}, which increased in intensity in parallel with the increase in the concentration of the oxidant, was associated with the stretching vibration mode of deprotonated S–O(H) functional group of cysteine sulfenic acid. Furthermore, there was no evidence that $S–O_2^-$ functional group of cysteine sulfinate was produced, this group should have had two intense broad bands in the range of 1250–1000 cm^{-1}[142]. By performing the oxidation in non-aqueous solvents without the LDH or dosing it as additive to the solution, it was not possible to produce any of the desired products selectively (Figure 42/D). In all cases, both cysteinate and cystinate as well as oxo acid forms were produced. Accordingly, the presence of the layered material providing confined space as molecular reactor with fixed cysteinate ion in it was a contribution of utmost significance in facilitating the selective oxidation.

Finally, by repeating the screening in acetone, completely different product selectivity was obtained. The ordered structure of LDH was not lost during oxidation, irrespective to the concentration of peracetic acid verified by the XRD patterns (Figure 43/A). Moreover, a new LDH phase was developed without eliminating the original one, *i.e.* staging occurred. The interlayer gallery for the new phase was enlarged (1.154 nm) compared to the cysteinate-containing counterpart (0.864 nm). Additionally, the ratio of new LDH phase to the original one grew in line with the increasing amount of added peracetic acid. (It is fair to mention though that a relatively strong and sharp reflection related to unidentified impurity arose at about 25° of 2θ values, the intensity of which increased with increasing concentration of peracetic acid. Since the other reflections are assigned to LDH structures, it is reasonable to assume that certain amount of the product formed was released from the interlayer space, and it might be adsorbed on the outer surface of the LDH resulting in the unidentified reflection).

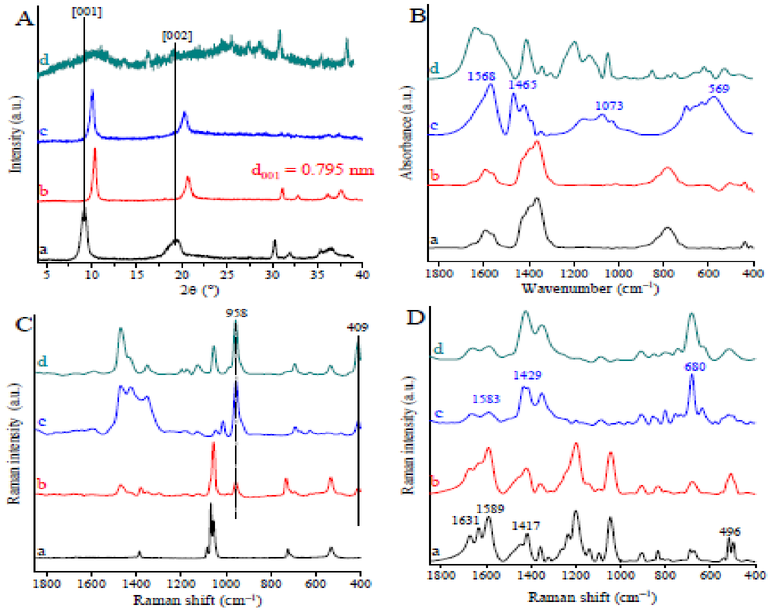


Figure 42: XRD patterns (A), IR (B) and Raman spectra (C) of CaAl–cysteinate–LDH (a) and CaAl–cysteinate–LDH (0.1 g) oxidized by peracetic acid using 0.4 M (b), 0.55 M (c) and 0.70 M (d) peracetic acid in methanol (100 cm^3). Raman spectra (D) of cysteine (1 g) oxidized by peracetic acid (0.4 M) in methanol (100 cm^3) with (a) or without (b) LDH (0.1 g) as additive as well as in acetone (100 cm^3) with (c) or without (d) LDH (0.1 g) as additive at 298 K. The reaction time was 60 min.

