THE RING CLOSURE REACTIONS OF AMIDOXIMES WITH *N*-SUBSTITUTED THIOUREA COMPOUNDS

ASLI AYCAN

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By

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Approval of the Graduate School of Natural and Applied Sciences.

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I certiy that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

Prof. Dr. Mahmut ACIMIŞ
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This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Sciences.

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3. **Doç. Dr. Özdemir ÖZARSLAN**

ABSTRACT

THE RING CLOSURE REACTIONS OF AMIDOXIMES WITH *N*-SUBSTITUTED THIOUREA COMPOUNDS

AYCAN, Aslı

M.Sc., Department of Chemistry

Supervisor: Prof.Dr.Yaşar DÜRÜST

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The major aim of this work is to try the cyclo condensation reactions of amidoximes and N-substituted thioureas under the effect of catalysts. For this purpose, first amidoximes were synthesized according to the literature procedures. The amidoximes were then reacted with N-substituted thioureas to give triazole-thione compounds. When KF/Al_2O_3 catalyst system was used in DMF medium a different and new type of heterocyclic ring; oxatriazine was obtained.

Another section of the work involved in the synthesis of some new SR derivatives of mercaptothiadiazole compounds. RX type compounds, some of which were synthesized in this work were used to react with

mercaptothiadiazole compounds. In addition, one sample reaction was carried out to obtain an organosulfur-mercury compound by the action of mercury (II) chloride with mercaptothiadiazole compound.

All of the compounds newly synthesized were identified by means of spectral measurements (IR,NMR,MS) and physical constants (e.g. melting points, Rf values) and in this regard, this work is an important contribution to the synthetic organic chemistry.

Keywords:Amidoxime,thiourea,triazole-thione,mercaptothiadiazole,
oxatriazine, spectroscopy,chromatography

ÖZET

AMİDOKSİMLERİN *N*-SÜBSTİTÜYE TİYOÜRE BİLEŞİKLERİYLE HALKA KAPANMASI REAKSİYONLARI

AYCAN, Aslı

Yüksek Lisans Tezi , Kimya Bölümü

Tez Danışmanı : Prof.Dr.Yaşar DÜRÜST

Eylül 2005, 106 sayfa

Bu çalışmanın amacı başlangıç maddeleri olarak amidoksimler ve (tiyo) üre bileşiklerinin çeşitli katalizörlerin etkisi ile halka kapanması reaksiyonlarını incelemektir. Bu amaçla sentezlenen amidoksimler önce N-substitue tiyoüre bileşikleri ile reaksiyona sokularak sübstitue triazol-tiyon bileşikleri elde edilmiştir.

Çözücü ve katalizör değiştirilmek suretiyle aynı başlangıç maddelerinden değişik halka sistemleri elde edilmiştir.

Çalışmanın bir diğer kısmı merkapto tiyadiazol bileşiklerinin RX tipi maddeler ile reaksiyonunu içermektedir ve bu şekilde SR bileşikleri sentezlenmiştir. Ayrıca merkapto tiyadiazol bleşiğinin civa(II) klorür ile reaksiyonundan organokükürt-civa bileşiği elde edilmiştir. Sentezlenen tüm bileşikler literatürde henüz mevcut olmayan bileşiklerdir ve bu anlamda sentetik organik kimyaya önemli bir katkıdır.

Yeni bileşiklerin yapıları IR,NMR (^{1}H, ^{13}C),Kütle Spektrumları ve fiziksel sabitler (erime noktası, Rf değerleri) yardımıyla aydınlatılmıştır.

Anahtar Sözcükler: Amidoksim, tiyoüre, triazol, tiyon, oksatriazin, tiyadiazol, merkaptotiyadiazol, spektroskopi, kromatografi

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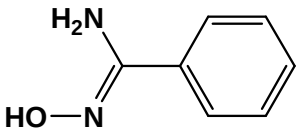

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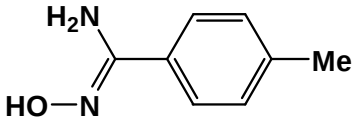

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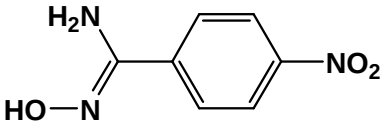

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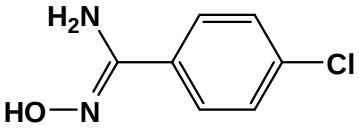

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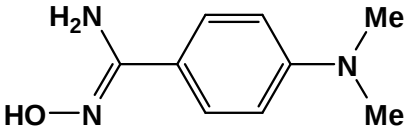

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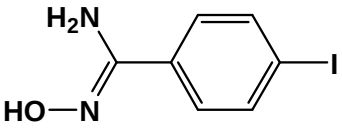

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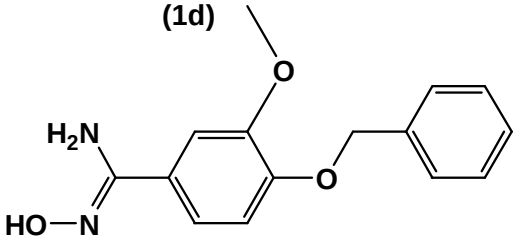

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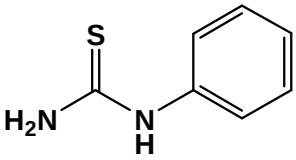

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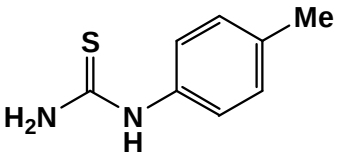

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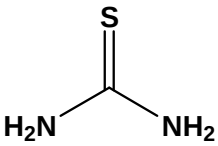

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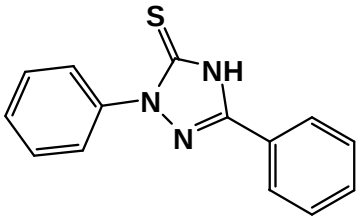

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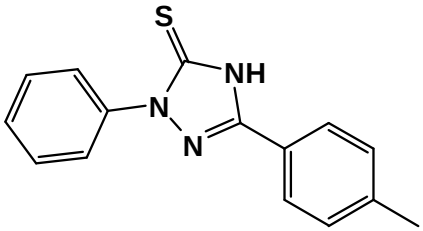

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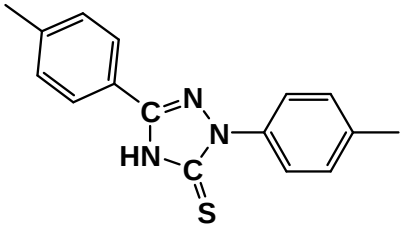

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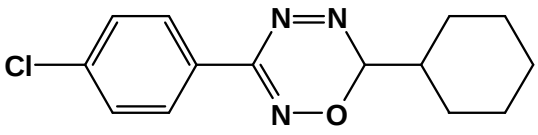

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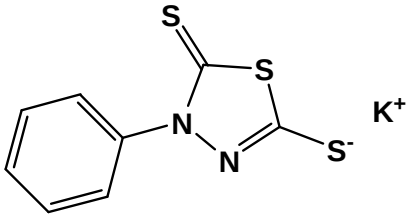

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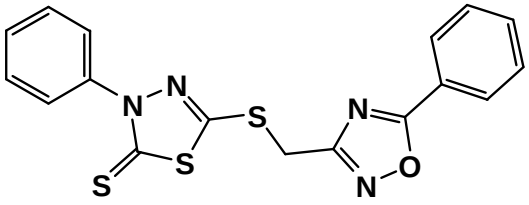

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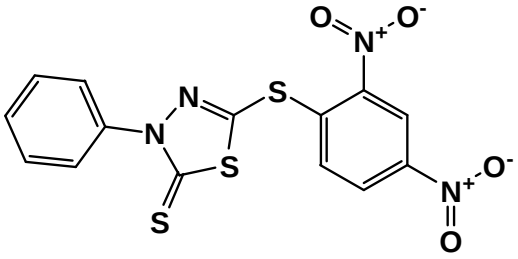

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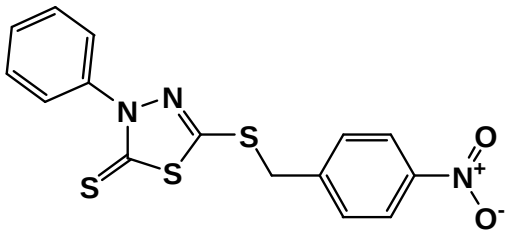

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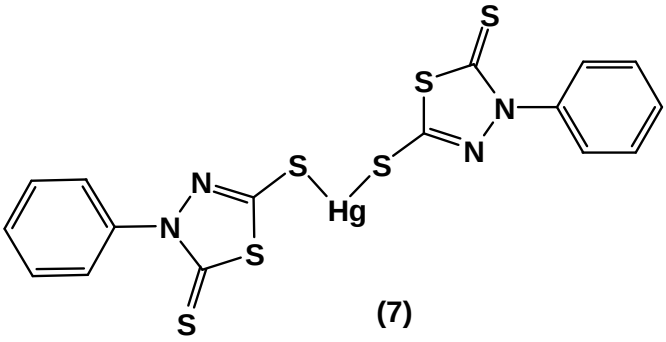

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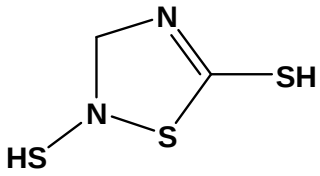

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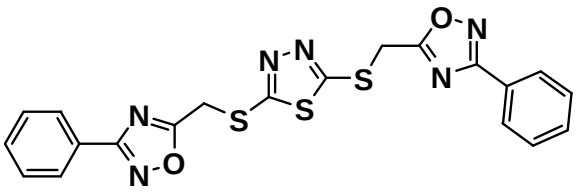

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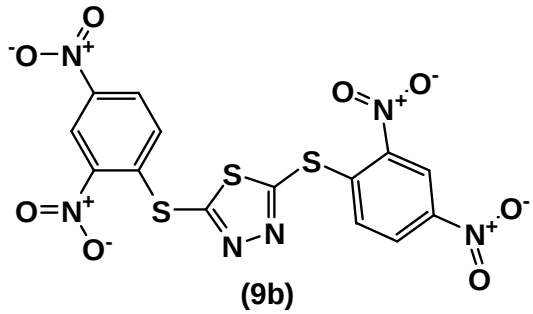


(9b)

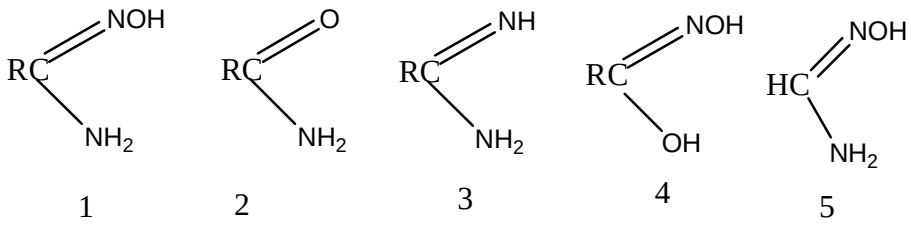
CHAPTER I

INTRODUCTION

1 .Amidoximes

1.1 Nomenclature of Amidoximes:

The amidoximes (1) can be considered as an amide (2) in which the oxygen atom of the carbonyl group has been replaced by an isonitroso group, or as an amidine (3) whose hydrogen atom of the imido group has been exchanged for a hydroxy radical. For this reason amidoximes are sometimes named oxyamidines. They are also related to the hydroxamic acids (4).



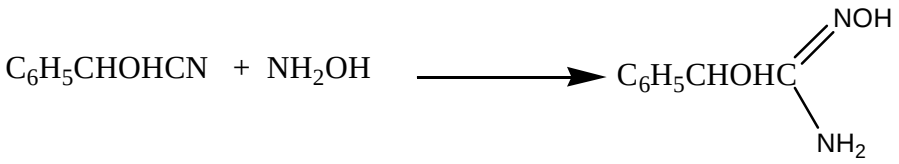
1 2 3 4 5

Figure 1.1:(1) Amidoximes, (2) Amide, (3) Amidine, (4) Hydroxamic acids

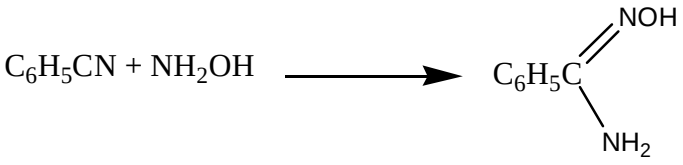
The first amidoxime was prepared in 1873 by Lossen and Schiffferdecker from hydrogen cyanide and hydroxylamine; these authors did not establish the structure of this compound. They called the lowest homolog (i.e., R = H) of the amidoxime “isuretin”. The name “amidoxime” was first used by Tiemann, who elucidated the structure of this class of compounds in 1884.

1.2 Molecular Structure

Tiemann prepared two related compounds (6 and 7).It was an addition reaction of hydroxylamine to benzaldehyde and to benzonitrile.



6,Mandelamidoxime



7,Benzamidoximes

Figure 1.2: Mandelamidoxime and Benzamidoxime

He proved the structure of the amidoxime by showing the simultaneous presence of NH_2 (amine) and NOH (oxime) groups. He found that benzamidoxime forms salts with metals and with mineral acids. The isonitroso group is identified by its acidic character and its reaction with nitrous acid brings out nitrous oxide.

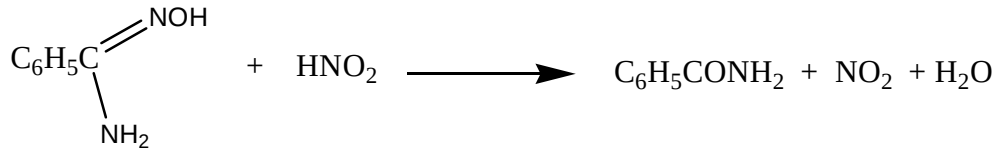


Figure 1.3

When the sodium salt of benzamidoxime is alkylated with methyl iodide the resulting compound reacts with nitrous acid to yield nitrogen, thus proving the presence of the amino group.

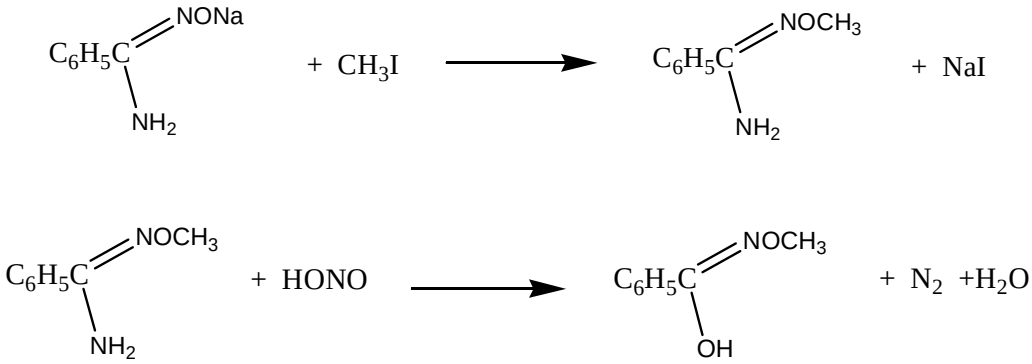


Figure 1.4

Tiemann recognized that amidoximes may be present in two tautomeric forms (8a and 8b), with former predominant.

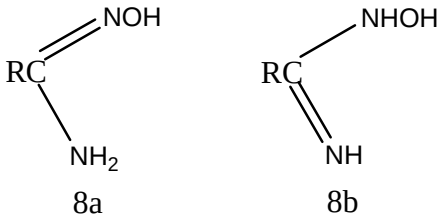
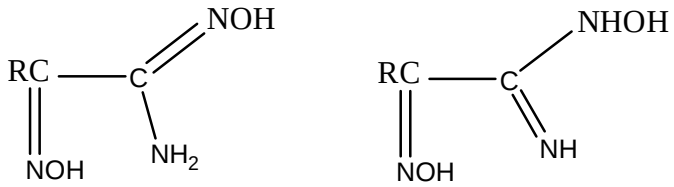


Figure 1.5: Tautomeric forms of amidoximes

Ponzio and his collaborators investigated the problem of tautomerism of aminoglyoximes. Several aminoglyoximes are known under two forms with

distinct physical properties. According to Ponzio they should be only two tautomers 9a and 9b.



9a 9b

Figure 1.6: Tautomerism of aminoglyoximes

The latter compounds can be transformed irreversibly into the former. However, only the more modern methods such as spectroscopy may finally settle the question of tautomerism in aminoglyoximes.

The greatest part of the work in the field of amidoximes was done by Tiemann and his co-workers at the University of Berlin. They prepared most of the amidoximes and related compounds known at present.

1.3 Synthesis of Amidoximes

1.3.1 Action of Hydroxylamine on Nitriles

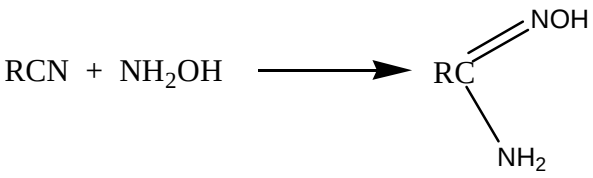
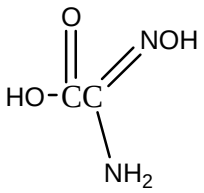


Figure 1.7

This is the most used process for the preparation of amidoximes.

1.3.2 Action of Hydroxylamine on Amides or Thioamides

Hydroxylamine does not react with amides. This method has only been reported for the preparation of the two amidoximes.



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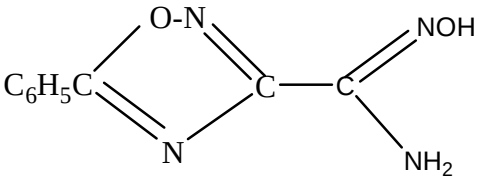

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Figure 1.8

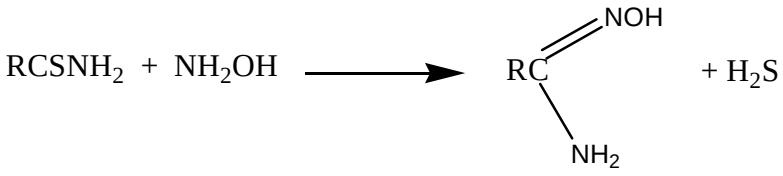

Figure 1.9

1.3.3 Reduction of Nitrosolic and Nitrolic Acid

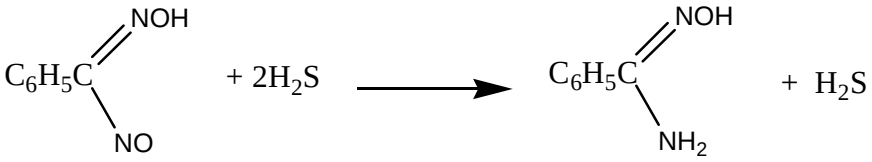

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Figure 1.10

1.3.4 Action of Ammonia on Hydroximic Acid Chlorides (Chloroximes)

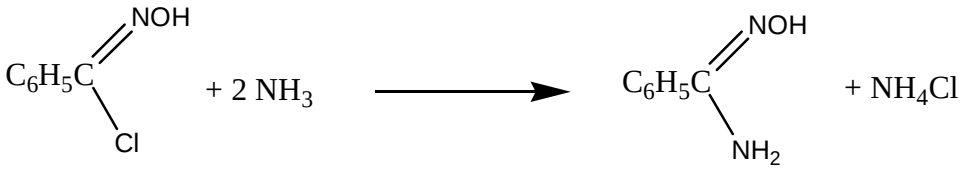

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Figure 1.11

1.3.5 Reduction of Oxyamidoximes

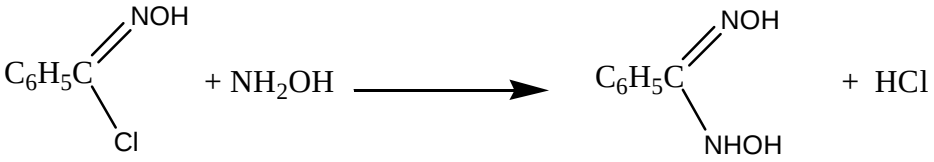

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Figure 1.12

1.3.6 Action of Hydroxylamine on Iminoethers

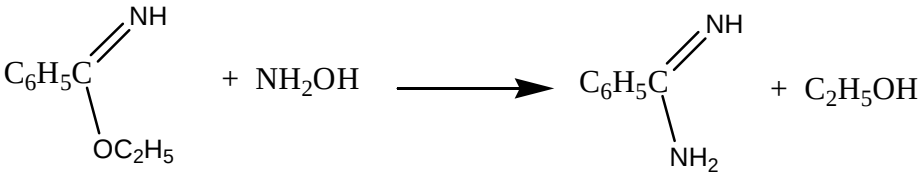

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Figure 1.13

1.3.7 Action of Hydroxylamine on Amidine Hydrochlorides

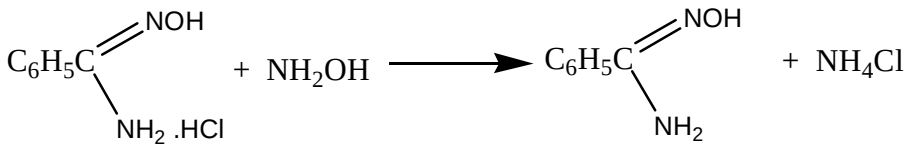

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Figure1.14

1.3.8 Action of Ammonia on Oximinoethers

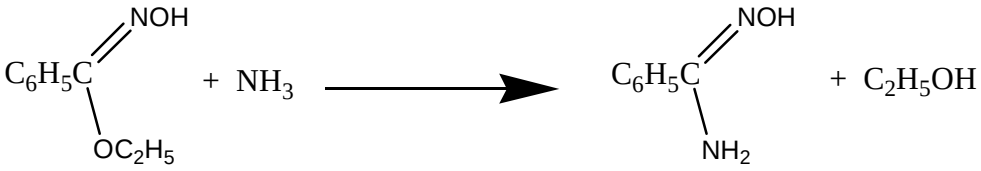

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Figure 1.15

1.3.9 Action of Formamidoxime on Aromatic Aldehydes

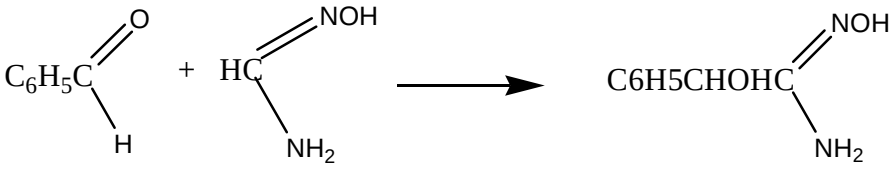


Figure 1.16

1.3.10 Action of Ammonia on Glyoxime Peroxides: (R' = H)

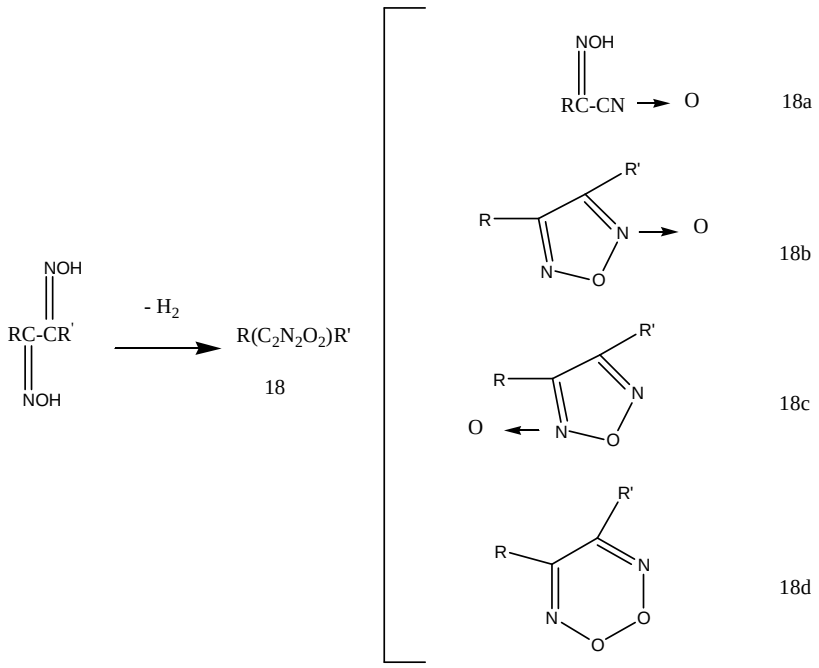


Figure 1.1

1.4 Properties and Reactions of Amidoximes

1.4.1 Physical Properties

The amidoximes are crystalline, colorless compounds which generally decompose when heated over their melting point. Aryl amidoximes are more stable than the aliphatic amidoximes.

The first members of the aliphatic series are soluble in water but their solubility decreases with increasing molecular weight. Aryl amidoximes are less or not soluble in water but soluble in alcohol and in most organic solvents. The IR spectra of the amidoximes show two well defined absorption bands: The first is a doublet at 2.87-2.93$\mu$and 2.96-3.03 μ , assigned to the two NH_2 streching modes; the second between 5.95 and 6.08 μ to the C=N streching. The OH

streching band of the NOH group is very broad and has its maximum at approximately 3.2μ .

1.4.2 Chemical Properties

1.4.2.1 Salt Formation

The amidoximes are amphoteric substances, soluble in dilute mineral acids as well as in aqueous alkaline solutions. The amino group in the molecule confers basic properties to the amidoximes. Salts of amidoximes with mineral or organic acids are known; they are crystalized easily and have well defined melting points. The hydrogen atom of the NOH group can be substituted by a metal. Many sodium and silver salts have been described. Amidoximes form colored crystalline compounds with the salts of some metals. Werner prepared a great number of such compounds with different amidoximes and proved that they are internal complexes in which the metal atom is linked to the oxime group as well as the amino group. These amidoximes have been used as analytical reagents for various cations. For example, oxamidedioxime "Niccolox" forms complex salts with Ni^{+2}, Cu^{+2}, Ag^{+}, Co^{+2} and has been applied in quantitative analysis. Nicotinamidoxime can be used for the spectrophotometric determination of uranium.

1.4.2.2 Organic Complexes

Amidoximes form with chloral bimolecular complexes, which are insoluble in water and organic solvents. They have sharp melting points and may be used for the identification of amidoximes.

1.4.2.3 Thermal Decomposition

Generally, amidoximes are decomposed when heated in the neighborhood of their melting point. Benzamidoxime is melting at 80^0C and stable up to 170^0C. At this temperature it decomposes, yielding several products which were identified as nitrogen, nitrous oxide, ammonia, water, benzonitrile, benzamide, diphenyl 1,2,4-oxadiazole, diphenyl-1,2,4-triazole and triphenyl-1,3,5-triazine.

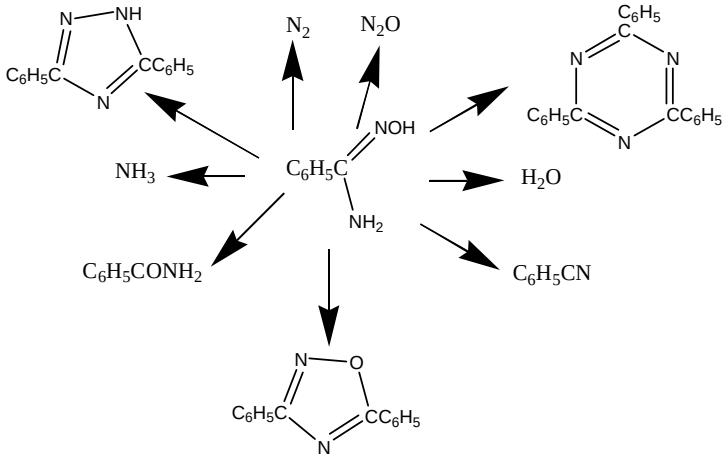


Figure 1.18

1.4.2.4 Hydrolysis

Many amidoximes, which at room temperature form soluble salts with dilute mineral acids and alkalies, are hydrolyzed completely when heated in the same media. Amides and hydroxylamine are formed, and under drastic conditions the amides are hydrolyzed into the corresponding acids;

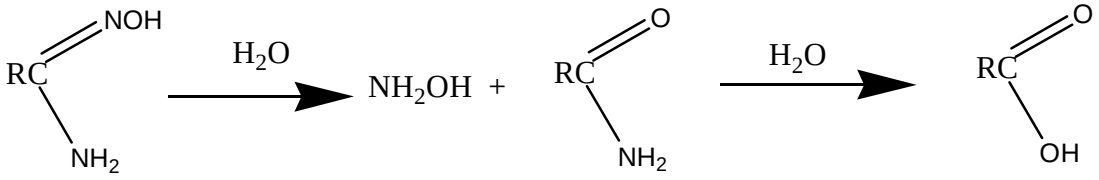


Figure 1.19

1.4.2.5 Reduction

The reduction of benzamidoxime with sodium amalgam produces ammonia and benzaldoxime with a yield of only 10 to 12 %; most of the amidoxime are unchanged.

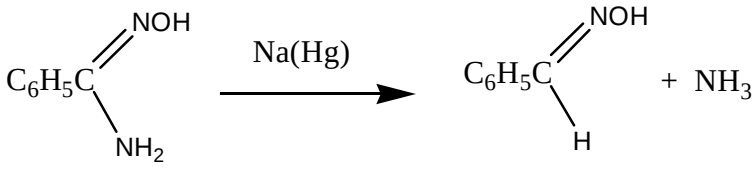
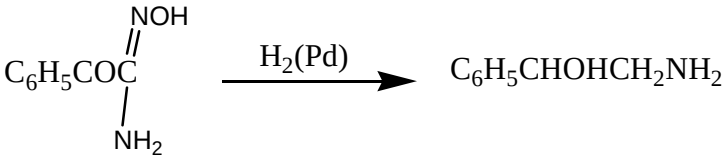


Figure 1. 20

Phenylglyoxalamidoxime has been reduced to phenylethanolamine on a palladium charcoal catalyst under 10 to 20 atmospheres of hydrogen.



19

Figure1.21

Amidines can be prepared by reduction of the corresponding amidoximes in the presence of Raney nickel at 30 atm. and 60-80^{0}C.

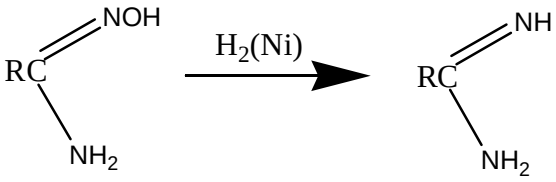
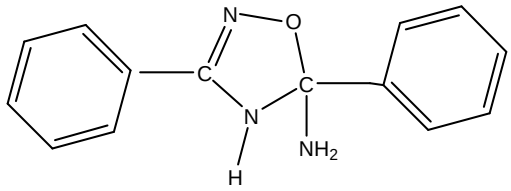


Figure 1.22

1.4.2.6 Oxidation

Oxidizing agents such as potassium ferricyanide, chlorine, or bromine in acetic acid, and iodine in aqueous bicarbonate react with benzamidoxime to yield a product $C_{14}H_{13}N_3O$ which corresponds to an aminohydrooxadiazole 20.



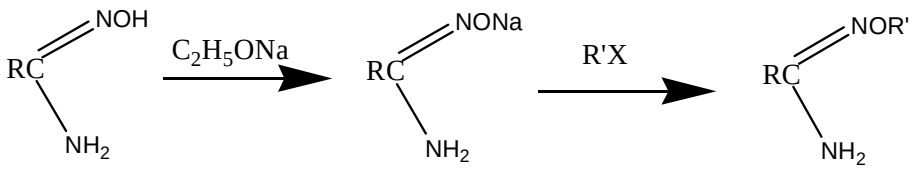
20

Figure 1.23

This compound (20) also is obtained together with nitrous oxide and aminodiazobenzene when benzenediazonium chloride or sulfonate reacts with benzamidoxime. The mechanism of formation of the compound is not known.

1.4.2.7 *O*-Alkylation

As it said before amidoximes and their N-substituted derivates exhibit acidic properties and form salts with metals. Sodium salts, readily (easily) obtained from sodium alcoholate, yield *O*-alkyl ethers (21) when treated with aliphatic halogen compounds.



21

Figure 1.24

Instead of sodium ethoxide, potassium or sodium hydroxide in aqueous alcolic solution can be used. The O-alkyl derivatives of aliphatic amidoximes are oily unstable compounds and they have not yet been obtained in a pure state. Those of aromatic amidoximes are low melting stable compounds, soluble in common organic solvents, and can be prepared in good yields.

1.4.2.8 Action of Nitrous Acid

The reaction of nitrous acid on benzamidoxime has been one of the methods which helped to elucidate the structure of the amidoxime group. Tiemann and Krüger identified the presence of the NOH group by the fact that benzamidoxime, as hydroxylamine itself, evolves nitrous oxide when treated with an equivalent amount of nitrous acid. Under these conditions, benzamidoxime is transformed into benzamide. Acetamidoxime react similarly yielding acetamide and nitrous oxide.

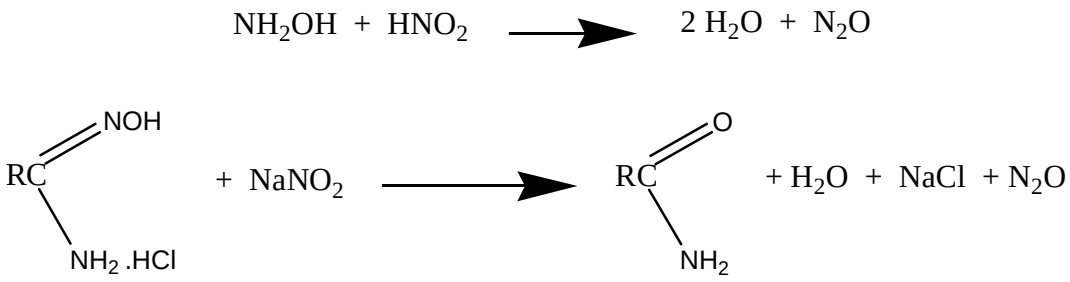
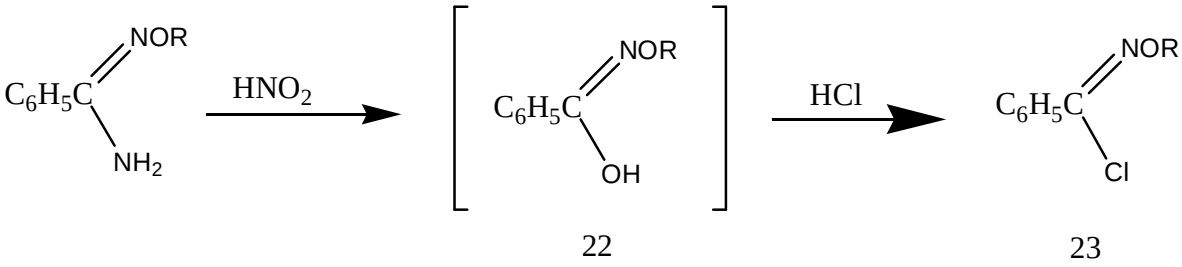


Figure1. 25

However, an O-alkylated benzamidoxime treated with nitrous acid evolves nitrogen, which proves that an amino group is present in the molecule. In this reaction the corresponding hydroximic acid is not isolated, but in the presence of an excess hydrochloric acid, the hydroximic acid chloride is formed in almost quantitative yields.



