SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME N-ALKOXY AND ACYLOXY α, β-UNSATURATED OXIME ETHERS

BY

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(B.Sc., M.Sc.)

Ph.D./CH/07/0472

OCTOBER, 2011.

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A thesis submitted to the School of Postgraduate Studies, Modibo Adama University of Technology, Yola, in fulfilment of the requirement for the award of the degree of Doctor of Philosophy.

Chemistry Department, School of Pure and Applied Sciences, Modibo Adama University of Technology, Yola.

OCTOBER, 2011.

Declaration Page

I hereby declare that this thesis was written by me and it is a record of my own research work. It has not been presented before in any previous application for higher degree. All references cited have been duly acknowledged.

…… Date……

Aliyu, Abdulraman Oiza Chogudo

Dedication

Dedicated to my mother, Otupe Rekiya Hanna
and brother, Mohammed.

Approval Page

This thesis entitled "Synthesis, Spectral Characterization And Antimicrobial Activity of Some N-Alkoxy and Acyloxy α, β-Unsaturated Oime Ethers" by Aliyu, Abdulraman Oiza Chogudo meets the regulations governing the award of the Degree of Doctor of Philosophy of Modibo Adama University of Technology, Yola, and is approved for its contribution to knowledge and literary presentation.

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Abstract

Several α, β-unsaturated oxime ethers were synthesized from cinnamaldehyde and crotonaldehyde by alkoxy amination and hydroxiamination of the aldehydes followed by alkylation or acylation of the oximes. The following compounds obtained from the reactions were characterized by ^{1}H-NMR, ^{13}C-nmr, as well as IR spectroscopy: *3-Phenylpropenal o-ethyl oxime (32a), 3-Phenylpropenal O-methyl oxime ether (32b), But-2-enal O-methyl oxime (32c), But-2-enal O-ethyl oxime (32d), O-Palmitoyl cinnamaldoxime ether(33a), O-Oleoyl cinnamaldoxime ether (33b), O-palmitoyl crotonaldoxime ether (33c), Crotonaldoximyl oleate (33d)* . Detailed structural elucidation of 32a and 32b was carried out by ^{1}H-^{1}H-coupling corelational spectroscopy (COSY), ^{13}C-NMR-DEPT (Distortionless Enhancement by Polarisation Transfer) and ^{1}H-^{13}C-HETCOR (Hetero-nuclear spectroscopy) to confirm the chemical structures of the compounds obtained and determine the most likely configuration. The compounds obtained from the synthesis were evaluated for bioactivity against selected microorganisms such as *Staphylococcus aurreus, Escherichia coli, Candidas albicans and Saccharomyces cereviciae* and compounds 32a, 32b, 33a and 33b were found to have some inhibitory anti-fungal effects against *C. albicans* and *S. cerevicea*. 32b was also found to have some activity against *S. aurreus* and *E. Coli* while 33b also had some activity against *S. aurreus.*

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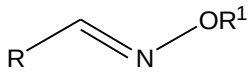
Chapter One

Introduction

1.1 Background of Study

Oxime ethers are compounds of the general form **1** and α, β-unsaturated oxime ethers are usually represented as **2** where R and R^1 can be alkyl, aromatic, heterocyclic or alicyclic groups which may be substituted (March and Smith, 2001).



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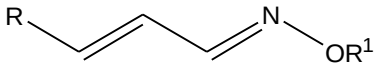

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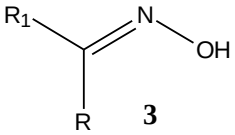
They are usually generally formed from either an oxime (**3**), or from the reaction of O-substituted hydroxyl amines, **4**, with aldehydes or ketones. R and R^1 could be substituents ranging from aliphatic, aromatic, heterocyclic or alicyclic compounds March and Smith, 2001; Morrison and Boyd, 2004).



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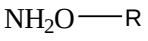

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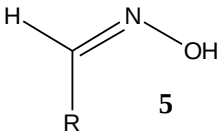

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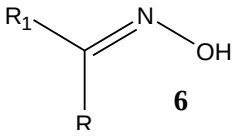

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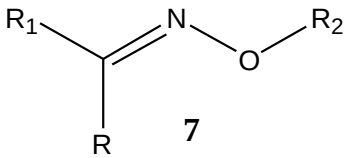
When the oximes are derived from aldehydes aldoximes are formed, **5** (RHCNOH) and when it is from ketones, ketoximes are formed, **6** (RR^1CNOH, where R and R^1 are not hydrogen). Oximes and oxime ethers, 2 or **7**, (RR^1CNOR^2) have important pharmaceutical and synthetic applications (Balsamo *et al*, 1990; Sun *et al*, 2008).



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The oxime (and oxime ether) functional groups have a wide range of potential biological activity and are incorporated into many organic medicinal agents, including some antibiotics (Fang *et al*, 2009; Frazen, 2000).

Oxime ethers have found many uses in recent years as non-steroidal anti inflammatory drugs, mould inhibitory active compounds in poultry science, anti-protozoan, insecticides, insect growth regulator, and herbicides and as various materials with steroidal effects (Khan, 2006). Oximes are usually prepared by the action of a hydroxyl amine on an aldehyde or ketone followed by dehydration (scheme 1.1), while oxime ethers are formed by several methods, two of the commonest are either by direct alkylation of the oximes or may be prepared by the action of an N-alkoxyamine on an aldehyde or ketone (Bozdag-Dunder, 2003; Sun *et al*, 2008).

1.2 Statement of the Problem

References to the potential of oxime ethers and their derivatives as anti-microbial drugs abound in literature. (Djik and Davies, 1976; Bozdag-Dunder, 2003; Balsamo *et al.*, 1990; Sun *et al.*, 2008 and Khan, 2006). However, most of the work done so far are on oxime ethers but very little on their α, β-unsaturated analogues.

^{1}H-NMR, ^{13}C-NMR, COSY and HETCOR as well as IR spectroscopic characteristics of this class of organic compounds are currently not well documented.

The spectral elucidation of the functional structure of the oxime or oxime ether group is important. The effect of the additional α, β-unsaturation on the spectral characteristics of this functional group needs to be captured, as it will provide valuable data for subsequent workers in this area.

Despite the growing list of antimicrobial agents, their clinical value has been limited by their relatively high risk of toxicity, the emergence of drug resistance, and insufficiencies in their antimicrobial activity. Since the environmental and economic requirements imposed on modern-day antibiotics are continually increasing, with regard to the spectrum of action, toxicity, selectivity, application rate, formation of residues, and favourable preparability, a constant task is to develop new antibiotics which in some areas at least have advantages over their known counterparts (Sharpless *et al*, 2001). This situation has led to an ongoing search for potent broad spectrum antimicrobial agents with low side effects, which can be administered both orally and parenterally (Sharpless *et al*, 2001).

1.3 Aim and Objectives of the Research

The aim is to design and synthesize a novel series of α, β-unsaturated oxime ethers and to evaluate their bioactivity against selected microorganisms through the following objectives:

i. To prepare a series of α, β-unsaturated oximes and their corresponding N-alkoxy α, β-unsaturated ethers from appropriate carbonyl

compounds such as cinnamaldehyde and crotonaldehyde using methods established in literature and slightly modified literature methods.

ii. To carryout spectral analysis of the compounds by means of ^{1}H-NMR, ^{13}C-NMR, and COSY, HETCOR as well as IR spectroscopy.

iii. To observe the direction of nuleophilic addition of hydroxylamines or alkoxyamines to α, β-unsaturated carbonyl compounds.

iv. To evaluate the bioactivity of the compounds on selected microorganisms such as *Staphylococcus aurreus, Escherichia coli, Candidas albicans and Sacharomyces cereviciae*

1.4 Significance of the study

As has been observed by Hammond in a Norris award lecture in 1968 (Sharpless *et al.*, 2001) the most fundamental and lasting objective of synthesis is not just the production of new substances but the production of substances with desired properties. An essential part of the search for new leads in drug design programme is the synthesis of new molecules which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features (Silverman, 1992). There are a few molecules containing these features which enable them to act as scaffolds or pharmacophores of a number of biologically active and medicinally useful molecules (Fang *et al.*, 2009; Franzen, 2000).

Numerous workers have shown that the oxime ether group is one such group that has biologically activity (Fang *et al.*, 2009; Frazen, 2000; Kast, *et al.*, 1995, Cukurovali *et al.*, 2005). Both *O*-alkly oximes and more recently *O*-aryl oximes have been demonstrated to be stable at physiological pH with *O*-alkyl oximes present in a number of approved drugs.

There are two main ways to form oxime ethers: one is to react aldehydes and ketones with hydroxyl amine and then alkylate or arylate the oxime with an alkyl or acyl halide; the other method is to react the aldehydes or ketone directly with an oxyimine. The one drawback for the oxyimine pathway is that while large numbers of aldehydes and ketones are readily available the oxyimine precursors are not.

It has been revealed that coupling of two or more biodynamic molecules result in enhanced biological activity (Kamble *et al.*, 2009) It is known that unsaturation introduces certain extra chemical and physical properties that may confer additional biological activity on a molecule. The introduction of α, β-unsaturation as well as alkyl and acyl fragments (Oleic acid and palmitic acid, e.g., **8** and **11**) from fatty acids of palm oil – an easily available natural substance – adjacent to the oxime ether moiety is expected to make the molecules more biologically active. The introduction of sites of unsaturation provide binding sites, or capacity for chelation; provides sites that are nucleophilic in a compound and are subject to attacks by free radicals and other

oxidising agents. The hydrophobic nature of the long alkyl groups of fatty acids is a useful property in some pharmacological media (Chern *et al.*, 2004).

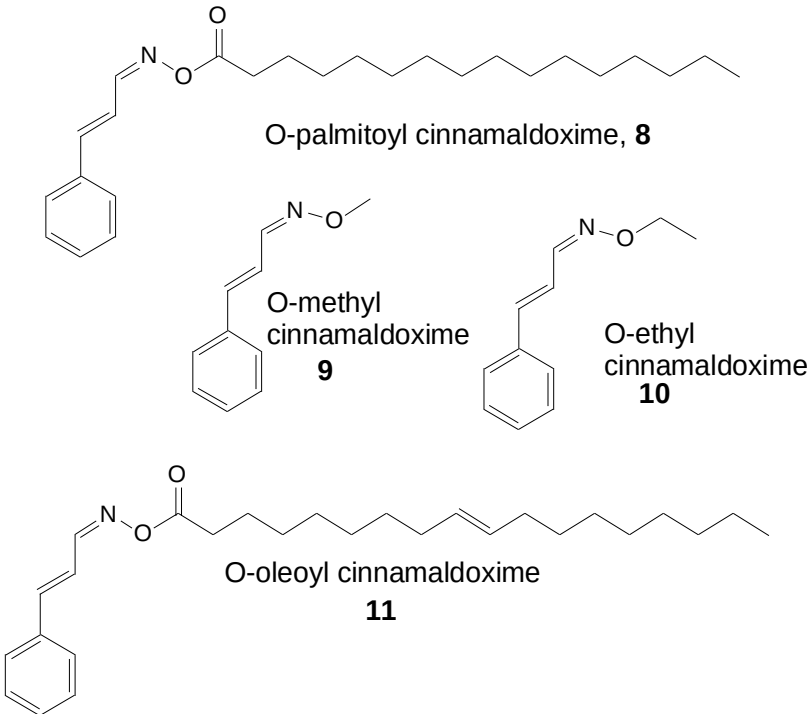


Fig. 1.1: Examples of some α, β-unsaturated oxime ethers

It is also hoped that the introduction of fatty acid derivatives obtainable from a substance such as palm oil which is already widely consumed and the effect of the additional α, β-unsaturation will enhance the feasibility of formation, as well as their antimicrobial activity and physiological tolerance in humans and other animals when formulated into ingestable drugs (Chern *et al*, 2004; Sharpless *et al*, 2004).

This work should also be able to ascertain whether nucleophilic addition of certain derivatives of amine such as hydroxyl amine or alkoxyamine to α, β-unsaturated aldehydes results in the formation of the corresponding α, β-

unsaturated oximes or whether the conjugate addition product, β-amino carbonyl compounds is the preferred product.

The study of these oxime ethers in this way will enhance capacity for designing, preparation and testing of other potentially more complex oxime ethers and drug candidates in future.

1.5 Scope of the study

This work is limited to the synthesis, spectral characterization and microbial activity of a series of N-alkoxy and acyloxy- α, β-unsaturated oxime ethers on selected microorganisms. Some of the N-acyloxy moiety will be derived from fatty acids. Cinnamaldehyde and crotonaldehyde will provide the α- and β-unsaturated fragments of the molecules. Instrumental techniques such as ^{1}H-NMR, ^{13}C-NMR, and COSY, HETCOR as well as IR spectroscopy will be used to study the spectral characteristics of this class of organic compounds.

The *in vitro* antibacterial activity of the oxime-ether derivatives will be evaluated by disk diffusion method against culture of *Staphylococcus aureus, Escherichia coli, Candida albicans and Sacharomyces cereviciea* using methods already established in literature.

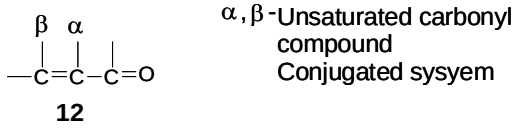
Chapter Two
Literature Review

2.1.0 α, β-Unsaturated Carbonyl Compounds

2.1.1Structure and properties

A compound that contains both a carbon-carbon double bond and a carbon-oxygen double bond has properties that are characteristics of both functional groups. At the carbon-carbon double bond an unsaturated ester or unsaturated ketone and other such compounds undergoes electrophilic addition of acids and halogens, hydrogenation, hydroxylation, and cleavage; at the carbonyl group it undergoes the nucleophilic substitution typical of an ester or the nucleophic addition typical of ketone (Morrison and Boyd, 2004).