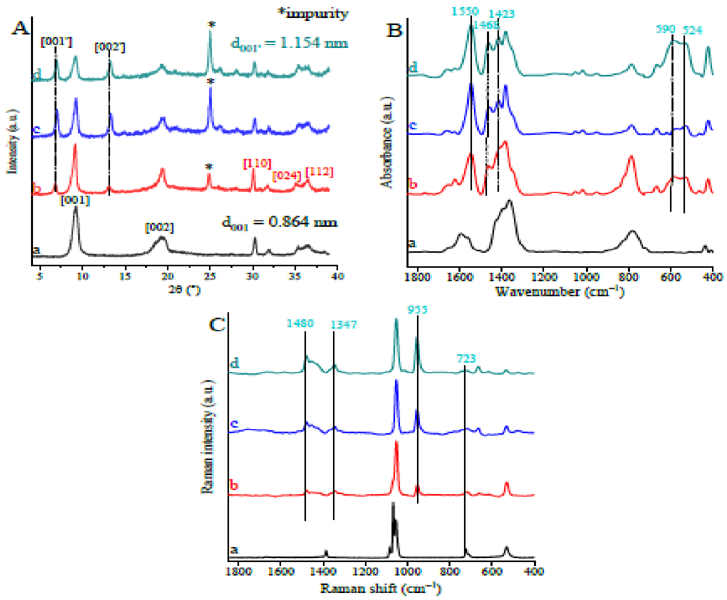


Figure 43: XRD patterns (A), IR (B) and Raman spectra (C) of CaAl–cysteinate–LDH (a) and CaAl–cysteinate–LDH (0,1 g) oxidized by peracetic acid upon using 0.4 M (b), 0.55 M (c) and 0.65 M (d) peracetic acid in acetone (100 cm^3) at 298 K.

A series of absorption bands in IR spectra appeared at 1550, 1468, 1423 and 590 as well as 524 cm^{-1}, they could be clearly attributed to the characteristic vibration modes of cysteine sulfenic acid[141a]. Distinct strong absorbances in the high-energy region (1620–1420 cm^{-1}) agreed well with the antisymmetric and symmetric vibration modes of carboxylate group overlapped with vibrations of sulfenyl group, while less intense bands at about 550 cm^{-1} could be related to the deformation mode vibrations of C–S bond. No evidence for the formation of cysteine sulfinate was found. Including strong peaks at 955, 1347 and 1480 cm^{-1} identified as stretching vibration mode of deprotonated S–O(H) and carboxylate functional groups, Raman spectra of the composites provided with clear, fingerprint-like evidence for the exclusive production of cysteine sulfenic acid[142].

In our view, the changes observed in the oxidation products on altering the solvent is due to the changes of hydration/dehydration state of the interlayer gallery. Water is an integral part of an LDH, attached to the wall of the layers and to each other by secondary, probably mainly hydrogen bonds. On changing the solvent from water to methanol or acetone, at least partial replacement of the interlayer water molecules took place, thus, the immediate environment for the reaction was modified significantly, while all the other parameters (the LDH, reaction temperature, reaction time, the oxidant) remained unaltered.

CHAPTER 4: CONCLUDING REMARKS

The history of the chemistry of sulfur-containing organic compounds was reportedly marked in 1920s. Since then, studies on these compounds have been continuously developed due to their unique properties as well as plentiful of applications found in broad range of fields. Currently, the chemistry of organosulfur compounds is still an important research area which draws the great deal of interests by chemists.

In the first work involved organosulfur compounds, we successfully synthesized 2-cyano-2-(hydroxyimino)dithioacetic acid, a thio-cyanoxime, *via* a three-step pathway with a total yield 27% from cyanoacetic acid methylester as starting material. After a failed attempt in the last step, thionation, using LR as the thionation agent that produced the unwanted product, we discovered that P_4S_{10} served as the excellent reagent to achieve the target product.