22 23

Figure 1.26

O-Alkyl hydroximic acid chlorides are very stable oils, and they can be steam distilled without decomposition. They are soluble in most organic solvents. Hydroximic acid bromides and flourides are prepared in a similar way if hydrobromic or hydrofluoric acid is used instead of hydrochloric acid.

Unsubstituted hydroximic acid chlorides generally are prepared by direct chlorination of aldoximes

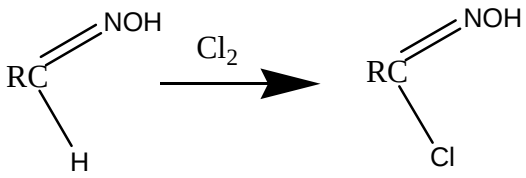


Figure1.27

Unsubstituted hydroximic acid chlorides are formed with NaN_3 azidoximes (azides of hydroximic acids)

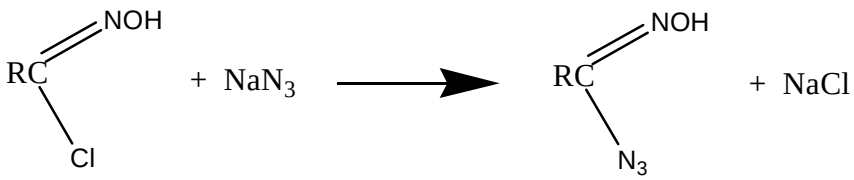


Figure 1.28

1.4.2.9 N-Substitution: This topic has been prepared into 4 sections.

1.4.2.9.1 Action of an amine on hydroximic acid halides is the usual way of preparing N-substituted amidoximes. Primary and secondary, aliphatic and aromatic amines have been used.

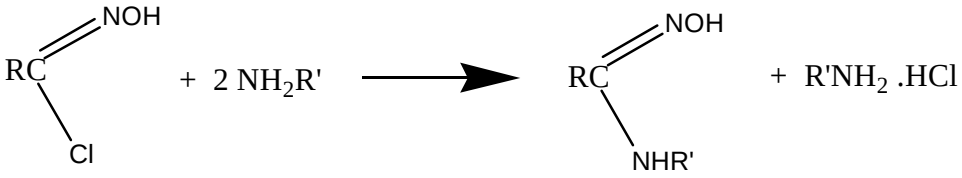


Figure 1.29

1.4.2.9.2 Action of hydroxylamine on N-substituted thioamides

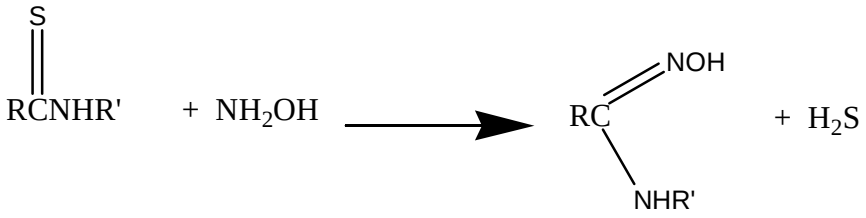
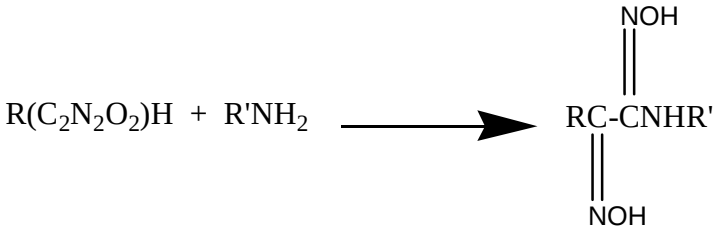


Figure 1.30

The yields are less than in the case of unsubstituted thioamides.

1.4.2.9.3 Action of amines on glyoxime peroxides yields N-substituted aminoglyoximes 24.



24

Figure 1.31

Different isomers of aminodioximes have been isolated but their configuration is not definitively established.

1.4.2.9.4 Action of Aniline on Amidoximes

Aniline is reported to react directly on acetamidoxime and formamidoxime hydrochloride; at 80-90^{0}C ammonia is evolved with formation of the corresponding N-substituted amidoximes

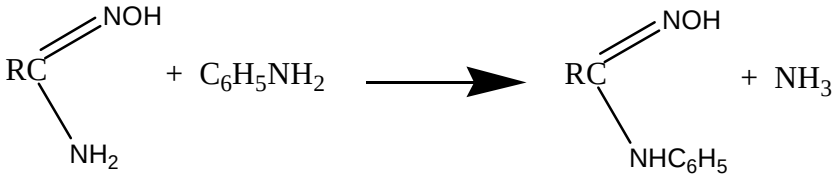


Figure 1.32

1.4.2.10 Action of Isocyanates and Isothiocyanates

According to the Tiemann cyanic acid and phenyl isocyanate react with benzamidoxime to yield ureide or phenylureide oximes.

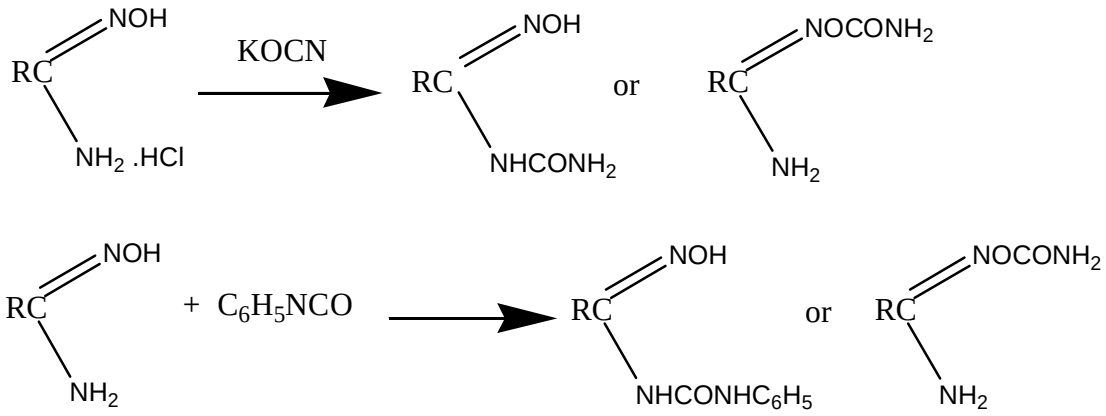


Figure1. 33

In the case of O-alkyl amidoximes, isocyanates can evidently yield only ureide oximes.

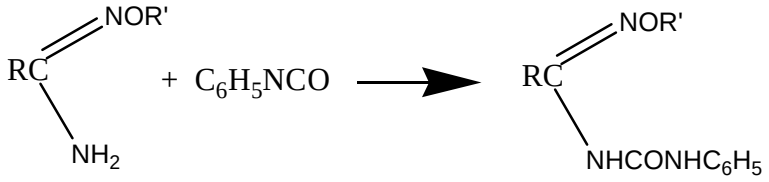


Figure1.34

1.4.2.11 Acylation

1.4.2.11.1 O-Acylated Amidoximes can be acylated readily at room temperature by acid chlorides or anhydrides.

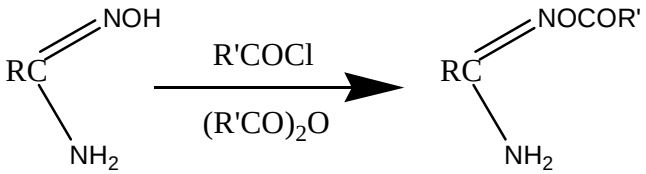


Figure 1.35

The IR spectra of the acyl derivatives show the presence of the NH_2 and -O-CO- groups and the absence of the broad OH-absorption band at about 3.2μ . The methods of acylation are all based on well- known classical procedures using either an acid chloride, or an anhydride. Instead of acid anhydrides and chlorides, other reagents have been used, such as ketene, mixed carboxylic-carbonic anhydres, carboxylic acid azides, and thioacetic acid.

Ketene reacts instantaneously (suddenly) with benzamidoxime in an inert solvent to give the O-acetylbenzamidoxime in quantitative yields

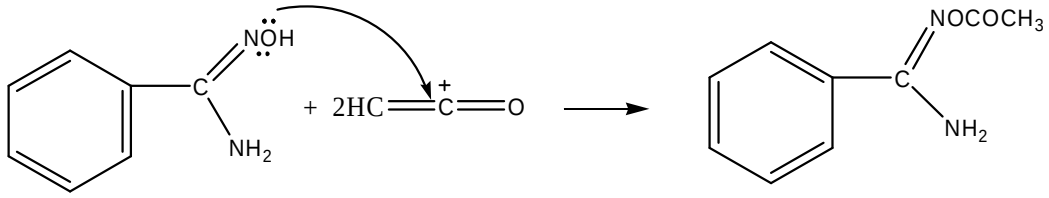
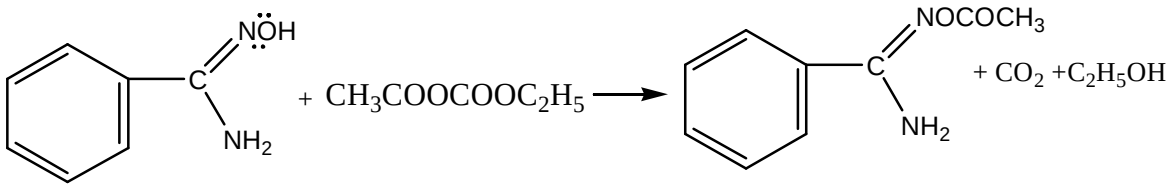


Figure 1.36

Benzamidoxime and acetamidoxime give the corresponding O-acetyl derivative quantitatively when treated at room temperature with an ethereal solution of acetic-ethylcarbonic anhydride.



25

Figure 1.37

Also carboxylic acid azides are very efficient acylation agents which react readily at room temperature with amidoximes.

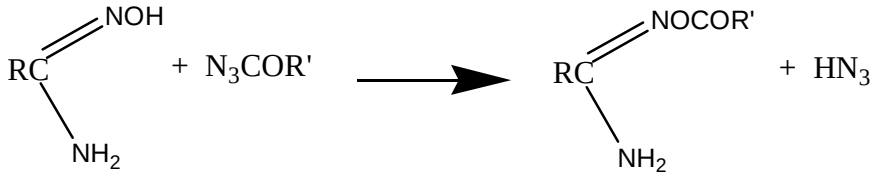
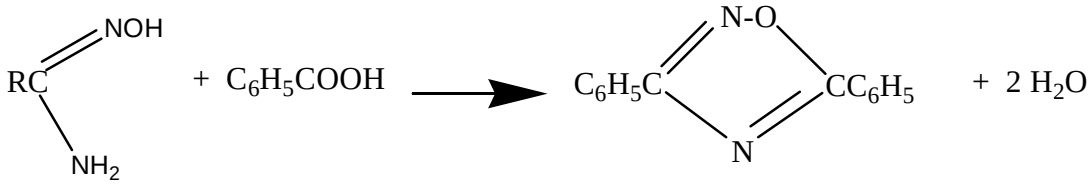


Figure 1.38

With thioacetic acid, benzamidoxime is aceylated at room temperature with evolution of hydrogen sulfide. The reaction can be conducted in water. However, sulfur appears during the reaction showing that simultaneously a reduction occurs. A by-product of the formula $C_9H_{12}O_2N_2$ can be isolated, which could be identified as a salt of benzamidine with acetic acid.

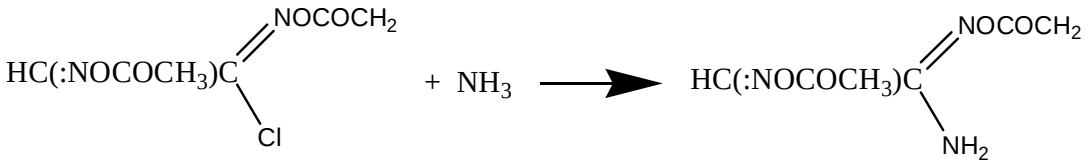
Benzamidoxime reacts on heating with benzoic acid. The acylated amidoxime cannot be isolated but its dehydration product 3,5-diphenyl-1,2,4-oxadiazole is formed.(26)



26

Figure 1.39

O-Acylated amidoximes also have been prepared from acylated hydroximic acid chlorides (27) and ammonia.



27

Figure 1.40

The formylation of amidoximes has been performed with the mixed anhydride of formic and acetic acids.

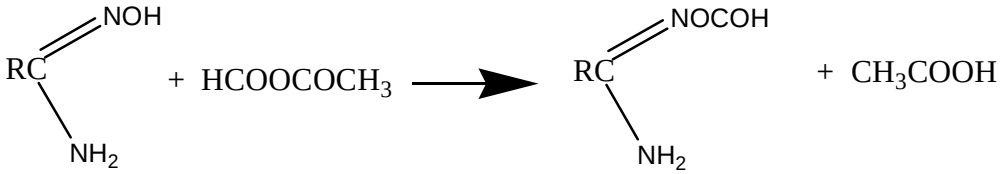
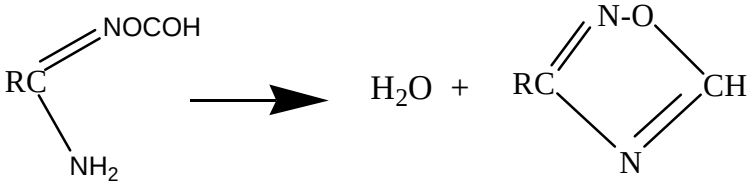


Figure 1.41

The formyl esters or formamidoxime,acetamidoxime,and benzamidoxime have been synthesized but they were immediately dehydrated into the corresponding 3-monosubstituted oxadiazoles(28)



28

Figure 1.42

By using mixed anhydride, the diformyl ester of oxamidedioxime could be prepared in good yields.

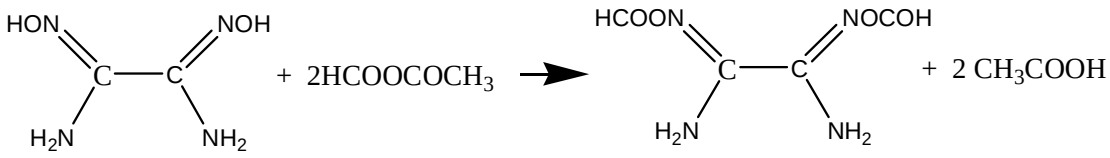
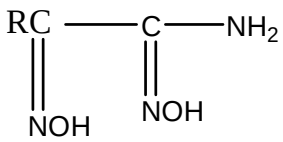


Figure 1.43

1.4.2.11.2*N*-Acylated Amidoximes

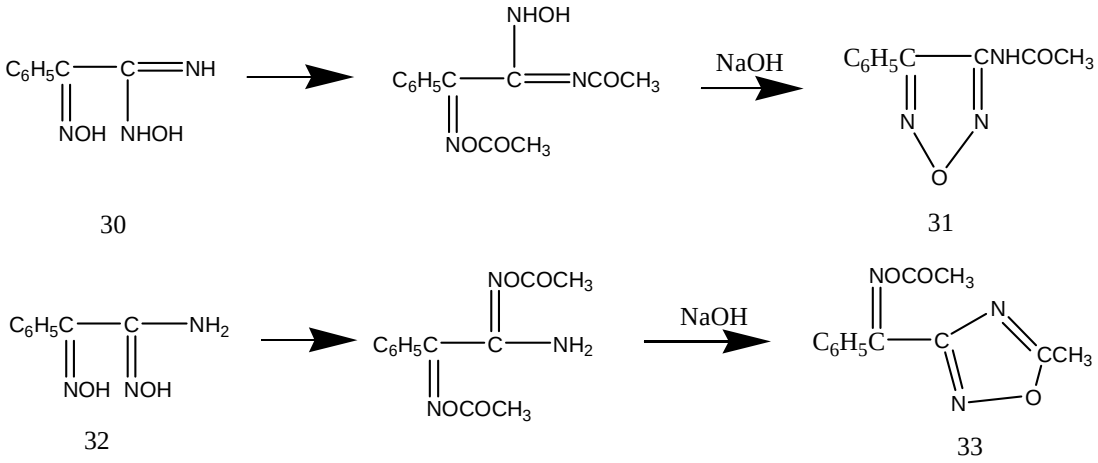
N-Acyl derivatives of oximes have been described by Ponzio and his collaborators. They have published papers about stereochemistry of α-dioximes.



29

Figure 1.44

Ponzio has claimed that the two isomers α and β of 1-phenyl-2-aminoglyoxime correspond to the structures 30 and 32, respectively, and that on acylation, the amidoxime of the former is *N*-acylated, while the latter undergoes O-acylation.



30 31

32 33

Figure 1.45

And he established the possibility of transformation of the oxadiazole into the corresponding furazan by treatment with alkali.

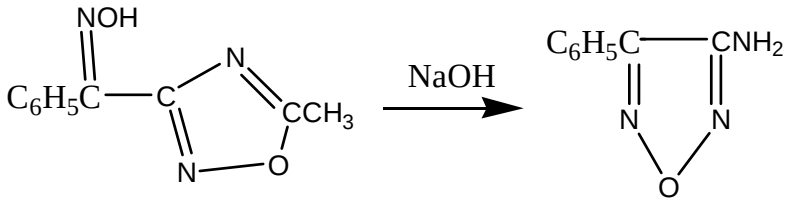


Figure 1.46

Recently, both N- and O-acetylated formamidoximes have been synthesized. When the acylation of formamide is carried out with mixed acetic ethylcarbonic anhydride, (34) the two isomers are present in almost equal quantities.

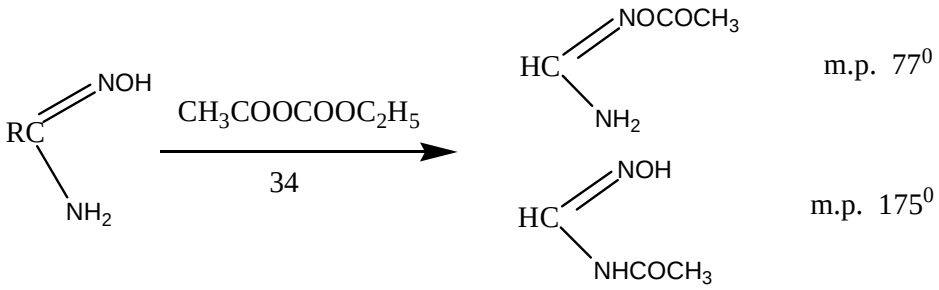


Figure 1.47

The infrared spectra of both isomers are quite distinct:NH_2 doublet is at 3295 and 3420 cm^{-1} and -OC=O band at 1735 cm^{-1} characterize the O-acytyl formamidoxime molecule, and N-acetylated compound shows only a simple band at 3335 cm^{-1} as well as a broad absorption region between 3300 and 2900 cm^{-1}. While the carbonyl absorption band of the amide function is visible at 1730 cm^{-1}.

Solubility and chemical behavior of the two isomers are also different: for example, O-derivative can be dehydrated into the 5-methyl-1,2,4-oxadiazole,whereas The N-derivative cannot.

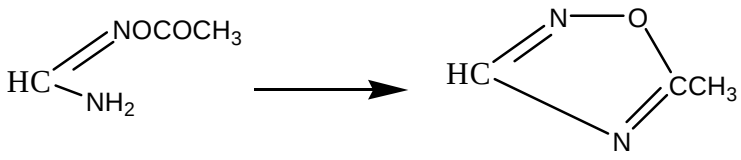


Figure 1.48

1.4.2.12 Carbonic Acid Derivatives of Amidoximes

Ethyl chloroformate reacts with the isonitroso group of the amidoximes to give carbonic acid derivatives.

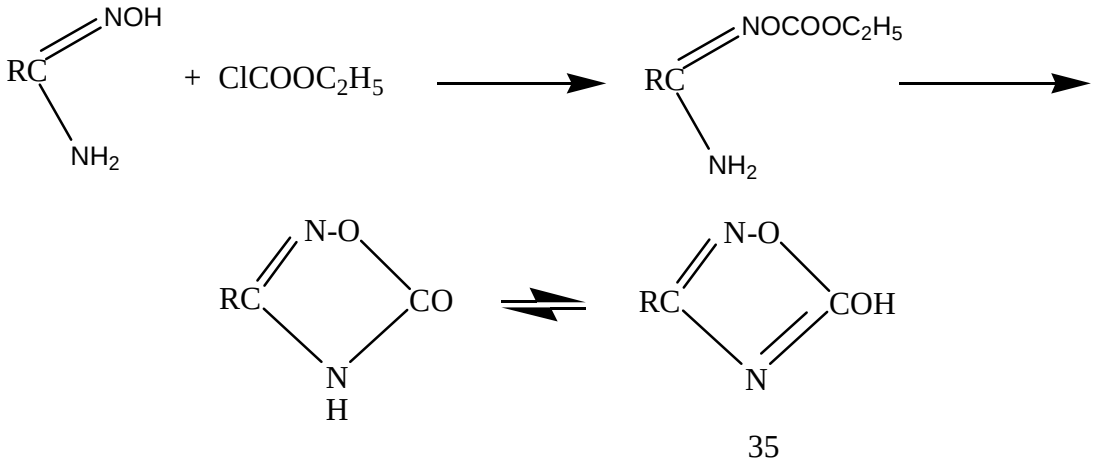


Figure1.49

On heating ethanol is eliminated and a 5-hydroxy-1, 2, 4-oxadiazole (35) is formed. N-substituted amidoximes react also in the same way. For example, N-dimethyl *m*-nitrobenzamidoxime treated with ethyl chloroformate yields a carbonic ester.

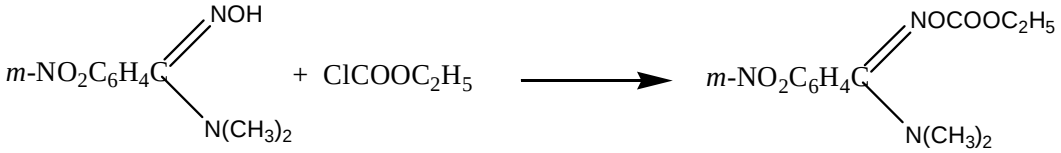


Figure 1.50

Phosgene reacts with amidoximes to give derivatives of carbonic acid; on cyclization one molecule of amidoxime is regenerated.

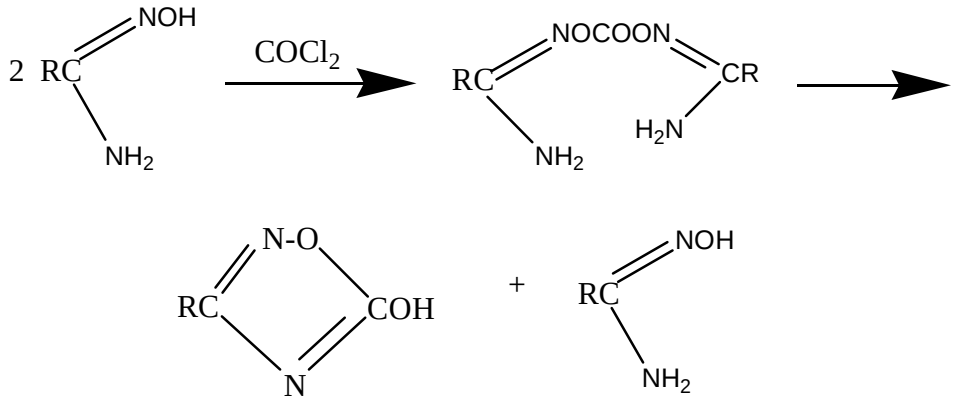


Figure 1.51

Thiophosgene and amidoximes yield derivatives of thiocarbonic acid, which on cyclization give 5-mercapto-1,2,4-oxadiazoles

1.4.2.13 Reaction with β-Ketocarboxylic Esters

Amidoximes are indifferent toward non-activated esters, they react on heating with an excess of ethyl acetoacetate. Water and ethanol are eliminated, and 5-aryl-3-acetonyl-1,2,4-oxadiazoles are formed

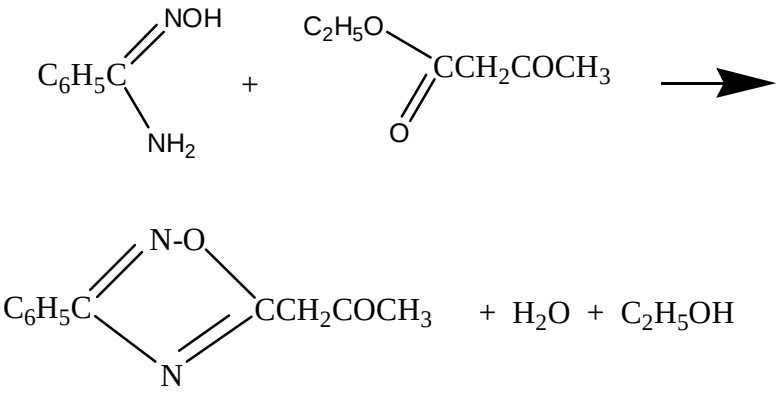


Figure1.52

Other β-Ketocarboxylic esters such as ethyl benzoylacetate,o-methoxybenzoylacetate,and acetonedicarboxylate react similarly with aromatic amidoximes,

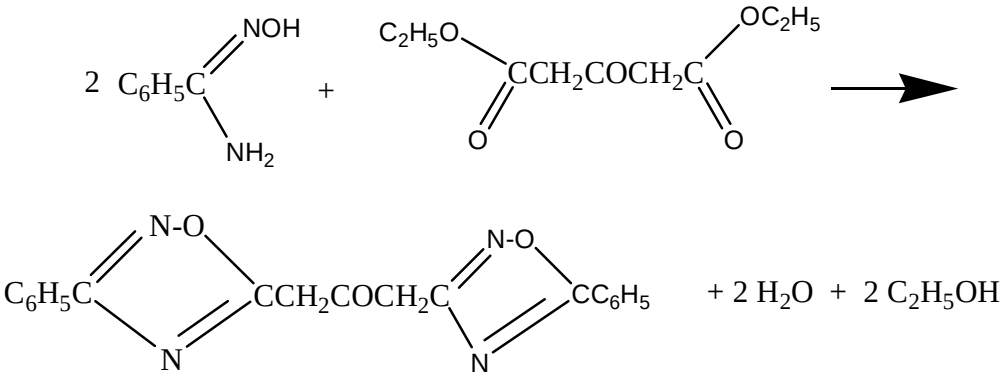


Figure 1.53

1.4.2.14 Reaction with Aldehydes

The aliphatic aldehydes react with amidoximes yielding 3,5-disubstituted 4,5-dihydro-1,2,4-oxadiazoles

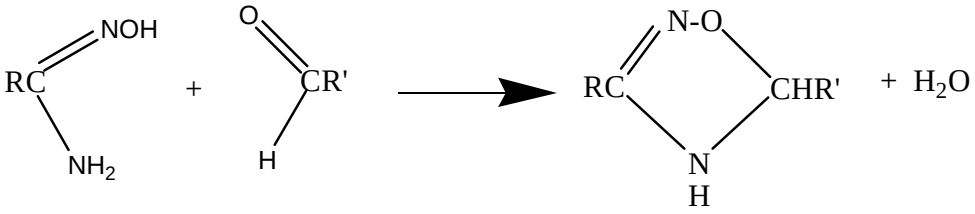
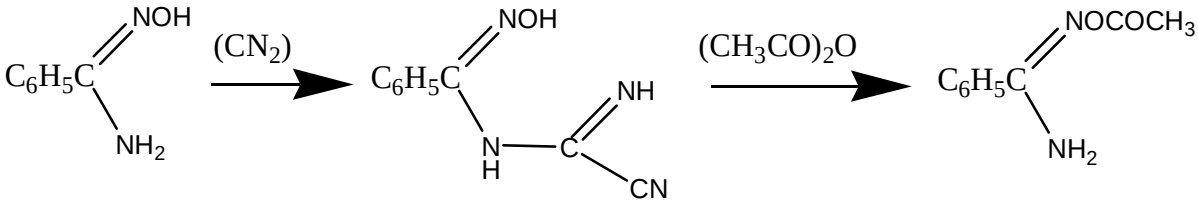


Figure1.54

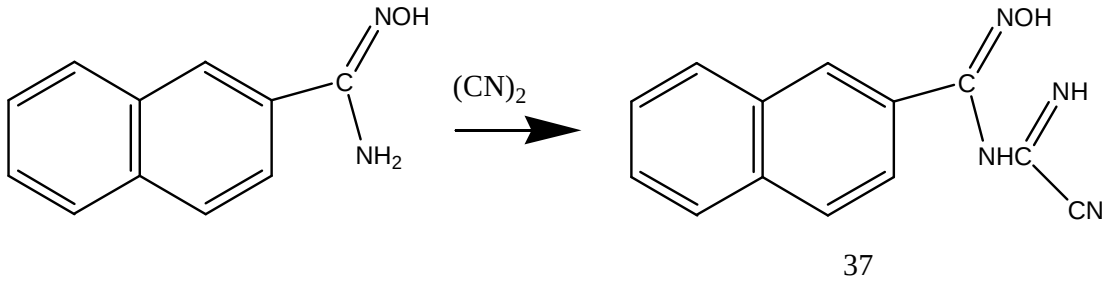
The dihydro-oxadiazoles are crystalline products with basic properties, forming salts with mineral acids. They are hydrolyzed with diluted acids and bases into the corresponding aldehydes and amidoximes and they are easily oxidized by potassium permanganate into the corresponding oxadiazoles.

1.4.2.15 Action of Cyanogen

Cyanogen and benzamidoxime or *β*-naphthalamidoxime yields addition products formulated as 36 and 37. They are rather unstable and hydrolyze readily into the original amidoximes. The same compounds treated with acetic anhydride give the corresponding *O*-acetylamidoximes.



36



37

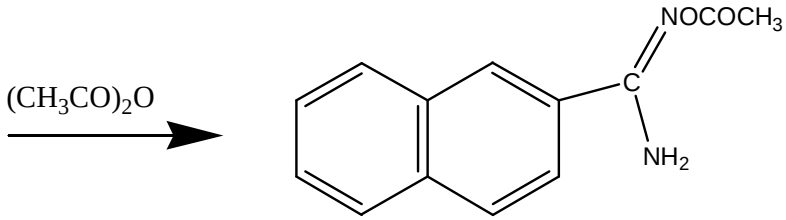
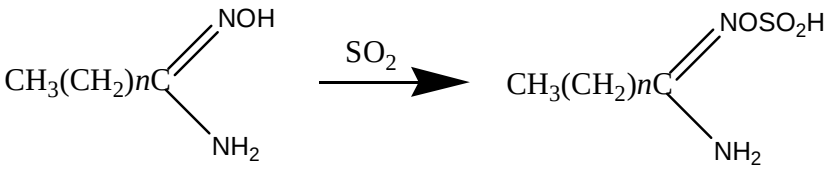


Figure 1.55

1.4.2.16 Action of Sulfur Dioxide

Sulfur dioxide gives with amidoximes derived from long chain fatty acids unstable addition compounds (38)

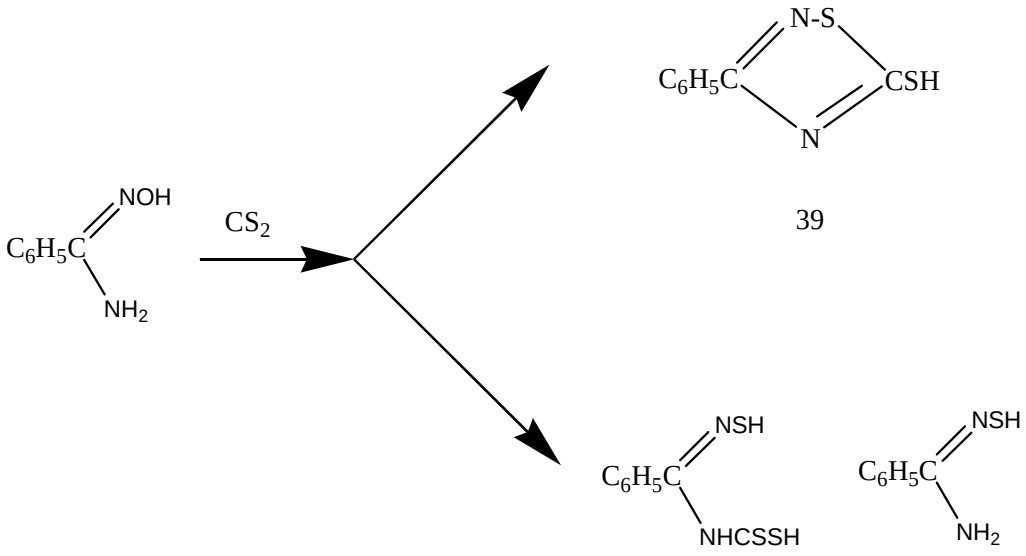


38

Figure 1.56

1.4.2.17 Action of Carbon Disulfide

The reaction of carbon disulfide with amidoximes in alkaline alcoholic solution produces cyclic compounds known as 5-mercapto-1,2,4-thiadiazoles(39). In boiling ethanol, benzamidoxime gives with an excess of CS_2 the thiobenzamidoxime salt of the thioloxime of benzoyldithiocarbamic acid (40). Dilute hydrochloric acid hydrolyzes this compound into benzamidine hydrochloride.



39

40

Figure1.57

Methylbenzamidoxime shows a similar behavior.

1.4.2.18 Action of Phenylhydrazine

Phenyl formazyl (41) is formed when benzamidoxime is refluxed with phenylhydrazine in dilute acetic acid.