In the α, β-unsaturated carbonyl compounds, the carbon-carbon double bond and the carbon-oxygen double are separated by just one carbon-carbon single bond; that is , the double bonds are conjugated, 12.



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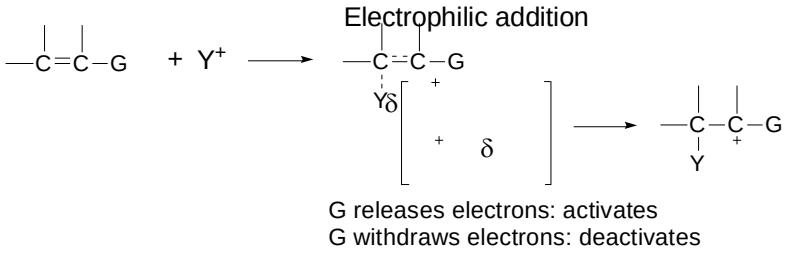
Because of this conjugation, such compounds possess not only the properties of the individual functional groups, but certain other properties, besides, that are as a result of the combination of the functional groups but are quite distinct from the properties each of the functional groups.

2.1.2Interaction of functional groups

Towards electrophilic addition, a carbon-carbon double bond is activated by an electron-releasing substituent and deactivated by an electron-withdrawing substituent. The carbon-carbon double bond serves as a source of electrons for the electrophilic reagent; the availability of its electrons is determined by the groups attached to it. An electron releasing substituent stabilizes the transition state leading to the initial carbocation by dispersing the developing positive charge, Eqn. 1.1; an electron withdrawing substituent destabilizes the transition state by intensifying the positive charge (Morrison and Boyd, 2004).



Eqn. 2.1

The C=O, -COOH, -COOR, and –CN groups are powerfully electron withdrawing groups, and therefore would be expected to deactivate a carbon-carbon double bond toward electrophilic addition. This is found to be true: α, β-unsaturated ketones, acid, esters or nitriles are in general less reactive than simple alkenes toward reagents like bromine and the hydrogen halides (Morrison and Boyd, 2004).

But this powerful electron withdrawal, which deactivates a carbon-carbon double bond towards reagents seeking electrons, at the same time activates towards reagents that are electron rich. As a result, the carbon-carbon double

bond of an α, β-unsaturated ketone, acid, ester or nitrile is susceptible to nucleophilic attack, and undergoes a set of reactions, nucleophilic addition, that is uncommon for the simple alkenes. This reactivity toward nucleophiles is primarily due not to a simple inductive effect of these substituents, but rather to their conjugation with the carbon-carbon double bond (Morrison and Boyd, 2004).

2.1.3 Nucleophilic addition to carbonyl carbon

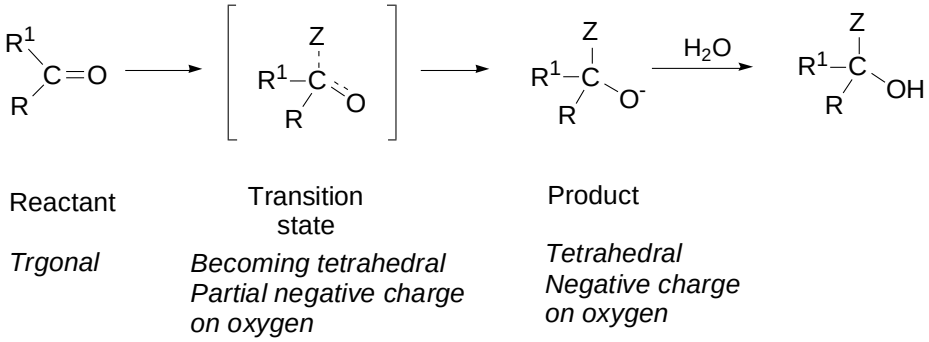
The carbonyl group, C=O, governs the chemistry of aldehydes and ketones. It does this in two ways: (a) by providing a site for nucleophilic addition, and (b) by increasing the acidity of the hydrogen atoms attached to the alpha carbon. Both of these effects are quite consistent with the structure of the carbonyl group and are, in fact, due to the same thing: the ability of oxygen to accommodate a negative charge (Morrison and Boyd, 2004).

The carbonyl group contains a carbon-oxygen double bond; since the mobile π electrons are pulled strongly towards oxygen, carbonyl carbon is electron- deficient and carbonyl oxygen is electron-rich. Because it is flat, this part of the molecule is open to relatively unhindered attack from above or below, in a direction perpendicular to the plane of the group. It is not surprising that this accessible, polarized group is highly reactive.

Since the important step in these reactions is the formation of a bond to the electron deficient (electrophilic) carbonyl carbon, the carbonyl group is most

susceptible to attack by electron-rich, nucleophilic reagents, that is, by bases. The typical reaction of aldehydes and ketones is nucleophilic addition.

Nucleophilic addition



Eqn. 2.2

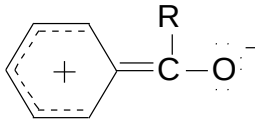
A truer picture of the reactivity of the carbonyl group can be seen by looking at the transition state for attack by a nucleophile. In the reactant, carbon is trigonal. In the transition state, carbon has begun to acquire the tetrahedral configuration it will have in the product; the attached groups are thus being brought closer together. At this stage, moderate steric hindrance is to be expected, that is, larger groups (R and R^1) will tend to resist crowding more than smaller groups. But the transition state is relatively roomy when compared with the transition state for an S_N2 reaction, which has a pentavalent carbon; it is this comparative uncrowdedness that is referred to when the carbonyl group is said to be accessible to attack (Morrison and Boyd, 2004).

In the transition state, oxygen has started to acquire the electrons- and the negative charge – that it will have in the product. It is the tendency of oxygen to acquire electrons –its ability to carry a negative charge- that is the real cause of

the reactivity of the carbonyl group toward nucleophiles. The polarity of the carbonyl group is not the cause of reactivity; it is simply another manifestation of the electronegativity of oxygen.

Aldehydes generally undergo nucleophilic additions more readily than ketones. This difference in reactivity is consistent with the transition states involved, and seems to be due to a combination of electronic and steric factors. A ketone contains a second alkyl or aryl group where an aldehyde contains a hydrogen atom. A second alkyl or aryl group of a ketone is larger than the hydrogen of an aldehyde, and resists more strongly the crowding together in the transition state. An alkyl group releases electrons, and thus destabilizes the transition state by intensifying the negative charge developing on the oxygen (Morrison and Boyd, 2004; Ternay Jr., 1979).

An aryl group has an electron-withdrawing inductive effect and might be expected to stabilize the transition state and thus speed up the reaction; however, it seems to stabilize the reactant even more, by resonance and thus cause net deactivation, 13.



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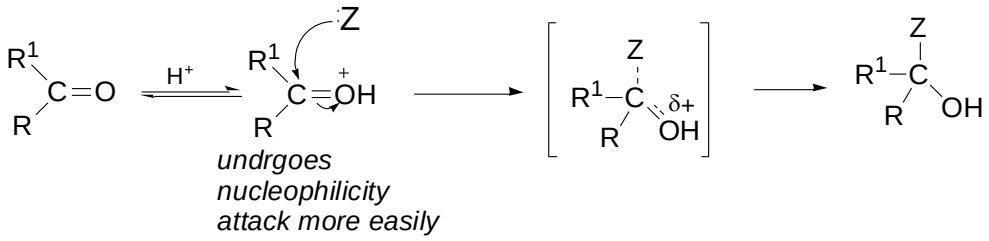
If acid is present, hydrogen ion becomes attached to carbonyl oxygen. This prior protonation lowers the activation energy, E_{act}, for nucleophilic attack, since it

permits oxygen to acquire the π electrons without having to accept a negative charge.

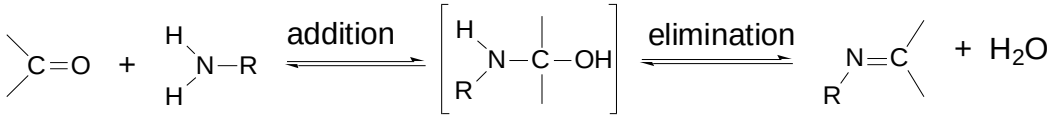


Eqn. 2.3

Thus nucleophilic addition can be catalysed by acids and sometimes by Lewis acids (Morrison and Boyd, 2004).

2.1.4Nucleophilic addition to the Carbonyl carbon by ammonia and its derivatives

Ammonia and many of its derivatives react with carbonyl groups. The products of these reactions contain a carbon-nitrogen double bond. There are two important phases to the reaction. In the first phase, the ammonia derivative adds an N-H fragment across the carbonyl group and forms an unstable adduct. This adduct loses a molecule of water in the second phase.



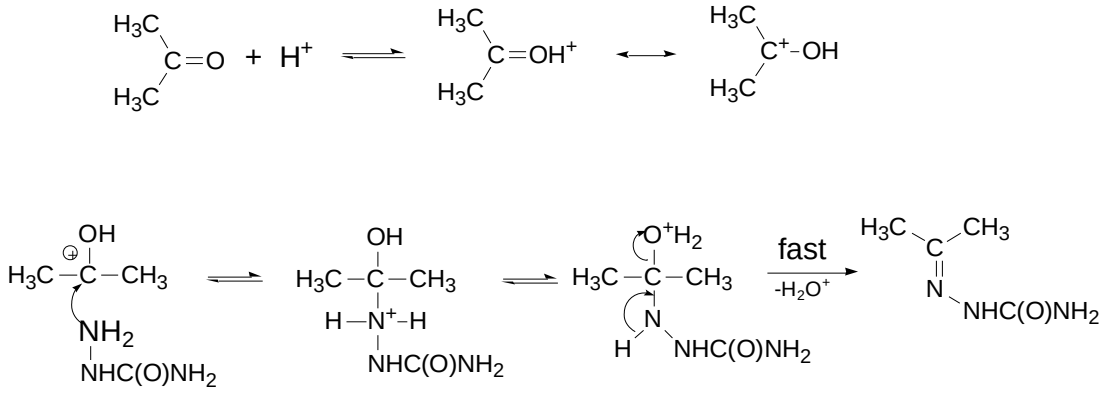
Eqn. 2.4

The product of this type of reaction is called an imine or Schiff base (Ternay Jr., 1979; Morrison and Boyd, 2004). Imines of the type C=N-H are called unsubstituted imines. They are unstable and tend to polymerize on standing. Imines of the type C=NR are substituted imines (or N-substituted imines). N-

substituted imines are comparatively more stable (R = substituents other than H usually alkyl or aryl).

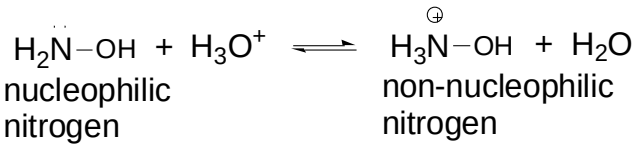
A host of ammonia derivatives other than amine also form condensation products with aldehydes and ketones. Included in this group are hydroxylamine (H_2N-OH), hydrazine (H_2N-NH_2), phenylhydrazine (H_2N-NHC_6H_5) and semicarbazide (H_2N-$NHC(O)NH_2$. The products that these form are called oximes, hydrazones, phenylhydrazones, and semicarbazones, respectively (Morrison and Boyd, 2004; Ternay Jr., 1979).

The condensation of carbonyl compounds with these reagents is normally carried out with the assistance of an electrophilic catalyst, most commonly a proton. The function of the catalyst is to coordinate with the carbonyl group, thus making it more subject to attack by a nucleophile. Attack by the most nucleophilic nitrogen, proton transfer and finally, a 1, 2-elimination produces the desired product. This entire sequence is outlined below for the reaction of acetone with semicarbazide (Morrison and Boyd, 2004).



Scheme 2.1

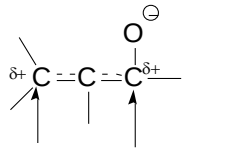
The use of large amount of acid may actually diminish the rate of reaction. This is due to the fact that the nucleophilic nitrogens also are bases and, in acidic solution, will be converted to non-nucleophilic cations.



Eqn. 2.5

2.1.5 Nucleophilic addition to α, β-unsaturated carbonyl compounds.

When a nucleophile adds to an α, β-unsaturated carbonyl compound, usually called an "enone", it may attack the carbonyl carbon or remote end of the double bond (Ternay, Jr., 1979; Morrison and Boyd, 2004).



Possible sites of nucleophilic attack

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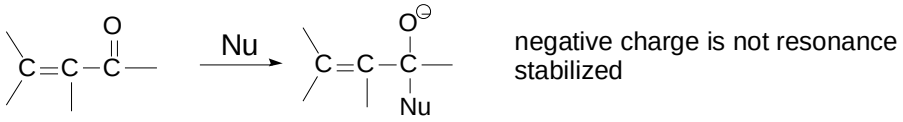
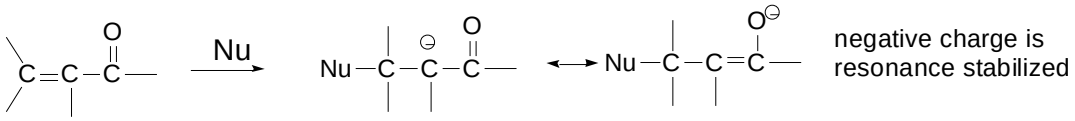


Eqn. 2.6

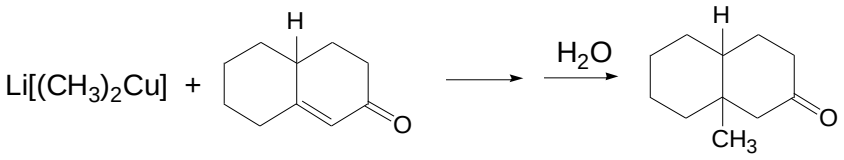


Eqn. 2.7

It might be imagined that resonance delocalization of charge should make the transition state leading to attack at C=C more stable than the transition state leading to attack at the carbonyl carbon. While this is very often the case (i.e. addition occurs preferentially at the C=C linkage), very reactive anions such as Grignard reagents give a fair amount of "direct addition" product (i. e., addition at carbonyl carbon, scheme 2.2).