We determined the H-bonding interactions of three imidazole-2-thione derivatives that are responsible for short-range and long-range ordering in solution, solid state and over polycrystalline gold surface by using the IR, Raman spectroscopies and the molecular modelling method, in the next stage of work. Accordingly, it was identified that the N-H…S and S-H…N hydrogen bonds were responsible for the short-range ordering in the solution and long-range ordering in the solid state and over polycrystalline gold surface, respectively. Moreover, the aggregation behavior of a derivative, 1,3-dihydro-1-ethyl-4,5-diphenyl-2*H*-imidazole-2-thione, over polycrystalline gold surface was also explored in which the S-Au strong coordination bonds were responsible for the formation of the first layer, then, sparingly pillars were grown where the major interacting force is the S-H…N hydrogen bonding being responsible for long range ordering.

Our last work focused on investigation of selective oxidation of L-cysteinate anions by anchoring them among interlayers of CaAl-LDHs. We examined various oxidizing agents such as peracetic acid, bromine or H_2O_2 at 298 K in water as solvent. The results showed that only peracetic acid oxidized cysteinate to cystinate selectively without losing the long-range order of the LDH while both bromine and hydrogen peroxide damaged the layered structure. Subsequently, the influence of solvent on the product selectivity was also evaluated by replacing water with organic solvents (methanol and acetone). We discovered that the oxidation in methanol displayed significantly lower extent in the degradation of LDH structure and notable decrease in the interlayer space. However, using methanol as solvent led to the formation of the formation of oxo acid anion mixture is suggested, the main product being double deprotonated cysteine sulfonic acid anions along with double deprotonated cysteine sulfenic acid and sulfinic acid anions, unexpectedly. In case of acetone as solvent, it was observed that the ordered structure of LDH was not lost during oxidation and a new LDH phase was developed without eliminating the original one. Furthermore, clear, fingerprint-like evidence for the exclusive production of double deprotonated cysteine sulfenic acid anions was confirmed by the IR and Raman spectral data.

Thanks to the above represented findings, we expect to make a contribution to the chemistry of sulfur-containing organic compounds.

CHAPTER 5: EXPERIMENTAL SECTION

5.1. Study on synthesis of 2-cyano-2-(hydroxyimino)dithioacetic acid and its complexes with metal ions

5.1.1. Materials

The reactants were either the products of Aldrich Chemical Co. (P_4S_{10}, cyanoacetic acid methylester, $NaNO_2$, KOH, NaOH) or VWR (HCl, H_3PO_4, glacial acetic acid). The solvents (toluene, methanol, ethanol, hexane, ethyl acetate and DMSO-d6) were purchased from VWR. They had over 98 % purity and were used without further purification. The thionation reactions were performed in Ar atmosphere. The reactions were followed by thin-layer chromatography (TLC, silica gel, Aldrich; eluent: n-hexane:ethyl acetate =1:1). The products were purified with column chromatography with the eluent used in TLC in solution or recrystallization when solid. TLC was performed on a plastic sheet precoated with silica gel 60 F_{254}. Silica gel (pore size 60 Å, 60–100 mesh particle size, Sigma-Aldrich) was used for column chromatography.

5.1.2. Methods for structural characterization

Infrared (IR) measurements were carried out on a Bio-Rad FTS-40 FT-IR spectrometer, working in the reflection mode, using 1 w/w% of the sample in KBr (spectroscopic grade, Aldrich Chem. Co.). 256 scans were collected for the spectra at 4-cm^{-1} resolution.

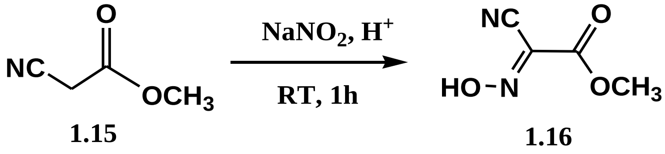
NMR measurements were performed in 0.5 mL DMSO-d6 or acetone-d6 (99.96 atom% D, from Sigma-Aldrich Chemical Co.) using Bruker Avance 500, 500-MHz NMR spectrometer with 5-mm glass NMR tubes from Wilmad.