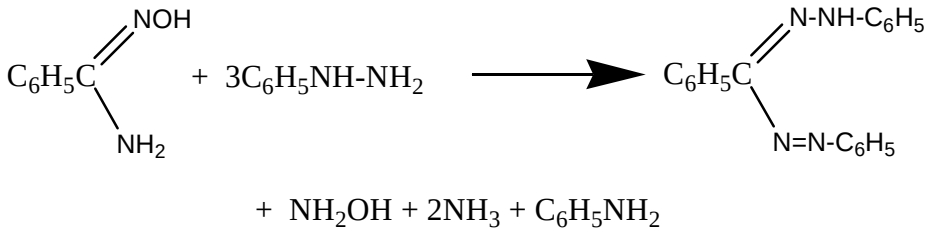


Figure 1.58

1.4.2.19 Beckmann Transformation

The presence of urea among the decomposition products of formamidoxime has been explained by a Lossen rearrangement, related to the Beckmann transformation.

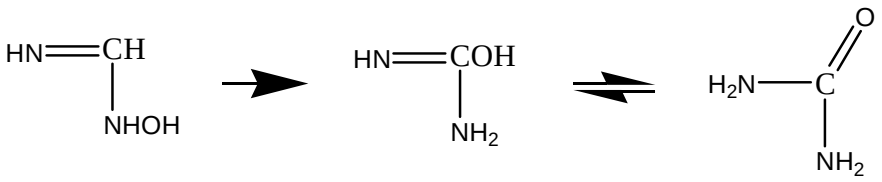


Figure 1.59

The formation of acetylurea when formamidoxime is aceylated with acetic anhydride also could be interpreted by a Lossen-Beckmann transformation.

Amidoximes have been converted into unsymmetrical ureas when treated first with benzenesulfonyl chloride and then with water.

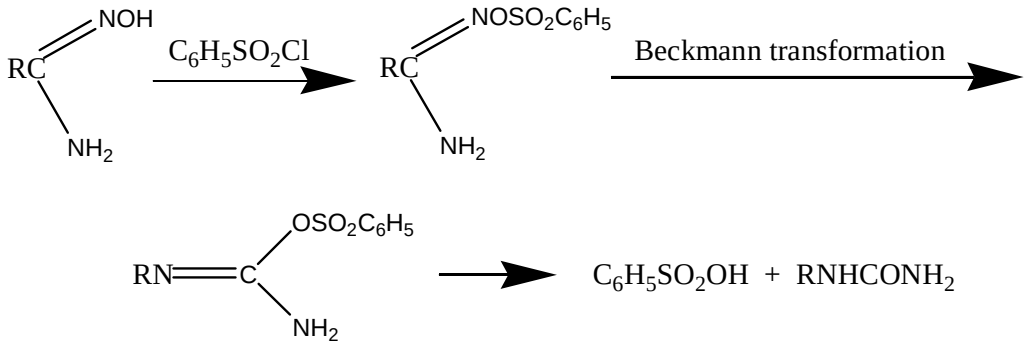


Figure 1.60

In support of this reaction mechanism it was found that certain amidoximes yielded isolable O-benzenesulfonyl derivatives which on heating with water gave the expected ureas (or their decomposition products) and benzenesulfonic acid.

Partidge and Turner claimed in 1953 that the isourea derivative (42) decomposes spontaneously into benzenesulfonic acid and a cyanamide (43). Hydrolysis of this cyanamide would then yield a urea, and its reaction with an amine yielded a guanidine derivative.

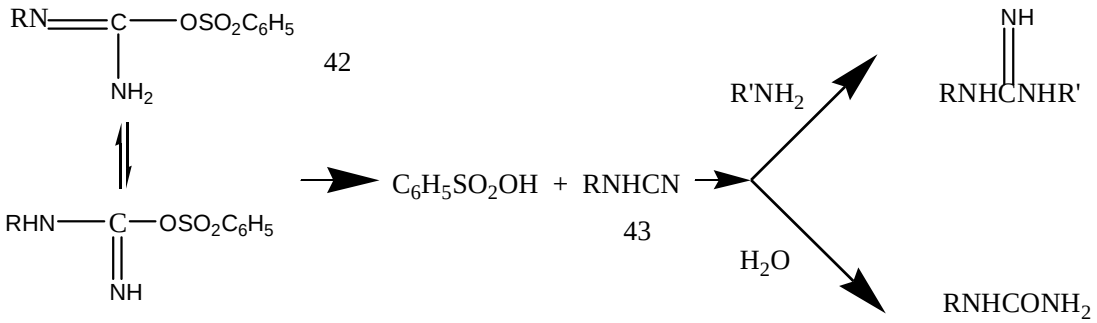


Figure1.61

The mechanism may be represented as an intramolecular process in which the hydrogen bond controls the subsequent electronic displacements.

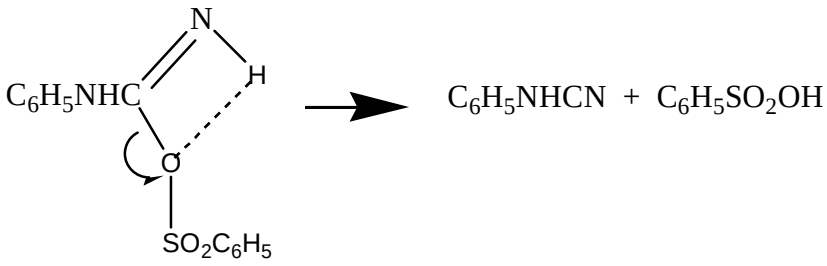


Figure 1.62

When the amino group is substituted by two methyl radicals, no transformation occurs and the O-benzene-sulfonyl derivative can be isolated easily **[1]**

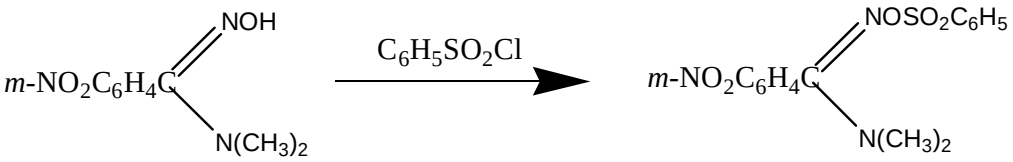


Figure 1.63

1.5 Uses of Amidoximes

Amidoximes are an important class of compounds in their own right and have been employed for the synthesis of a variety of valuable compounds. Many benzamidoximes have exhibited biological activities, for example, as trypanocides, antituberculars, and hypotensives. It has been found that halogenated as well as alkoxy benzamidoximes have a moderate effect on the nervous system. Some of the other pharmacological properties of amidoximes have been found that bactericidal and fungicidal, local anaesthetics, fibrinogen receptor antagonists **[2]**. There are several papers which concerning the anti-bacterial activity of amidoximes, compared with amidines. For example, *p*-

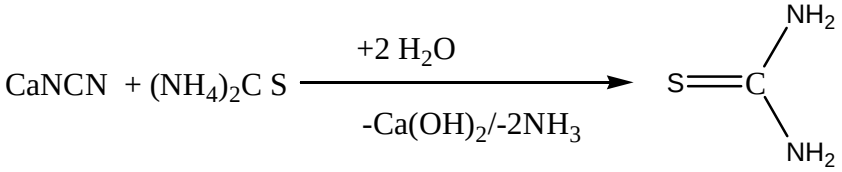
Sulfamidobenzamidoxime has a slightly superior activity over the corresponding amidine on experimental typhus infection in mice. However, in most cases, the introduction of the oxygen atom decreases the anti-bacterial power of the amidines, together with their toxicity. Lamb and White have studied the trypanocide activity of several diamidoximes and there are some amidoximes, which are patented as products having pharmacological properties and useful in thrapeutics. Some halogenated phenols carrying amidoxime group are active against Mycobacterium tuberculosis **[1].**

2. Thiourea

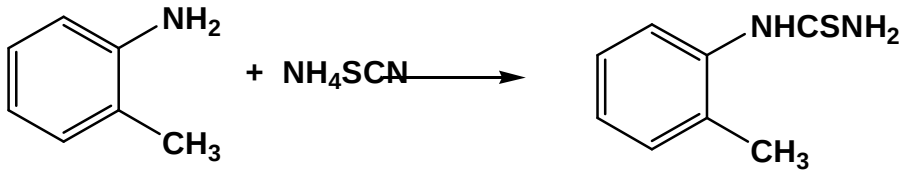
2.1 Properties and Reactions of Thiourea

The thiourea was synthesized first by heating ammonium thiocyanate in 1869, which was similar with Wöhler's urea synthesis **[2]**.

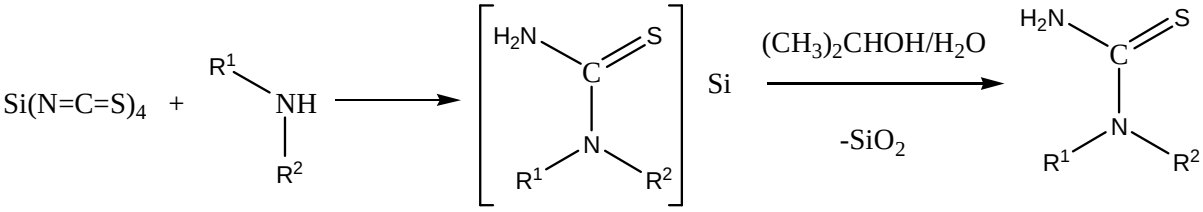
The synthesis of thiourea was also reported by reacting calcium cyanamidine with ammonium sulfide as shown below **[2]**.



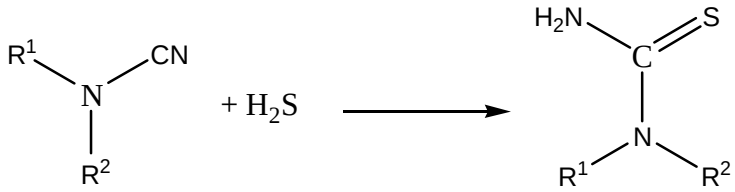
By heating of an aromatic amine with ammonium thiocyanate **[3]**



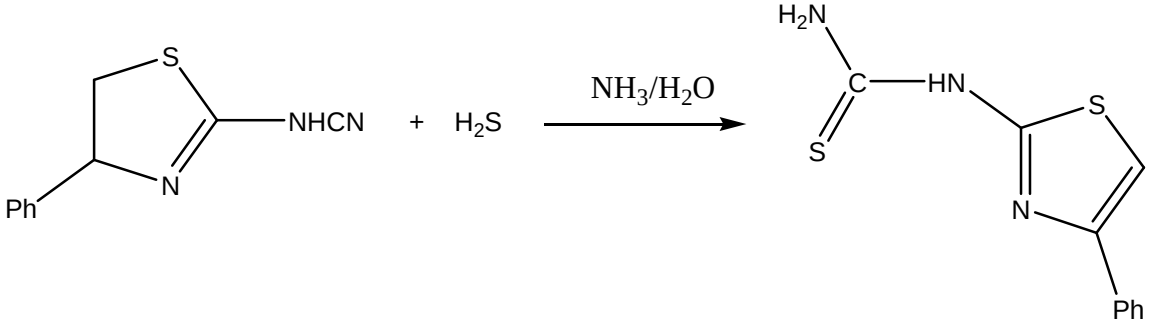
By the reaction of silicon thiocyanate with amine



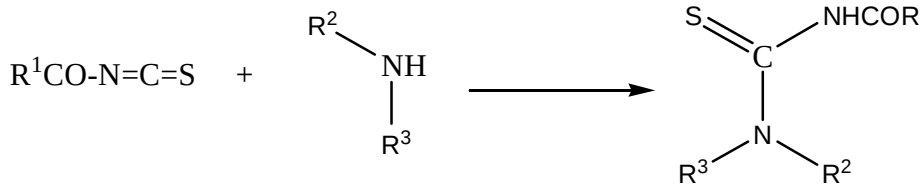
From the action of alkyl cyanamide on hydrogen sulfide **[4, 5]**



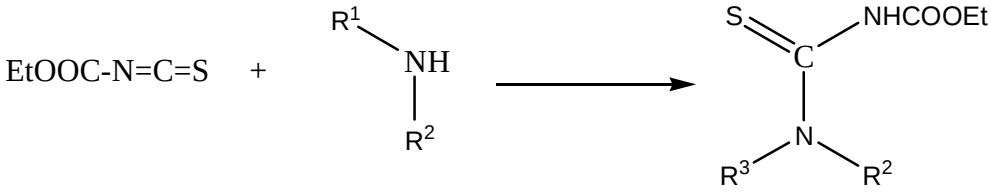
By the reaction of cyanamide thiazole with hydrogen sulfide **[6]**



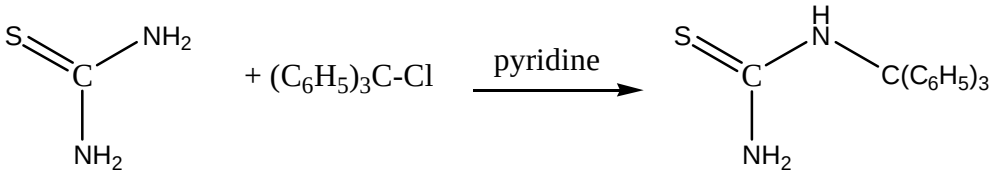
By the reaction of benzylisothiocyanate with primary or secondary amine



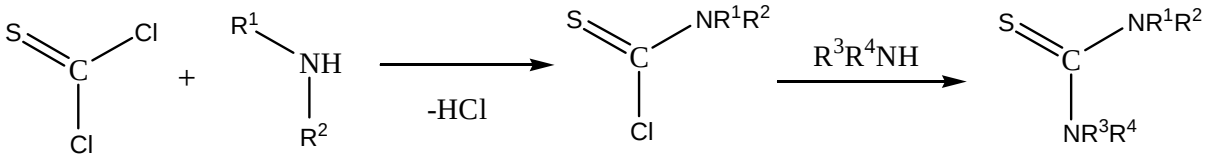
From the reaction of ethoxycarboyl isocyanate with amine



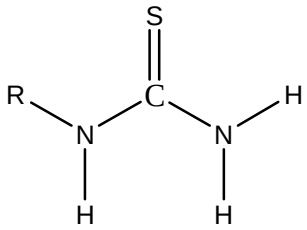
Alkylation of thiourea **[7]**



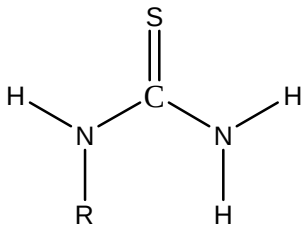
From thiophosgene and amine **[8,9]**



Monoalkylsubstituted thiourea compounds were found to exist in *E* and *Z* form in solution The compounds which have aromatic groups were reported most stable because of the intramolecular hydrogen bonds **[10]**.



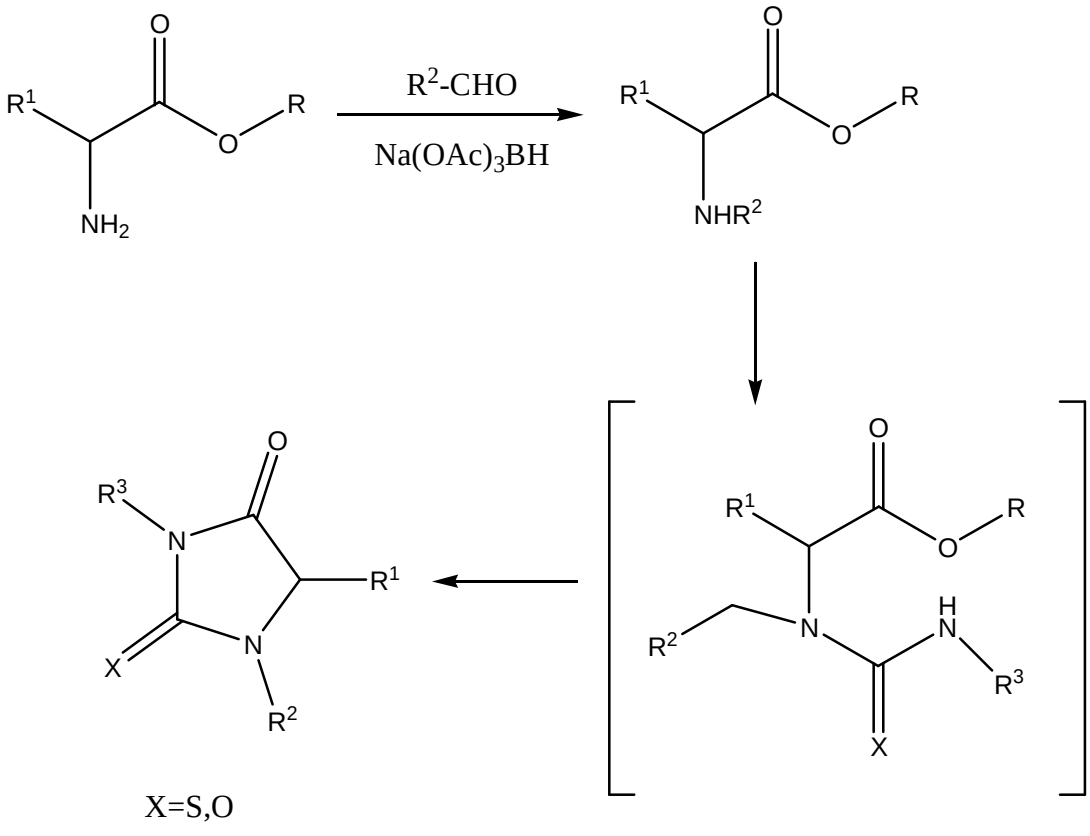
Z-FORM



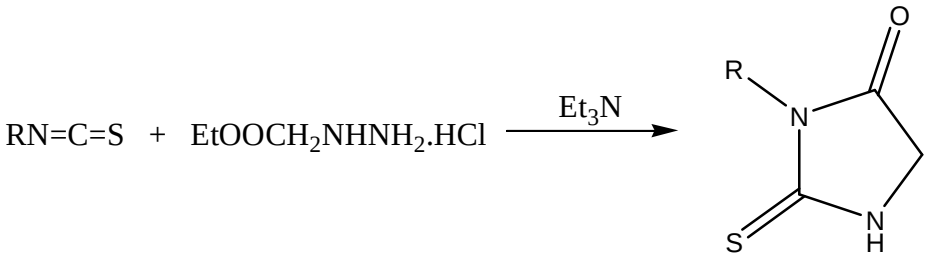
E-FORM

It was reported that a number of substituted thiourea compounds have been found to exhibit anti-viral and anti-corrosive activity **[11, 12]**. Also anti-microbial effect of N-[4-(3H-1, 3, 4-oxadiazolin-2-thion-5-yl] phenyl)-N'-substitute thiourea compounds was also described **[13]**.

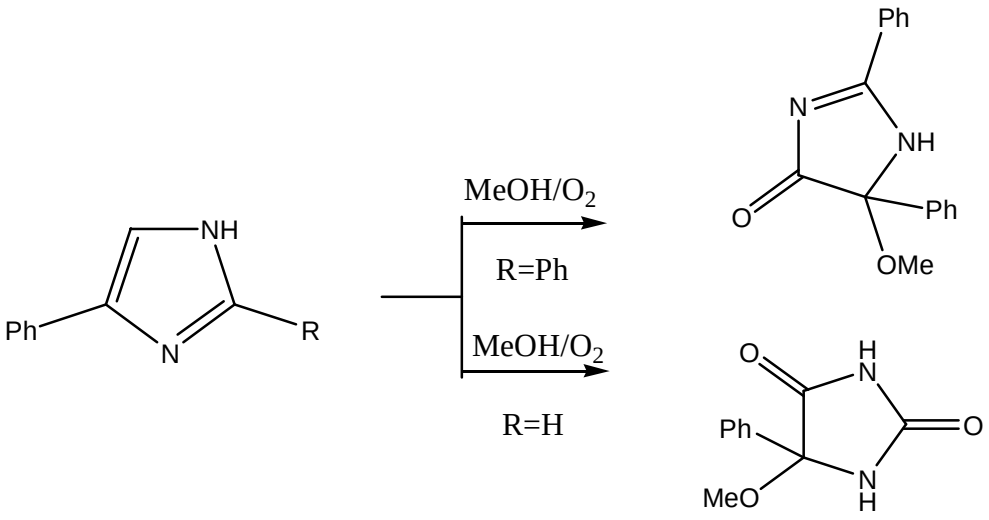
The syntheses of imidazolidin-dione (also known as hydantoin) and imidazolidin-2-thion-4-on (also known as thiahydantonin) were carried out as below **[14]**:



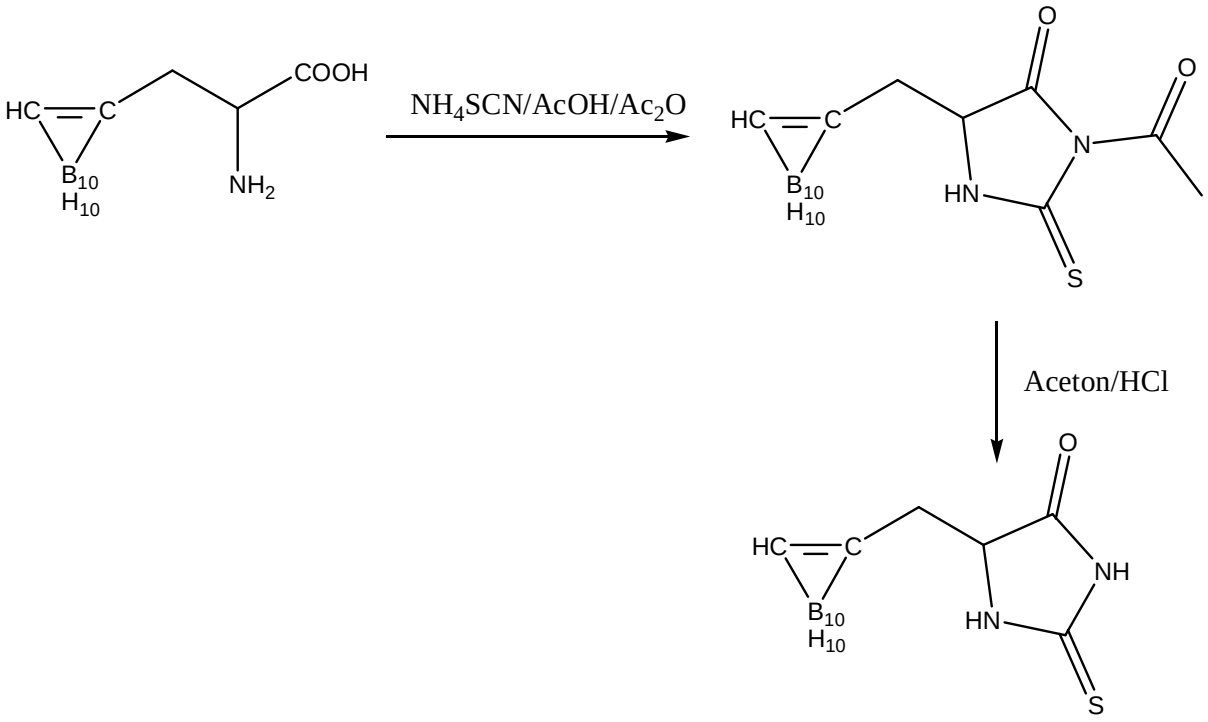
3-Substituted-1-amino-2-thioxo-4-imidazolinon was synthesized from alkyl or aryl isothicyanate with the action of ethyl hydrazinoacetate hydrochloride in triethylamine solution **[15]**.



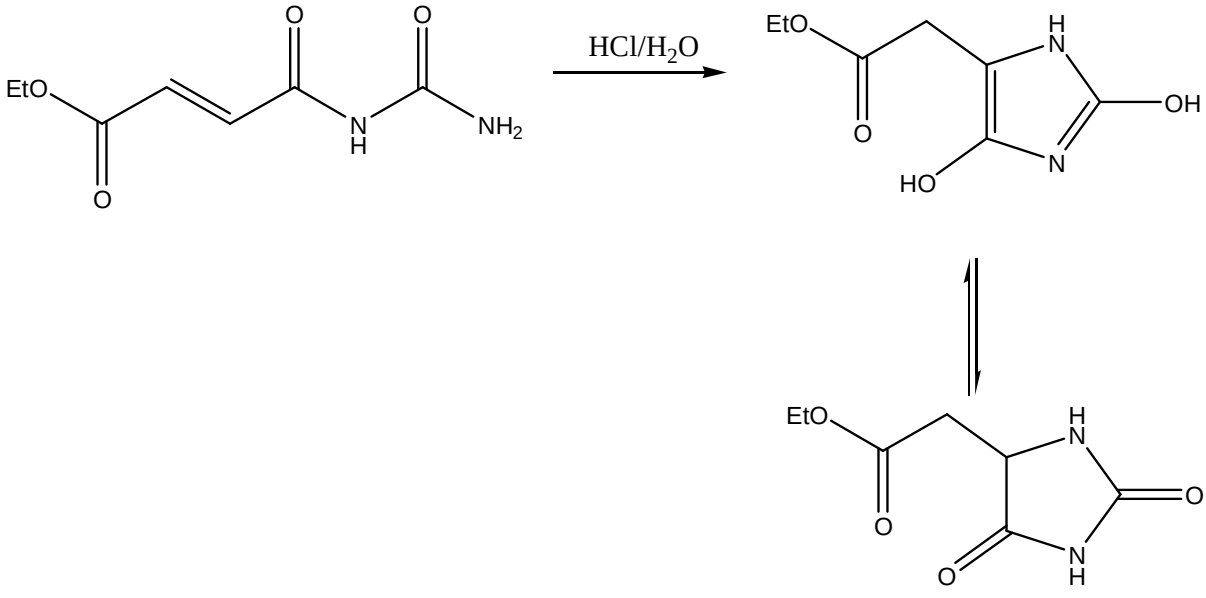
Imidazolidine dione compounds and 3-aryl imidazolidine dione were synthesized by the oxidation of pyrazole ring **[16]**.



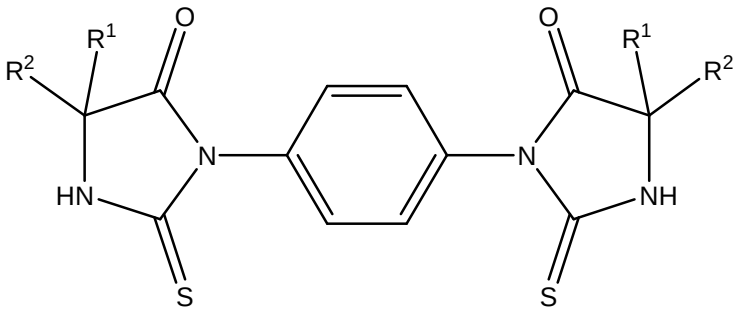
Synthesis of carboranyl substituted imidazolidin-2-thion-4-on compounds were obtained as follows **[17]**.



İmidazolidin dion compounds which contaning carbethoxy groups were synthesized by the action of hydrochloric acid on substituted urea.



The synthesis of bisthiohydantoin from *p*-phenylenediamine and ammonium thiocyanate was reported by Acharya et. al**. [18]**



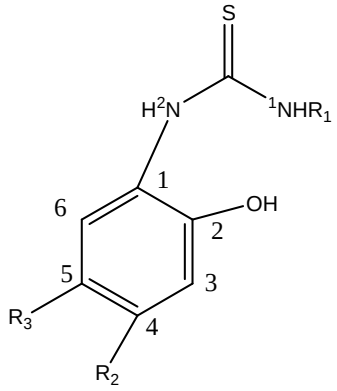
*N-A*cyl thiohydantoin derivates, which have anti-diabetic activities, were synthesized from ammonium thiocyanate and glycine by Zubenko and Turkevic **[19]** the anti-myolitic and local anesthetic activities of some thiohydantoin derivatives were claimed by W.Chiti **[20].** Lempert and Nyitrai **[21]** reported the synthesis of dithiohydantoin and alkylthio derivatives in 1965 and Lempert **[22]** ac hieved the preparation of S-methyl hydantoin derivatives in 1962. Girard and Dreux **[23]** carried out research on the synthesis and tautomeric equilibria of some thiahydantoin compounds in 1968.

2.2 Synthesis of *N*-substituted thiourea compounds

2.2.1 N^1 N^2 –Diaryl and N^1-Alkyl- N^2- Arylthioureas

The N^1 N^2- disubstituted thioureas can exist in solution as an equilibrium mixture of three conformers EZ, ZE and EE, because the fourth conformer ZZ (with voluminous substituents at the same side of the C=S group) is unstable due to the steric hindrance. Interesting model compounds for the study of

structural effects are the N-phenyl thioureas with *ortho* hydroxyl substituent to the phenyl ring, because OH and NH proton-donor groups can be involved in different intra and/or intermolecular hydrogen bonding. In Wawer and his collaborators studies on substituted thioureas compounds have been synthesized with methyl or propene(allyl)substituent at N^1 and with 4-methyl or 5-methyl group in addition to 2-hydroxyl at aromatic ring at N^2. **[24]**



1 $R_1=CH_3$, $R_2=H$, $R_3=CH_3$
2 $R_1=CH_3$, $R_2=CH_3$, $R_3=H$
3 $R_1=CH_2CH=CH_2$, $R_2=H$, $R_3=CH_3$
4 $R_1=CH_2CH=CH_2$, $R_2=CH_3$, $R_3=H$

Figure 2.1: The structure of compounds **1-4**.

The few data only for thioureas can be understood by known in collecting reflexes from sulphur atoms (high scattering factor and absorption coefficient). According to the Wawer the molecules differ only by the position of the methyl substituent to the phenyl ring, which is meta or para with respect to the thiourea moiety. Both compounds have the EZ location of phenyl and methyl substituents with respect to thiocarbonyl group.

The thiourea fragments are almost planar (torsional angles 1.6.0 deg), but the twist angles of aromatic rings are 59.8 and 61.9 deg for the product **1** and **2**.The geometry of phenyl ring is typical, with the small deviations of angles at the position of substituents, the presence of electronegative methyl group (Walsh-Bent rule) results in a decrease of valence angle.

The comparison of bond lengths with the average ones reveals that C=S bond in the compound 1and 2 is longer than the average, the N^2-CS bond in the compound 1 is longer and the N^1-CS in the compound 2 is shorter than the respective average bonds in N^2-phenylthiourea. The conjugation of lone electron pairs of nitrogen atoms with π-electrons of the C=S double bond is usually illustrated by the resonance structures I, II, and III

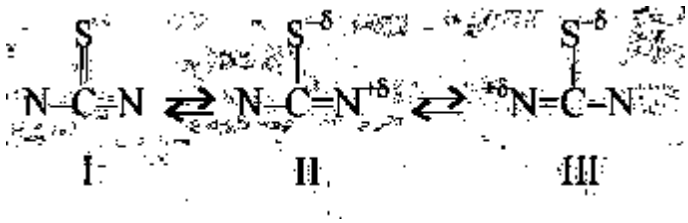


Figure 2.2

Optimal values of C-N and C=S bond lengths are 1.334 and 1.677 A^0 .The deviations from optimal values may be a measure of delocalization of π-electrons over the above molecular fragment. In both compounds the C=S bond is longer than the optimal value; in the compound 1 the N^2-CS bond is longer and in the compound 2 the N^1-CS is shorter than optimal C-N bond. The results of comparison with optimal bond lengths, as well as with the average ones, indicate that the polar structures II and III, with longer C-S bond, describe better the real geometry of thioureas compound 1 and 2 than the structure I **[25]**.

2.2.2 Synthesis of Thiols

Alkyl halides react with thiourea to form stable S-alkylisothiouronium salts. These salts can be used to prepare thiols **[26]**.

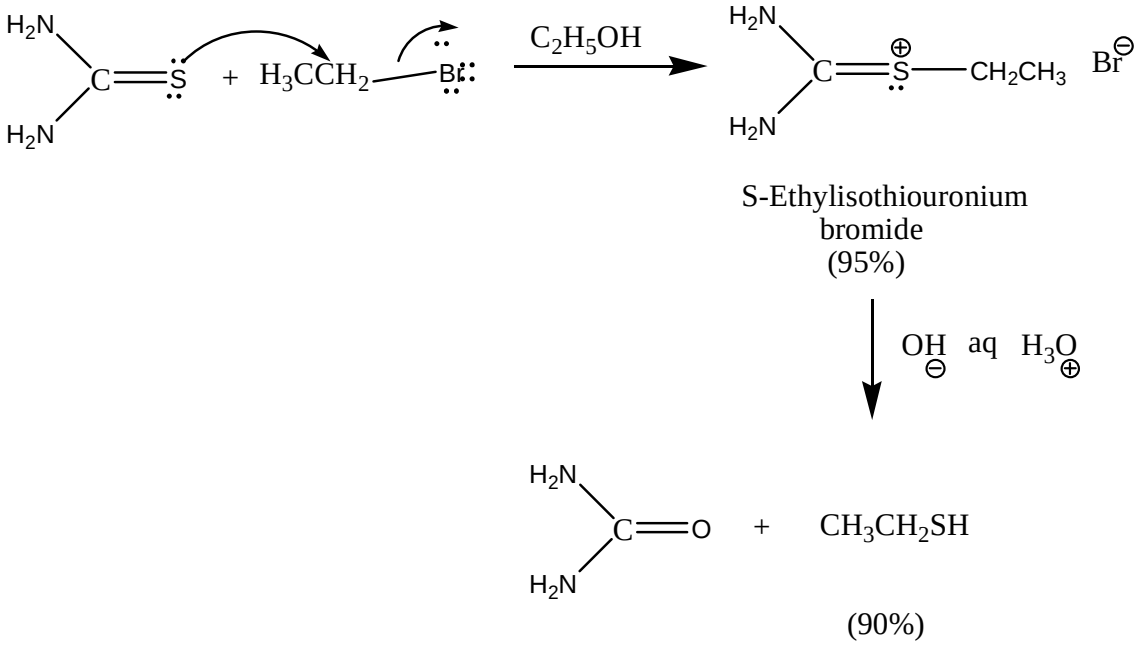


Figure 2.3

2.2.3 One –pot Synthesis of *N*,*N*'-Disubstituted Acylguanidines

An efficient method for the synthesis of acylguanidines is to use thioureas and cyanoguanidines. More recently, several reports have demonstrated that an acylthiourea can be converted to corresponding acylguanidine by the EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) coupling reaction with an amine.