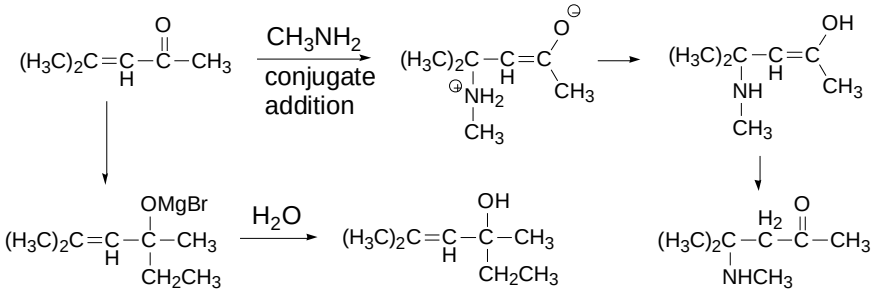
It is possible, however, to alter this preference of the Grignard reagent so that "conjugate addition" is observed. All that is required is the presence of Cu (I) during the addition (scheme 2.3, TernayJr., 1979).

The addition of copper (I) salts converts the Grignard reagents to complex organocopper reagents. And it is these organocopper compounds which actually are responsible for the conjugate addition. The conjugate addition of copper-containing compounds is also demonstrated directly. In the example below, (Eqn. 2.8) lithium dimethylcuprate is the reagent being added to the conjugated system.

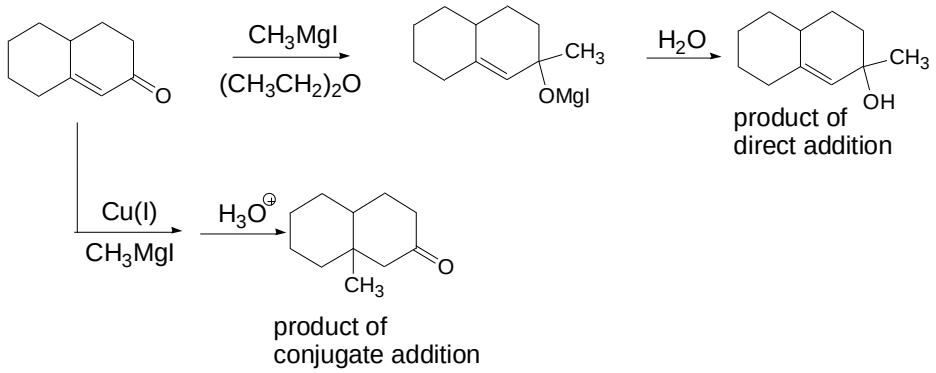


Eqn. 2.8

And it is these organocopper compounds which actually are responsible for the conjugate addition (Ternay, Jr., 1979).

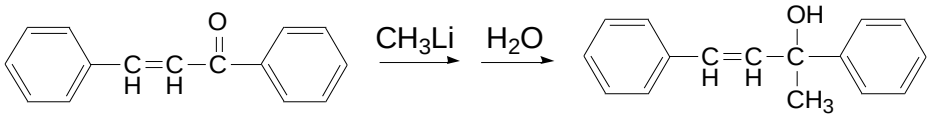


Scheme 2.2



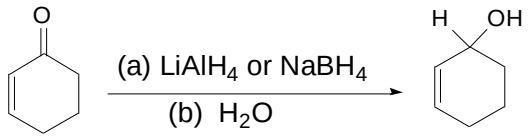
Scheme 2.3

Organolithium compounds almost always add to the carbonyl group of an α, β-unsaturated aldehyde or ketone. The addition of methyllithium shown below is a typical example (Eqn. 2.9).



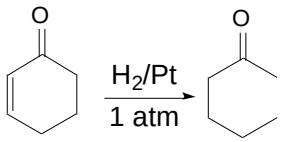
Eqn. 2.9

When an α, β-unsaturated carbonyl compound is reduced with $LiAlH_4$ or $NaBH_4$, the product usually is that from direct addition to carbonyl carbon (Eqn. 2.10).



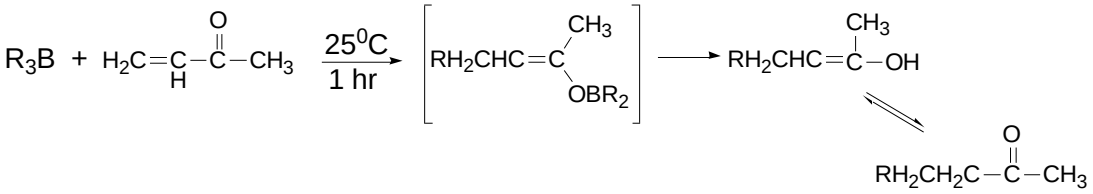
Eqn. 2.10

Catalytic reduction with one mole of hydrogen, on the other hand, reduces the C=C unit selectively (Eqn. 2.11, Ternay Jr., 1979). This probably has to do with the fact that the hydride anion in $LiAlH_4$ and $NaBH_4$ is more Nucleophilic than the neutral hydrogen of H_2/Pt reagent.

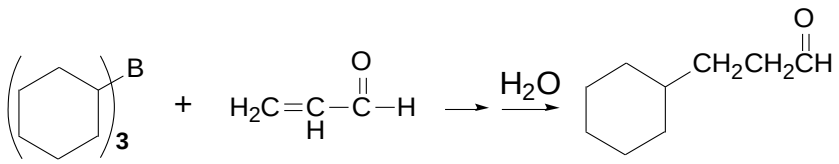


Eqn. 2.11

Conjugate addition of trialkylboranes to α, β-unsaturated carbonyl compounds produce aldehydes or ketones that are alkylated at the double bond (scheme 2.4).



Scheme 2.4

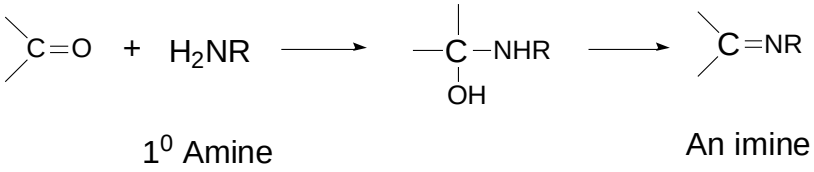


Eqn. 2.12

While the reaction is wasteful, in that only one of the groups bonded to boron is used in the alkylation, the simplicity of operation makes this a highly desirable procedure.

2.1.6 Formation of Imines and Enamines

In the examples given so far, the nucleophilic reagent is either the strongly basic anion or a neutral base like ammonia and its derivatives, NH_2-G or NH_2-OH. Amines react with carbonyl compounds by nucleophilic addition. If the amine is primary, the initial addition product undergoes dehydration to form a compound containing a carbon-nitrogen double bond, an imine (scheme 2.13, Morrison and Boyd, 2004).

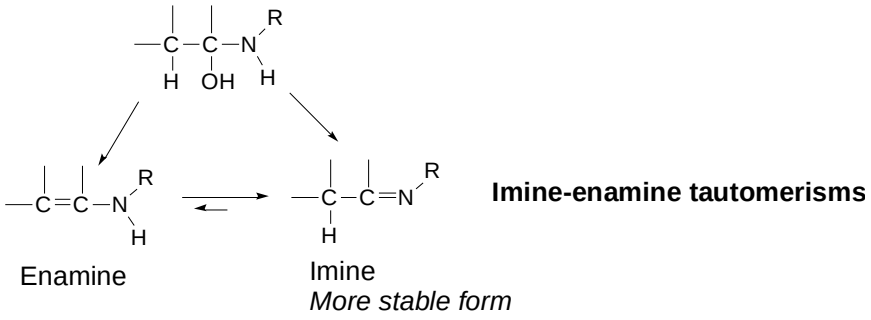


1^0 Amine

An imine

Eqn. 2.13

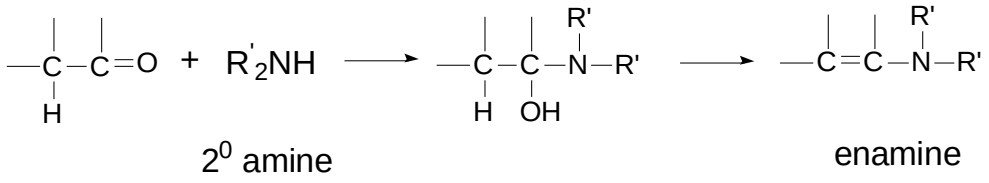
Elimination occurs with this orientation even if the carbonyl compound contains an α- hydrogen: that is, the preferred product is the imine rather than the enamine (Eqn. 2.14).



Eqn. 2.14

If some enamine should be formed initially, it rapidly tautomerizes into the more stable imino form as shown in Eqn. 2.14(Morrison and Boyd, 2004).

A secondary amine, too, can react with a carbonyl compound, and to yield the same kind of initial product. But here there is no hydrogen left on nitrogen; if dehydration is to occur, it must be in the other direction, to form a carbon-carbon double bond. A stable enamine is the product (Eqn. 2.15).



Eqn. 2.15

In literature (Morrison and Boyd, 2004; March and Smith, 2001; Zhang *et al*, 2001, etc) there seems to be confusion as to the nature of the addition of

ammonia or certain derivatives of ammonia to α, β-unsaturated carbonyl compounds with respect to the product formed. Morrison and Boyd (2004) concluded that β-amino carbonyl compounds were the products and then adds that "indeed, nucleophilic reagents rarely add to the carbon-carbon double bond of α, β-unsaturated aldehydes, but rather to the highly reactive carbonyl group".

The only literature that claims direct oximation (rather than conjugate addition) of an α, β-unsaturated carbonyl compound was a patent claim by Zhang *et al.*, 2001, that draws heavily on the description of oxime formation between carbonyls and hydroxyl amine by March and Smith (2001). These authors' description is exclusively for simple aldehydes and ketones and no mention is made about the oximation of α, β-unsaturated carbonyl compounds in the text book. Infact, it is stated in March and Smith (2001) that as regards Nucleophilic addition to α, β-unsaturated carbonyl compounds, "the mechanism is 1, 4 nucleophilic addition", i.e., conjugate addition!

Ternay Jr. (1979) gives a detailed account of how the direction of addition is influenced by organometallic reagents as was mentioned in earlier sections (Grignard reagents and organolithium reagents favouring direct carbonyl carbon addition while organocopper favoured conjugate addition) but fails to make clear the distinction between nucleophilic addition to the carbonyl carbon of an α, β-unsaturated aldehyde and ketone rather than a conjugate addition at the β-carbon in the absence of organometallic reagents.

2.2.0 Chemistry of Formation of Oximes

Oximes can be prepared by the addition of hydroxylamine to aldehydes or ketones (March and Smith, 2001). Hydroxyl amine is a derivative of ammonia and is therefore, basic and reacts with acids to form salts, hydroxyl amine hydrochloride. The salt is less easily oxidised by air than the free base and it is in this form that the reagent is best preserved and handled (Morrison and Boyd, 2004). When needed, the basic reagents are liberated from their salts in the presence of the carbonyl compound by addition of a base, usually sodium acetate.

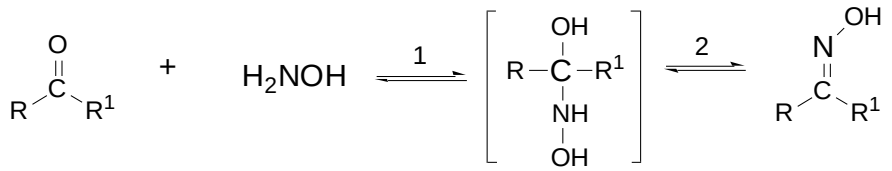
Addition involves nucleophilic attack by the basic nitrogen compound on carbonyl carbon. Protonation of carbonyl oxygen makes carbonyl carbon more susceptible to nucleophilic attack; i.e. as far as the carbonyl carbon is concerned, addition will be favoured by high acidity. But the ammonia derivative, H_2N-OH can also undergo protonation to form the ion, H_3N^+-OH, which lacks unshared electrons and is no longer nucleophilic; i.e. as far as the nitrogen compound is concerned, addition is favoured by low acidity.

The conditions under which additions proceeds most rapidly are thus the result of a compromise: the solution must be acidic enough for an appreciable fraction of the carbonyl compound to be protonated, but not so acidic that the concentration of the free nitrogen compound is too low.

It has been shown that the rate of formation of oximes is at a maximum at a pH that depends on the substrate but is usually about 4, and that the rate

decreases as the pH is raised or lowered from this point (March and Smith, 2001). Oximes are formed by nucleophilic attack of hydroxylamine at the carbonyl carbon (CO) of an aldehyde or ketone to give an unstable carbinolamine intermediate (Eqn. 2.16).

Since the breakdown of the carbinolamine intermediate to an oxime is acid catalyzed, the rate of this step, 2, is enhanced at low pH (Rossi *et al.*, 1990; Pliego *et al.*, 1999).



Carbinolamine intermediate

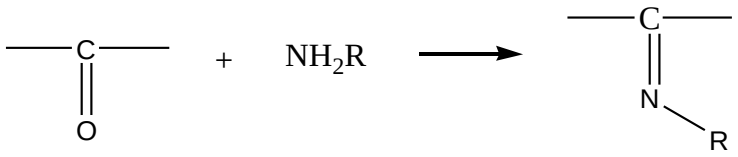
Eqn. 2.16

At low pH values step 2 (Eqn. 2.16) is rapid (because it is acid catalysed), and step 1 (Eqn. 2.16) is slow (and rate determining) because under this acidic conditions, most of the NH_2OH molecules have been converted to the conjugate NH_3OH^+ ions, which cannot attack the substrate. As the pH increases the fraction of free NH_2OH molecules increases and consequently, so does the reaction rate, until maximum rate is reached at about pH = 4 (March and Smith, 2001). As the rising pH has been causing an increase in the rate of step 1, it has also been causing a decrease in the rate of the acid catalysed step 2, although

this later process has not affected the overall rate since step 2 was still faster than step 1.