Electrospray ionization mass spectrometric (ESI-MS) measurements were performed using a Micromass Q-TOF Premier (Waters MS Technologies) mass spectrometer equipped with electrospray ion source. The sample was introduced into the MS by applying direct injection method: the built-in syringe pump of the instrument with a 25 mL Hamilton syringe was used. The electrospray needle was adjusted to 3 kV and N_2 was used as nebulizer gas. The computer program used to simulate the theoretical isotope distributions is included in the Masslynx software package.

5.1.3. Synthetic procedures

5.1.3.1. Pathway for synthesis of 2-cyano-2-(hydroxyimino)dithioacetic acid 1.18 as ligand for coordination chemistry

Preparation of 2-cyano-2-(hydroxyimino)acetic acid methylester 1.16

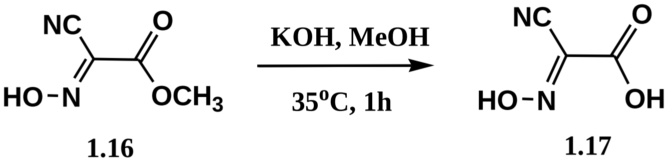


Scheme 20: Reaction for preparation of 1.16 from 1.15

Phosphoric acid (4 mL) was added drop-wise to a 0°C suspension of methyl cyanoacetate (10 g) and sodium nitrite (6 g) in H_2O (80 mL). The reaction was allowed to warm up to 40°C in 1h. The mixture was then cooled and *cc.* HCl (8 mL) was added gradually. The solution was extracted with ethyl acetate, and the organic phase was collected, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the product, which was purified by recrystallization from toluene. White crystals were collected with a yield of 91%.

Preparation of 2-cyano-2-(hydroxyimino)acetic acid 1.17

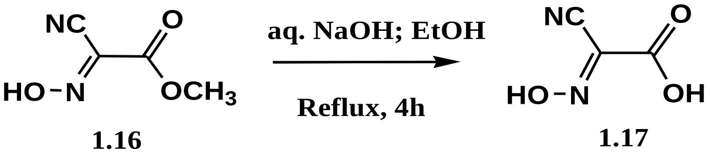
- ✓ *Method 1:*



Scheme 21: The hydrolysis of 1.16 by method 1

A mixture of 3 g of 2-cyano-2-(hydroxyimino)acetic acid methylester 1.16 and 12 mL of methanol was stirred and maintained at 40°C in a 50-mL two neck round-bottom flask; 2.65 g of KOH was added and the contents were stirred for 2 h and then were concentrated *in vacuo*. Twenty-five millilitres of water was added. The mixture was acidified to pH = 2 with 6M HCl extracted with ethyl acetate. After drying over Na_2SO_4, the solvent was evaporated and the crude 2-cyano-2-(hydroxyimino)acetic acid 1.17 was obtained. It was purified by column chromatography (eluent: n-hexane: ethylacetate = 1:1). White crystals were obtained with a yield of 76%.

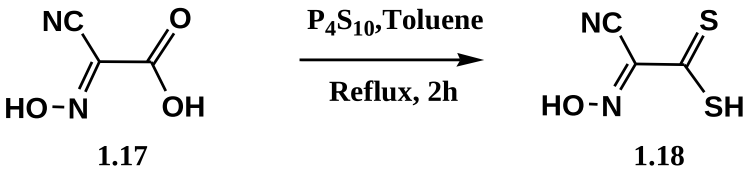
- ✓ *Method 2:*



Scheme 22: The hydrolysis of 1.16 by method 2

A mixture of 4.3 g of 2-cyano-2-(hydroxyimino)acetic acid methylester 1.16 in 40 mL of ethanol was added to a solution of 8g of NaOH in 80mL of H_2O. The mixture was refluxed for 4h, then cooled to room temperature and diluted with 40 mL of THF and acidified to pH = 2 with 6M HCl. The mixture was then extracted with ethyl acetate. The organic fraction was separated, dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the crude of 2-cyano-2-(hydroxyimino)acetic acid 1.17, which was refined the same way as in *method 1*. White crystals were also obtained with a yield of 74%.