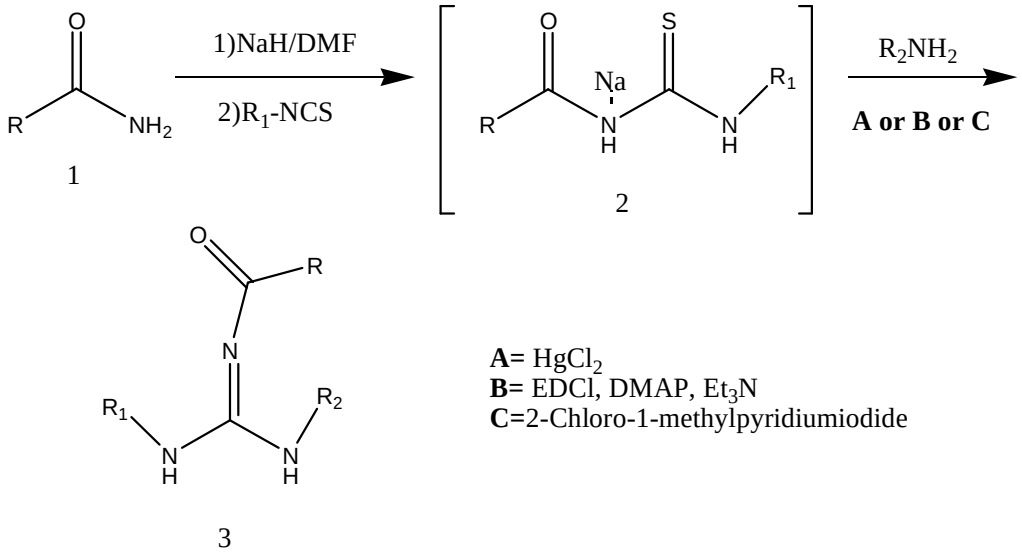


Figure 2.4

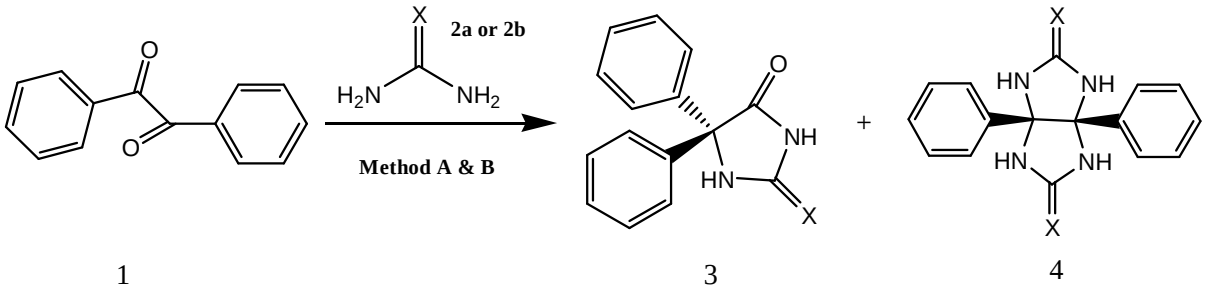
In this reaction the intermediate acylthiourea anion (2), generated by the reaction of a primary amide anion with an isothiocyanate, and the action of a thiocarbonyl activating reagent and a requisite amine provide an N, N'-disubstituted acylguanidine. Intermediate 2a (R_1= phenyl) was synthesized from benzamide anion and phenyl isocyanate in 30 minutes at 60^0C **[27]**.

2.2.4 Synthesis of Hydantoins and Thiohydantoins

The imidazolidine-2, 4-dione, or hydantoin nucleus is a common 5-membered ring containing a reactive cyclic urea core. This heterocycle is present in a wide range of biologically active compounds including antiarrhytmics, anticonvulsant and antitumor agents. Due to the growing interest of medicinal chemist in the hydantoin scaffold, Muccioli and his collaborators developed an efficient and rapid synthesis of phenytoin and related compounds using microwave activation. Microwave activation has received increasing interest in

organic synthesis because of rapid reaction rates, increased yields and cleaner reaction conditions.

The most straightforward condition for the synthesis of phenytoin is the base-catalyzed condensation using benzil (1) and urea. (2a, X=O), known as the Biltz synthesis of phenyltoin(3).



1 3 4

Figure 2.5: Synthetic routes to diphenylhydantoin and diphenylthiohydantoin.

Method A: Conventional route known as Biltz's synthesis of pheyltoin and diphenylthiohydantoin, obtained from benzil and urea or thiourea in absence or presence of microwave activation.

Method B: Two-step procedure for preparing phenytoin following the microwave-assisted condensation of benzil and thiourea giving diphenylthiohydantoin followed by H_2O_2 oxidation in DMF/acetic acid at room temperature **[28]**

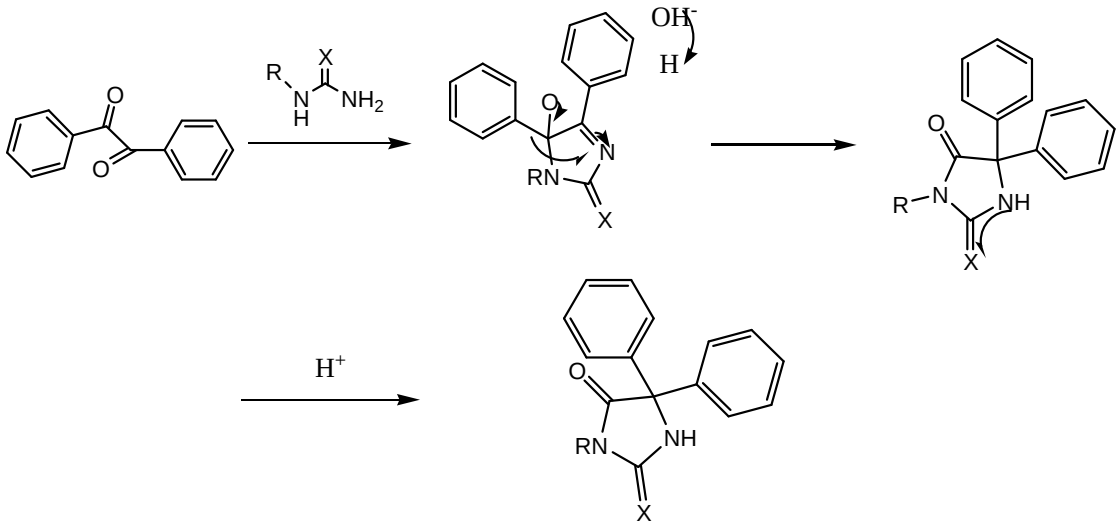


Figure 2.6: Proposed mechanism of condensation of benzile and alkylurea by the benzylic rearrangement**.**

2.2.5 Ferrocene Derivatives

The thiazole ring is very important in nature. It occurs, in thiamine, a coenzyme required for the oxidative decarboxylation of α-keto acids. A tetrahydrothiazole also appears in the skeleton of penicillin which is one of the first and still most important of the broad-spectrum antibiotics. Thiazolamines are key intermediates for synthesizing many pharmaceuticals. Some thiazolidones are valuable medicines. It is obvious that compounds with the thiazole ring have potential biological activity. Also it is known that some Schiff bases are effective antitumor drugs and antibacterials. The search for biologically active ferrocene derivatives has attracted considerable attention. Also, Zakaria and Chohan reported antimicrobial and antibacterial ferrocene derivatives. Huairang Ma and his coworkers synthesized series of ferrocene derivatives with strong biological activity. They have been prepared 4-ferrocenyl-2-thiazilamine with chloroacetyl ferrocene and thiourea **[29]**.

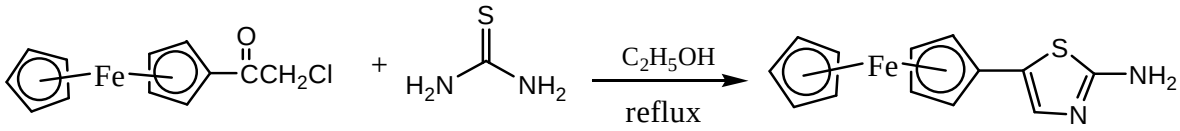


Figure 2.7

With the presence of several electron-donating atoms, acyl thiourea compounds are known for their coordination particularly with transition metals studied the crystal structure of a series of acylthioureas and their complexes with platinum-group metals. Beer reported a ferrocenyl-containing acyl thiourea containing a strong intramolecular hydrogen bond and proposed that the hydrogen bond prevents it from binding $H_2PO^-_4$ as a host.

Intramolecular hydrogen bonding between acyl and hydrogen atom on N'(ferrocene-containing mono-substituted acyl thiourea derivatives **1** and ferrocene-containing disubstituted acyl thiourea derivatives **2**) was found to be common in this kind of compound by Ling-yun Zhang and his coworkers. A planar six-membered ring was often observed. While in the absence of hydrogen atom on N', another inter-side chain hydrogen bond forms between carbonyl and hydrogen on *N*-(1-[*N* –formyl - *N′*, *N′*-disubstituted thiourea]-1'-[*N′*, *N′*-disubstituted amide]ferrocene derivatives 3 **[30]**.

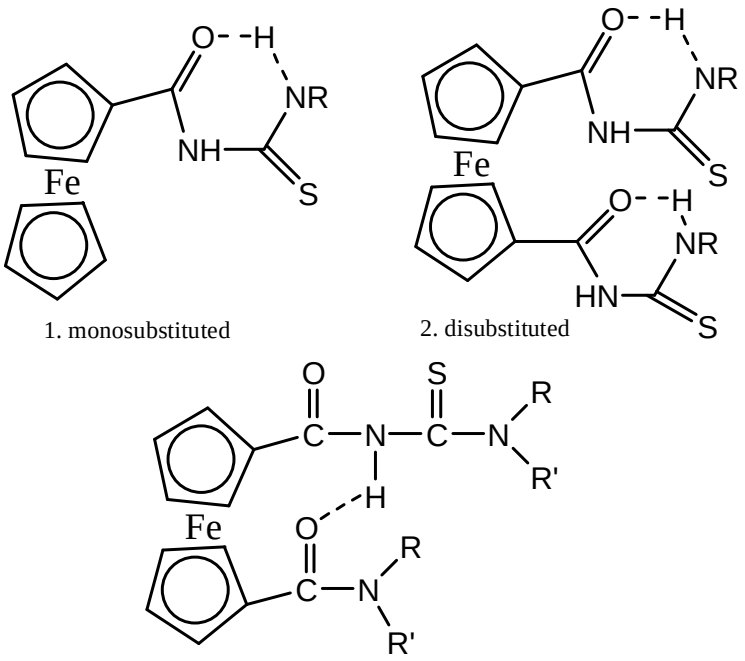
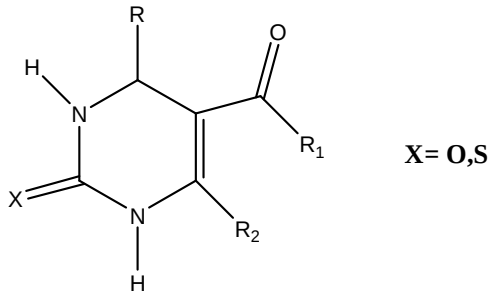


Figure 2.8: Intramolecular hydrogen bonding behavior in ferrocene-containing acyl thiourea derivatives: monosubstituted (1), disubstituted (2), inter-side-chain hydrogen bonding (3).

2.2.6 Biginelli Compounds

In recent years 5-acyl-1, 2, 3, 4-tetrahydropyrimidine-2-thiones/ones **1** (Biginelli Compounds) have received significant attention owing to their diverse range of biological properties. For example, some of these compounds are very potent calcium channel blockers. The presence of several interacted functional groups in Biginelli compounds determines also their great synthetic potential.



X= O,S

1

Figure 2.9

This very simple method of the synthesis of 5-acyl-1, 2, 3, 4-tetrahydropyrimidine-2-thiones/ones involves acid-catalyzed three-component condensation of (thio)ureas, aldehydes and β-oxoesters or 1,3-dicarbonyl compounds. This method is known as Biginelli Reaction.

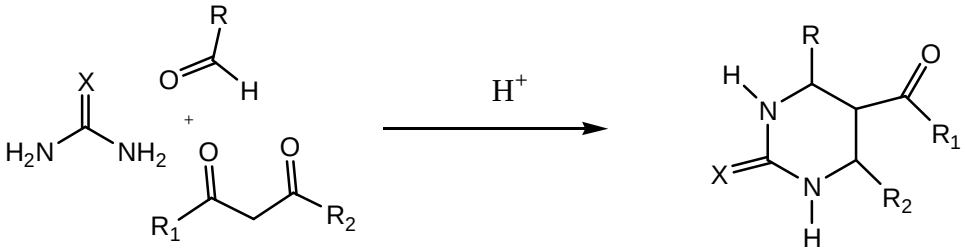


Figure 2.10

Very attractive approach to the synthesis of Biginelli compounds was developed by Atwal and co-workers (Figure 2.9). This approach is based on the reaction of α-arylidene-β-oxoesters with S-(4-methoxybenzyl)isothiourea or O-methylisourea in the presence of sodium bicarbonate followed by transformation of the obtained 2-(-4-methoxybenzylthio)- or 2-methoxy-1,4-dihydropyrimidine-5-carboxylates into 2-thioxi- or 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates.

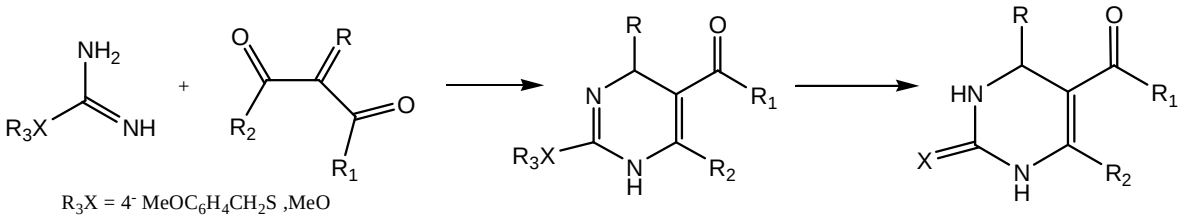
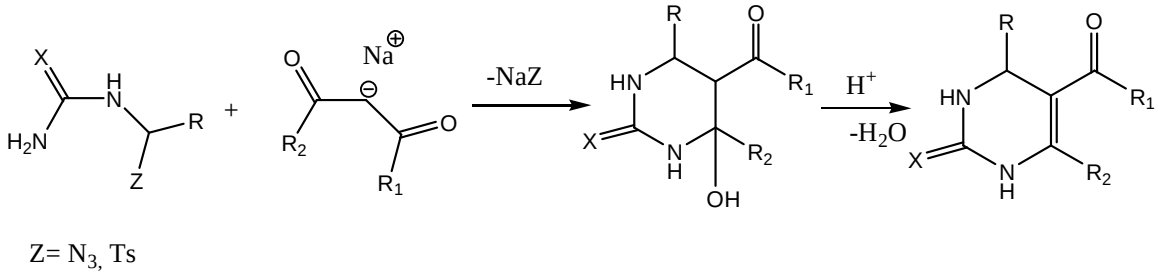


Figure 2.11

Also Shutalev claim that Biginelli compounds can be easily prepared by reaction of α-azido or α-tosyl substituted thioureas and ureas with sodium enolates of β-oxoesters or 1, 3-dicarbonyl compounds followed by acid-catalyzed dehydration of the obtained 5-acyl-4-hydroxyhexahydropyrimidine-2-thiones/ones (Figure 2.11). This method is very flexible and gives possibility to prepare a large number of 1, 2, 3, 4-tetrahydropyrimidine-2-thiones/ones bearing various subtituents in pyrimidine ring **[31].**



Z= N_3, Ts

Figure 2.12

2.2.7 Ring Closure of *N*-(2-Hydroxyethyl)- *N′*-phenylthioureas:

The 2-aminothiazoline ring system has gained much interest as biologically active molecules such as potent inhibitors of human nitric oxide synthase, octopaminergic-agonists, anthelmintics, and anti-inflammatory agents. These compounds are usually prepared by the hydrochloric acid-catalyzed cyclization

of *N*-(2-hydroxyethyl) thioureas or the cyclization of hydrogen sulfate of thioureas in aqueous basic conditions. These methods give low yields for the formation of 2-aminothiazolines and are not applicable to the acid sensitive or racemization-prone substrates due to the vigorous acidic conditions. Alternatively, treatment of aromatic amines with 2-haloalkyl isothiocyanates gives 2-aminothiazolines. This method, however, has some limitations in the scope of aromatic amines.

Recently, Taek Hyeon Kim and his coworkers reported that 2-methylaminothiazolines were synthesized by the intramolecular Mitsunobu reaction conditions (DEAD/TPP). In this report in the cyclization reaction of N-(2-hydroxyethyl) - *N′*-phenylthioureas, they found that that one-pot reaction of *N*-(2-hydroxyethyl) ureas proceeded in the presence of TsCl and some bases to give N-cyclized products in good yields. Thioureas **2** proceeded through mild nucleophilic attack upon the tosylate intermediate in the presence of a base either by the sulfur atom to provide **3** or by the nitrogen to give the 2-imidazolidinethiones **4** depending on the structure of thioureas (**Figure 2.13**).

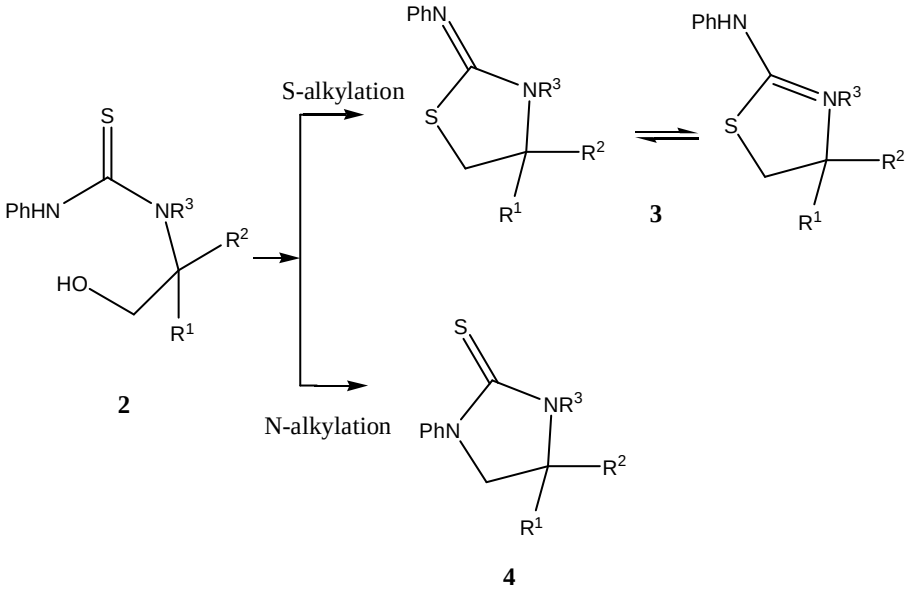


Figure 2.13

The synthetic method of 2-phenylaminothiazolines **3** from the corresponding *N*-(2-hydroxyethyl) thioureas **2** is described in detail in **Figure 2.12 [32]**.

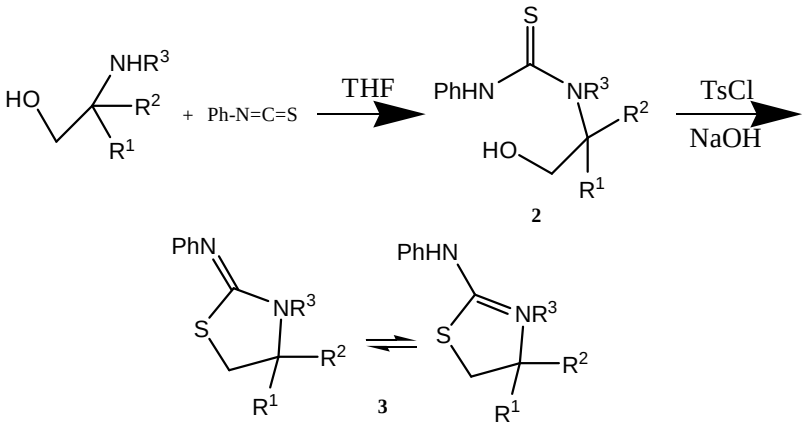


Figure 2.14

2.3 Reactions of Amidoximes with Thioureas

2.3.1 Photocyclization to 1,2,4-triazolo [3,4-*b*]-1,3-(4*H*)-benzothiazines via 1,2,4-triazole-3-thiones

Generally 1, 2, 4-triazole fused heterocyclic ring systems are found to be associated with diverse (various) pharmacological activity. IDPH-791 an analogue of triazolobenzothiazine is a well known centrally acting muscle reactant. Few methods have been reported for the synthesis of 1, 2, 4-triazolobenzothiazine analogs. And photochemical ring expansion of 1, 2-benzisothiazole to 1, 3-benzothiazine and photocyclization of 2-chloroindole-3-thiocarbamate to thiazino indole have been reported. Also, Senthilvelan and his coworkers have reported the photochemical synthesis of triazolobenzothiazole.

The required starting materials, 4-(2-halobenzyl)-5-substituted-1, 2, 4-triazole-3-thiones **1a-e**, were synthesized by refluxing the respective 4-(2-halobenzyl)-1-benzoyl thiosemicarbazide obtained from *o*-halobenzyl isothiocyanate and an acid hydrazide, using a 10% K_2CO_3 solution. **[33]**

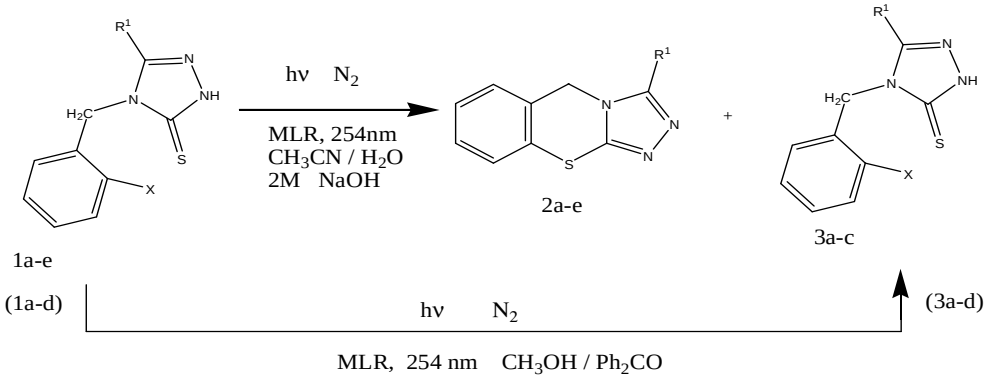
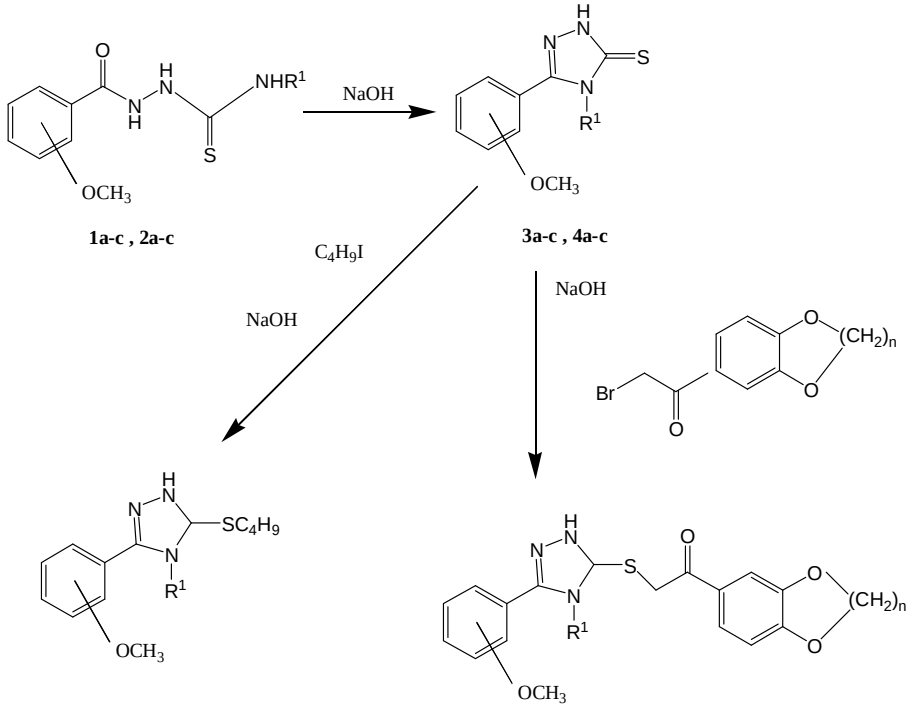


Figure 3.1

2.3.2 Anti-inflammatory Activities of 1,2,4-Triazole Thione and derivatives

3-Aryl-4*H*-1, 2, 4-triazole derivatives are known for their anti-inflammatory activity. Alkylthio-3-(3, 4-dimethoxyphenyl)-4*H*-1, 2, 4-triazole derivatives can exhibit high anti-inflammatory activity and low acute toxicity.



1, 3, 6 : R^1 = H
2, 4, 7, 8 : R^1 = C_8H_5
7 : n = 1 ; 6, 8 : n = 2 ; 9 : n = 3
1-9 : a: 2 - OCH_3 ; b: 3- OCH_3 ; c: 4-OCH_3

Figure 3.2

CHAPTER II

RESULTS AND DISCUSSION

Both amidoximes and thioureas are important starting materials for assembling the heterocyclic compounds with O, N, and S atoms: triazole-thiones, thiazoles. Many of these types of compounds were found to have shown pharmacological activities. Also they were assayed for various industrial and analytical purposes. **[34-54]**

On the other hand, to our best knowledge of literature survey based on the electronic databases; Science Finder Scholar, Web of Science, Science Direct, Beilstein Crossfire Commander, there are no examples of the cyclocondensation reactions of amidoximes and (thio)urea compounds. In this study, various amidoximes were reacted with thioureas under various conditions to obtain triazole-thiones **(3a-d)**, oxatriazine **(4)** ring, carrying a cyclohexyl substituent. The present study is essentially consisted of five sections.

A) Synthesis of amidoximes

B) Reaction of amidoximes with *N*-substituted thioureas

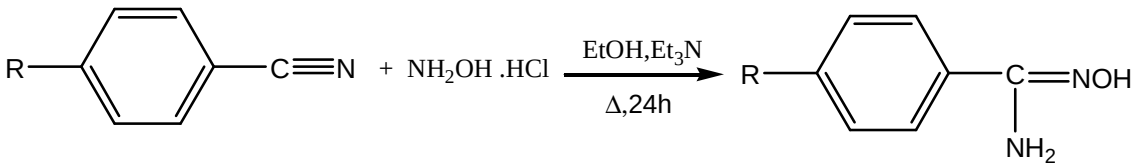
C) Reaction of 3-phenyl mercaptothiadiazole with R-X compounds

D) Reaction of dimercaptothiadiazole with R-X compounds

E) Reaction of 3-phenyl mercapto thiadiazole with mercury (II) chloride

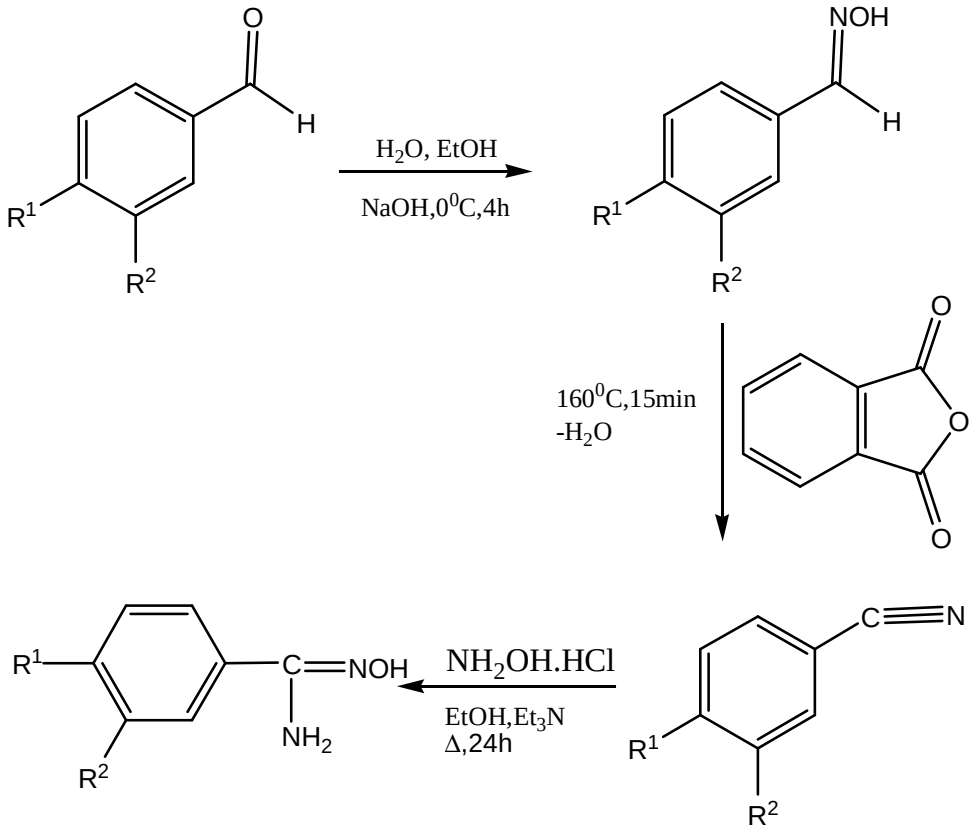
A) Synthesis of amidoximes

Amidoximes were prepared according to the literature procedures starting from nitriles or aldehydes. **[55-59]**



R= $N(CH_3)_2$, I

Scheme 1.1



R^1= MeO, R^2= $PhCH_2O$

Scheme 1.2

These compounds were easily characterized by their physical and spectral data and comparison with the literature values if they were recorded.

In this regard , three new amidoximes were obtained.

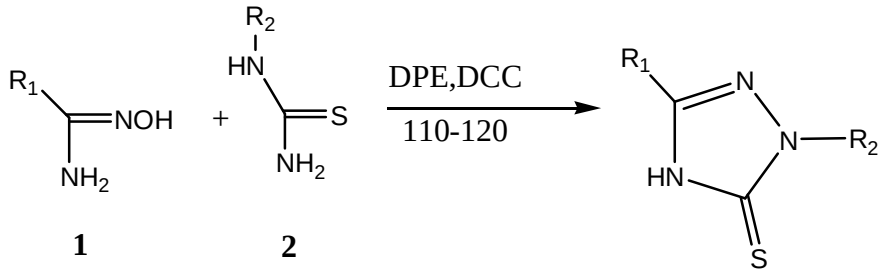
4-Dimethylamino benzamidoxime **(1e)**

p-Iodo benzamidoxime **(1f)**

4-Benzyloxy-3-methoxy benzamidoxime **(1g)**

B) Reaction of amidoximes with *N*-Substituted thioureas

Amidoximes were reacted with thioureas in the presence of DCC in DPE and recovered the triazole-thiones (**Scheme 2.1**).

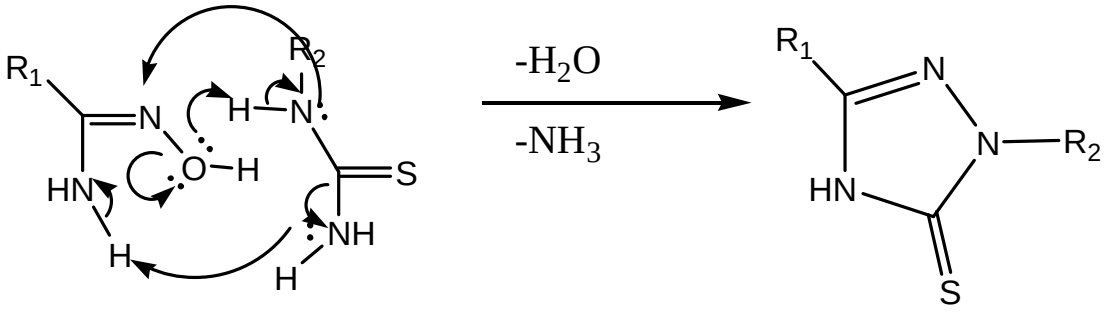


1 **2** **3**

	R_1	R_2
3a	Ph	Ph
3b	p-Me-C_6H_4	Ph
3c	p-Me-C_6H_4	p-Me-C_6H_4
3d	p-NO_2-C_6H_4	Ph

Scheme 2.1

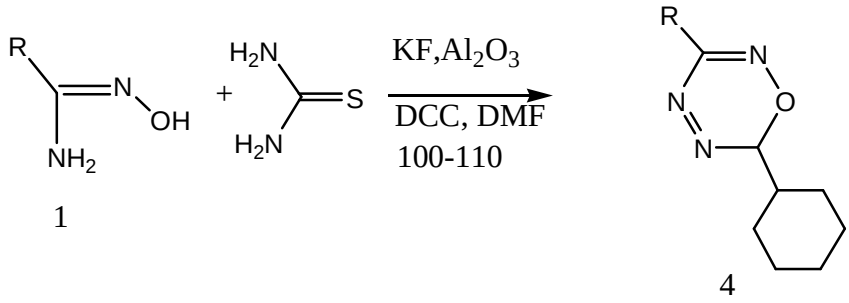
One possible mechanism for this cyclocondensation of amidoximes may be depicted as follows:



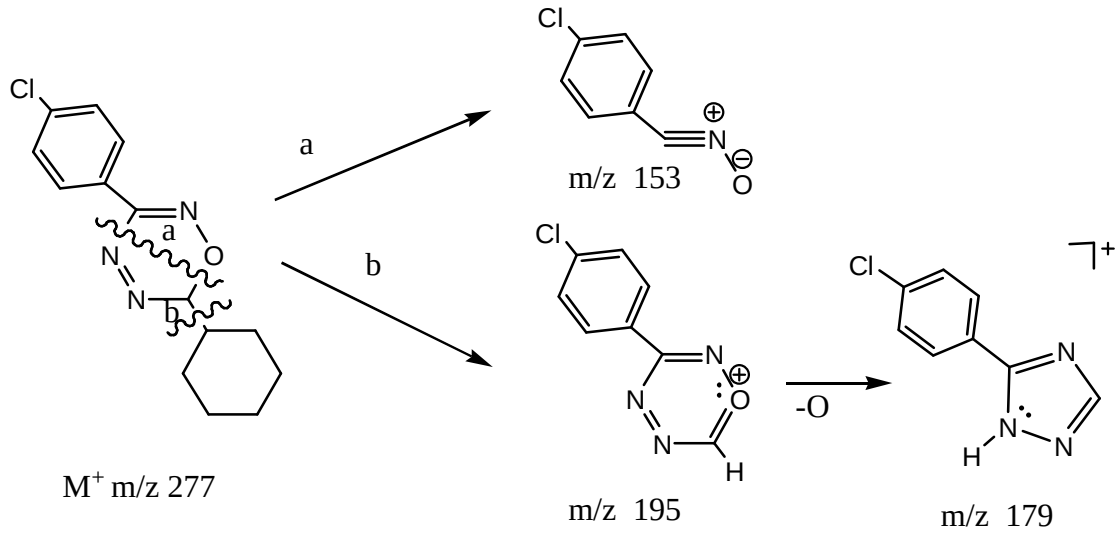
1 **2** **3**

Use of DCC may be considered as facilitating the water release from the reaction. In addition a dense ammonia vapor release during the reaction was observed.