However, when the pH goes above about 4, step 2 becomes rate determining, and although the rate of step 1 is still increasing (as it will until all the NH_2OH has been unprotonated), it is now step 2 that determines the rate, and this step is slowed by decrease in acid concentration. Thus the overall rate decreases as the pH rises beyond about 4. The pH of the reaction medium also has some stereochemical implications. The pathways and conditions for certain stereochemical outcomes will be discussed in section 2.5.

Similar results are expected for the reactions involving aldehydes and ketones with amines (Eqn. 2.17).



Eqn. 2.17

2.2.1 Addition of Primary Amines to Carbonyl Compounds

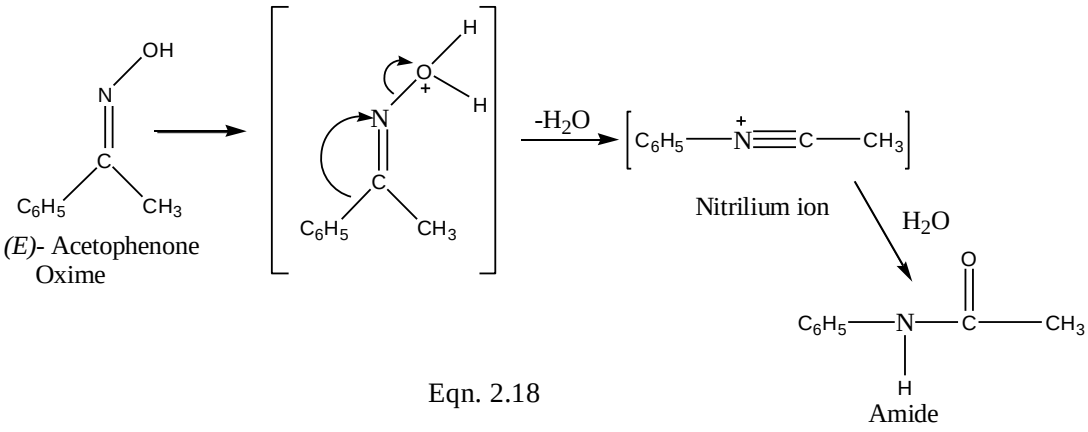
Addition reactions of carbonyl compounds with primary amines give imines that are stable under an inert atmosphere. In the presence of oxygen or water, such imines will quite readily hydrolyze or oligomerize. However, with an aryl group or certain stabilizing alkyl substituents on nitrogen, the imine formed is stable to oxygen and water and is called a Schiff base. In contrast, imine

condensations using ammonia and a carbonyl compound do not lead to stable imines - the imine formed quickly oligomerizes such as in the reaction of formaldehyde and ammonia which gives hexamine instead of the corresponding imine. (www.absoluteastronomy.com/ imine facts).

2.2.2 Beckman Rearrangement

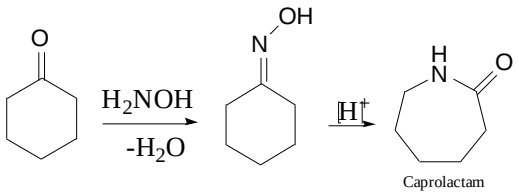
Perhaps it is pertinent to note that excessively low pH during oxime formation may induce the Beckman rearrangement of oximes (Gawley, 1988). One of the best-known reactions of oximes is their rearrangement to amides. This reaction, the Beckmann rearrangement, can occur with a variety of reagents [such as phosphorus pentachloride (PCl_5), concentrated sulfuric acid (H_2SO_4), and perchloric acid ($HClO_4$)] that induce the rearrangement by converting the oxime hydroxyl group into a group of atoms that easily departs in a displacement reaction (a good leaving group such as water which is stable and is capable of freely existing) by either protonation or formation of a derivative as shown in eqn. 2.18 (Gawley, 1988).

The Beckmann rearrangement has been shown to be a stereo-specific process in which the group *anti* to the leaving group undergoes a 1, 2-shift to give a nitrilium ion. The nitrilium ion reacts with water to form the amide as shown in eqn. 2.18 (Gawley, 1988). The water molecule (in case of simple protonation) eliminated in an earlier step in the reaction becomes the nucleophile that attacks the nitrilium ion (eqn. 2.18).



Eqn. 2.18

Similarly, the oxime of cyclohexanone is easily converted into caprolactam, a cyclic amide, in the presence of sufuric acid as catalyst (eqn. 2.19).

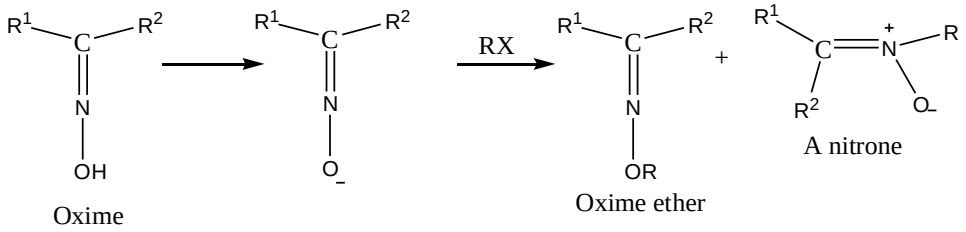


Eqn. 2.19

2.3 Chemistry of Formation of Oxime ethers

2.3.1 Alkylation of Oximes

An oxime can act as both a weak acid and a weak base (p*Kb*～=12 and p*Ka*～=11). Oxime anions (generated by the action of an alkali-metal base, eqn. 2.20) are capable of reacting at two different sites with alkyl halides (R-X).



Eqn. 2.20

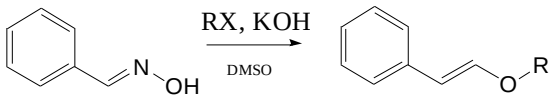
Oximes are referred to as ambident (literally, two-sided tooth) nucleophiles. In the case of oxime anions, the reaction with an alkyl halide (an alkylation reaction) can give oxime ether or a nitrone (eqn 2.20). Oxime can be alkylated by alkyl halides or sulphates (eqn 2.20). N-Alkylation is usually a side reaction, yielding a nitrone (eqn. 2.20).

The relative yield of oxime ether and nitrone depends on the nature of the reagents, including the configuration of the oxime, and on the reaction conditions. For example, *anti*-benzaldoxime gives nitrones, while the *syn* isomers give oxime ethers (March and Smith, 2001).

However, Agho *et al* (2003) reported the formation of aldoxime ethers from oximes by using Ag_2O as base to prevent nitrone formation regardless of whether *anti* or *syn* isomers were used while Olofsson *et al* (2005) prepared (3-Chloro-N'-(2-(methoxyimino)-1-phenylethylidene) benzohydrazide from 3-Chloro-N'-(2-(hydroxyimino)-1-phenylethylidene) benzohydrazide with silver(I)oxide as base and or oxidising agent. In the reaction, the methylation of the oxime was carried out with methyl iodide to obtain a product yield of 37%. The reaction mixture was stirred at room temperature for 4 days.

There are various methods, reaction conditions and reagents reported in the literature for the formation of oxime ethers (Li *et al*, 2002). For example, they have been made under anhydrous conditions using strong bases such as NaH (sodium hydride) or sodium alkoxides. They have also been made with weak bases like pyridine to realize the substitution reaction between alkyl halide and oximes.

Li *et al.*, 2002, reported a convenient and simple procedure for the preparation of oxime ethers. With aqueous Dimethyl sulfoxide as solvent, KOH, alkyl halide (or methyl sulfate) and oximes were reacted together in the presence of a strong base (Potasium hydroxide) at room temperature for 5 to 70 minutes as the case may be which on work-up gave oxime ethers in excellent yields - 70 to 96% (eqn. 2.21). The results are summarized in Table 1.



Benzaldehyde oxime

R = Me, Et, Bu, Ar etc

Eqn. 2.21

Table 1. Preparation of Oxime ethers with Dimethyl sulfoxide (DMSO) as Solvent and Potasium hydroxide as base.

Yield (%) and reaction time (minutes) of oxime ethers

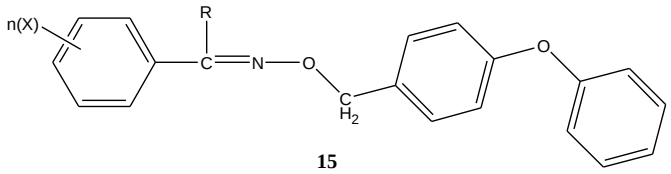
RX	acetophenone oxime		benzaldehyde oxime	
	% yield	rxn time	% yield	rxn time
CH_3I	87	5	76	5
Me_2SO_4	72	10	82	30
EtBr	74	5	72	10
BuBr	80	60	85	70
$CH_3(CH_2)_6Br$	77	5	81	10
$Br(CH_2)_3Br$	96	35	70	5
iPrBr	83	15	70	15
BzCl	76	50	96	60

Acetophenone oxime and benzaldehyde oxime were used as representative carbonyl compounds. The amounts of halides and methyl sulphate used were 1.2 equivalents and 1.6 equivalents respectively, whereas, 0.5 g of KOH was used for 1 mmol of oxime.

Replacing KOH with NaOH and DMSO with DMF in the reactions to prepare oxime ethers gave similar results as checked between benzaldehyde oxime and ethyl bromide (Li *et al*, 2002). The authors did not state the effect of

the stereochemical configuration of the substrate on the outcome i.e. whether a nitrone or an oxime is favoured.

Henry (1978) prepared oxime ethers of the form, **15**, by effecting reaction between an alkali metal salt of the appropriate ketoxime and 3-phenoxybenzyl bromide.



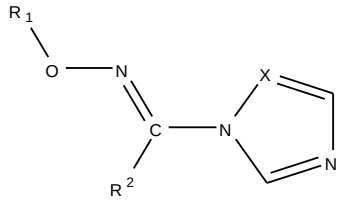
15

R = alkyl or alkenyl; X = halogen; n = 0,1 or 2

This reaction can be effected in some cases by treating a stirred mixture of the appropriate oxime and 3-phenoxybenzyl bromide in a solvent such as tetrahydrofuran or acetonitrile, or dimethylformamide in toluene, with sodium hydride. The reaction suitably can be conducted at or somewhat above room temperature, for example 15^{o}-70^{o}C. In some cases, it may be found to be desirable to first form the metal salt by treatment of the oxime with the hydride, and then bring the salt and the bromide together at a temperature of about 100^{o}-110^{o}C. In other cases, the reaction can be effected by treating a mixture of the oxime and an alkali metal base, such as potassium hydroxide, in water, with a solution of the bromide in a water-immiscible solvent, such as, toluene, in the presence of a suitable phase transfer catalyst. The catalyst can be any compound which would accelerate interphase reactions in two phase-systems.

Tetrabutylammonium bromide is an example. Temperatures of between 80^{o}-100^{o}C are usually suitable.

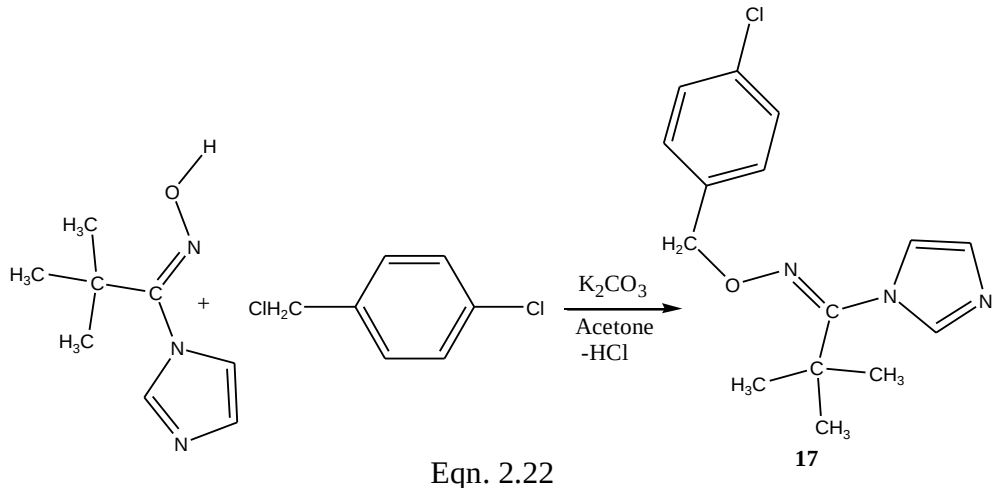
Schmeizer *et al.*, 1986, synthesized 1-azolyl-substituted oxime ethers of the general formula, 16,



16

in which R represents alkyl, alkoxyalkyl, alkenyl, alkinnyl, cycloalkyl, aralkyl, phenoyalkyl or phenyl groups while R^2 repesented alkyl, alkenyl, alkinyl and substituted aralkyl and heteroalkyl groups. X represented Nitrogen or the CH_2 group.

The compounds of this general formular were reported to have powerful fungicidal properties. If for example, 2,2-dimethyl-1-oxyimino-1-(N-imidazolyl)-propane and *p*-chlorobenzyl chloride are used as starting substances, the preparation of the compound, 17, may be prepared according to eqn. 2.22.