Synthesis of 2-cyano-2-(hydroxyimino)dithioacetic acid 1.18



Scheme 23: The thionation of 1.17 to produce the product 1.18

A mixture of 0.34 g of 2-cyano-2-(hydroxyimino)acetic acid 1.17 and 0.4 g of phosphorus pentasulfide in 20 mL of anhydrous toluene was refluxed for 2h. After cooling to room temperature, the reaction mixture was placed on silica gel column and the toluene was eluted with n-hexane. The product 2-cyano-2-(hydroxyimino)dithioacetic acid 1.18 formed was then eluted with n-hexane:ethylacetate = 2:1. A crystalline orange-coloured product with a yield of 39% was achieved.

5.1.3.2. Preparation of complexes of the ligand 1.18 with metal ions

$$\underset{\textbf{1.18}}{\textbf{LH}} + \textbf{MCl}_2\textbf{.xH}_2\textbf{O} \xrightarrow[\substack{\text{1. Reflux in 5h} \\ \text{2. RT in 15h}}]{\text{EtOH 96\%}} \underset{\textbf{1.20-1.22}}{\textbf{ML}_2} + \textbf{2HCl} + \textbf{xH}_2\textbf{O}$$

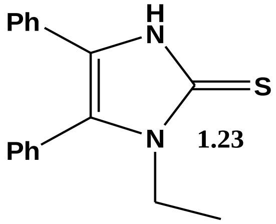
(M = Co, Ni, Cu)

Scheme 24: General reaction for synthesis of complexes 1.20-1.22

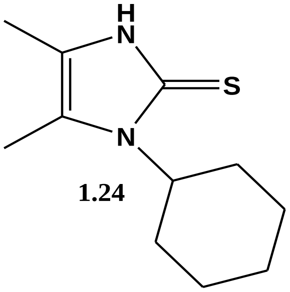
1 mmol of ligand (1.18; LH) was dissolved in 20-25 ml ethanol 96% and stirred at 50-70^{0}C. Solutions of 0.5 mmol of metal salts ($MCl_2.xH_2O$; M = Co, Ni, Cu) in 15ml ethanol were slowly added. The mixtures were then refluxed in 5h and stirred further (overnight) at RT. The obtained precipitates were filtered, washed with ethanol and diethylether and dried in desiccator.

5.2. *Study of the secondary interactions and aggregation behavior of imidazole-2-thione derivatives*

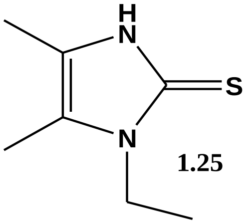
5.2.1. Materials


1.23

1,3-dihydro-1-ethyl-4,5-diphenyl-2H-imidazol-2-thione


1.24

1,3-dihydro-1-cyclohexyl-4,5-dimethyl-2H-imidazol-2-thione


1.25

1,3-dihydro-1-ethyl-4,5-dimethyl-2H-imidazol-2-thione

Figure 44: Imidazol-2-thione derivatives in the study

The compounds studied 1.23 – 1.25 were synthesized via the reaction of azole N-oxides and thioketones[120]. All chemicals used were of analytical grade Sigma-Aldrich products, and were applied without further purification.

5.2.2. Preparation of the self-assembled layers

5.2.2.1. Preparation of gold surfaces

The polycrystalline gold surfaces were made using the gold-coating facility of a SEM-EDX (Röntec QX2 energy dispersive X-ray analyzer coupled to the scanning electron microscope) instrument on quartz slides.

5.2.2.2. Procedure for creating the self-assembled layers

Metal layers were washed with chloroform to remove all impurities before the experiments. Dilute (~0.1 M) solutions containing compounds 1.23 or 1.24 or 1.25 were prepared first using chloroform as the solvent. Films of compounds 1.23 or 1.24 or 1.25 were deposited onto the polycrystalline gold surface by the dip-coating technique. For thickening the film formed, the procedure was repeated several times.