When amidoximes **(1d)** were reacted with thiourea in the presence of alumina,potassium fluoride and DCC in DMF , a new type heterocyclic ring (1,2,4,5-oxatriazine) is formed.



Scheme 2.2



M^+ m/z 277

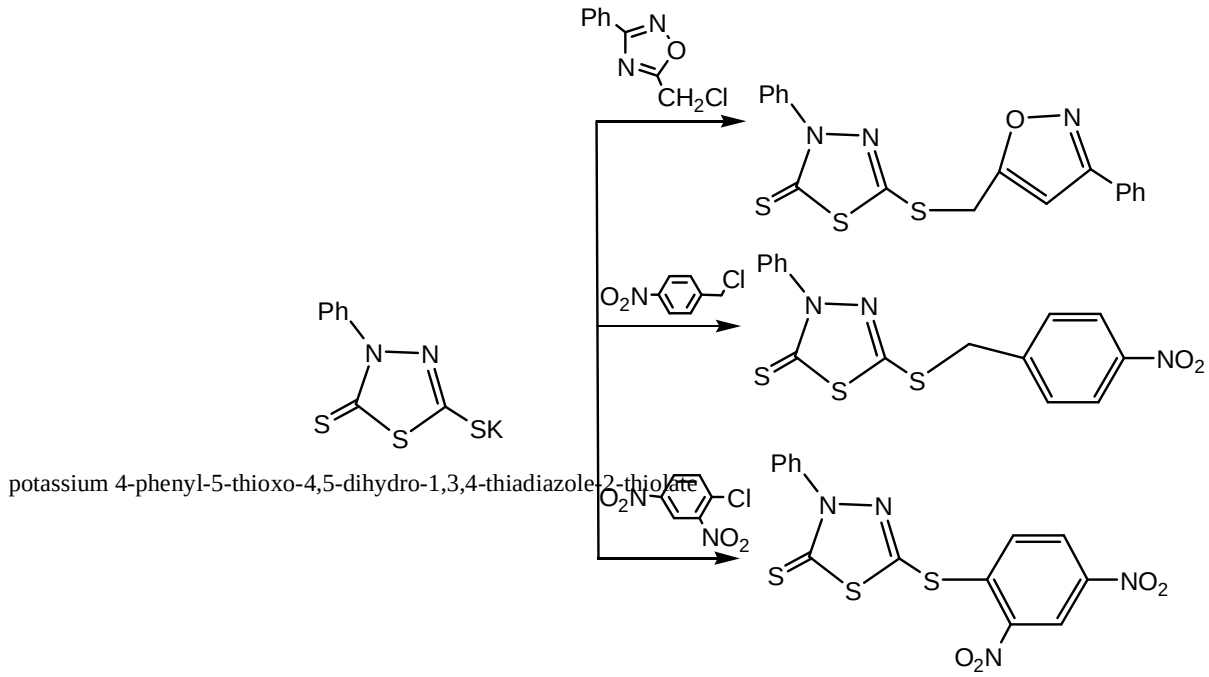
3-(4-chlorophenyl)-6-cyclohexyl-6*H*-1,2,4,5-oxatriazine

Scheme 2.3: Mass spectral fragmentation pathways of compound (4).

Mass spectral fragmentations with m/z 153; 195 and 179 can be attributed to the substituted benzonitrile oxide,oxatriazinium ion and triazole species, respectively.

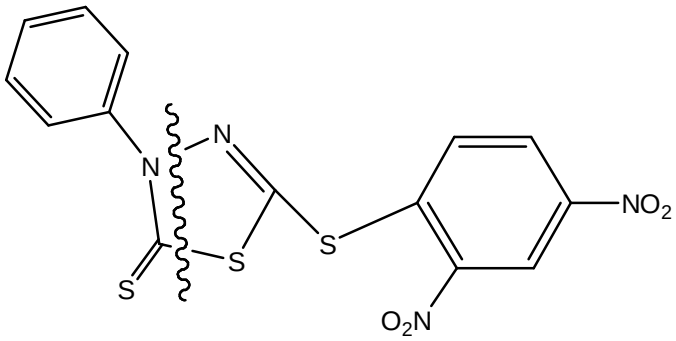
C) Reactions of 5-phenyl mercapto thiadiazole 3-thione with RX

In recent years, heterocyclic thiones have attracted much interest especially to obtain their metal complexes and various derivatives for assaying against bacteria and fungi species. **[60-61]**. Thiones were known to be thiol tautomeric form **[62-69]** in solution which leads to thiolate and progressively reacting with RX type compounds to give SR products instead of NR products. **[70-.74]**



Scheme 3.1

Mass spectral fragmentations are shown below (Scheme 3.2) Fragment with m/z 135 can be considered as phenyl isothiocyanate species. **[75-76]**

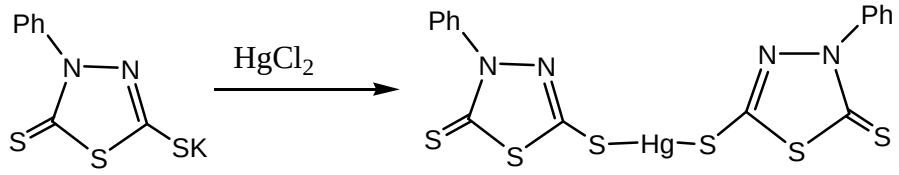


m/z 135

Scheme 3.2

This compound was reacted with RX compounds to give the products, respectively. They were identified by spectral and physical methods. Data were in accord with the specified structures.

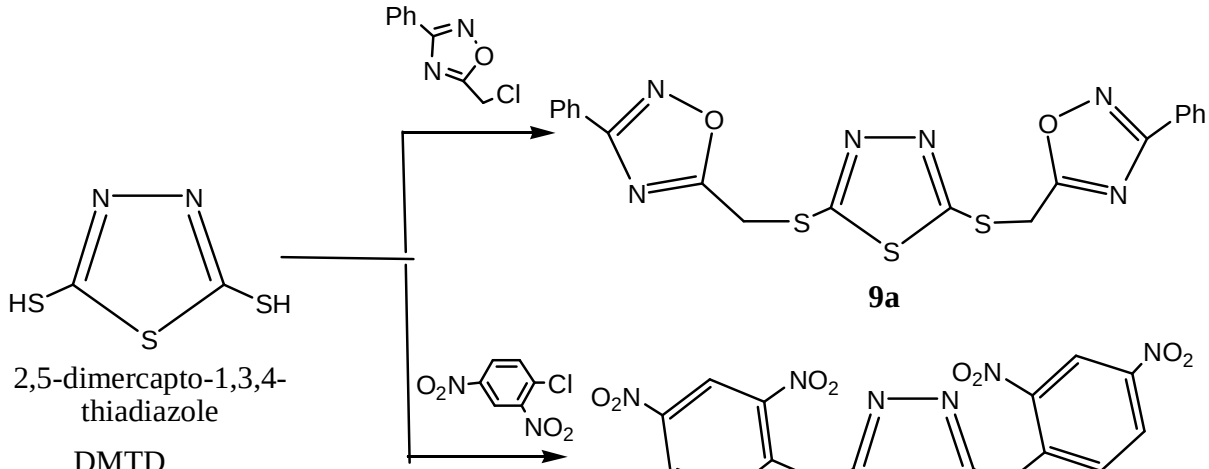
In addition, an organo-mercury derivative was prepared by reacting thiolate **(5) [77, 78]** with mercury (II) chloride according to a very recent procedure reported by us **[70] (Scheme 3.3).**



Scheme 3.3

D) Reaction of Dimercapto-1, 3, 4-thiadiazole with R-X Compounds

Another entry is dimercapto-1, 3, 4-thiadiazole (DMTD). DMTD was reacted with RX compounds to give compounds **(9a, 9b)**.

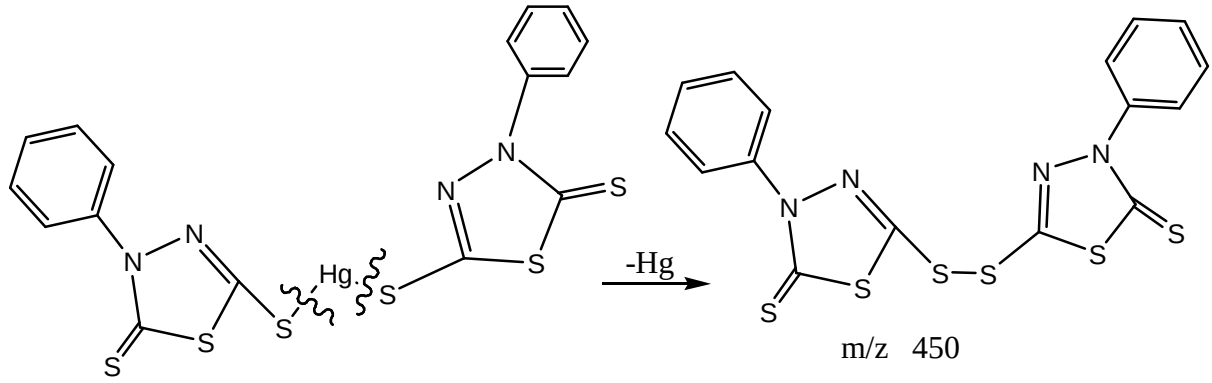


Scheme 3.4

E) Reaction of (5) with Mercury (II) chloride

Bis-mercapto-thiadiazole mercury compound was obtained structure determined spectroscopically.

Mass spectral fragmentation for compound **(7)** is given below.



It is easily seen that a disulfide formation (m/z 450) occurred during electron impact.

Scheme 3.5

CHAPTER III

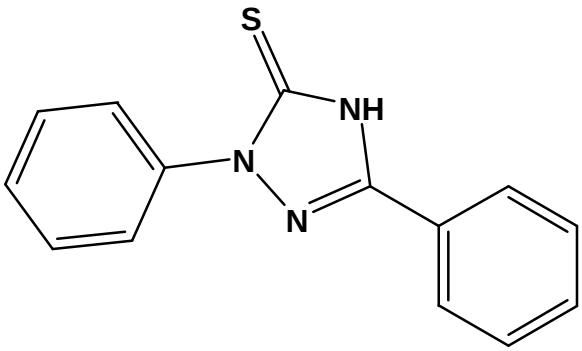
EXPERİMENTAL

^{1}H and ^{13}C NMR spectra were recorded on BRUKER and VARIAN spectrometers. IR

Spectra were recorded on a JASCO 430 FT/IR instrument (KBr pellet in case of solids and neat for oil or liquids using NaCl discs). Mass spectra were run on ZABSpec VG7070E instrument. Melting points were determined on a Meltemp apparatus and uncorrected. Flash Column chromatography was performed on Silica Gel (Merck, 230-400 mesh). TLC was done using precoated plates with fluorescent indicator (Merck 5735).

2.1 Synthesis of Triazole-thiones (3a-d)

2.1.1. 2, 5-Diphenyl-*2H*-1, *2, 4*-triazole-3(*4H*)-thione (3a)



A mixture of benzamidoxime **(1a)** (408.5 mg, 3 mmol) and N-phenylthiourea **(2a)** (457mg, 3 mmol) and Dicyclohexylcarbodiimide (62 mg, 0.3 mmol) in diphenylether (853 mg, 5 mmol) was heated at $140^{0}C$ with vigorous stirring for six hours. Ammonia gas was observed during the reaction. Reaction was

monitored by TLC. The mixture was extracted with petroleum ether to remove DPE. The residual material was purified by flash column chromatography (n-hexane: ethyl acetate; 4:1) to give **(3a)** and recrystallized from benzene (Yield: 111mg, 14.6 %). mp:177-178.5^{0}C. (Lit.191-193^{0}C **[78];** Lit. 179-182^{0}C **[79]**)

Rf : 0.75(Ethyl acetate-n-hexane; 1:1)

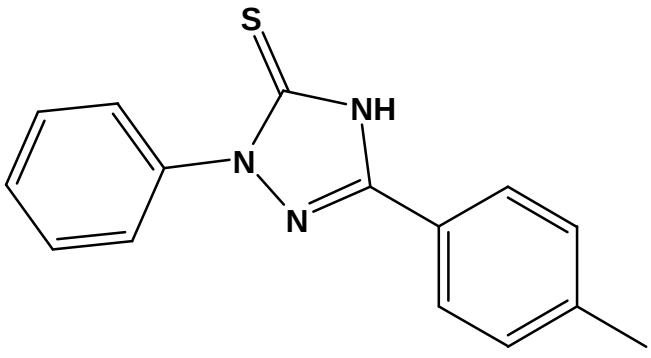
IR (KBr) υ (cm^{-1}) : 3230 (N-H) , 1603 and 1564 (C=N) , 1354 and 1309 (N-C=S)

^{1}H NMR ($\delta_{H,}$ 300MHz, $CDCl_3$): 8.23 (m, 1H), 7.47 (m, 2H), 7.22(m, 4H).

^{13}C NMR ($\delta_{C,}$ 75MHz, $CDCl_3$): 182, 170, 139, 132, 128,128.2,124.

MS (m/z, %): 253 (M^+, 92), 150 (91), 135 (100), 103 (83), 77 (91), 51 (73)

2.1.2. 2-Phenyl-5-*p*-tolyl-*2H*-1, 2, 4-triazole-3(*4H*)-thione (3b)



A mixture of p-toluamidoxime **(1b)** (302 mg, 2 mmol) and *N*-phenylthiourea **(2a)** (304 mg, 2 mmol) were added to a suspension of Al_2O_3 (2g) and KF (2g) in acetonitrile (10mL).The mixture was heated under reflux with vigorous

stirring for three days. Reaction monitored by TLC. The reaction mixture was dissolved in acetone and filtered to remove inorganic parts. The residual product was purified by flash column chromatography (n-hexane: ethyl acetate; 4:1) to give **(3b)** and crystallized from benzene. (Yield: 494mg, 93 %). mp: 186.7-188.8^{0}C.

Rf : 0.63 (Ethyl acetate-n-hexane; 1:2)

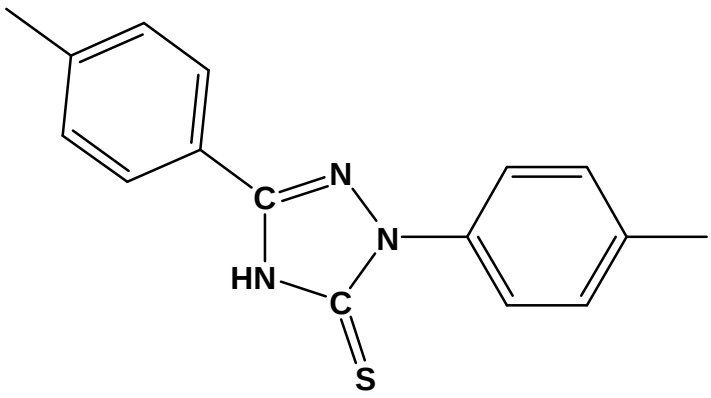
IR (KBr) υ (cm^{-1}) : 3229 (N-H) , 1601 and 1565 (C=N) , 1349 (N-C=S)

^{1}H NMR (δ_H, 400MHz, $CDCl_3$): 8.13-8.08(m, 2H), 7.45-7.16 (m, 7H), 2.89-1.85 (m, 2H).

^{13}C NMR ($\delta_{C,}$ 100 MHz,$CDCl_3$):140.32, 139.17, 130.26, 129.86, 129.28, 127.94, 124.28, 118.37, 21.47.

MS (m/z, %) : 266.7 (M^+ , 51) ,150.149 (64) , 149.1 (100) , 117.15 (32) , 105.15 (6) , 91.15 (34) , 77.1 (21) , 65.1 (16).

2.1.3. 2, 5-di*p*-tolyl-*2H*-1, 2, 4-triazole-3(*4H*)-thione (3c)



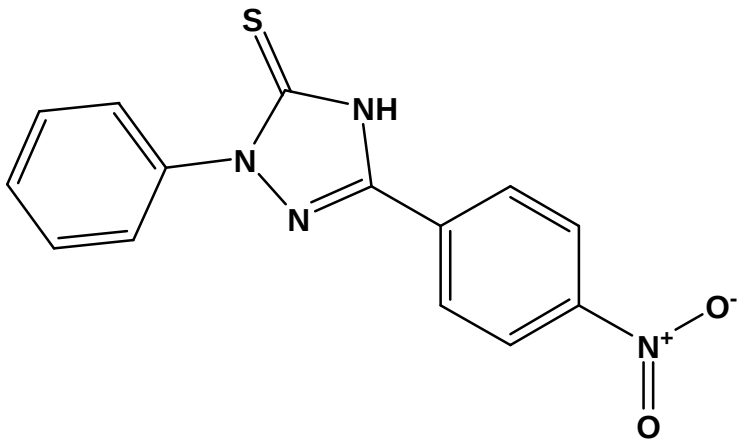
A mixture of p-toluamidoxime **(1b)** (302 mg, 2 mmol) and *p* -tolylthiourea **(2b)** (332.5 mg, 2 mmol) were added to a suspension of Al_2O_3 (2g) and KF (2g) in acetonitrile (10mL).The mixture was heated under reflux with vigorous stirring for a week. Reaction monitored by TLC. The reaction mixture was dissolved in acetone and filtered to remove inorganic parts. The residual product was purified by flash column chromatography (n-hexane: ethyl acetate; 4:1) to give **(3c)** and recrystallized from benzene. (Yield: 443mg, 78.7%). mp: 179.6-182.6^{0}C.

Rf : 0.67 (Ethyl acetate-n-hexane; 1:2)

IR (KBr) υ (cm^{-1}) : 3238 (N-H) , 1602 (C=N) , 1559 ,1442 , 1335 (N-C=S)

MS (m/z, %) : 281.75 (M^+ 21) , 280.75 (100) ,164.15 (76) , 149.15 (100) ,131.15 (21) , 117.15 (42) , 105.15 (9) , 91.15 (48) ,77.1 (21) ,65.1 (15).

2.1.4. 5-(4-nitrophenyl)-2-phenyl-*2H*-1, 2, 4-triazole-3(*4H*)-thione (3d)



A mixture of p-nitrobenzamidoxime **(1c)** (181 mg, 1 mmol) and *N*-phenylthiourea **(2a)** (152 mg, 1 mmol) were added to a suspension of Al_2O_3 (1g) and KF (1g) in acetonitrile (5 mL).The mixture was heated under reflux

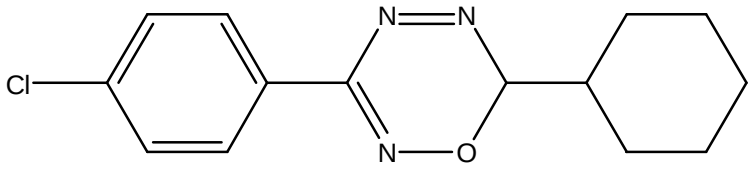
with vigorous stirring at 90^0C for a day. Reaction monitored by TLC. The reaction mixture was dissolved in acetone and filtered to remove inorganic parts. The residual product was purified by flash column chromatography (n-hexane: ethyl acetate; 6:1) to give **(3d)** and recrystallized from benzene and petroleum ether. (Yield: 110mg, 37%). mp:191-192.7^0C.

Rf : 0.90 (Ethyl acetate-n-hexane; 1:2)

IR (KBr) υ (cm^{-1}) : 3380 (N-H), 1646 (C=N), 1587,1552,1533 (N-C=S)

2.2 Synthesis of 1,2,4,5-Oxatriazine (4)

2.2.1. 3-(4-Chlorophenyl)-6-cyclohexyl-*6H*-1, 2, 4, 5-oxatriazine



4-Chlorobenzamidoxime **(1d)** (137.5mg, 1 mmol) and thiourea **(2c)** (76 mg, 1 mmol) were dissolved in DMF (5mL) and the mixture was added to a suspension of Al_2O_3 (0.5g) and KF (0.5g) in DCC (5 mL). The mixture was heated under reflux with vigorous stirring at 120^0C for a day. Reaction monitored by TLC. The reaction mixture was dissolved in water (100mL) and extracted with CH_2Cl_2 (20mL×6) to remove inorganic parts. The organic parts were collected and were dried under vacuum to remove CH_2Cl_2. The residual product was purified by flash column chromatography (n-hexane: ethyl acetate; 6:1) to give **(4)**. (Yield: 210mg, 99.5 %). mp:176-178.5^0C.

Rf: 0.74 (Ethyl acetate-n-hexane; 1:2)

IR (KBr) υ (cm^{-1}) : 3286 and 3229 (NH), 1638 (C=N), 1578,1523, (N-C=S)

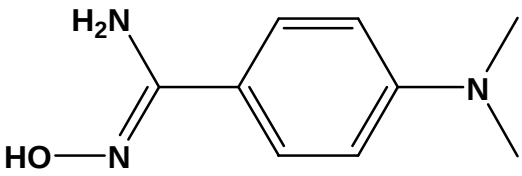
^{1}H NMR ($\delta_{H,}$ 300MHz, $CDCl_3$): 7.96 (d,*J*=2.4 Hz 2H), 7.44 (d,*J*=2.4 Hz 2H), 5.1(d, *J*=7.6 Hz,1H), 3.7 (m, 1H) 2.1(m, 2H), 1.8-1.1 (m, 2H).

^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d6): 170.5, 167.4, 136.7, 128.8, 128.5, 126.3, 96.1, 77.2, 76.9, 76.6, 52.9, 33.3, 29.7, 25.4, 24.6,

MS (m/z, %):278 (M^+ 6), 277 (30), 195 (55), 179 (26), 153 (71), 137 (36), 111 (29), 97 (37), 83 (22), 75 (35), 67 (19), 55 (100)

2.3 Synthesis of Oximes 1e-g

2.3.1. 4-(Dimethylamino)-*N′*-hydroxybenzamidine (1e)

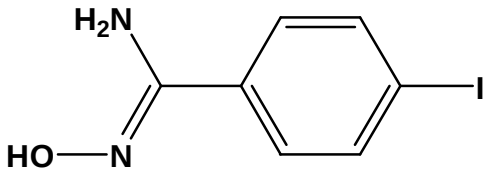


4-Dimethylaminobenzonitrile **(**3000mg, 20mmol) and triethylamine (6mL, 360mmol) were dissolved in ethanol (75 mL). $NH_2OH.HCl$ (2085mg, 300mmol) was added drop wise into the prepared suspension by stirring and the mixture was refluxed for 24 hours. After reflux all solvents was removed off under vacuum and mixture was put in desiccators to dry for one day period. All the mixture was dissolved in water (50mL) and was extracted with CH_2Cl_2 (3x25mL) then combined organic parts were washed by 5% NH_3 solution and brine water (15mL) and dried with Na_2SO_4. CH_2Cl_2 was removed under vacuum and product was dried in dessiccator for 15min. The residual product

was recrystallized from benzene and petroleum ether to give **(1e)**. (Yield: 295.1mg, 20%). mp:154-158.5^{0}C.

IR (KBr) υ (cm^{-1}) : 3498 (N-H) , 3369 (N-H) , 1652 (C=N)

2.3.2. 4-Iodobenzamidoxime (1f)

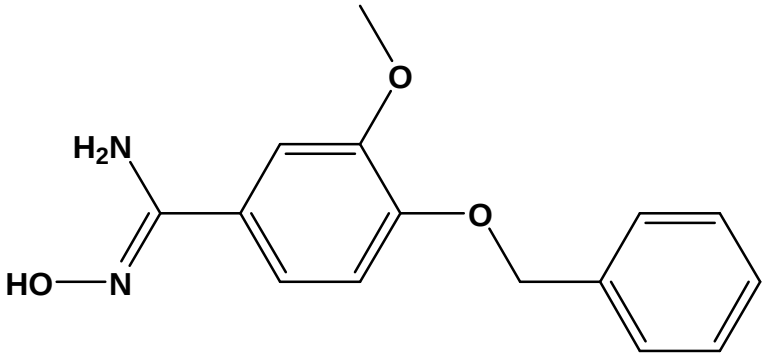


4-Iodobenzonitrile (3000mg, 13mmol) and triethylamine (5mL, 235mmol) were dissolved in ethanol (75 mL). $NH_2OH.HCl$ (1360mg, 300mmol) was added drop wise into the prepared suspension by stirring and the mixture was refluxed for 24 hours. After reflux all solvents was removed off under vacuum and mixture was put in desiccators to dry for one day period. All the mixture was dissolved in water (50mL) and was extracted with CH_2Cl_2 (3x25mL) then combined organic parts were washed by 5% NH_3 solution and brine water (15mL) and dried with Na_2SO_4. CH_2Cl_2 was removed under vacuum and product was dried in dessiccator for 15min. The residual product was recrystallized from benzene and petroleum ether to give **(1f)**. (Yield: 298 mg, 99%). mp:146.3-149.3^{0}C.

Rf : (Ethyl acetate-n-hexane; 1:2)

IR (KBr) υ (cm^{-1}) : 3484 and 3366 (NH) , 1659 (C=N).

2.3.3. 4-(Benzyloxy)-3-methoxybenzamidoxime (1g)



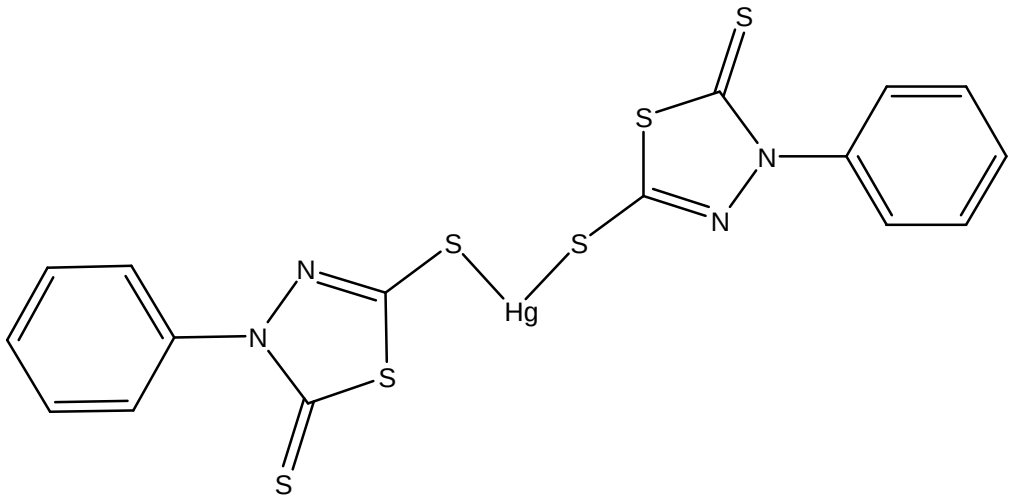
4-Benzyloxy-3-methoxy benzaldehyde (1g, 0.45mmol) in ethanol (5mL) was added into $NH_2OH.HCl$ (0.35g, 5mmol) and NaOH (2g, 50mmol) and water (100 mL) in EtOH (20 mL) cold solution by dropwise. Mixture was stirred at 0^0C for 4 h, then at room temperature for 1 h. Ethanol was removed under vacuum and white solid, (*E*)-4-benzyloxy-3-methoxybenzaldehyde oxime was obtained. Aldoxime was reacted with phthalic anhydride in a sand bath at 150^0C for 15 min. Then mixture was dissolved in CH_2Cl_2 and filtrated. The solution was extracted with 5% NH_3 solution (3x 25 mL) to give 4-benzyloxy-3-methoxy-benzonitrile. IR spectrum showed the was C=N stretching at $2219cm^{-1}$. 4-Benzyloxy-3-methoxy-benzonitrile (4mg, 18mmol) and triethylamine (6mL, 360mmol) were dissolved in ethanol (75 mL). $NH_2OH.HCl$ (1.9g, 27mmol) was added dropwise into the prepared suspension by stirring and the mixture was refluxed for 24 hours. After reflux all solvents was removed off under vacuum and mixture was put in desiccators to dry for one day period. All the mixture was dissolved in water (50mL) and was extracted

with CH_2Cl_2 (3x25mL) then combined organic parts were washed by 5% NH_3 solution and brine water (15mL) and dried with Na_2SO_4. CH_2Cl_2 was removed under vacuum and product was dried in dessiccator for 15min. The residual product was crystallized from benzene to give **(1g)**. (Yield: 415.3mg, 20%). mp:157.5-159.9^{0}C.

IR (KBr) υ (cm^{-1}) : 3839 and 3482 (NH) , 1646 (C=N).

2.4 Synthesis of Organosulfur-Mercury Compound (7)

2.4.1. Bis (3-phenyl-2-thioxo-1, 3, 4-thiadiazol-5-thiolato) mercury (II)



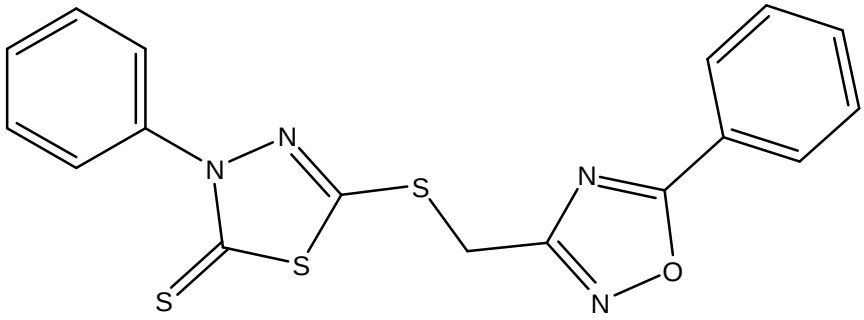
$HgCl_2$ solution in aqua EtOH (10mL) was added drop wise to a solution of potassium 4—phenyl-5-thioxo-4,5-dihydro-1,3,4-thiadiazole-2-thiolate **(5)** (264mg,1mmol) in EtOH (mL). The reaction mixture was stirred in room temperature for one day. EtOH was taken by evaporation and mixture was dissolved in THF by heating. The solution was filtrated and evaporated to give **(7)** (Yield: 300 mg, 46%) mp: 185.5-186.8

IR(KBr) υ (cm^{-1}) : 1628 , 1492 and 1438 (C=N).

MS (m/z, %) : 450.2 (M^+, 9) , 314.35 (3) , 226.8 (2) , 225.8 (9) , 135.15 (37) , 105.15 (29) , 91.25 (26) , 77.1 (100) , 63 (95).

2.5 Synthesis of S-R Products (6a-c)

2.5.1 3-phenyl-5-((5-phenyl-1, 2, 4-oxadiazol-3-yl) methyl-thio) 1,3,4-thiadiazole-2(3*H*)-thione (6a)



Potassium-4-phenyl-thioxo-4, 5-dihydro-1, 3, 4-thiadiazole-2-thiolate **(5)** (260 mg, 1.34 mmol) and 3-(chloromethyl)-5-phenyl-1, 2, 4-oxadiazole (353.76mg, 1.34mmol) were dissolved in THF (5mL). Both of the solutions were mixed by drop wise. The reaction mixture was stirred at room temperature for one day. Mixture was crystallized with hexane and the undissolved parts were crystallized with benzene to give **(6a)**. (Yield: 400 mg, %) mp: 84.6-85^{0}C

Rf: 0.57 (Ethanol-n-hexane; 3:1)

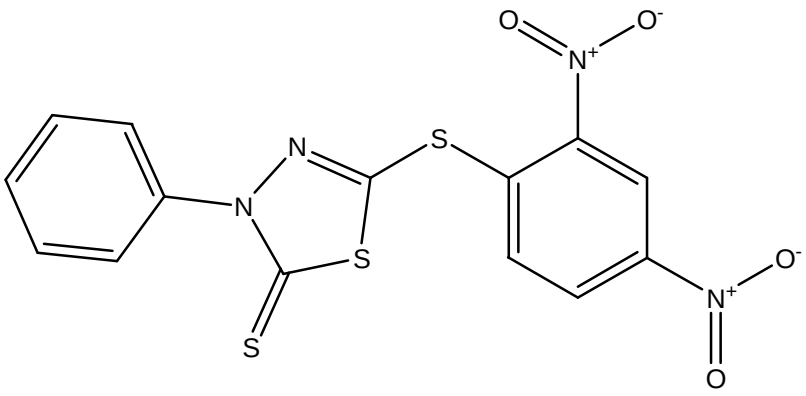
IR (KBr) υ (cm^{-1}) : 2929 , 1498 , 1359.

^{1}H NMR ($\delta_{H,}$ 400MHz, $CDCl_3$): 8.28 (m, 2H) 7.74 (m, 2H,), 7.48-7.41 (m, 6H) 4.7(s, 2H).

^{13}C NMR ($\delta_{C,}$ 100MHz, $CDCl_3$):185.6, 174.27, 168.70,151.94, 138.27, 131.45, 128.90, 128.82, 127.52, 126.27, 125.38, 96.18, 26.79.