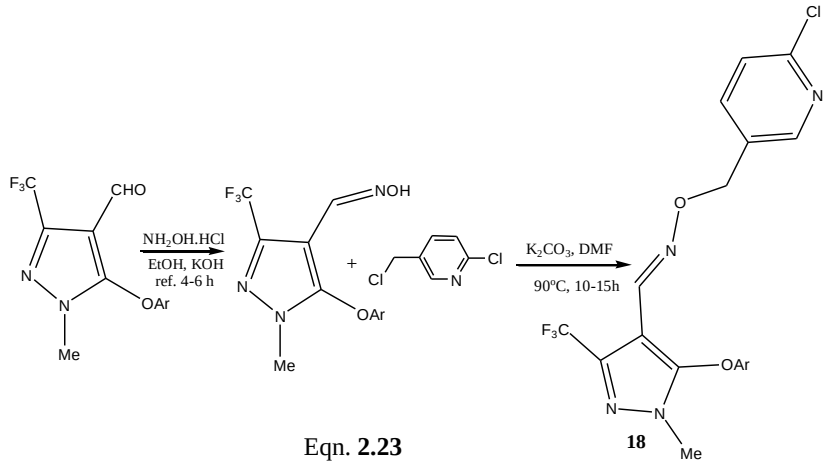


17

Eqn. 2.22

Another method reported in the PhD thesis of Khan (2006) is the treatment of the aldehydes or ketone with an alkyl halide in the presence of sodium methoxide with methanol as solvent (eqn. 2.29).

Fang *et al.*, 2009, discovered that the best results for the etherification of oximes were obtained when the reactions were carried out with K_2CO_3 in DMF at 90 °C. Fang *et al.*, 2009, converted aldehydes to the corresponding oximes with hydroxylamine under basic conditions, and further etherification of oximes under several base promoting conditions, including K_2CO_3 in DMF at 90 °C, generated a series of oxime ethers, 18 (eqn. 2.23 and Table 2). Consequently, K_2CO_3 and DMF were chosen as the best base and solvent, respectively, to further synthesize other compounds in satisfactory yields (Fang *et al.*, 2009).



Eqn. **2.23**

Table 2: The effects of bases and solvents on the synthesis of products

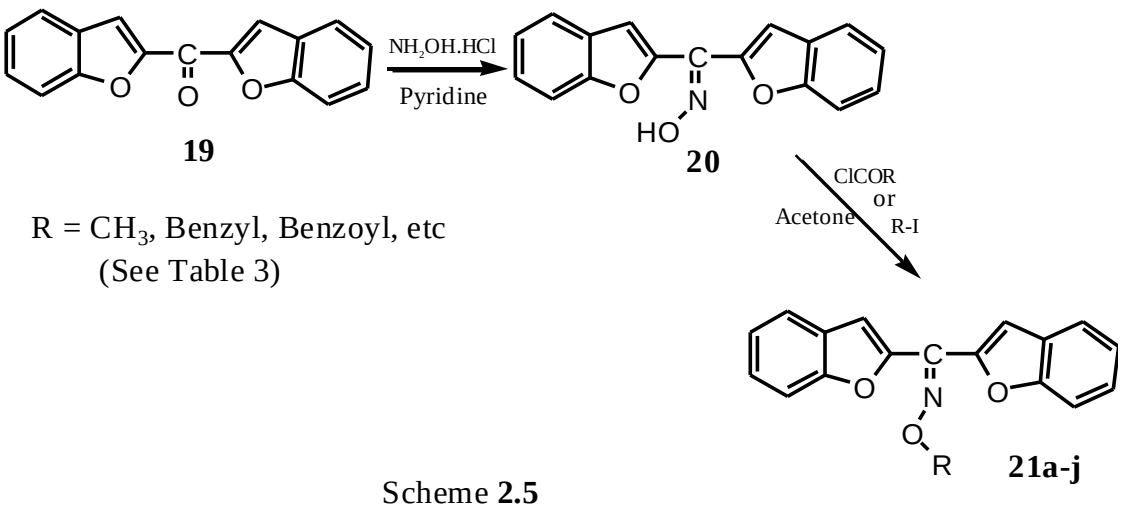
Entry	Temperature (°C)	Time(h)	Base	Solvent	Yield (%)
1	90	12	Et_3N	DMF	0
2	90	12	NaOAc	DMF	22
3	90	12	NaOEt	DMF	26
4	90	12	NaH	DMF	49
5	90	12	KOH	DMF	8
6	90	12	K_2CO_3	DMF	88
7	90	12	Pyridine	DMF	11
8	90	12	K_2CO_3	Me_2SO	41
9	90	12	K_2CO_3	Dioxane	38
10	90	12	K_2CO_3	CH_3CN	44
11	90	12	K_2CO_3	Butanone	40
12	90	12	K_2CO_3	Toluene	37

Abele *et al.*, 2007, used similar methods (reaction of alkyl halides, in K_2CO_3/DMF, NaH/DMF, and KOH/DMSO systems) to transform the oximes of

five-membered heterocyclic compounds with two hetero atoms into ethers of pyrazole, imidazole oxime ethers.

Examples of oxime ether formation involving the **acylation** of oximes also abound in literature. Cukurovali *et al.*, 2005, carried out a reaction between bisbenzofuran-2-yl-methanone, **19**, (scheme 2.5) with $NH_2OH{\cdot}HCl$ in pyridine to give its oxime derivative **20**. Reactions of **20** in acetone with appropriate alkyl iodides or bromides, or **acyl chlorides** in the presence of K_2CO_3, gave the oxime ether compounds (**21a-j,** scheme 2.5). The use of acetone as solvent provides relatively mild temperature conditions for the formation of the expected substances in excellent yields (Cukurovali *et al.*, 2005).

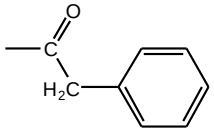
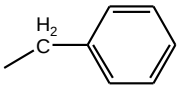
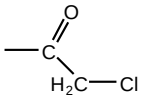
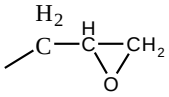
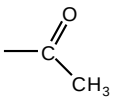
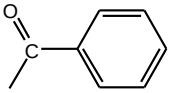
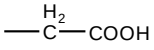
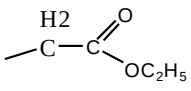
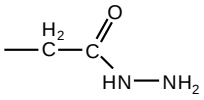
The compounds, except **21i**, were tested by Cukurovali *et al.*, 2005 against bacteria and fungi. The test results obtained are listed in Table **5**.



Scheme **2.5**

R in **21** consists of the following groups shown in the Table 3: All the compounds synthesized here are solid substances, stable at room temperature and not affected by atmospheric conditions over at least two weeks (scheme 2.5, Table **3**; Cukurovali *et al.*, 2005).

Table 3: Alkoxy substituent groups in Bis-benzofuran oxime ethers

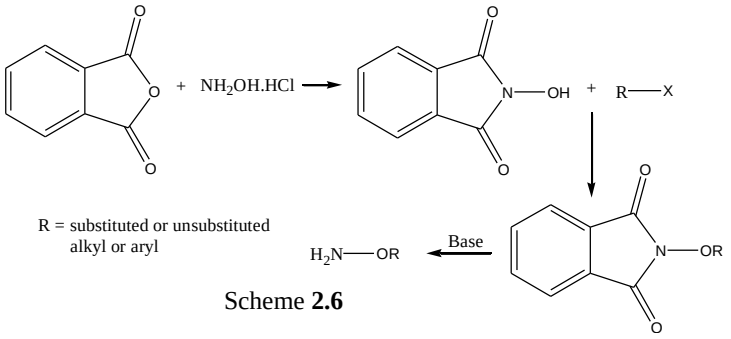
Substance	**R**	Substance	**R**
21a	CH_3	21f	
21b.		21g	
21c		21h	
21d		21i	
21e		21j	

2.3.2 Reaction of carbonyls with O-substituted amines

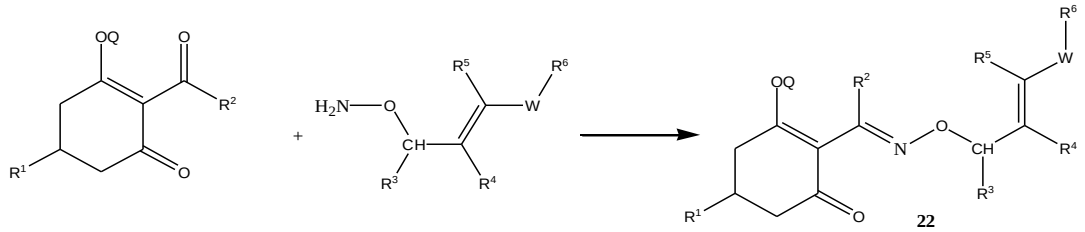
O-substituted amines are alkoxy or aryloxy amines like CH_3-O-NH_2 which are usually prepared by reacting phthalic anhydride with the appropriate amine (Kast *et al.*, 1995; Zhang and Shaber, 2001). Kast *et al.*, 1995, provided an

example of the alternative reaction (schemes 2.6 and 2.7) in which the oxime ether formation is a reaction between O-substituted alkoxy amine and an appropriate carbonyl compound. This way, Kast *et al.*,(1995) prepared a series of cyclohexenone oxime ethers, 22 (scheme 2.7), which are active as herbicides, (schemes 2.6 and 2.7) by reacting an alkylcarbonyl-substituted cyclohexanedione with an O-substituted hydroxyl amine. The reaction mixture, as earlier mentioned, can be in one or two phases, depending on the solvent used. Examples of bases that have been used for this kind of reactions include alkali metal or alkaline earth metal carbonates, bicarbonates, oxides, hydroxides and acetates of sodium, potassium, calcium as well as amines such as triethylamine, pyridine, dimethyl amino pyridine (Kast *et al.*,1995; Zhang and Shaber, 2001).

The hydroxylamine component is usually prepared by the reaction of an appropriate alkyl halide with N-hydroxy phthalimide which is usually prepared by the action of hydroxyl amine hydrochloride on phthalic anhydride (scheme 2.6).



Scheme **2.6**

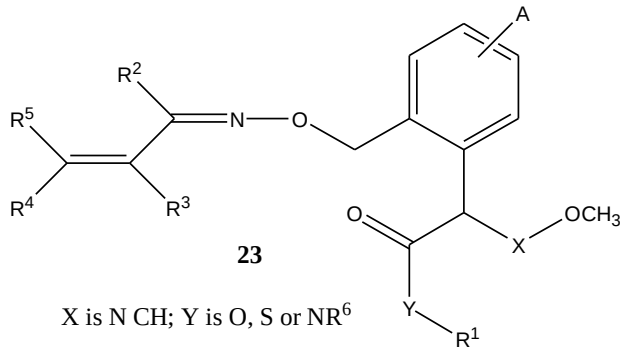


Q = H, alkylcarbonyl, benzoyl
W = -C=C-, alkynyl
R^1 = substituted or unsubstituted cycloalkyl , phenyl, pyridyl etc
R^2 = alkyl
R^3 = H, alkyl
R^4 = H, X, alkyl
R^5 = H, alkyl
R^6 = H, alkyl etc

scheme 2.7

Zhang and Shaber, 2001, used both methods, that is, reaction between carbonyl compound and an oxime as well as reaction between carbonyl and an O-substituted hydroxyl amine to prepare a series of one of the very few α, β-unsaturated oximes that have been synthesized, **23**. R^1-R^5 (23) can be a great variety of substituents. These series of compounds possess broad-spectrum fungicidal properties (Zhang and Shaber, 2001).

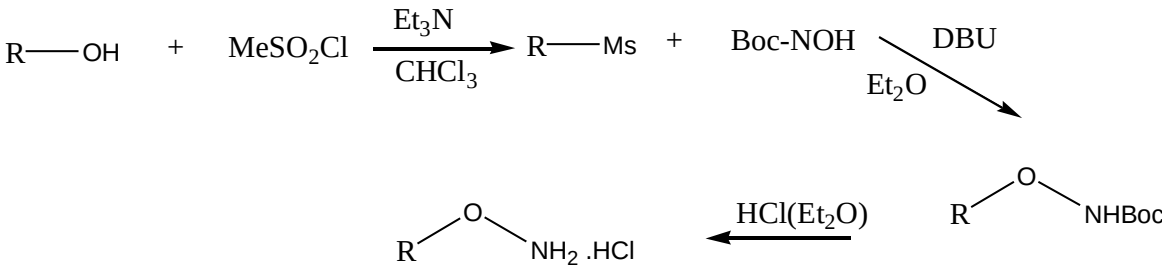
A variation of this method is the direct preparation of O-substituted hydroxylamines from alcohols which is achieved by O-alkylation of *tert*-butyl *N*-hydroxy carbamate with the methanesulfonates of respective alcohols, followed by acidic N-deprotection (scheme **2.8**, Defoin *et al*, 2006).



23

X is N CH; Y is O, S or NR^6

Such O-substituted hydroxylamines can then be reacted with aldehydes and ketones to give oxime ethers as in scheme **2.7**.



Scheme **2.8**

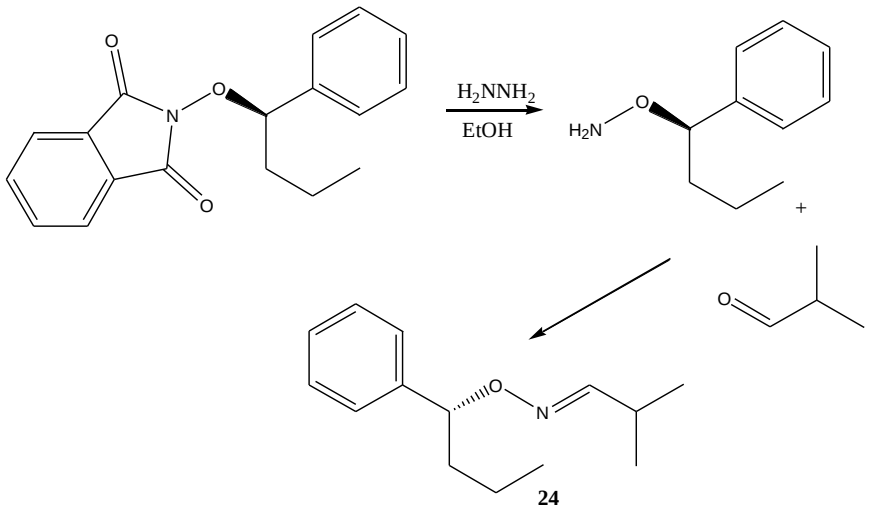
2.3.3 Some synthetic techniques for preparation of oxime ethers

In the direct alkoxyamination of carbonyls, Holan, et al (1986), used equimolar quantities of ketone or aldehydes and O-substituted hydroxylamine hydrochlorides (e.g. O-(4-fluoro-3-phenoxybenzyl) hydroxylamine hydrochloride) in dry methanol at 10-50^{o}C.