5.2.3. Instrumental methods

5.2.3.1. Methods for structural analysis

Infrared spectroscopy (IR)

The IR spectra were registered on a BIO-RAD Digilab Division FTS-65A/896 FT-IR spectrophotometer with 4 cm^{-1} resolution. The 4000–600 cm^{-1} wavenumber range was recorded. 256 scans were collected for each spectrum. The spectra of the solid samples were taken in the diffuse reflectance mode using DTGS detector.

Raman spectroscopy

The Raman spectra were recorded on a Thermo Scientific TM DXRTM Raman microscope at an excitation wavelength of 635 nm applying 10 mW laser power and averaging 20 spectra with an exposition time of 6 seconds.

Nuclear magnetic resonance (NMR) spectroscopy

^{1}H NMR measurements were performed in 0.5 mL CDCl3, from Sigma-Aldrich Chemical Co.) using Bruker Avance 500, 500-MHz NMR spectrometer with 5-mm glass NMR tubes from Wilmad.

Mass spectrometry (MS)

Electrospray ionization mass spectrometric (ESI-MS) measurements were performed using a Micromass Q-TOF Premier (Waters MS Technologies) mass spectrometer equipped with electrospray ion source. The sample was introduced into the MS by applying direct injection method: the built-in syringe pump of the instrument with a 25-mL Hamilton syringe was used. The electrospray needle was adjusted to 3 kV and N_2 was used as nebulizer gas. The computer program used to simulate the theoretical isotope distributions is included in the Masslynx software package.

5.2.3.2. Surface inspection methods

Scanning Electron Microscopy (SEM)

The gold surfaces were studied by scanning electron microscopy (SEM−Hitachi S-4700 instrument, accelerating voltage of 18 kV) in the pristine forms to check the homogeneity of the surface.

Atomic Force Microscopy (AFM)

The topology of the adsorbed molecular layers on gold surfaces was studied by atomic force microscopy (AFM) using an NT-MDT Solver AFM microscope working in the “tapping” mode (the frequency of the cantilever was 278 kHz). The AFM needle 5 (manufactured by Nanosensors, Inc.) was an SSS-NCH-type 15 µm long silicon needle with 10° half cone angle and 2 nm radius of curvature.

Infrared mirospectroscopie (IRM)

The success of immobilization was checked by infrared microspectroscopy (IRM). The measurements were carried out on a Bruker Vertex 70 IRM instrument collecting the spectra in total reflection mode from the focused area of the proper surface (1−0.1 mm^2). A liquid nitrogen cooled MCT detector was used to collect observable intensities. Each spectrum was created from 1024 accumulated scans with 2cm^{-1} resolution in the 4000−400 cm^{-1} region.

5.2.4. Molecular modelling method

Molecular modelling calculations were performed at the B3LYP/6-31++G (d,p) level using the Gaussian 2009 Rev. E.01 package.

5.3. Study on the oxidation process of L-cysteinate-intercalated CaAl-LDH

5.3.1. Materials

L-cysteine, $Ca(NO_3)_2 \times 4H_2O$, $Al(NO_3)_3 \times 9H_2O$, NaOH, peracetic acid, bromine, hydrogen peroxide, methanol and acetone were purchased from Sigma Aldrich and used without further purification.

5.3.2. Synthesis of nitrate-containing and L-cysteinate-intercalated CaAl-LDH

A modified co-precipitation method was used for the synthesis and the intercalation process. Firstly, the organic compounds (most often 6.0×10^{-3} mol, but other quantities were also used, see later) were dissolved in 65 cm^3 of methanol, then 100 cm^3 aqueous solution containing $Ca(NO_3)_2 \cdot 4H_2O$ (0.3 M) and $Al(NO_3)_3 \cdot 9H_2O$ (0.15 M) was added, and the pH of 13.1 was set with NaOH solution (3 M). The mixture was stirred at 65°C for 3 days. Then the suspension was filtered, washed with water and methanol several times and dried at 85°C overnight. Nitrate-containing LDH was produced in the same way without adding organic phase to the slurry. All operations were performed under nitrogen atmosphere to minimize carbonate intercalation from the airborne CO_2.