MS (m/z, %) : 383.1 (M^+, 45) , 135.15 (14) , 119.15 (6) , 105.15 (32) , 91.15 (19) , 77.1 (100) , 64.1 (13) , 51.1 (17)

2.5.2 5-(2, 4-Dinitrophenylthio)-3-phenyl-1, 3, 4-thiadiazole-2(3*H*)-thione (6b)



Potassium-4-phenyl-thioxo-4, 5-dihydro-1, 3, 4-thiadiazole-2-thiolate **(5)** (396 mg, 1.5 mmol) was dissolved in THF (5mL) and also 1-chloro-2, 4-dinitrobenzene (303.84mg, 1.5mmol) was dissolved in THF (5mL). The second solution was added by drop wise in to the first one. The reaction mixture was stirred at room temperature for one day. Reaction mixture was dissolved in water and extracted with CH_2Cl_2 (3×25mL) and dried with Na_2SO_4.The product was obtain as yellow powder. **(6b)** (Yield: 730 mg,) mp: 172.6-174.8^{0}C

Rf: 0.24 (Ethanol-n-hexane; 2:1)

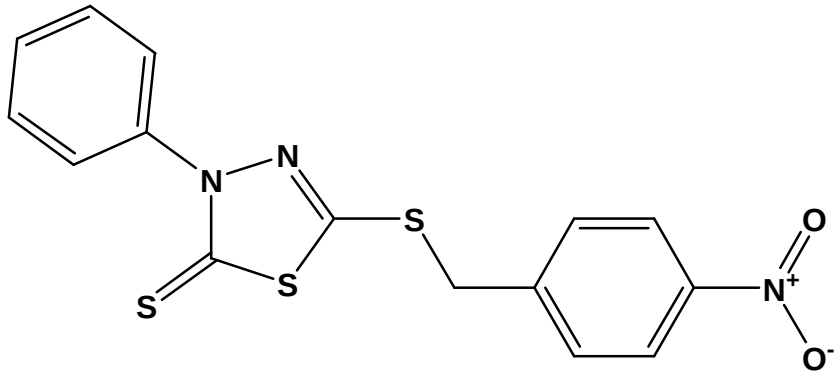
IR (KBr) υ (cm^{-1}) : 1594 , 1535 , 1338, 1224.

^{1}H NMR ($\delta_{H,}$ 400MHz, $CDCl_3$): 9.32 (s,broad,1H) , 8.47 (s,broad,1H) , 7.55 (m, 6H).

^{13}C NMR ($\delta_{C,}$ 100 MHz,$CDCl_3$):129.69, 129.25, 128.08, 125.61, 121.63.

MS (m/z, %): 391.1 (M^+, 21) , 183.2 (14) , 135.15 (18) , 105.15 (19) , 91.25 (43) , 77.1 (100) , 64.1 (22).

2.5.3 5-(4-nitrobenzylthio)-3-phenyl-1, 3, 4-thiadiazole-2(3*H*)-thione (6c)



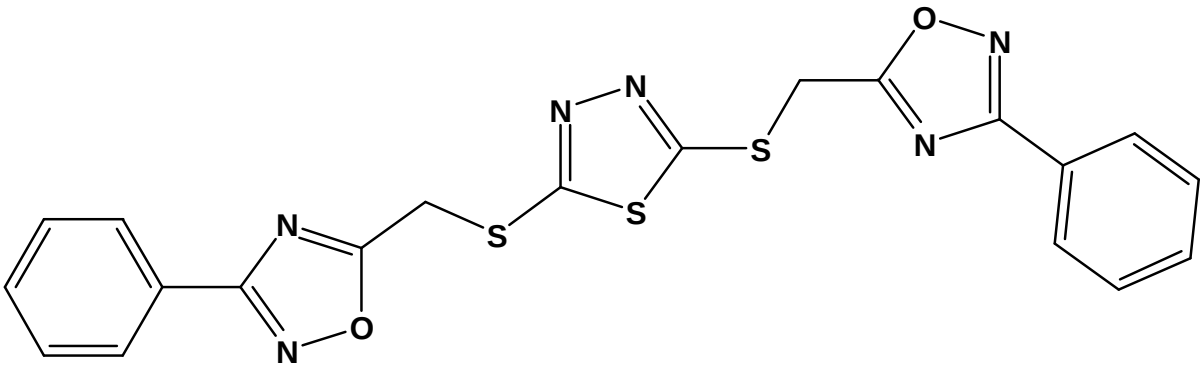
Potassium-4-phenyl-thioxo-4, 5-dihydro-1, 3, 4-thiadiazole-2-thiolate **(5)** (260 mg, 1.5 mmol) was dissolved in THF (5mL) and a solution of a 1-chloromethyl-4-nitrobenzene (396mg,1.5mmol) in THF(5mL) was added by drop wise in to the first solution. The reaction mixture was stirred at room temperature for one day. THF was evaporated and reaction mixture was put in desiccator. The product was obtained as yellow powder **(6c)**. (Yield: 672.3 mg, %) mp: 108-113.2^{0}C

Rf: 0.29 (Ethanol-n-hexane; 2:1)

IR (KBr) υ (cm^{-1}) : 1595 , 1513 , 1490 , 1342 , 1225 .

2.4. Synthesis of Dimercapto-thiadiazole Derivatives (9a, 9b)

2.4.1 3-phenyl-5-((5-((3-phenyl-1, 2, 4-oxadiazol-5-yl)methylthio)1,3,4-thiadiazol-2-ylthio)methyl)-1,2,4-oxadiazole (9a)



5-(Chloromethyl)-3-phenyl-1,2,4-oxadiazole (260mg,1.34mmol) in THF (5mL) was added drop wise into a solution of 1,3,4-thiadiazole-2,5-dithiol **(8)** (100mg,0.67mmol) in EtOH (5mL) containing KOH (75mg,1.34mmol) stirred at room temperature for one day. The mixture was evaporated to dryness. The yellow solid was taken into the water (50mL) and extracted with CH_2Cl_2 (3×20mL). Combined organic parts were dried over anhydrous Na_2SO_4 and crystallized from EtOH to give **(9a)** mp: 103-105.6^{0}C.

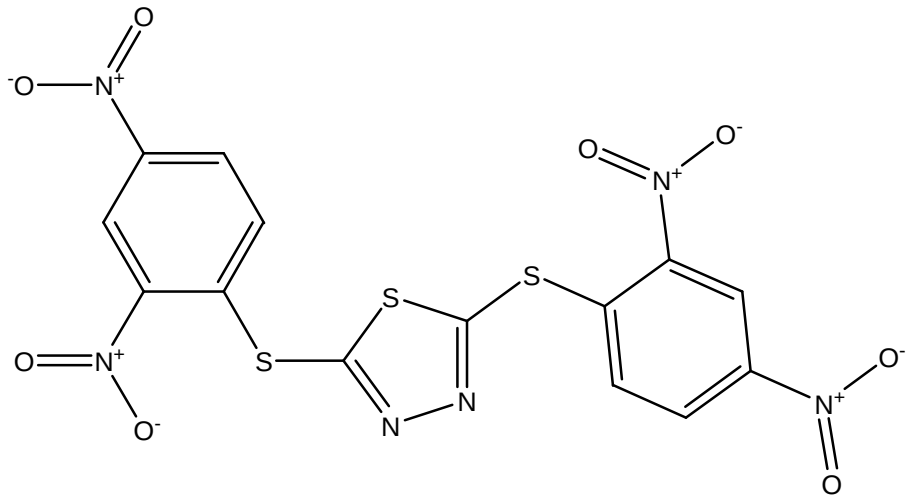
IR (KBr) υ (cm^{-1}) : 1600, 1490, 1410, 610,600.

^{1}H NMR ($\delta_{H,}$) : 7.76 (m,4H) ,7.58 (m,6H) 4.96 (d,4H,2xCH_2)

^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 189.2, 176.9, 176.8, 168.3, 164.7, 155.9, 132.7, 132.2, 132.1, 129.8, 129.7, 128.8, 127.5, 126.3, 40.6, 40.4, 40.2, 40, 39.8, 39.6, 39.3, 28.4, 27.9. .

MS (m/z, %) : 466 (M^+10) , 308 (14) , 191 (10) , 145 (24) , 129 (95) , 103 (100) , 76 (74) , 64 (46) , 51 (62).

2.4.2 2, 5- Bis (2, 4-dinitrophenylthio) 1, 3, 4-thiadiazole (9b)



1-Chloro-2,4-dinitrobenzene (602.68mg,3mmol) in alcohol (5mL) was added drop wise into a solution of 1,3,4-thiadiazole-2,5-dithiol **(8)** (225mg,1.5mmol) in alcoholic solution of NaOH (120mg,3mmol/5mL). Two solutions were mixed at room temperature and stirred for one day. An orange solution was obtained. Precipitation was begun after 20 min. After two hours color was changed to yellow. The mixture was evaporated to dryness. The product was taken into the water (50mL) and yellow precipitate was filtrated. The crude product was crystallized from hot dioxane to give **(9b)**. (Yield:) mp: 235.8-237^{0}C

IR (KBr) υ (cm^{-1}) : 1590, 1508,1349, 1035, 835, 739.

MS (m/z, %): 482 (M^+,26), 436 (66), 183 (95), 137 (100), 95 (64), 63 (81).

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APPENDICES: IR, NMR (^{1}H, ^{13}C) AND MASS SPECTRA