For alkylation of oximes, Holan *et al*, 1986, in an inert gas atmosphere sodium hydride was suspended in dry acetonitrile. To the suspension was added, drop wise, a solution of the oxime in dry acetonitrile. After 1 hour at room temperature a solution of an alkyl halide (e.g. 4-fluoro-3-phenoxybenzyl-

bromide in dry acetonitrile was also added drop wise to yield the desired oxime-O-alkyl ether.

(*R*)-*O*-(1-Phenylbutyl)isobutyraldehyde oxime, 24, is obtained by the phthalimide pathway from a suspension of (*R*)- or (*S*)-*N*-(1-phenylbutoxy)phthalimide in ethanol and heating until the phthalimide dissolves. Hydrazine hydrate is added at this elevated temperature. The aldehyde is then added at room temperature and the suspension is stirred until the reaction is adjudged complete by TLC (typically 2–16 h, Hunt *et al.*, 1999).



24

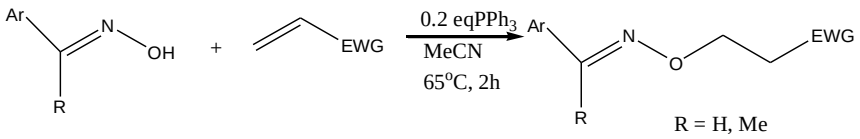
Eqn. **2.24**

(*R*)-*O*-(1-Phenylbutyl)isobutyraldehyde oxime, 24. Obtained from the cleavage of (*R*)-*N*-(1-phenylbutoxy)phthalimide and subsequent condensation of the hydroxylamine with isobutyraldehyde, as a colourless oil (54%, Hunt *et al*, 1999).

Oxime ether formation from Acyl halides was achieved by the reaction of 4-chloro-2, 2-substituted chromeno-3-aldoximes with acyl chlorides or ethyl chloroacetate. The appropriate acyl chloride (acetyl chloride, chloroacetyl chloride, benzoylchloride) or ethyl chloroacetate was added to a solution of 4-

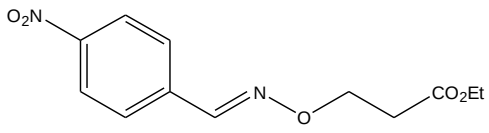
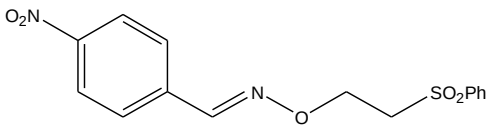
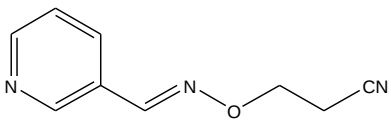
chloro-2, 2--substituted chromeno-3-aldoxime in dry toluene containing redistilled dry pyridine. The reaction mixture was refluxed for 5h, The solvent was evaporated under reduced pressure to give the corresponding oxime ethers, respectively (Cukuruvali *et al.*, 2005; Mohamed, *et al.*, 2008).

Bhuniya *et al.*, 2003, discovered a new reaction condition for Michael addition of oximes onto activated olefins by using a catalytic amount of triphenylphosphine. Various aldoximes and ketoximes were reacted with different Michael acceptors in good yields (eqn. 2.25).



Eqn. 2.25

Table 4: Michael addition of oximes to activated olefins

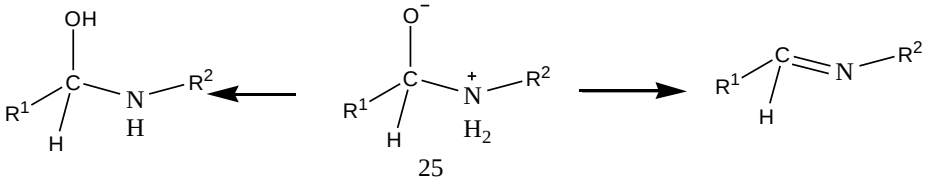
Product	Yield (% iso.)
	85
	90
	65

The reaction between benzaldehyde oxime and ethyl bromide may serve as a typical procedure for the alkylation of Oximes in DMSO or DMF with KOH. To the stirred mixture of benzaldelyde oxime and KOH in DMSO and 2 mL of H_2O were added ethyl bromide. The reaction was monitored by TLC and was completed in 35 min (Li *et al.*, 2002).

2.4.0 Stereochemistry and Spectral Characterization of Oximes and oxime ethers

2.4.1 Stereochemistry of oximes and oxime ethers (mechanistic study)

The reaction mechanism of amine addition to carbonyl compounds in aqueous solution has been studied at the experimental level, and some theoretical studies have been reported (Pliego *et al.*, 1999). A general mechanism has been proposed for this reaction in aqueous solution and at variable pH. The first step can be catalyzed by H_3O^+ at low pH, forming the aminoalcohol intermediate. Increasing the pH, a competitive uncatalyzed mechanism can take place, which occurs through the formation of a supposed zwitterion tetrahedral intermediate, 25.



25

Tetrahedral zwiterion

R^1 and R^2 = substituted or unsubstituted alkylor aryl groups

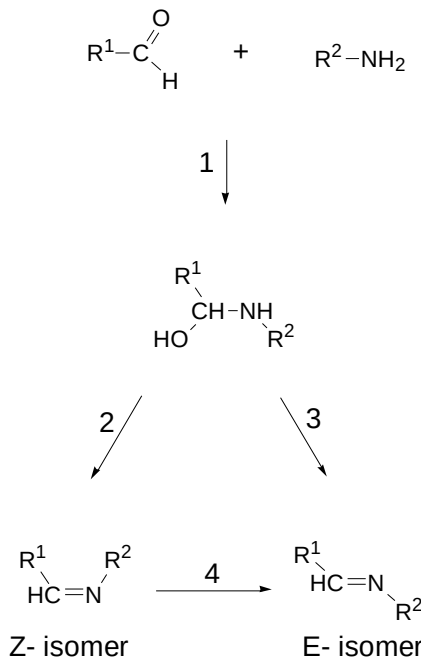
Eqn. 2.26

This species could dissociate backward, or rearrange to aminoalcohol in an acid catalyzed or uncatalyzed mechanism. Support for this mechanism was provided

by the pH dependent rate profile (Pliego *et al,* 1999). However, *ab initio* studies for the addition of several amines to carbonyls do not support this proposed mechanism. The zwitterion intermediate, **25 (eqn. 2.26)**, is not a minimum energy structure on the potential energy surface, and some workers have found a four-center transition state for this step, thus generating directly the aminoalcohol (Pliego *et al*., 1999).

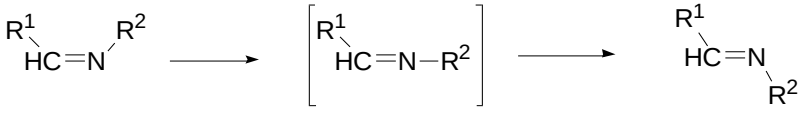
Another *ab initio* study of the NH_3 addition to HCHO has shown that one or two water molecules can act as a catalyst through a cyclic transition state. These results raise doubts about the formation of the zwitterion intermediate, and point out that the uncatalyzed mechanism in reality is water catalyzed (Pliego *et al.*, 1999).

The second step of the reaction is the water elimination of the aminoalcohol, forming the imine. This step can be acid catalyzed in low pH, and presents a competitive uncatalyzed mechanism, which can become important when the pH increases. So, in the case of a reaction involving amine and aldehyde in a neutral and low polarity medium, which is the interest of the study by Pliego, *et al.*, 1999, the overall mechanism can be represented by scheme 34, where they have included the possibility of the formation of both *E*- and *Z*- isomers.



Scheme 2.9

The interconversion from *E*- to *Z*-isomers of imines has been the object of many theoretical and experimental studies which have addressed questions on the mechanism, kinetics and thermodynamics of this process. These studies pointed out that in aprotic medium, isomerization occurs by inversion of the nitrogen atom, as indicated in eqn. 2.27 (Pliego *et al.*, 1999).



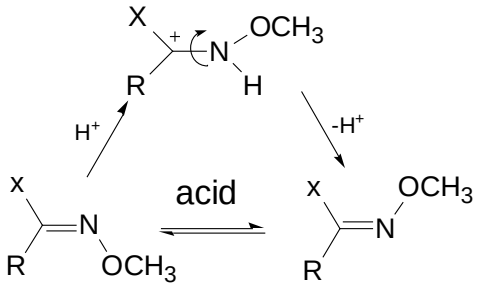
Eqn. 2.27

For the prototypical methylimine species, *ab initio* calculations have indicated a barrier of 30.5 kcal/mol (Pliego *et al.*,1999) exists between the two forms (*E* and *Z* isomers). With the increase of the groups bonded to nitrogen and carbon,

this barrier can decrease by up to 15 kcal/mol, as found in experimental studies. In thermodynamic terms, either *E*- or *Z*-isomers can be the more stable, depending on the substituent groups. For aldimines, *E*-isomers in general present lower free energy. As an example, experimental and theoretical data have been combined to obtain the heat of formation of (*E*)- and (*Z*)-N-methyl-acetaldimine, and it was found that the *E*- isomer is more stable by 4.4 kcal/mol (Johnson *et al*, 2001). Another pathway to isomerization is by enamine formation in protic medium (Pliego *et al*, 1999).

Johnson *et al*., 2001, in their kinetic studies of the interconversion reactions between *E* and *Z* isomers also indentified the several ways by which these interconversions could occur.

The kinetics of *Z*/*E* isomerisation of these imines have been studied in glacial acetic acid and in dioxane solutions containing HCl, trifluoromethanesulfonic acid, or tetrafluoroboric acid (scheme 2.10).



X = Cl, R = YC_6H_4 or $C_6H_5CH=CH$

Scheme 2.10

The isomerisation takes place by either (a) rotation about the carbon-nitrogen double bond of the protonated imine (iminium ion rotation (scheme 2.10) or (b)

nucleophilic attack on the protonated imine to form a tetrahedral intermediate that undergoes stereomutation and loss of the nucleophile (nucleophilic catalysis). The hydroximoyl chlorides only isomerise by the nucleophilic catalysis mechanism. Some of the hydroximates appear to be capable of isomerizing by either mechanism, while some hydroximate may be isomerising only by iminium ion rotation. Theoretical calculations support the notion that increased conjugation in the protonated imine increases the rate of iminium ion rotation (Johnson *et al.*, 2001).

In summary, both isomers are always formed in most oximation reactions. In both protic and aprotic media and there is interconversions between E and Z isomers to the most stable isomer. There are three ways by which this conversion may occur:

i. By inversion of nitrogen atom in aprotic solvent
ii. Rotation about the C=N double bond of the protonated iminium ion in protic solvent
iii. Stereomutation of the tetrahedral intermediate formed Nucleophilic attack on iminium ion.

2.4.2 Spectral studies of oximes and oxime ethers

The NMR technique is a versatile tool for the structural elucidation of most organic compounds and it is useful for the conformational analysis of compounds also. ^{1}H NMR and ^{13}C NMR techniques have been extensively

applied in deriving stereodynamical information about a wide variety of systems. For example, the conversion of the carbonyl group into the oxime, C=N-OH, and oxime ether C=N-OR etc exhibit an abrupt change in the NMR chemical shifts and infra-red bands (Rani *et al.*, 2008; Kabilan *et al.*, 2008).

In a wide search for new and efficient antimicrobial agents, Kabilan *et al.*, 2006, synthesized a series of substituted piperidin-4-one oxime ethers. The structures of these oxime ethers and their relative stereochemistries were investigated by nuclear magnetic resonance spectroscopy. In all the oxime ethers synthesized, the orientation of the N-O bond of the oxime ether moiety, the *E*-configuration, was deduced based on ^{1}H NMR and ^{13}C NMR spectra (Kabilan *et al.*, 2006).

Many of the original (prior to 1921) assignments of configuration of the *Z* and *E* isomers were based on chemical reactions (the Beckman rearrangement) and were in error because of incorrect assumptions concerning the stereochemistry of these reactions (Johnson *et al.*, 2001). The *E* and *Z* isomers of oxime ethers are known to be resistant to thermal isomerisation. The assignment of configurations of oximes, when both isomers are available, can be made from ^{1}H and ^{13}C nuclear magnetic resonance spectra by noting that, *E* and *Z* isomers of oxime ethers exhibit two signals for the C=N-O-CH_2- protons at 4.35-4.45 ppm (*E* -isomer) and 4.20-4.30 ppm (*Z*- isomer), O-CH_2 resonance for *E* isomer occurs at higher δ ppm values than for the *Z* isomers (Karabatsos and Hsi, 1967; Haney *et al*, 1977; Boschmann and Winter, 1980).

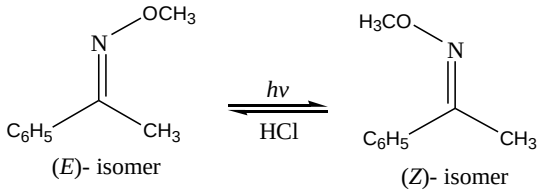
In their study on the synthesis of some novel Oxime ether derivatives, Buzdag-Dundar *et al.* (2003) observed C=N-O-CH_2- protons at 4.1-4.31 ppm but did not state whether the products were *Z* or *E* isomers. But from the aforementioned observations, they are *Z*-isomers. But it seems that both isomers have to be present in other to distinguish one from the other.