5.3.3. Interlayer oxidation of L-cysteinate

During the oxidation process, the oxidizing agent (peracetic acid, bromine or hydrogen peroxide) was applied in various concentrations (from 0.4 M to 0.7 M) by dropwise addition of them into the suspensions containing the intercalated LDH suspended in water, methanol or acetone (100 cm^3). The suspensions were stirred for 60 min, then they were filtered and dried at 353 K. The amount of the intercalated LDH (0.1 g) and the temperature (298 K) were the same in all cases.

5.3.4. Methods of structural characterization

Powder X-ray patterns were recorded by a Rigaku XRD-6000 diffractometer using CuK_α radiation ($\lambda = 0.15418$ nm) at 40 kV and 30 mA with 2°/min scan speed.

The instrument for recording the IR spectra was a Bruker Vertex 70 spectrophotometer equipped with a single reflection diamond ATR accessory. Spectra were recorded in the 4000–400 cm^{-1} wavenumber range, but only the most informative wavenumber ranges will be displayed and discussed in the paper. 256 scans were collected for each spectrum, and the resolution was 4 cm^{-1}.

Raman spectra were recorded with a Raman Senterra II (Bruker) microscope at an excitation wavelength of 765 nm applying 12.5 mW laser power and averaging 20 spectra with an exposition time of 20 sec.

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ACKNOWLEDGEMENTS

I wish to convey my foremost gratitude toward my 1st supervisor, the late Professor Palinko Istvan, for the warmth welcoming me to the group, for his valuable advice, guidance and kind support. From bottom of my heart I cannot thank him enough, he has been more than a supervisor.

My particular gratitude also goes to my 2nd supervisor, Professor Sipos Pal, for his encouragement, friendliness, especially his kind support at the end of my PhD journey.

I would like to express my appreciation to the Material and Solution Structure Research Group (MASOST):

- Gabor Varga for his kind helps in consulting, recording and analyzing spectral data during my research work. For me, he is just like my 3rd supervisor.
- Dudas Csilla for her openness as well as kind help for the issues I encountered in my life in Szeged.
- Zita Timar for her huge contribution in my third article.
- Zita Csendes and Krisztian Jozsef Csanko for their helpful advice and guidance at my first times in the Group.
- Adel Adam, Akos Bucko, Szabolcs Murath, Bence Kutus, Marton Szabados for their friendly conversations and sharing me interesting things during my time in Szeged.
- Other colleagues who contributed to make my time in Szeged as wonderful as possible.

I would also like to thank the Department of Organic Chemistry, University of Szeged for the good working environment.

My great appreciation sends to The Public Tempus Foundation, Hungary and Ministry of Education and Training, Vietnam for the scholarship.

I would like to express my gratitude to Laboratory of Organic Synthesis, Institute of Natural Products Chemistry (Vietnam Academy of Science and Technology) for allowing me to apply the scholarship and enroll my PhD program in the University of Szeged.

Certainly, I wish to thank my family and friends for their caring and encouragement.

Last but not least, my special words go to the most important person in my life, my love, my wife, Nguyen Hong Linh for her accompanying, unconditional love, and patience during my challenging and long-lasting PhD journey.

PUBLICATIONS

This thesis is based on the following three articles:

[1] **Truong N.H.**, Ádám A. A., Varga G., Dudás Cs., Kele Z., Sipos P., Pálinkó I.:
Thionation of cyanoxime derivative to form the sulphur-containing derivative, a novel ligand for complexation with transitional metal ions,
Structural Chemistry **28**, 475–478 (2017)
Impact factor: 1.997_{2017}

[2] **Truong N. H.**, Varga G., Kónya Z., Kukovecz Á., Kozma G., Havasi V., Sipos P., Mloston G., Pálinkó I.:
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Journal of Molecular Structure, **1180**, 26-30 (2019)
Impact factor: 2.120_{2019}

[3] **Truong N. H.**, Varga G., Kónya Z., Kukovecz Á., Kozma G., Havasi V., Sipos P., Mloston G., Pálinkó I.:
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Materials, **14** (5), 1202 (2021)
Impact factor: 3.623_{2020}