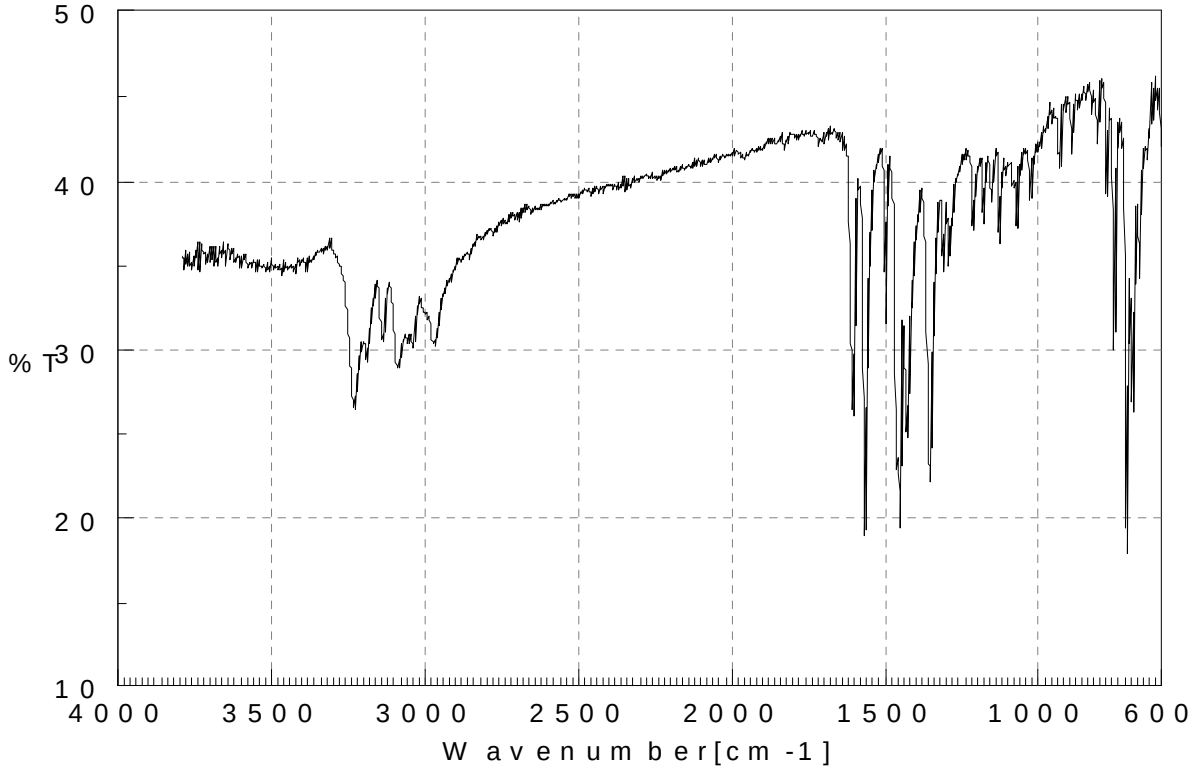


Figure 4.1: IR spectrum of **3a**

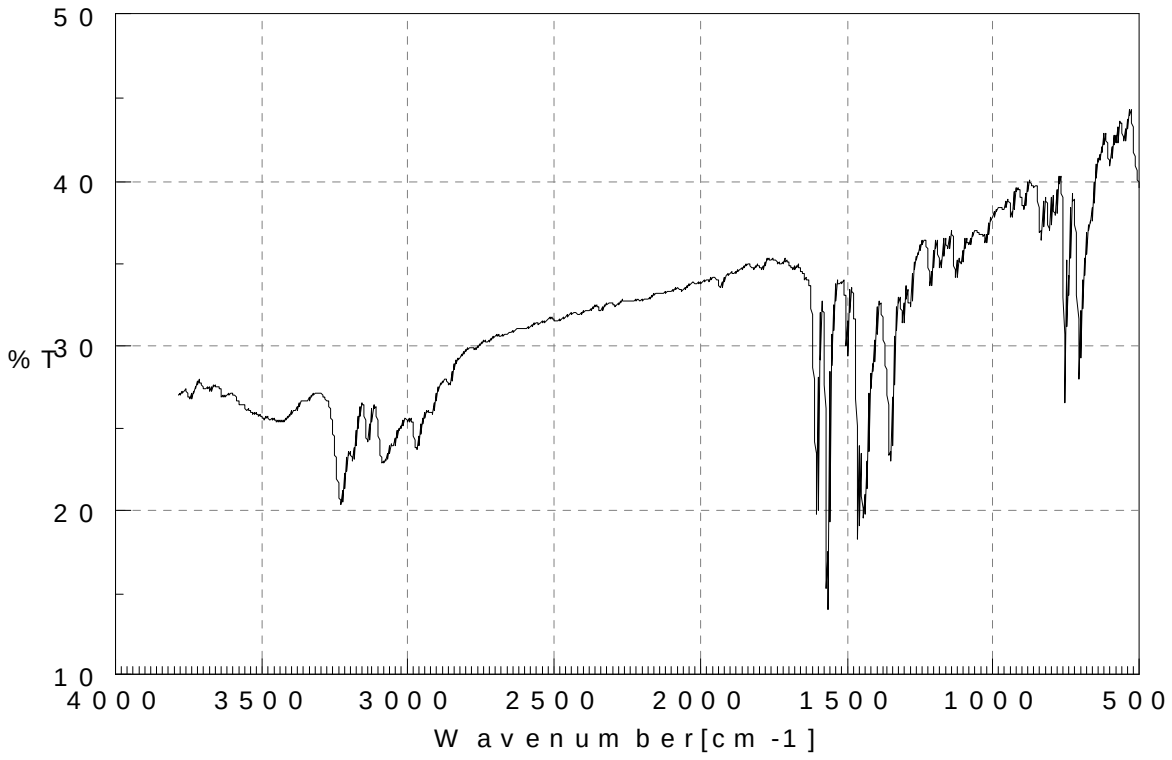


Figure 4.2: IR spectrum of **3b**

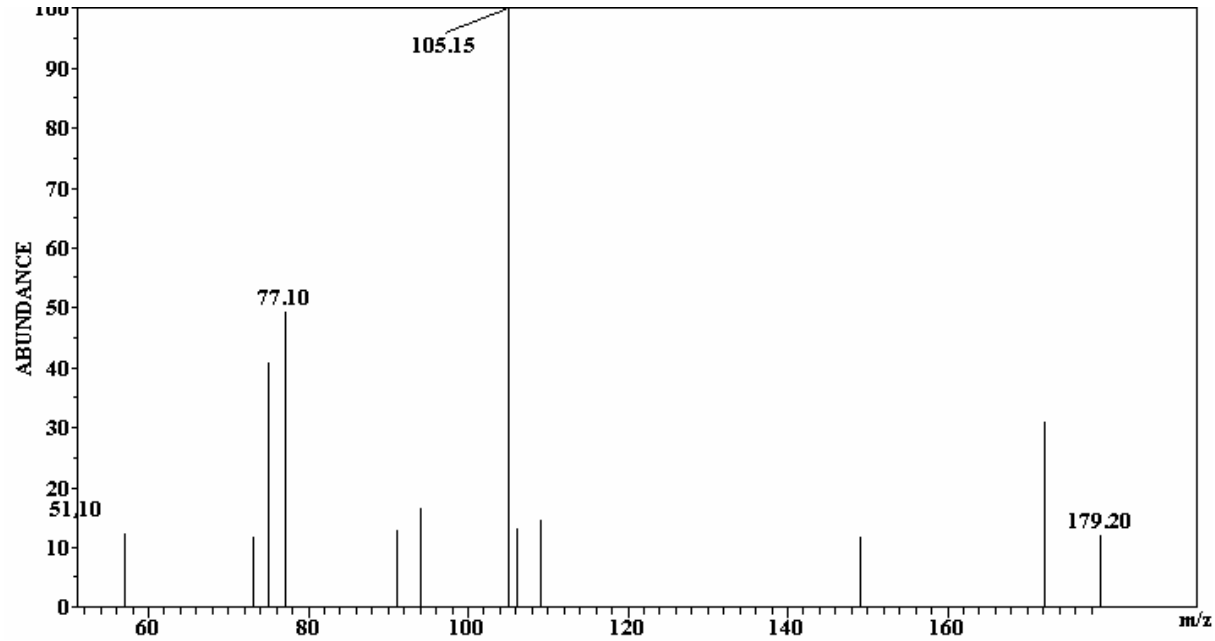


Figure 4.3: Mass spectrum of **3b**

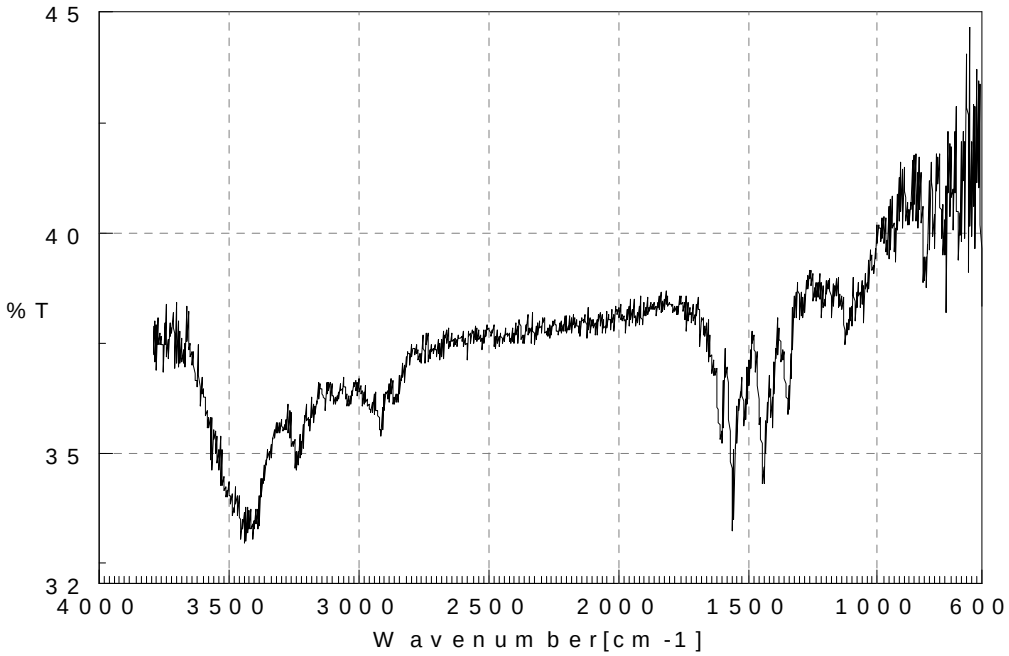


Figure 4.4: IR spectrum of **3c**

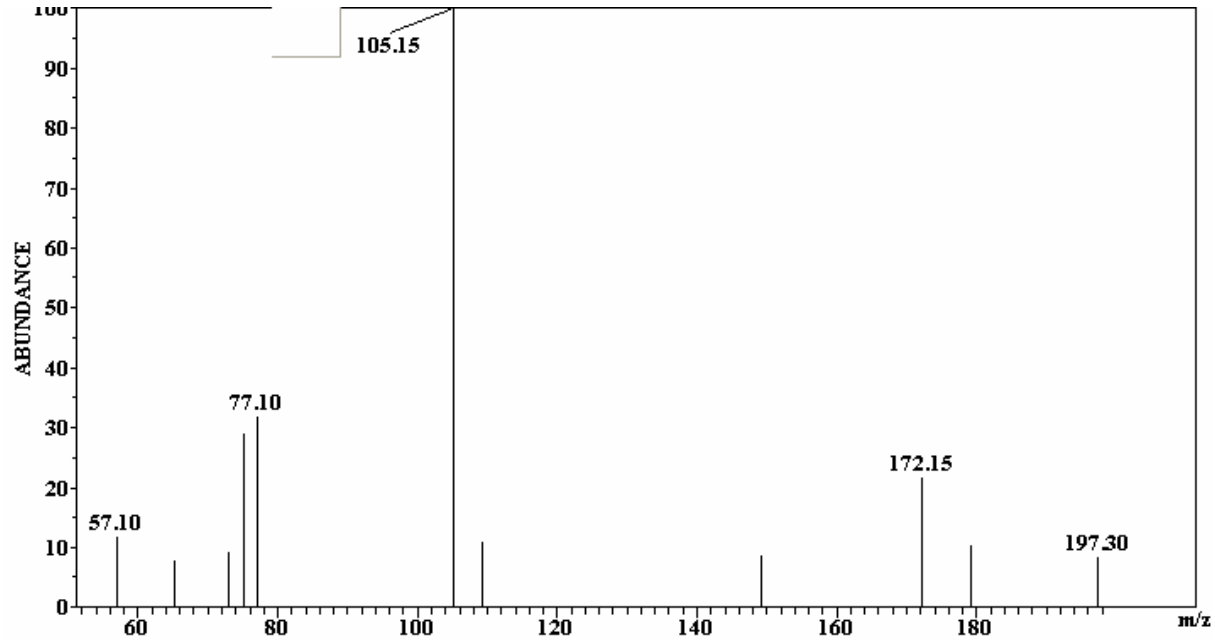


Figure 4.5: Mass spectrum of **3c**

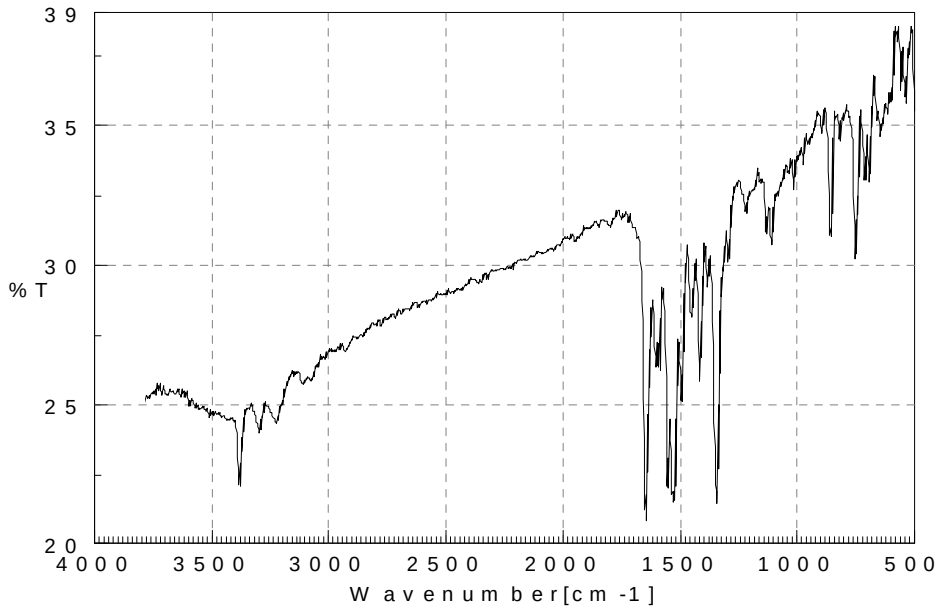


Figure 4.6: IR spectrum of **3d**

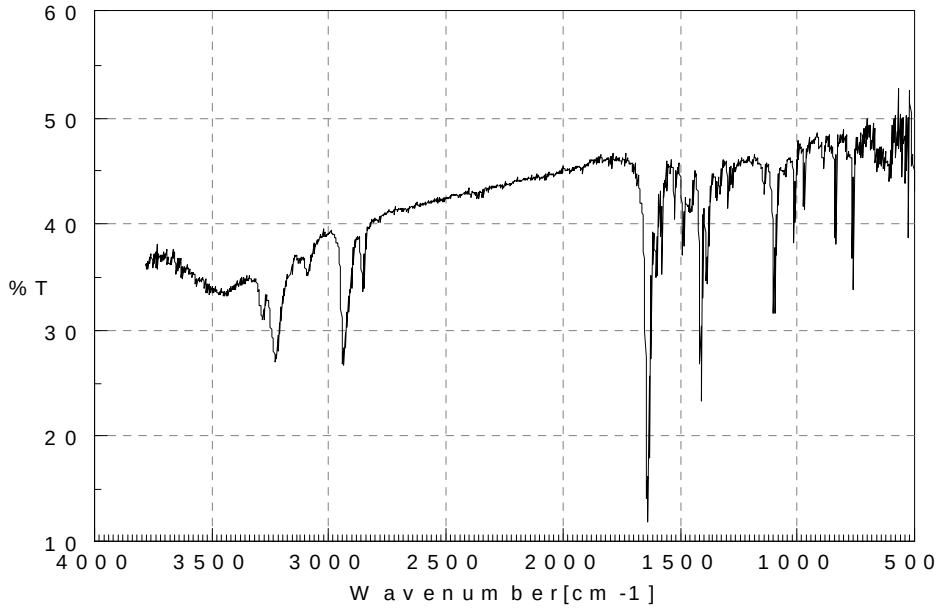


Figure 4.7: IR spectrum of **4**

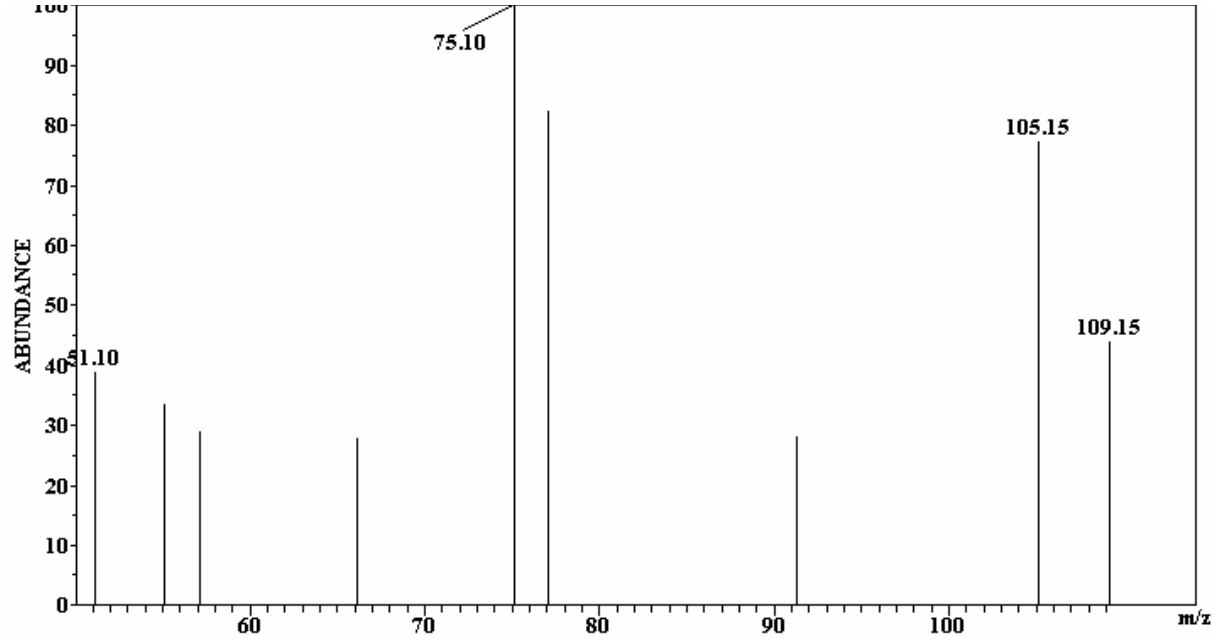


Figure 4.8: Mass spectrum of **4**

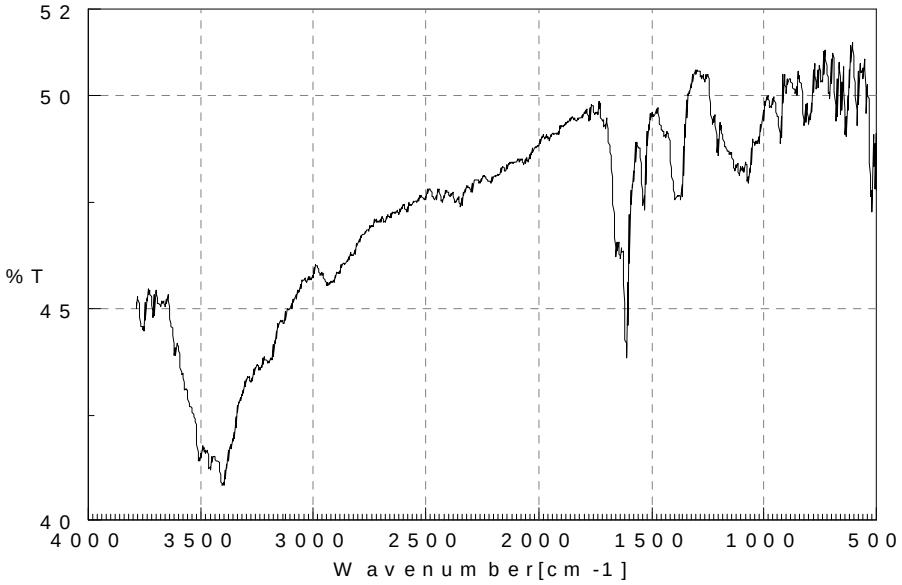


Figure 4.9: IR spectrum of **1e**

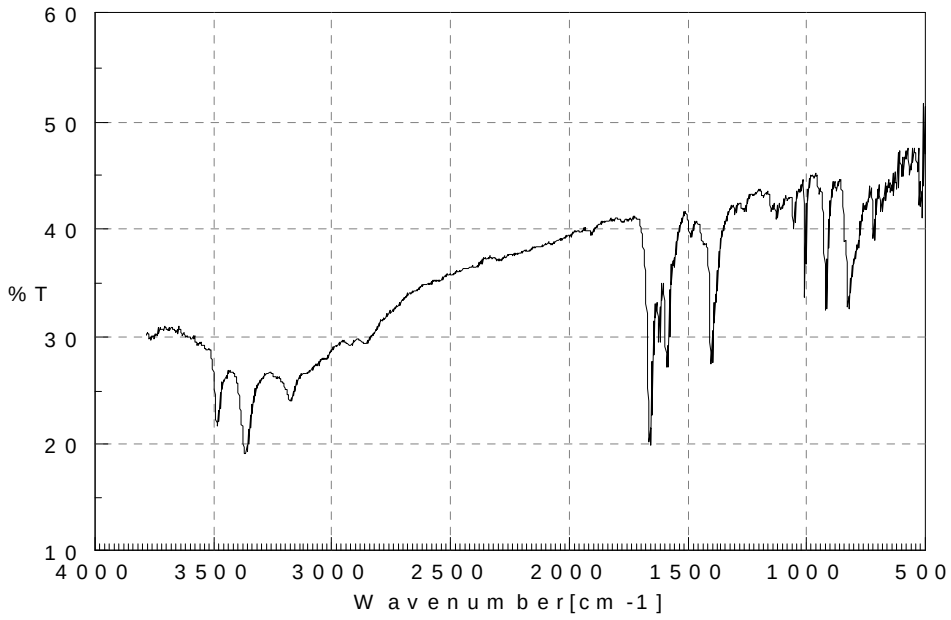


Figure 4.10: IR spectrum of **1f**

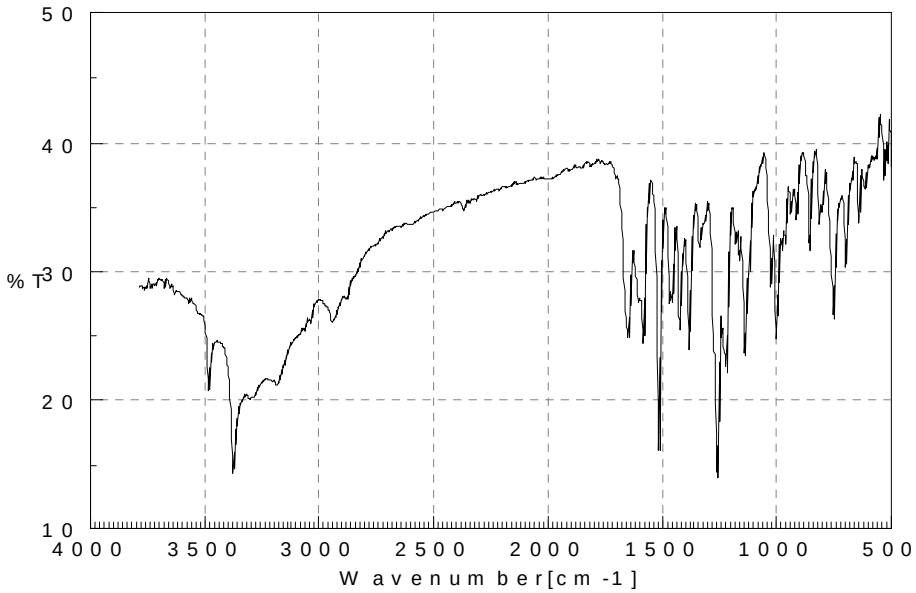


Figure 4.11: IR spectrum of **1g**

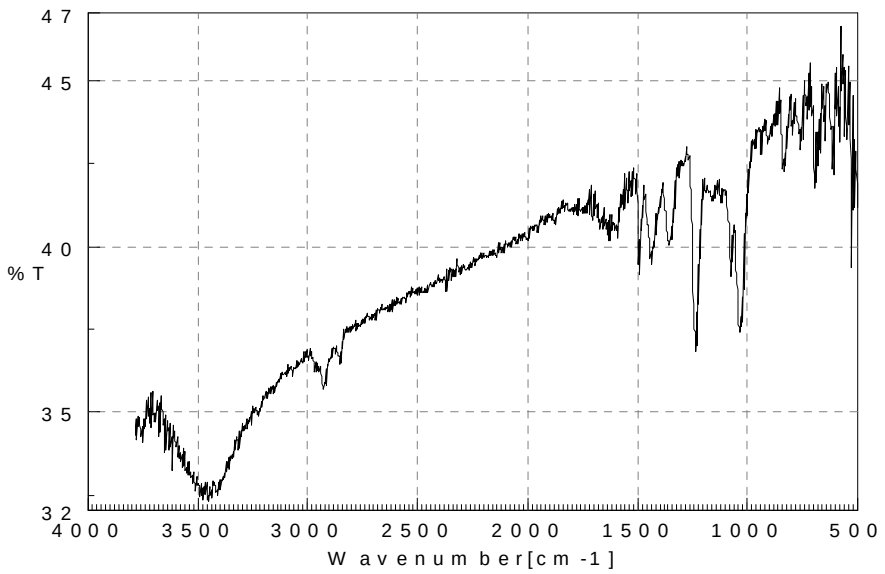


Figure 4.12: IR spectrum of **7**

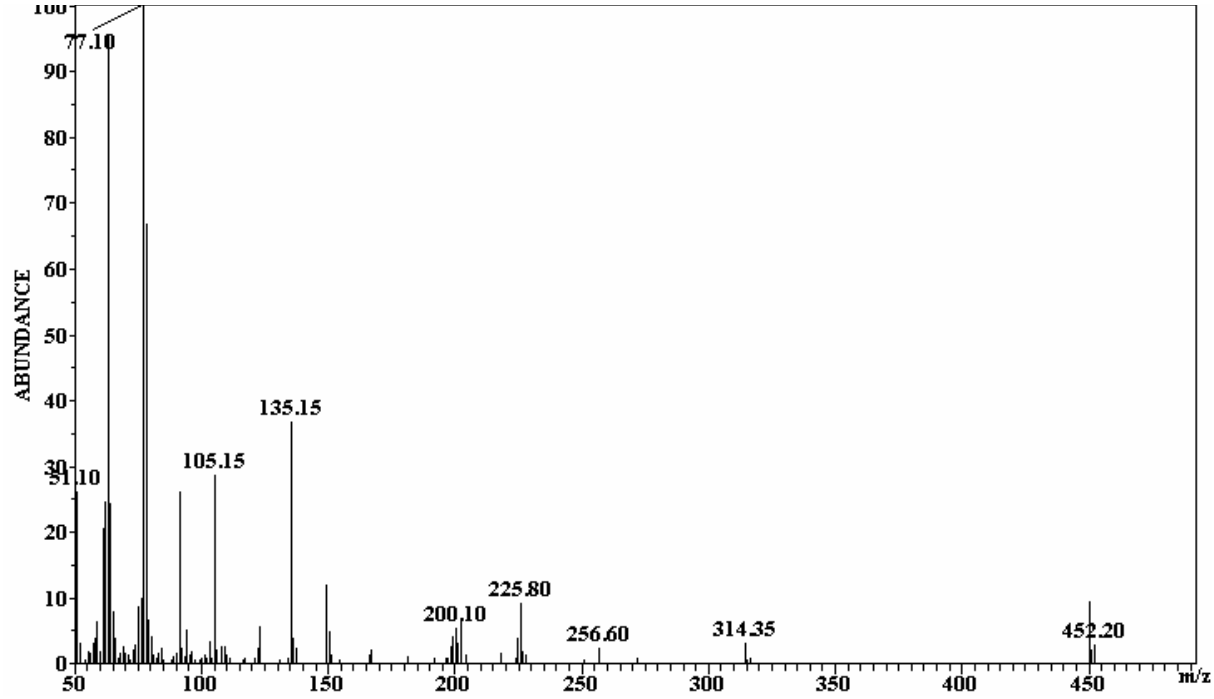


Figure 4.13: Mass spectrum of **7**

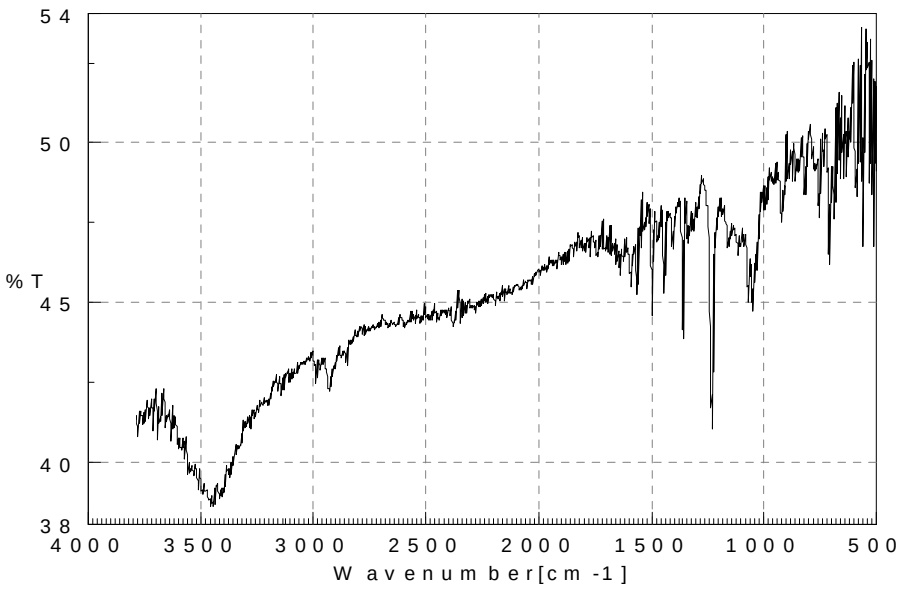


Figure 4.14: IR spectrum of **6a**

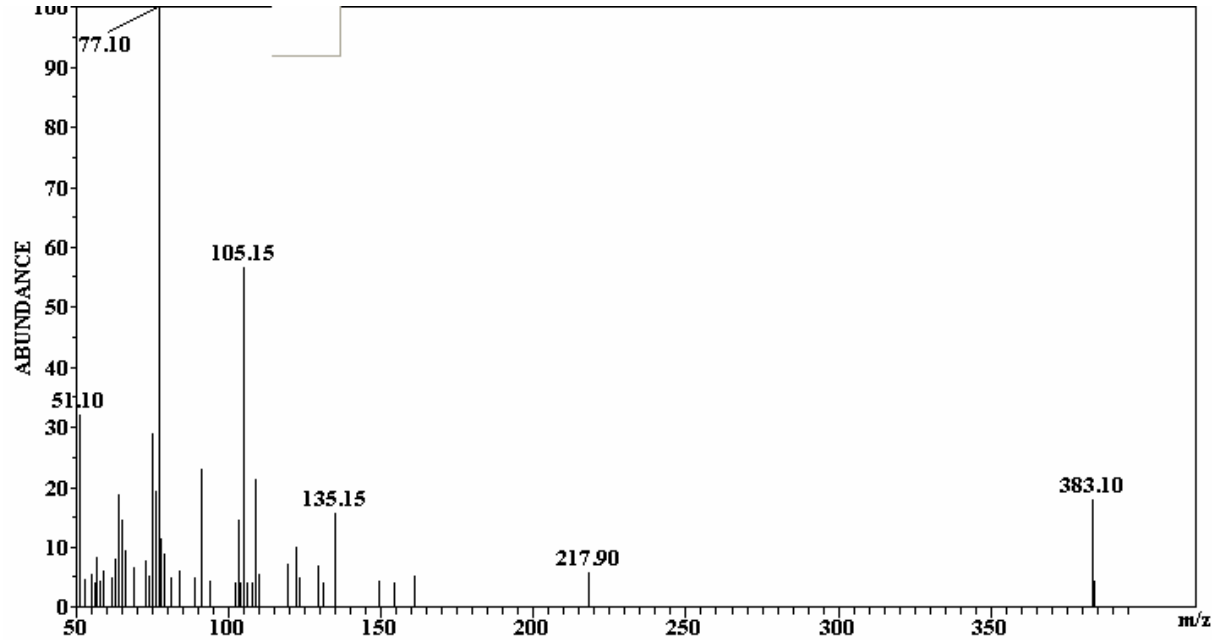


Figure 4.15: Mass spectrum of **6a**

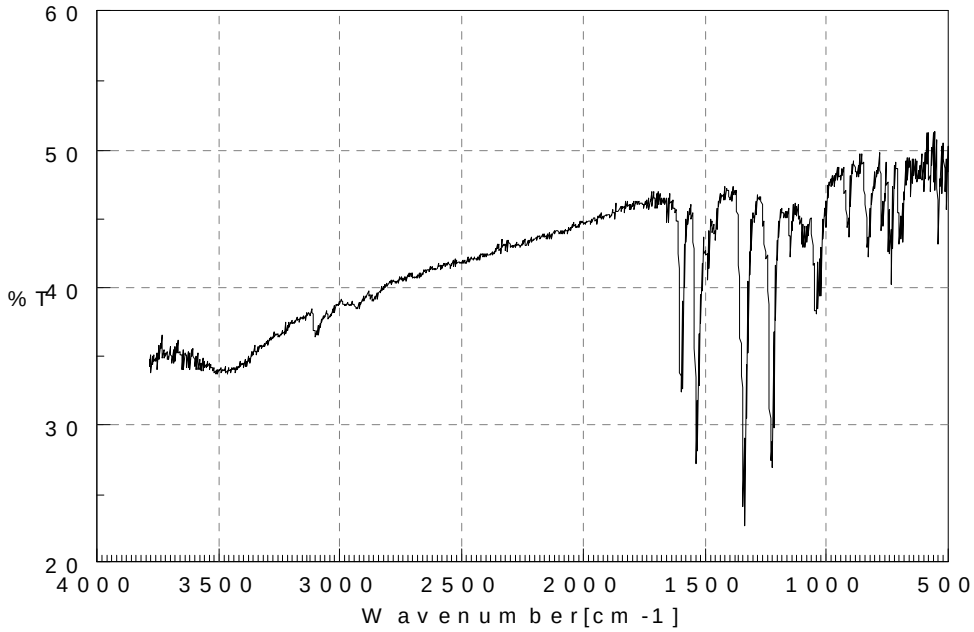


Figure 4.16: IR spectrum of **6b**

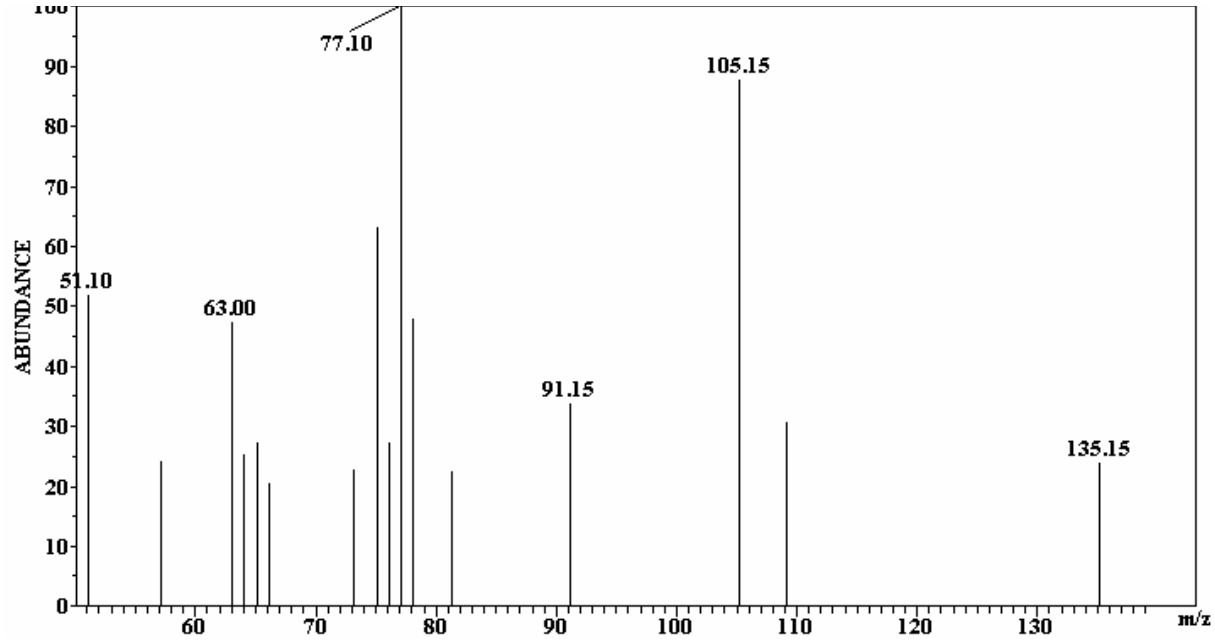


Figure 4.17: Mass spectrum of **6b**

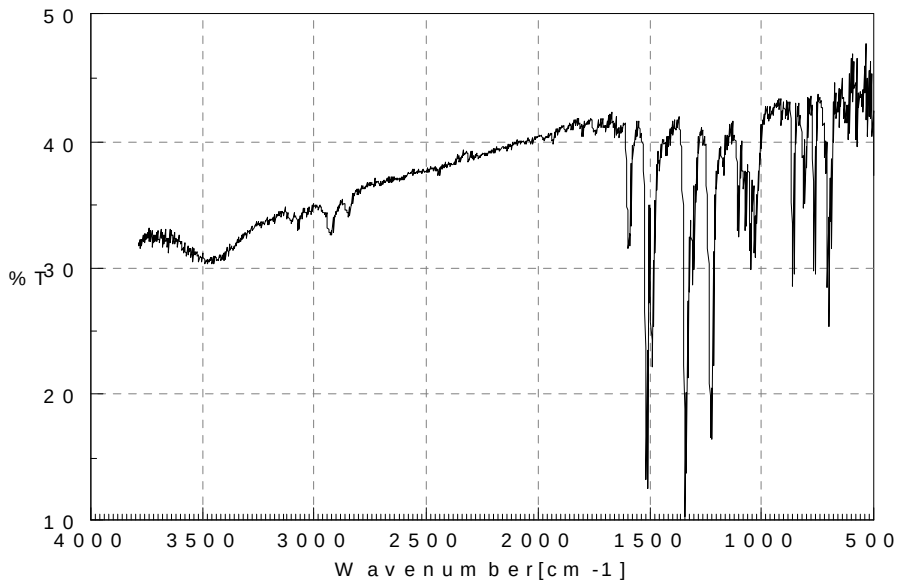


Figure 4.18: IR spectrum of **6c**

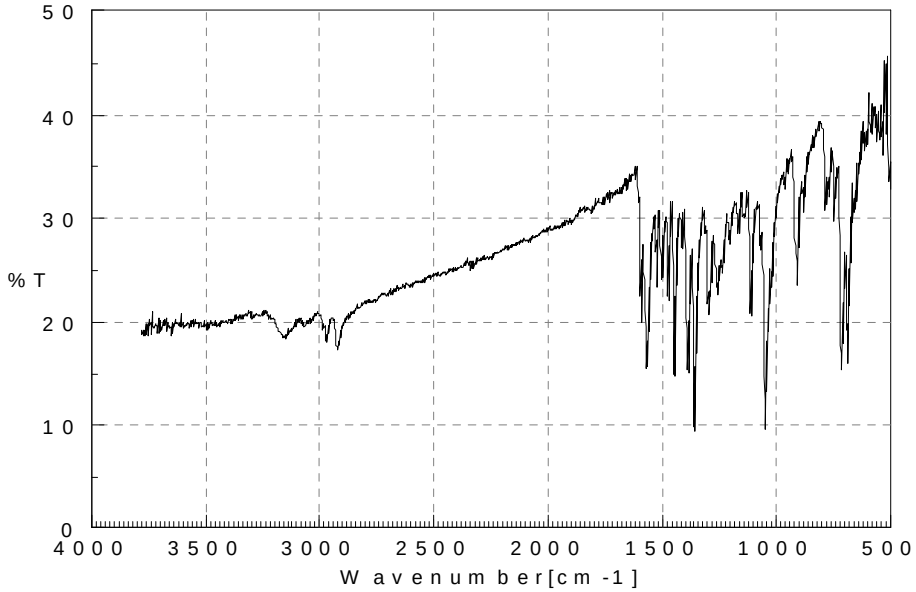


Figure 4.19: IR spectrum of **9a**

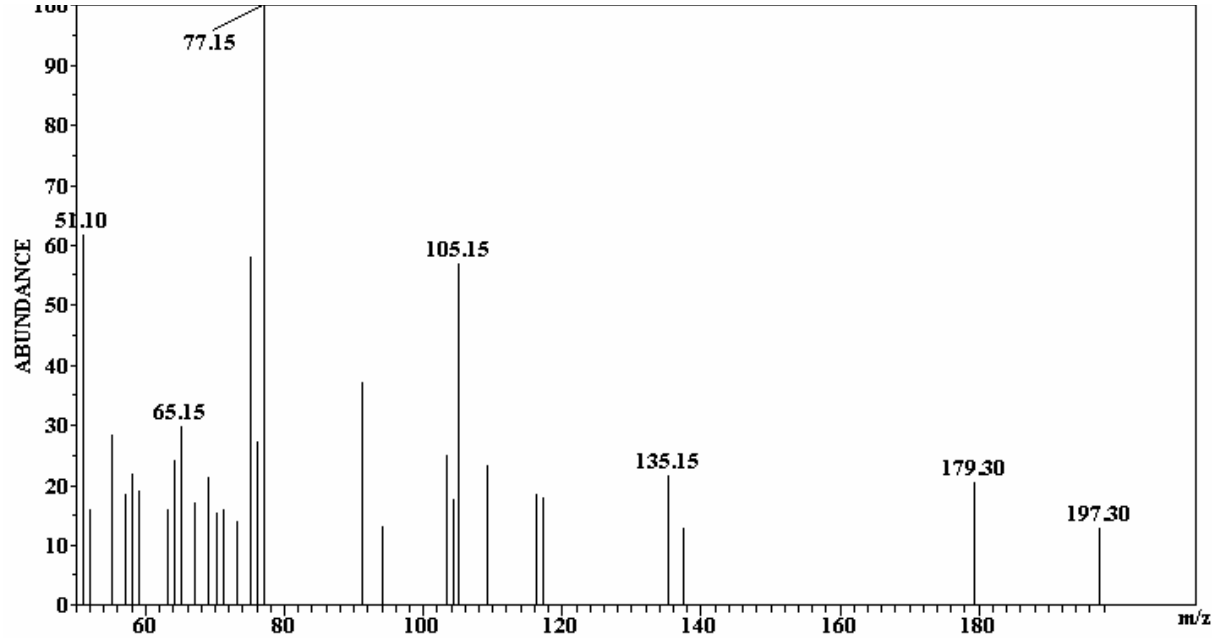


Figure 4.20: Mass spectrum of **9a**

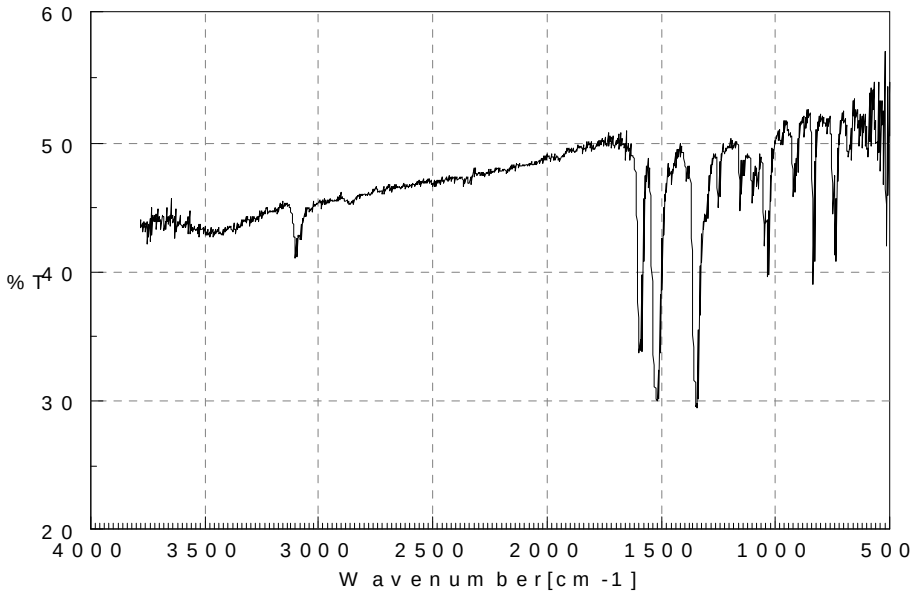


Figure 4.21: IR spectrum of **9b**

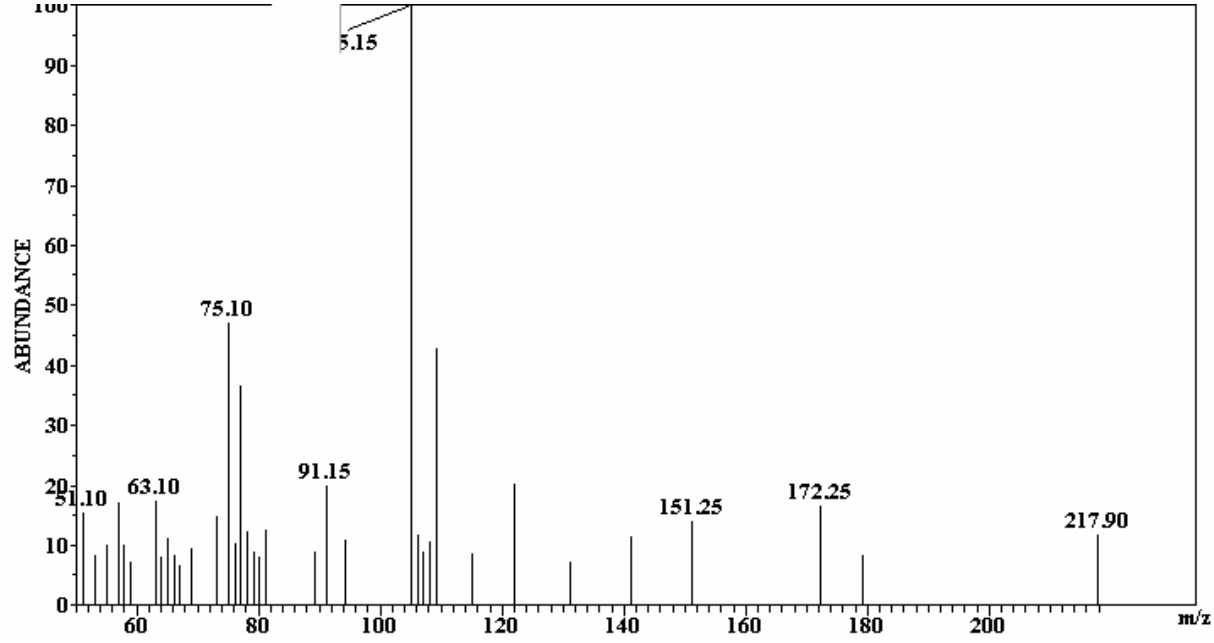


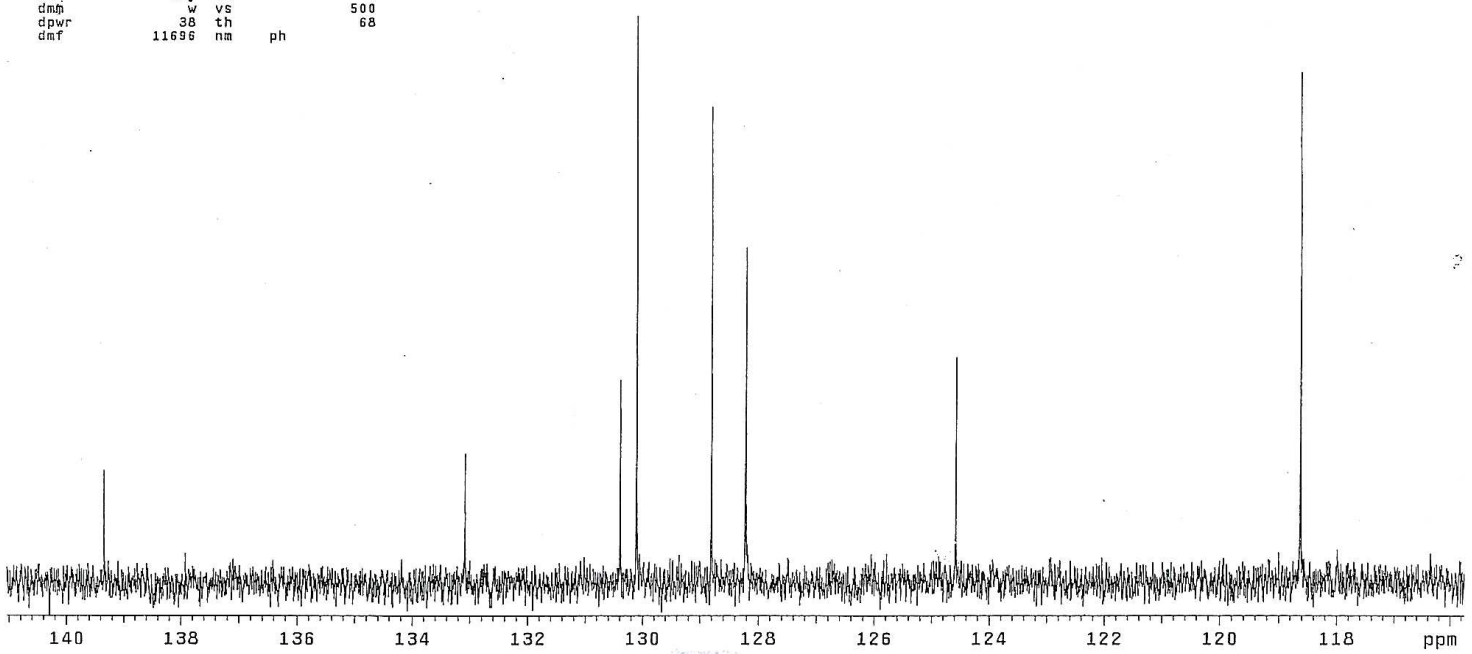
Figure 4.22: Mass spectrum of **9b**

Figure 4.23: ^{13}C NMR Spectra of 3a

AA1

exp3 s2pul

SAMPLE		SPECIAL	
date	Aug 8 2003	temp	25.0
solvent	CDCl3	gain	not used
file	/export/home/~	spin	22
vnmr1/Burcin/C13ID~		hst	0.008
	_AA1.fid	pw90	8.200
ACQUISITION		alfa	10.000
sw	31409.5	FLAGS	
at	1.300	il	n
np	81694	in	n
fb	17000	dp	y
bs	64	hs	nn
d1	1.000	PROCESSING	
nt	4096	lb	0.50
ct	2052	fn	not used
TRANSMITTER		DISPLAY	
tn	C13	sp	14543.6
sfrq	125.665	wp	3178.1
tof	1883.2	rfl	1883.2
tpwr	55	rfp	0
pw	4.100	rp	-42.4
DECOUPLER		lp	-259.2
dn	H1	PLOT	
dof	0	wc	250
dm	nny	sc	0
dmm	w	vs	500
dpwr	38	th	68
dmf	11696	nm	ph



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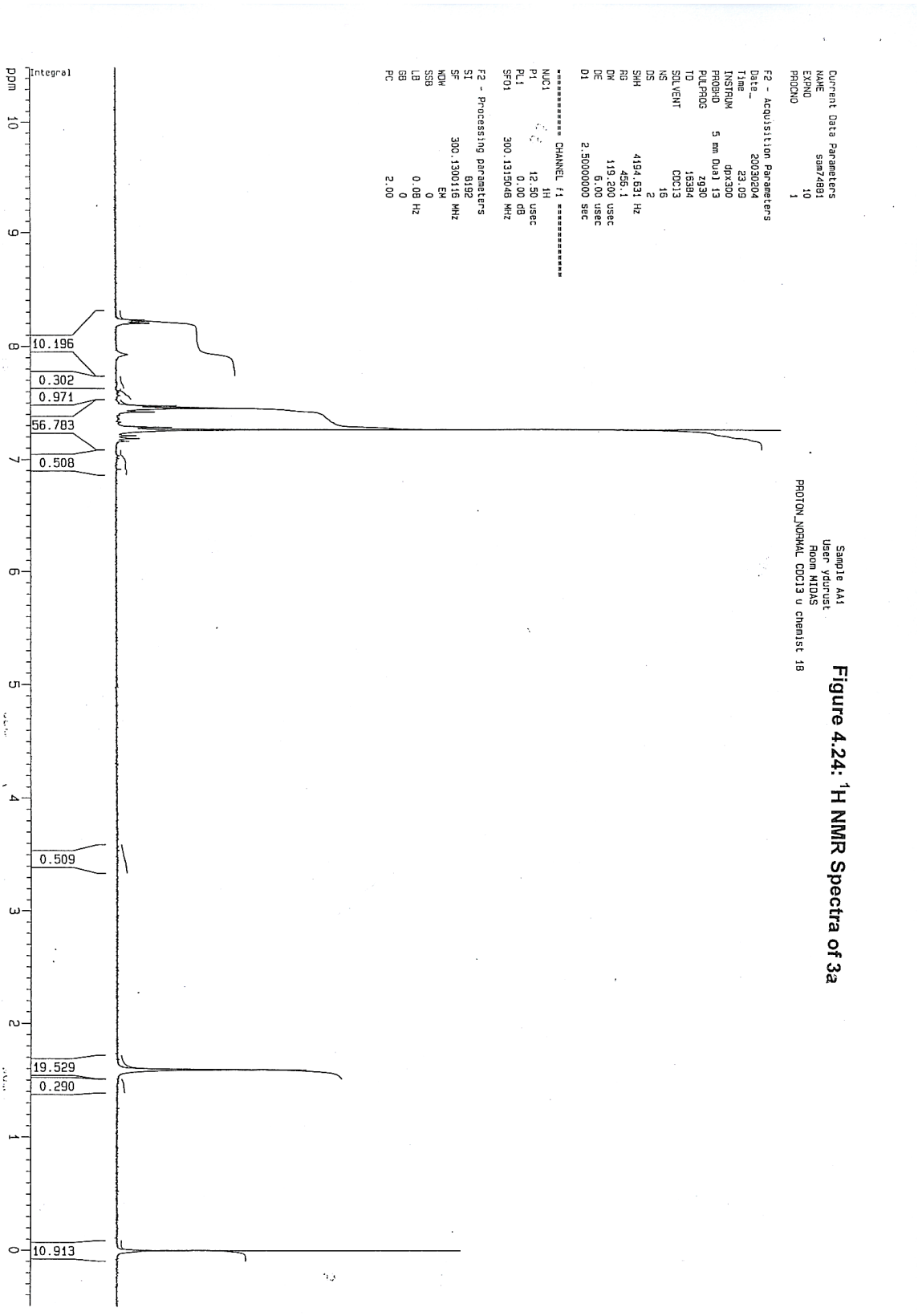