Cukurovali *et al.*, 2005, monitored the reaction for oxime formation from aldehydes and ketones and were able to verify the completion of oxime formation by using the absence of the C=O band of the carbonyl compound, **19** (scheme 2.5), and the existence of a broad =N-OH band centred around 3166 cm^{-1} in the IR spectrum of **20**, the corresponding oxime, to confirm the formation of the compound (scheme 2.5). The oxime –OH proton appears as a broad singlet at 13.01 ppm in the corresponding ^{1}H-NMR spectrum (scheme 2.5, Cukurovali *et al.*, 2005).

The *O*- methyloxime prepared from reaction of acetophenone with hydroxylamine followed by alkylation with methyl iodide has the *E* configuration (OCH_3 and C_6 H_5 groups on opposite sides of the double bond (eqn. 2.28, Johnson *et al.*, 2001).

Ultraviolet irradiation of benzene solution of the *E* isomer gives a mixture of the *E* and *Z* isomers from which the *Z* isomer is obtained by chromatography. Reversion to the more stable *E* isomer can be accomplished by acid-catalyzed

isomerisation (hydrogen chloride in dioxane) of the *Z* form (eqn. 2.28, Johnson *et al.*, 2001).



Eqn. **2.28**

Aromatic A and B ring protons were seen at 6.89-7.03 and 7.12-7.35 ppm, respectively (*E* and *Z*-isomers, eqn. 2.28).

2.4.3 Hydrogens bonded to heteroatoms

The chemical shifts of hydrogen bonded protons, O-H protons in alcohols and N-H protons in amines, depend on the concentration. In concentrated solutions, these protons are deshielded by hydrogen bonding when these absorb at lower field (δ 3.5 amine N-H, δ 4.5 for an alcohol O-H). When the alcohol or amine is diluted with a non-hydrogen bonding solvent, hydrogen bonding becomes less important and consequently these resonances are observed around δ 2.0.

Hydrogen bonding and the proton exchange that accompanies it leads to a broadening of the signal corresponding to the resonance of a O-H or N-H proton. Abroad peak is observed since, protons are exchanging from one molecule to another during the PMR resonance. The protons pass through different environments during this exchange, giving absorptions over a wider range of frequencies and field strengths.

2.4.4 Chemical Equivalence and magnetic equivalence

In benzene all six hydrogens are chemically equivalent. For example, in *p*-xylene, there are two sets of chemically equivalent protons, thus one would expect two signals. Often the protons attached to the aromatic ring, particularly when the substituent is an alkyl group may have similar chemical shifts.

Protons are magnetically equivalent if they have the same chemical shift and are coupled equally to other nuclei in the molecule. This is similar to chemical equivalence but it is a more rigorous definition of equivalence.

To be magnetically equivalent, the nuclei must be chemically equivalent and magnetically equivalent nuclei must have the same coupling constant to any other nucleus in the molecule (Kalsi, 2004).

2.4.5 Vicinal Coupling And Stereostructure

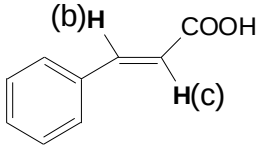
The difference between J_{cis} and J_{trans} is an important tool for distinguishing between *cis* and *trans* alkenes. Although the ranges of both sets overlap (*J*, coupling constant), for a pair of isomeric *cis* and *trans* alkenes J_{trans} is invariably greater than J_{cis} (Kalsi, 2004).

In alkenes, J_{cis} is in the range 5-14 Hz and J_{trans} is in the range 11-19 Hz and these ranges slightly overlap. It may not be possible to assign stereochemistry from the H NMR spectrum of just one stereoisomer. Thus for example no conclusion may be drawn about stereochemistry from observed coupling

constant of 13 Hz. If the H NMR spectra of both stereoisomers are available, the *cis* stereochemistry can be assigned to the one with smaller *J* value.

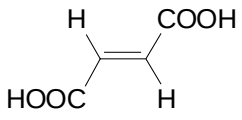
Terminal alkene hydrogens (RR-C=CH_2) give signals around δ 4.6-5.0 and their internal counterparts (RCH=CHR^1) at δ 5.2-5.7.

Unsymetrically substituted double bonds contain non-equivalent alkenyl hydrogens that are coupled to each other. This is so in the case of *trans* cinnamic acid in which the alkenic protons (b,δ 7.8) and (c, δ6.5) appear as doublets. The coupling constant (17 Hz) is in keeping with the fact that these hydrogens are *trans* arranged. These alkenic protons give rise to an AB 'quartet'. There is a multiplet (5 protons) around δ 7.4 due to the phenyl group. The COOH proton signal is usually around δ12.

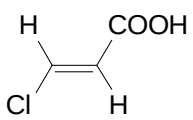


Cinnamic acid
(E)-3-phenylpropenoic acid

When two protons are equivalent by symmetry they do not display spin-spin splitting and appear as a singlet. The H NMR spectrum of benzaldehyde usually shows the chemical shift positions of aldehydic proton at between δ 9-10.



symmetrical



unsymmetrical

The H NMR spectra of 2-butenal (crotonaldehyde) is a system which is further complicated due to additional coupling with the aldehydic proton (fig. 2.1). A complete analysis of the spectrum is given by Kalsi (2004). The multiplet at low field (H_a) is two overlapping quartets. These occur from the coupling of the proton (H_a) with the methyl protons H_c to give to give a quartet which is subsequently split into a pair of quartets by coupling with proton H_b. The methyl group at δ 2.0 in crotonaldehyde gives a more complex pattern expected of terminal methyl group than would be expected for splitting by one adjacent proton.

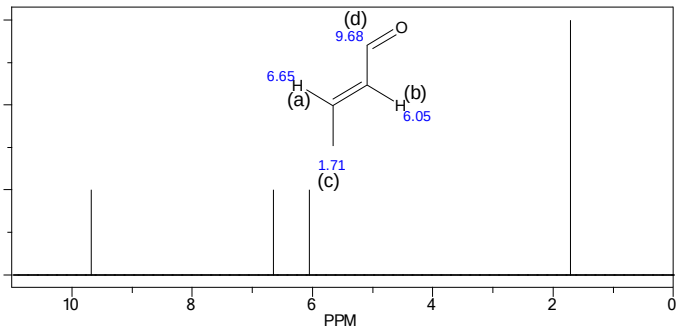


Fig. 2.1: Approximate Chemical shift positions for crotonaldehyde

The expected doublet (J = 7Hz) is further split (long range coupling J = 1.0 Hz) by H_b, i.e., proton on C-2. The aldehydic proton is the expected doublet at around δ 9.5.

Kalsi, 2004, also gave a complete interpretation of ^{1}H NMR spectrum of *trans*-cinnamaldehyde as follows (fig. 2.2):

- The aldehyde proton H^d is at δ 9.6 and is a doublet (J = 7 Hz) being split by H^b.
- All the five aromatic protons overlap to give a broard singlet at δ7.4.
- The alkenic proton H^a (vinylic proton) being β-placed to α, β-unsaturated carbonyl system is deshielded from the normal alkenic region (moreover proton H^a is also further deshielded being placed next to the aromatic ring). Its signal δ7.42 is split into a doublet by H^b with J = 15 Hz.
- The alkenic proton H^b at δ 6.6 gives four lines since it is coupled to two non-equivalent protons H^a and H^c and the coupling constants $J_{ab} \neq J_{bc}$. Ignoring the intervening signals for five aromatic hydrogens the multiplets can be best studied as their spin-spin splitting diagram.

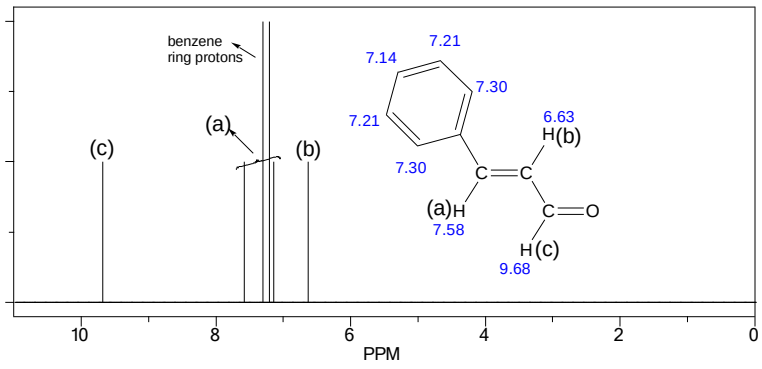


Fig.2.2: Approximate chemical shift positions for Cinnamaldehyde

2.5.0 Two Dimensional NMR Spectroscopy (2-D NMR)

A conventional ^{1}H NMR spectrum has a frequency axis and an intensity axis, 2-D NMR spectra have two frequency axes and one intensity axis. The common 2-D NMR spectra are ^{1}H-^{1}H shift correlation in which both frequency axes

show ^{1}H chemical shifts. This is known as ^{1}H-^{1}H shift correlated spectroscopy, which is known by the acronym COSY (Correlated SpectroscopY). COSY identifies pairs of electrons which are coupled to each other.

Two-dimensional NMR leads to the development of chemical shifts (and coupling constants) into two dimensions and to resolve overlap of resonances which enables the correlation of interacting nuclei to be determined. 2-D NMR can thus be applied to complex spectra which are difficult to analyse by conventional methods.

The following is the pointwise discussion of how a COSY spectrum is interpreted:

- In the COSY spectrum, the conventional ordinary one-dimensional spectrum is shown along both the horizontal and vertical axes.
- Along the diagonal is a view which corresponds to looking down on the conventional one-dimensional spectrum as if each peak were a mountain.
- The one –dimesional counterpart of each peak on the diagonal lies directly below that peak on each axis.
- The off diagonal peaks (also called cross-peaks) provide useful information. The presence of a cross-peak normally indicates that the protons giving the connected resonances on the diagonal are geminally or vicinally coupled. Long range couplings normally do not give significant cross-peaks

- One starts at a given cross-peak and imagines two perpendicular lines, one horizontal and the other vertical, are drawn back to the diagonal. The peaks which are intersected on the diagonal by these lines are coupled.
- Cross-peaks are usually found on both sides of the diagonal. For interpretation, only cross-peaks on one side of the diagonal (below or above the diagonal) may be used. The intensities of the cross-peaks provide some indication about the order of the coupling constant.

Thus from a COSY spectrum, one can know which hydrogens are coupled to each other.

2.5.1 HETCOR Spectra.

2D-NMR spectra that display ^{13}C-^{1}H shift correlations are called HETCOR (from Hetero nuclear Correlation) spectra. HETCOR spectra shows coupling between protons and the carbon to which they are attached. In a HETCOR spectra,

- A ^{13}C spectrum is illustrated along one axis and a ^{1}H spectrum on the other.
- There is no diagonal spectrum in the X-Y field as is in COSY experiment.
- The 2-D spectrum is composed only of cross-peaks, each one relating a carbon to its directly bonded protons.
- Quaternary carbons are invincible to the technique.

2.6.0 Carbon-13 NMR Spectroscopy

In comparison to Proton NMR (^{1}H NMR) spectroscopy, ^{13}C NMR spectra are more easily interpreted and give the following information:

- The common range of energy absorptions for ^{13}C is wide δ 0-200 relative to TMS, contrasted with δ0-15 for ^{1}H NMR. Thus fewer peaks overlap in ^{13}C spectra.
- Because only 1.1% of carbon in a compound is ^{13}C, ^{13}C- ^{13}C coupling is negligible and is usually not observed. Therefore, in one type of ^{13}C spectrum (proton decoupled), each magnetically non-equivalent carbon gives a single unsplit peak. Just like hydrogen, two adjacent carbons, if magnetically non-equivalent split each other. In practice however, such splitting is not observed, since coupling can only occur if two ^{13}C isotopes come to lie next to each other. Due to abundance of ^{13}C in the molecule at 1.11 %, this situation has a very low probability (1 in 10,000). Most ^{13}C nuclei are surrounded by only ^{12}C nuclei, which having no spin, do not give rise to spin-spin splitting.

2.6.1 Chemical Shifts of alkanes in ^{13}C NMR

Alkyl carbons display themselves in the most up field positions, carbons attached to an electronegative element such as oxygen are shifted downfield, i.e.,

away from Tms, the carbons of an aromatic ring appear farther downfield, and so on. (See fig. 2.3: correlation chart for ^{13}C chemical shifts).

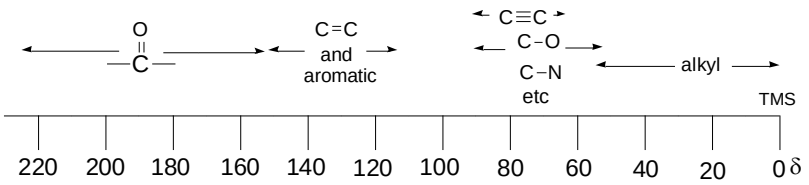
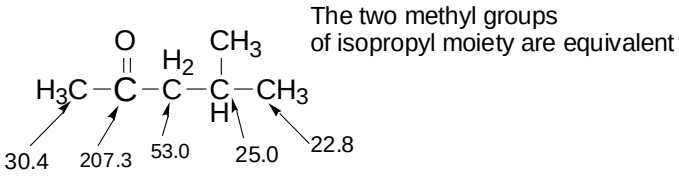


Fig. 2.3:

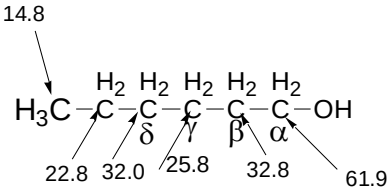
2.6.2 Deshielding effect of electronegative moiety

An electronegative substituent such a carbonyl group or hetero-atom on a carbon atom brings about a downfield shift in the resonance, relative to a saturated hydrocarbon. This effect is caused by the deshielding effect of the electronegative moiety.



4-Methyl-2-pentanone

An electronegative atom brings about a deshielding at the α and β carbons, however, there is often a small upfield shift for the ϒ-carbon.