Figure 4.24: ^{1}H NMR Spectra of 3a

96

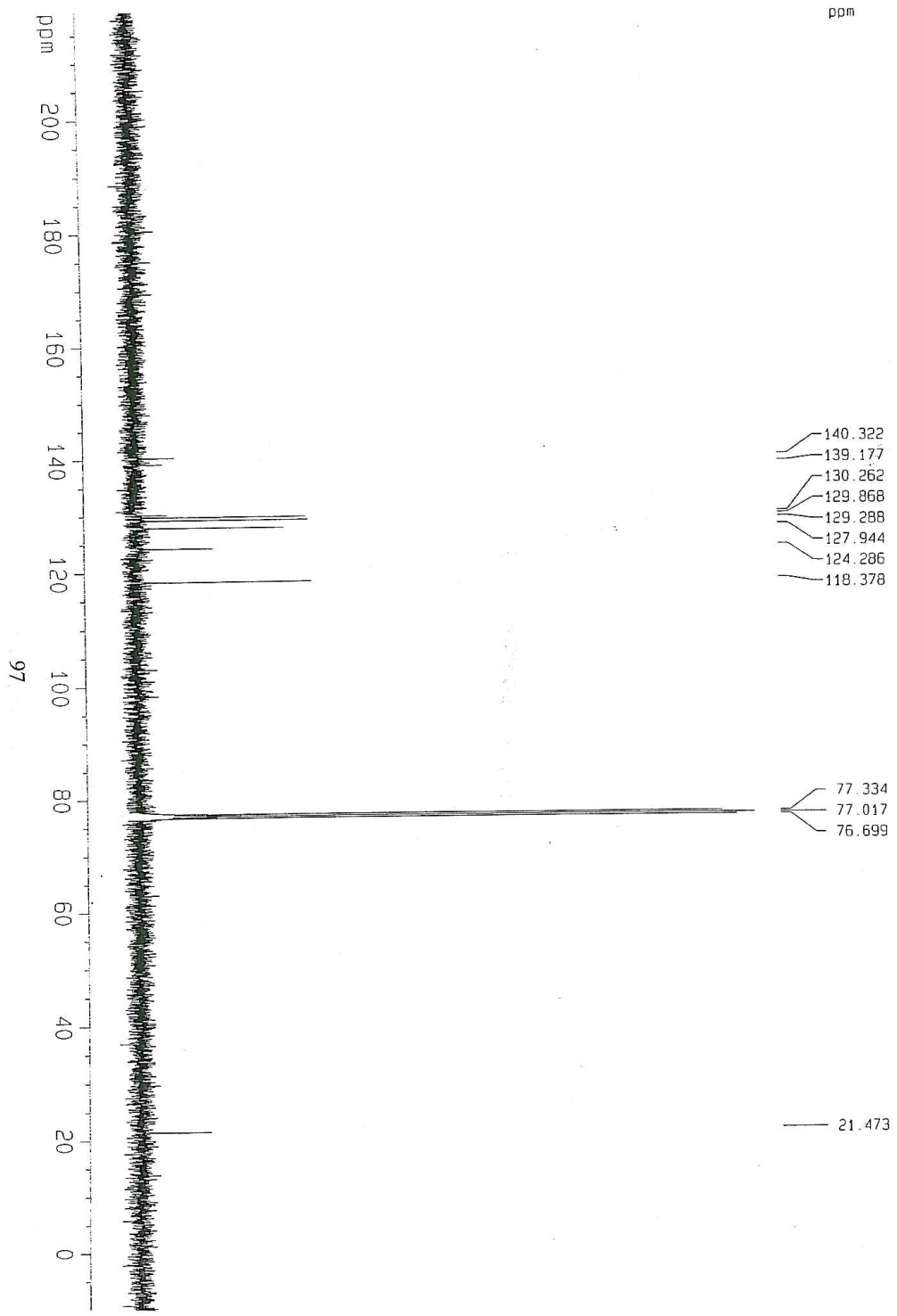


Figure 4.25: ^{13}C NMR Spectra of 3b

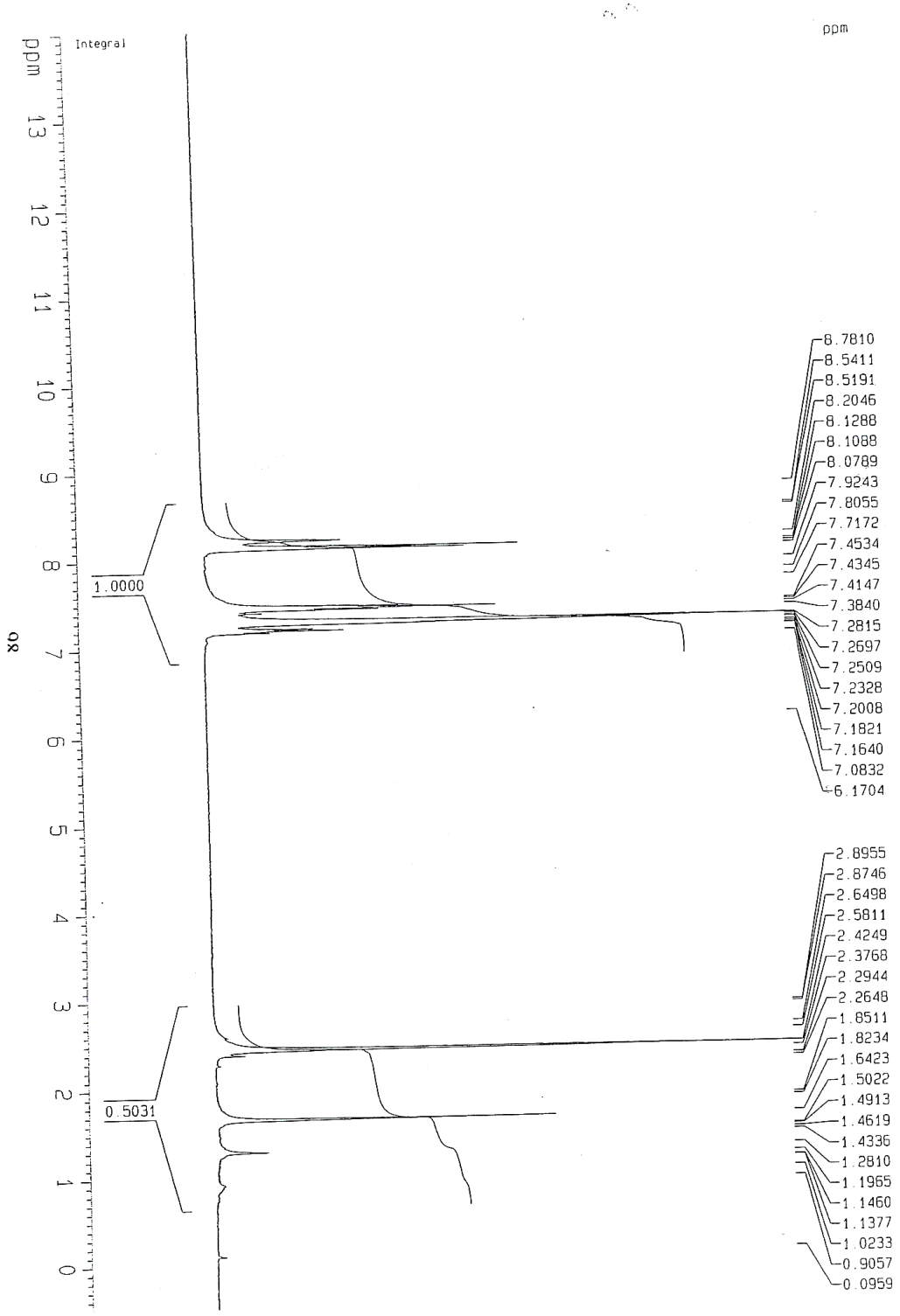


Figure 4.26: ^{1}H NMR Spectra of 3b

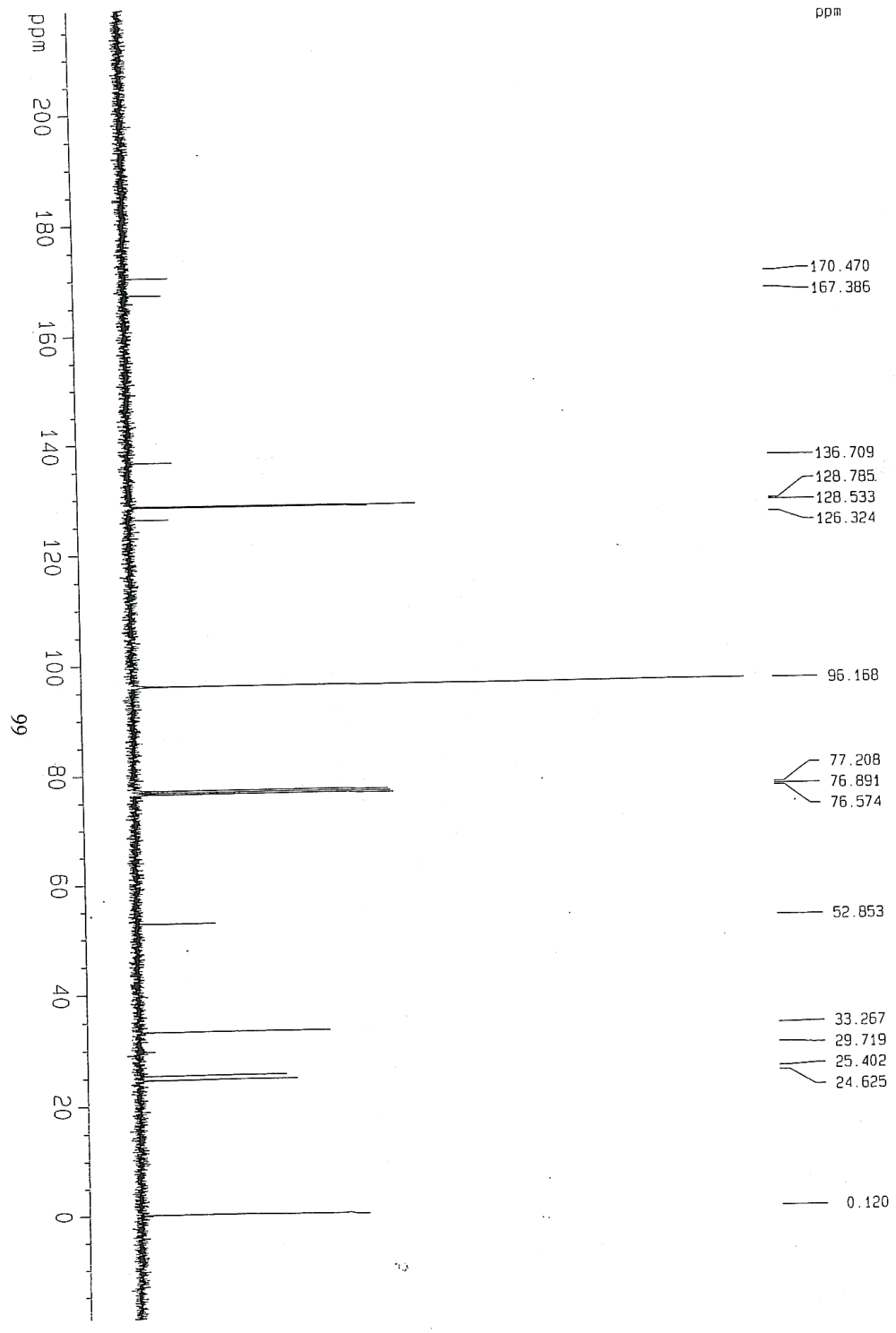


Figure 4.27: ^{13}C NMR Spectra of 4

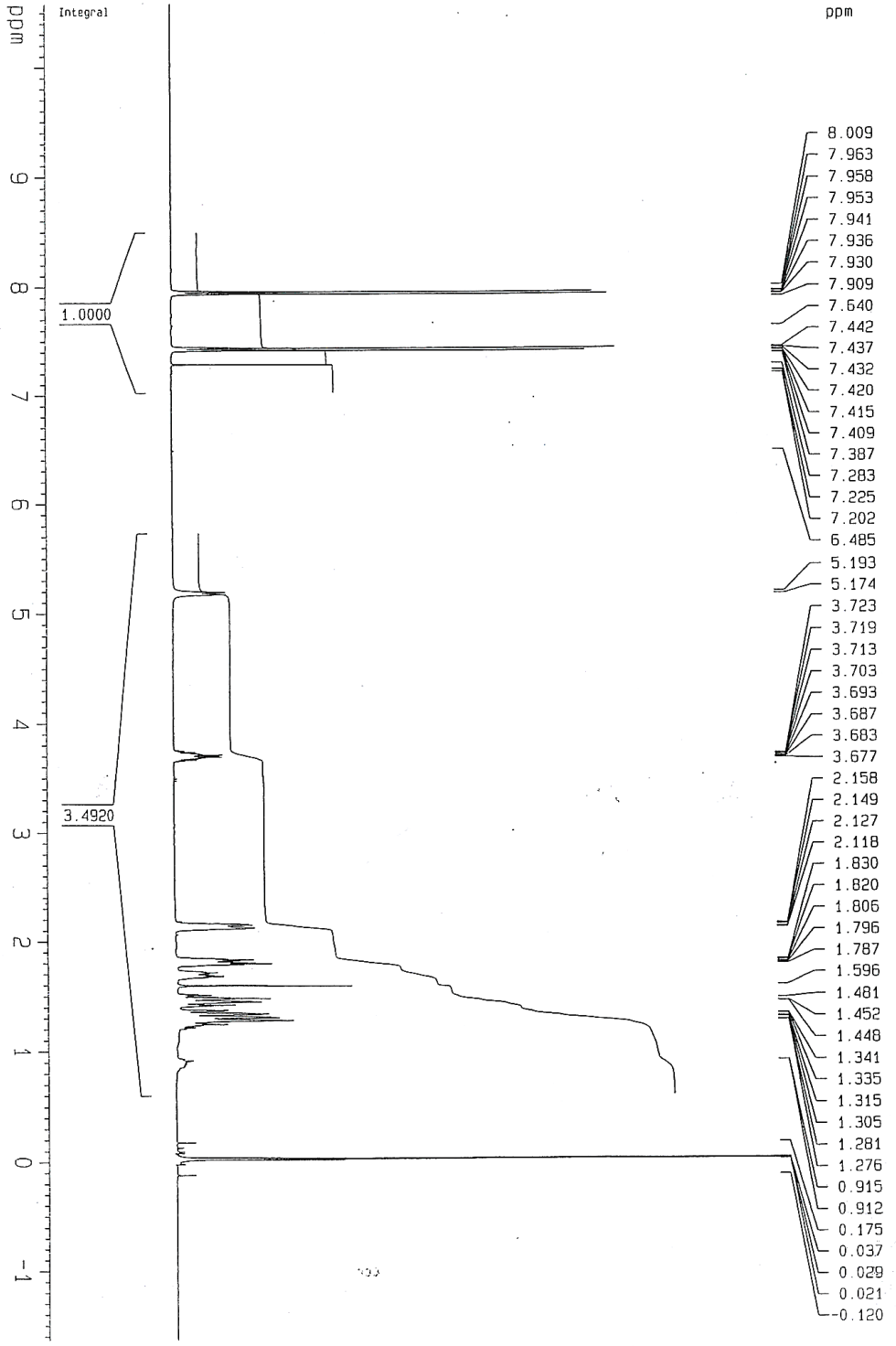


Figure 4.28: ^{1}H NMR Spectra of 4

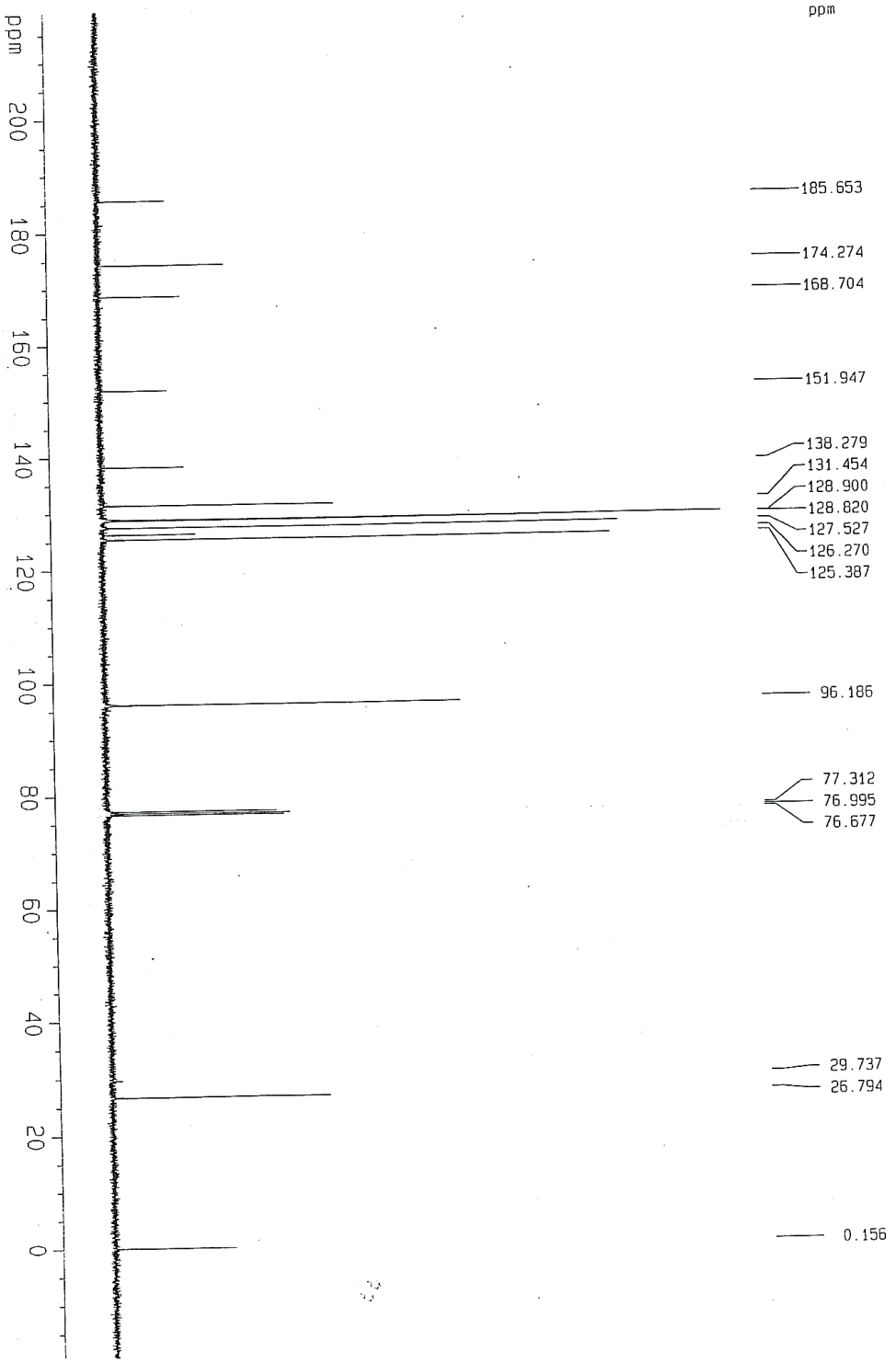


Figure 4.29: ^{13}C NMR Spectra of 6a

101

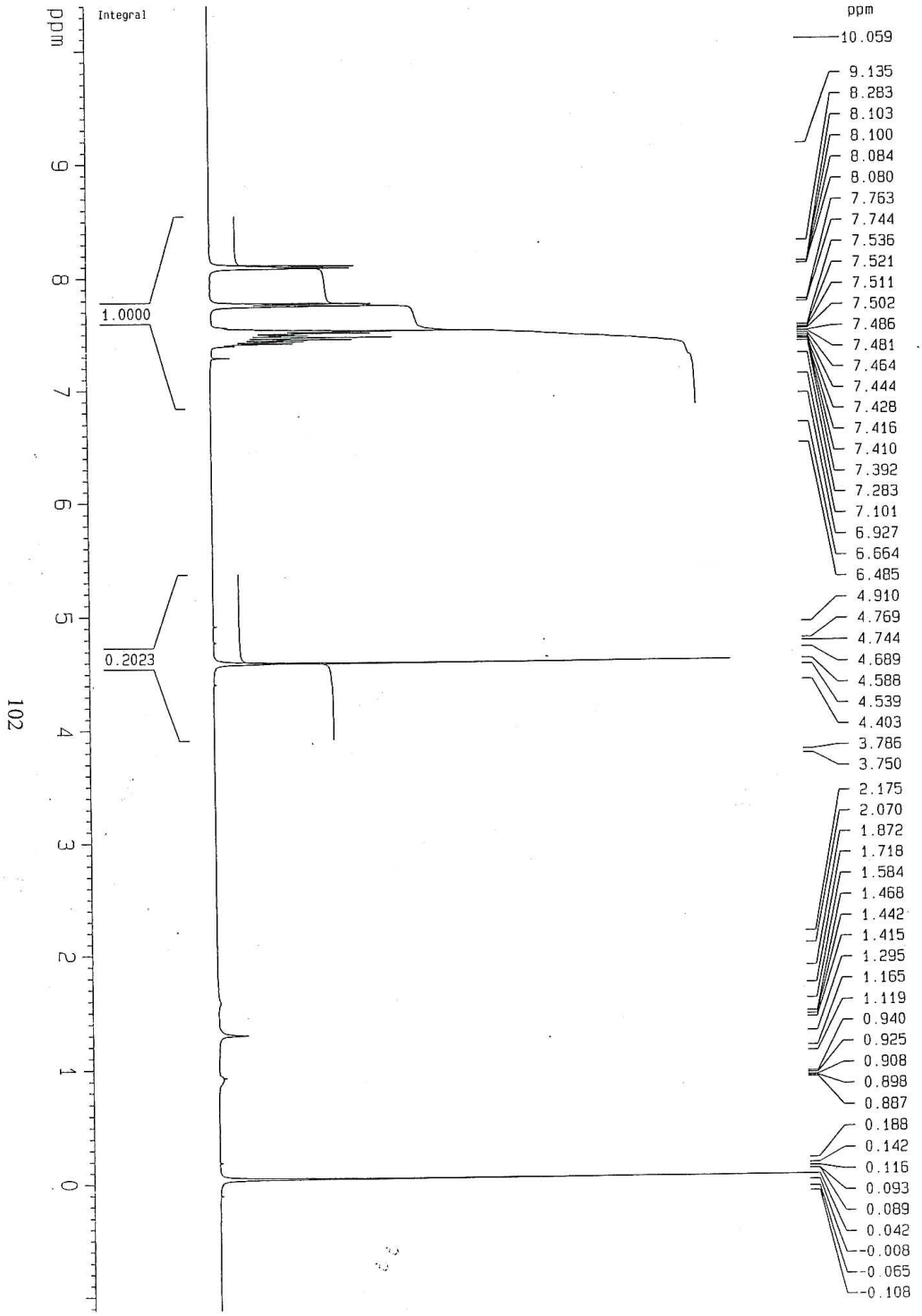
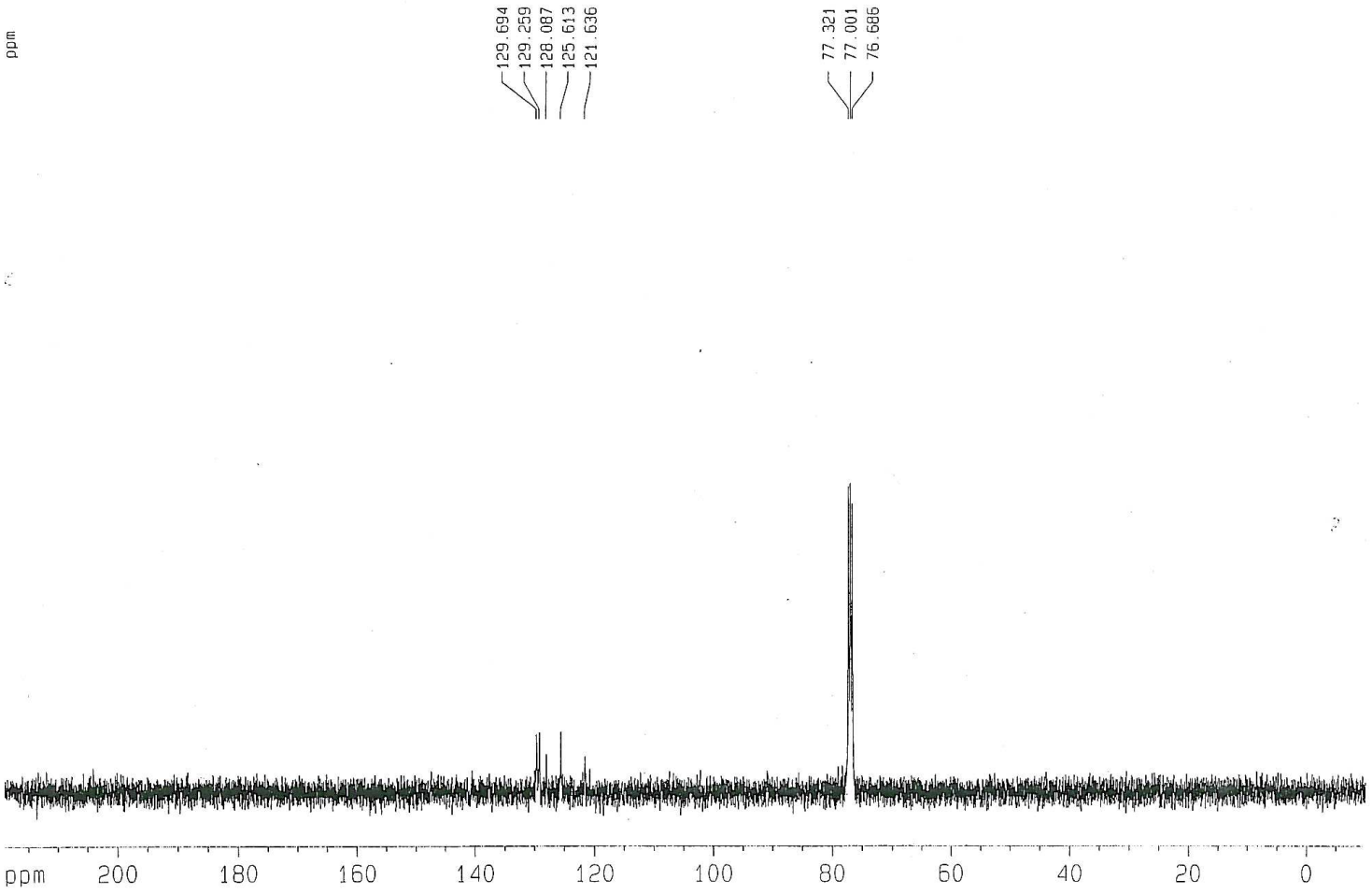


Figure 4.30: ^{1}H NMR Spectra of 6a

Figure 4.31: ^{13}C NMR Spectra of 6b



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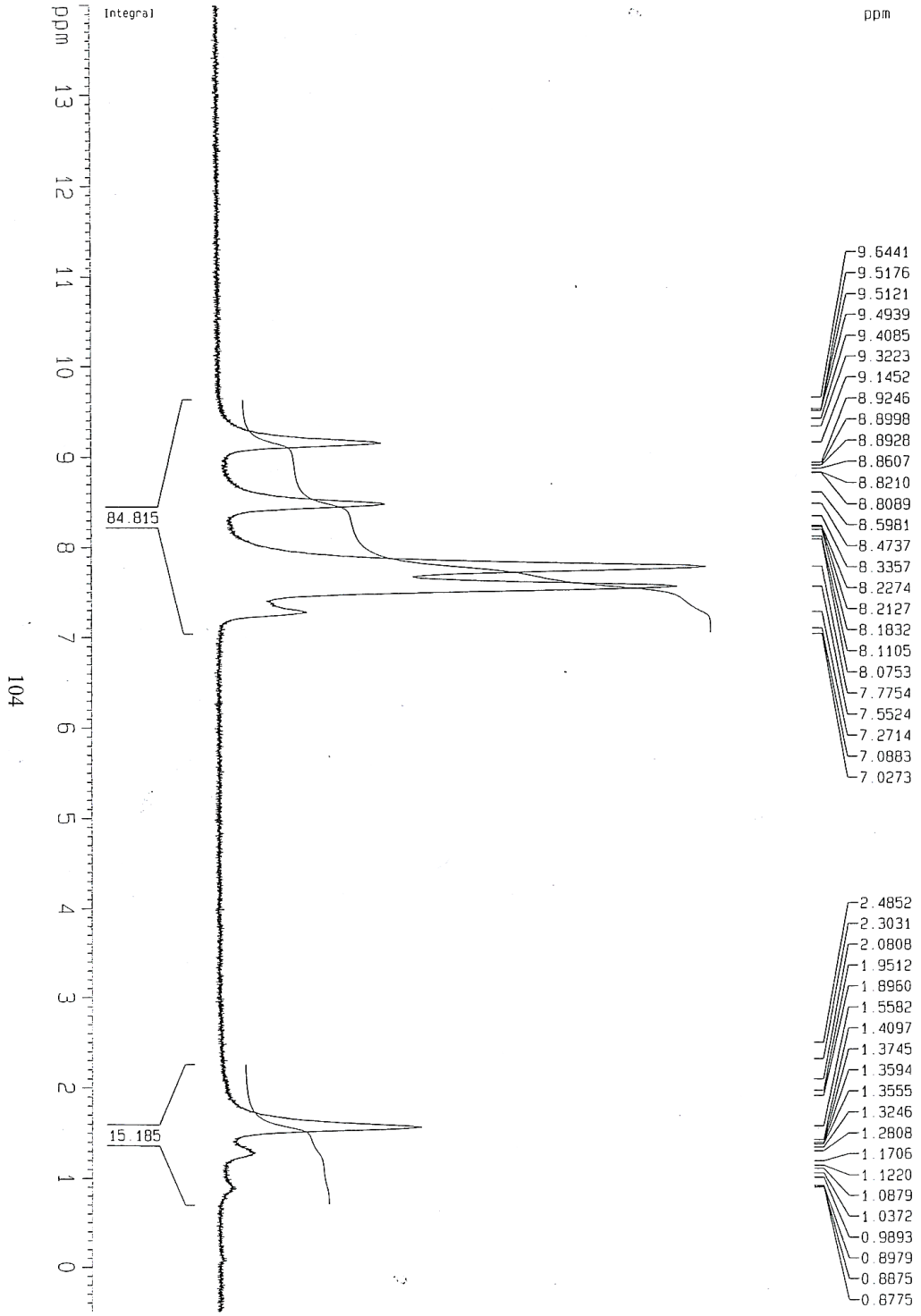

Figure 4.32: ^{1}H NMR Spectra of 6b

104

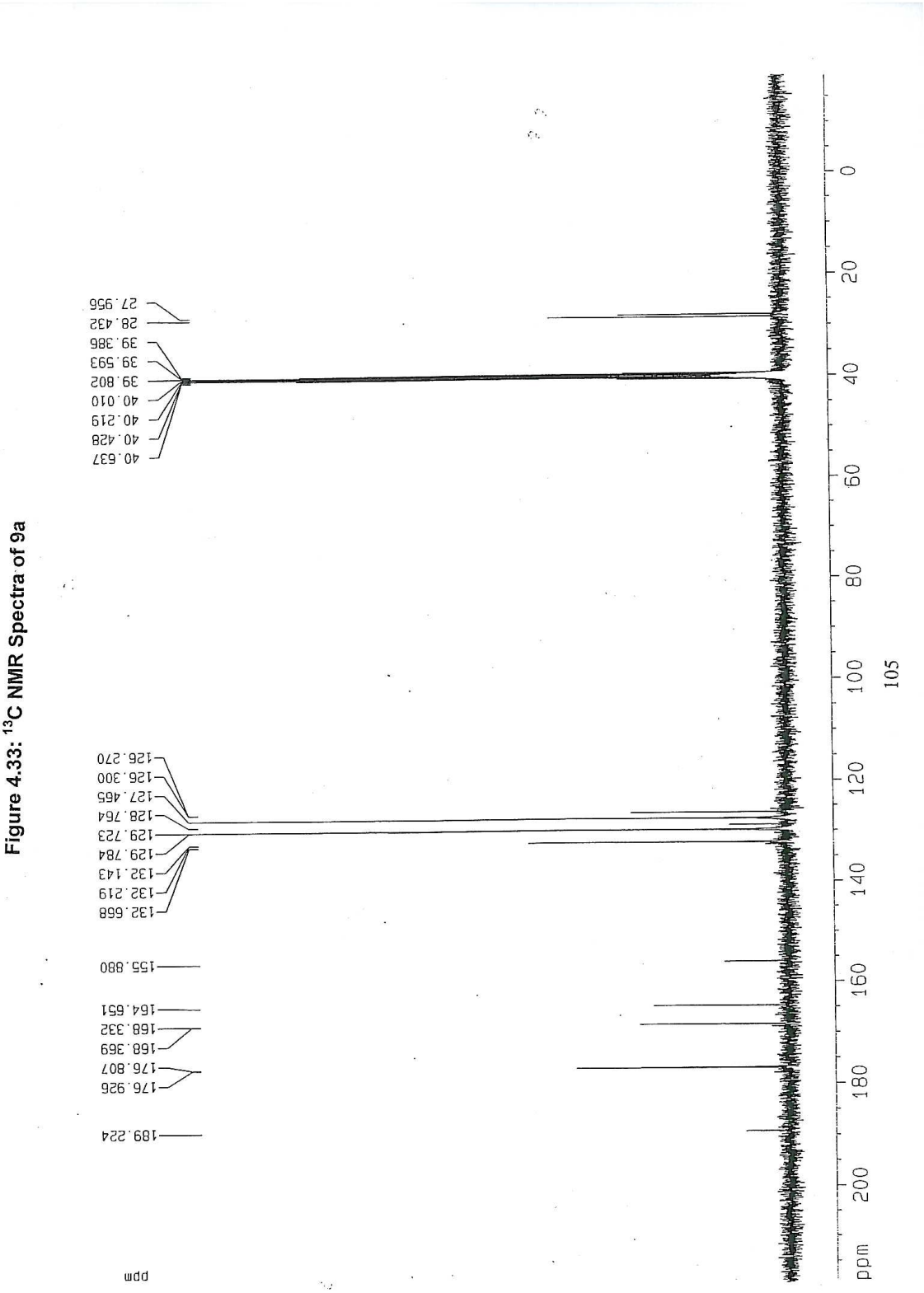

Figure 4.33: ^{13}C NMR Spectra of 9a

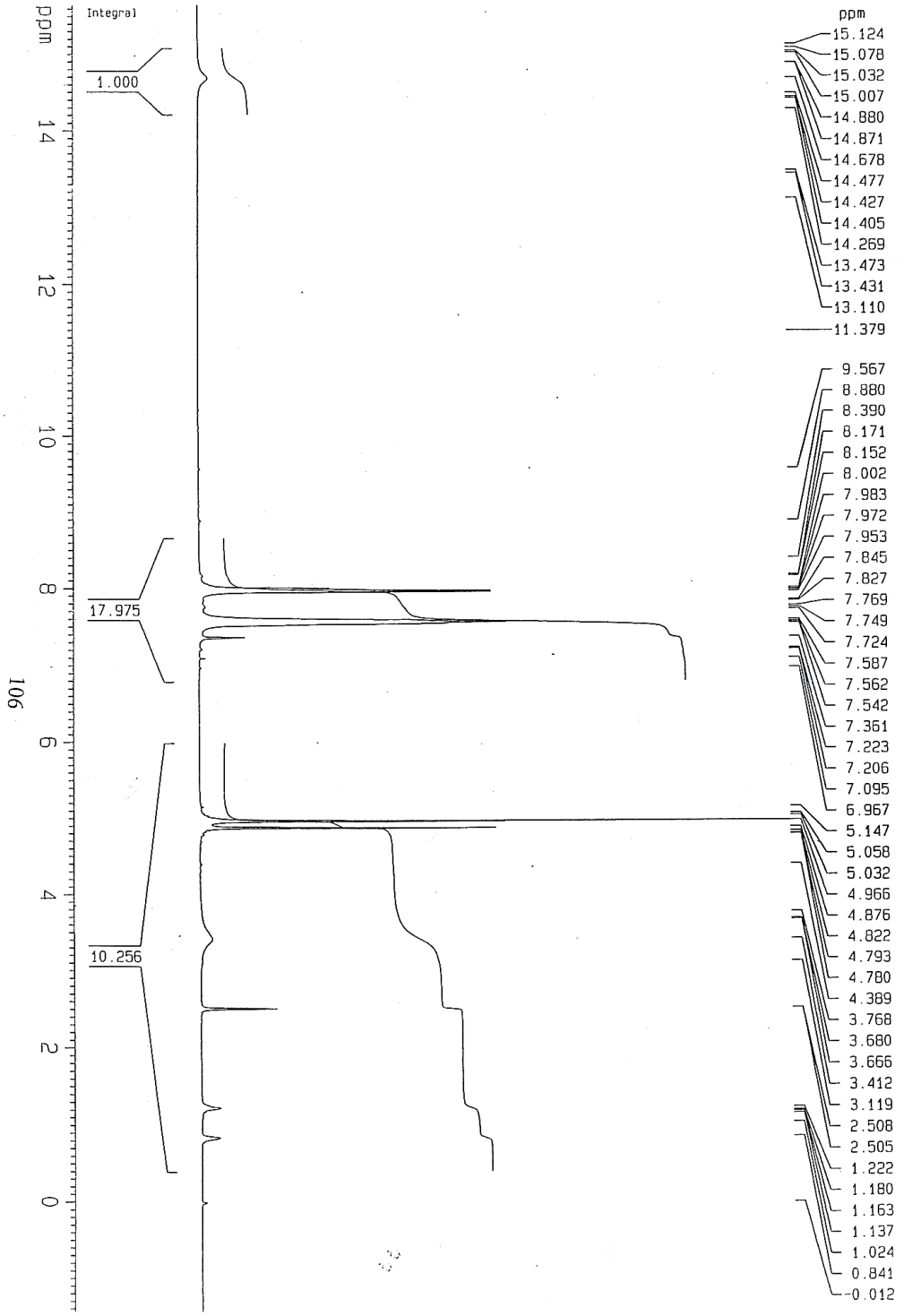

Figure 4.34: ^{1}H NMR Spectra of 9b