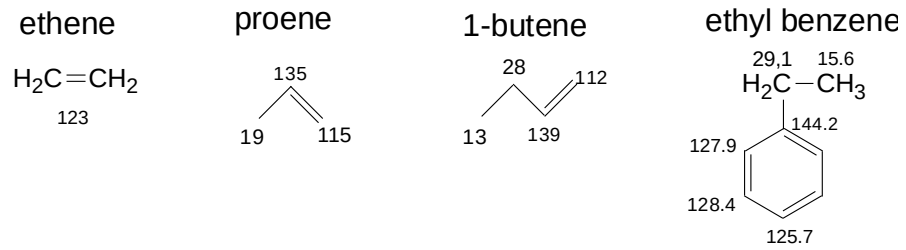


Hexanol

In ^{13}C NMR, an electronegative element also causes a downfield at α and β carbons but often leads to a small upfield shift for the γ carbon

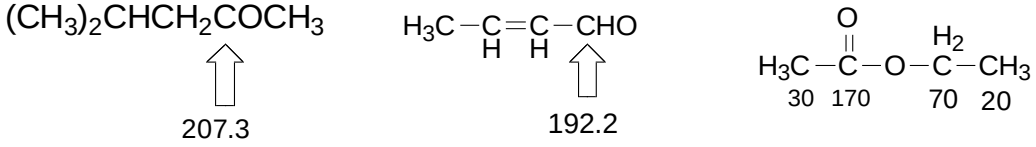
The sp^2 hybridised carbon atoms in alkenes and benzenoid hydrocarbons appear in the same general region of the ^{13}C NMR spectrum. Therefore proton NMR is more useful in making a distinction between the two types of unsaturation.

An inspection of scheme below shows that the double bond effect only slightly affects the shift of sp^3 carbons in a molecule, the methyl signal of propene is at 19.0 ppm, and of propane is at 16.0 pmm (Kalsi, 2004).



2.6.3 Carbonyl carbon atoms

The ^{13}C chemical shifts of carbonyl carbons vary from 150 to 220 ppm. This depends on the decrease of electron-donating or shielding ability of the attached atoms as shown in the scheme below for ketone, aldehyde and ester.



2.6.4 DEPT ^{13}C Spectra

In a DEPT (Distortionless enhanced polarization transfer) experiment, three spectra are obtained. One is a normal broadband decoupled spectrum. The second spectrum (DEPT 90^{o} spectrum) is obtained under special conditions in which only carbons bonded to single hydrogen (CHs) appear. A third spectrum (DEPT 135^{o} spectrum) is obtained under conditions in which CH and CH_3 carbons appear as normal signals, but CH_2 carbons appear as negative absorptions, and no peaks for quaternary carbons (Kalsi, 2004).

2.7.0 Separation of Isomers of oxime ethers

It has been found that geometrical isomers of chemical compounds containing the oxime group can be separated by a novel process using non-functional macroreticular adsorption resins.

Sometimes, isomers are distinguished by the difference in their bioactivity. For example, the more active isomers of 4-fluorophenoxy-benzyl ethers of oximes of substituted phenyl halo-methyl ketones, **21**, are distinguished by a powerful insecticidal and acaridical activity. In particular the compounds show powerful activity against cotton bud worm (*Heliothis Punctigera*) an important agricultural pest (Holan *et al.*, 1986).

The *syn*-isomers of cephalosporin compounds containing the oxime group exhibit superior antibacterial activity to the corresponding *anti*-isomer, so that

the oxime group-containing cephalosporin antibiotics are generally obtained and used in the form of their *syn*-isomers.

In some compounds the inactive isomer can be partly converted to the active isomer by gently heating it in a polar solvent, e.g. methanol, or by applying ultra violet radiation. The isomers can be separated by any conventional method, e.g., high performance liquid chromatography (Holan *et al.*, 1986; Robinson *et al.*, 1988).

The separation of *syn* and *anti* isomers of oxime compounds by chromatography on silica gel is known (Robinson *et al.*, 1988). However, the separation achieved by this method depends to a large extent on the solvent system employed to elute the isomers and the separation of isomers of different compounds often require quite different solvents systems (Robinson *et al.*,1988).

A further method in the art for the separation of *syn* and *anti*-isomers of oxime compounds is fractional crystallization whereby one of the isomers is crystallized from a solution of the mixed isomers while the other isomer is left in solution. However, it has been found that this technique does not achieve satisfactory separation of isomers of oxime cephalosporins. Robinson *et al.*, 1998, have found that the geometrical isomers of oxime group containing compounds can be separated with high efficiency, using aqueous elution from non-functional macroreticular adsorption resins.

A solution containing the isomers to be separated is brought into contact with the non-functional macroreticular adsorption resin in any desired way,

most suitably by loading it into a column or bed of granular resin e.g. in conventional bead form.

Where the resin is used in the form of a column, the separation may be chromatographic. Thus, elution will tend to separate the isomers into bands which may be eluted as separate peaks. The desired *syn*-isomers surprisingly always elute first (Robinson *et al.*, 1988).

2.7.1 X-Ray Crystallography of oxime ethers

One of the most versatile methods for studying the stereochemical properties of a compound is by X-ray crystallography. The X-ray crystal structures of typical oxime ethers are shown in Figs. 2.4 and 2.5 and they not only confirm the *E*-geometry about the C=N bond, but also the preferred *trans*-arrangement about the N–O bond (Hunt *et al.*, 1999; Fang *et al*, 2009) (for (R)-O-(1-phenylbutyl)hydroxyl amine). In both structures, i.e., *E* and *Z* (and also in the (*R*)-O-(1-phenylbutyl) hydroxyl amine oxime of cinnamaldehyde), the phenyl ring of the auxiliary adopts a conformation in which it is almost perpendicular to the planar CH=N–O oxime unit.

Calculations at the semi-empirical level (MOPAC Version 6.0) support the fact that (in the gas phase) the *trans* orientation about the N–O bond is the more stable, and that there is a high barrier to rotation about the N–O bond — ≈32 kJ mol^{-1} for the oxime ether $MeCH{=}{=}NOCH_2Ph$ (Hunt *et al*, 1999). Interestingly, they also show that the conformation adopted by the phenyl ring (as shown in

the X-ray crystal structures, figs 2.4 and 2.5) is the minimum energy conformation in the gas phase, and hence, in view of the low solvating power of toluene, probably also in solution (Hunt *et al.*, 1999).

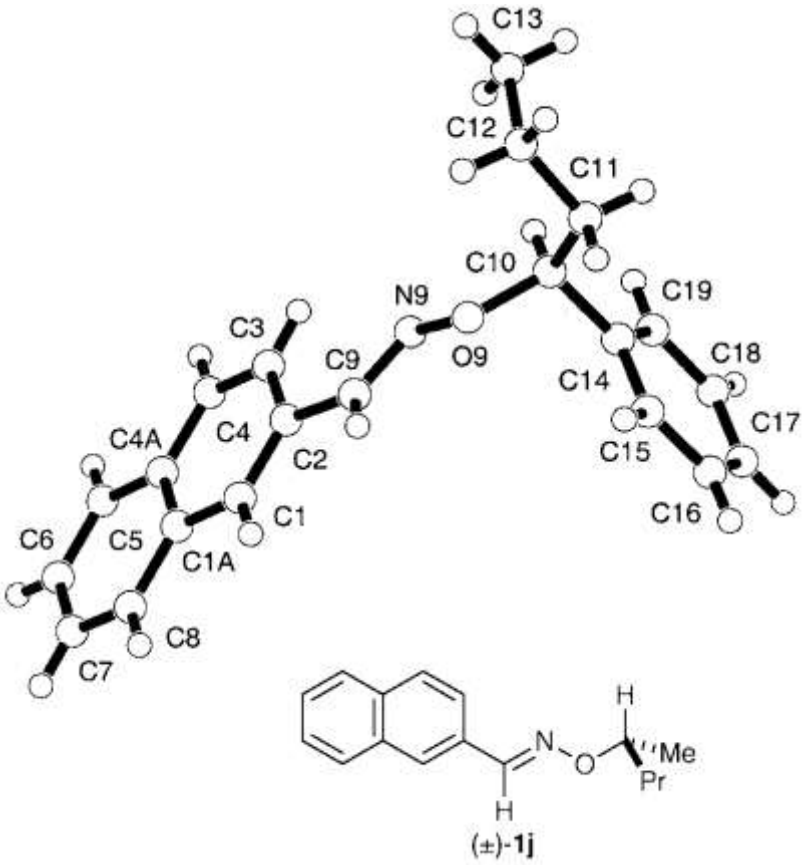


Fig. 2. 4: X-Ray molecular structure of (±)-*O*-(1-phenylbutyl)-2-naphthaldehyde oxime, with crystallographic numbering scheme (Hunt *et al*, 1999).

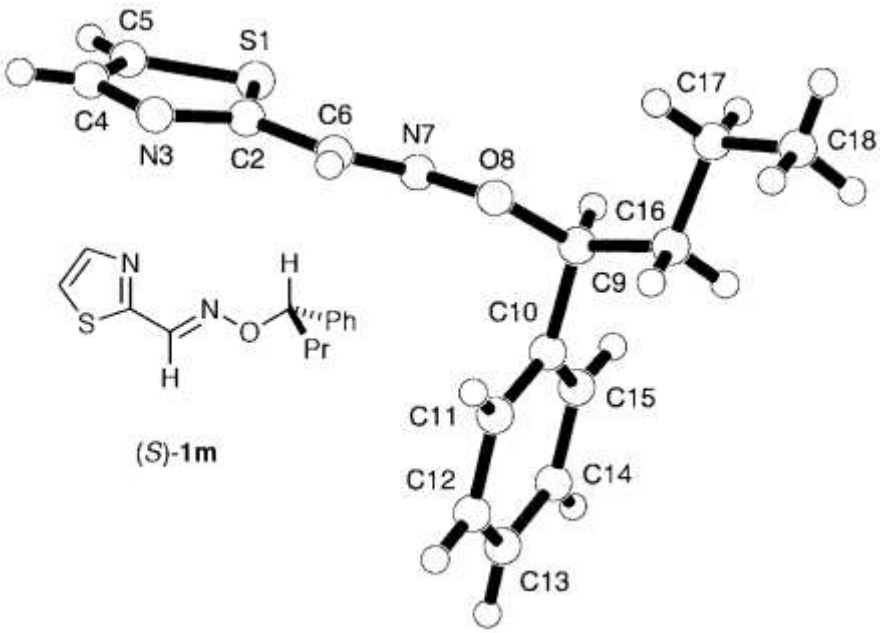


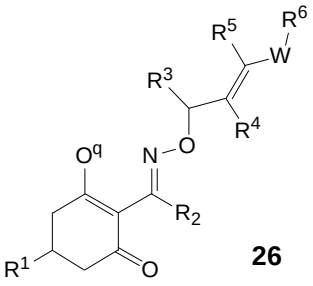
Fig. 2. 5: X-Ray molecular structure of (*S*)-*O*-(1-phenylbutyl)thiazol-2-ylcarbaldehyde oxime with crystallographic numbering scheme (Hunt *et al*, 1999).

2.8.0 Bioactivity of Oxime ethers

Most of the references to oximes and oxime ethers in literature are usually to oximes and oxime ethers rather than to α, β-unsaturated oximes and oxime ethers. Reference to the potentials of oxime ethers and their derivatives as biologically active compounds and drugs abound in literature (Olofsson *et al*., 2005). Oxime ethers have been reported to posses anti depressant (Dijk and Davies, 1976), anticonvulsant (Philips, 1967, Karakurt *et al*., 2006), antifungal (oya Bozdag-Dunder *et al*., 2003), antibacterial (Brain *et al*., 1989; Balsamo *et al*., 1990, Kabilan *et al*., 2006, 2008, 2009), antiviral (Wikel *et al*., 1980; Chern *et al*., 2004), anti-inflammatory (Lapucci *et al*., 1994; Olofsson *et al*., 2005), antihistaminic (Gootjes *et al*., 1972), antiandrogenic (Villani *et al*., 1969) and to have smooth muscle relaxant activities (oya Bozdag-Dunder *et al*., 2003), as

juvenoids (Wimmer *et al*., 1990) as insecticides and acaricides (Bull *et al*., 1980; Henry,1978).

It has also been observed that certain oxime-ethers show a synergistic effect when used with insecticidally and/or acaricidally active substances (Henry, 1978). Kast *et al.*, 1995 (scheme 2.3 and eqn. 2.9), reported that certain unsaturated cyclohexenone oxime ether derivatives, 26, are suitable as herbicides especially for controlling graminaceous plants (grasses).

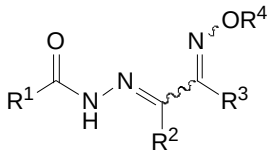


26

q = H, alkyl carbonyl, benzoyl, alkali metal or alkaline earth metal ion, substituted or unsubstituted ammonium ion, phosphonium ion, sulphonium ion, sulfoxonium ion, an equivalent of a transition metal cataion; w = -C≡C- or –CH=CH-. R^1= substituted or unsubstituted cycloalkyl, cycloalkenyl or 6-membered heterocyclic group which has 1-2 oxygen and/ or sulphur atoms and can be saturated or partially unsaturated; substituted or unsubstituted 5-membered heteroaromatic group with 1-2 nitrogen atoms and or 1oxygen or sulphur atom; substituted or unsubstituted phenyl, pyridyl group; R^2= alkyl; R^3= H, alkyl; R^4= H, halogen, alkyl; R^5 = H, alkyl; R^6 = H, alkyl etc.

They are reported to be generally tolerated and are thus selective for broad-leaved crops and for monocotyledonous crops which do not belong to the family of *Graminaceae*. Kast *et al.*, 1995, suggested that certain derivatives of cyclohexenone oxime ethers may display selectivity for *Graminaceae* which makes specific control for unwanted grasses possible. They are usually applied in the form of directly sprayable solutions, powders, suspensions etc.

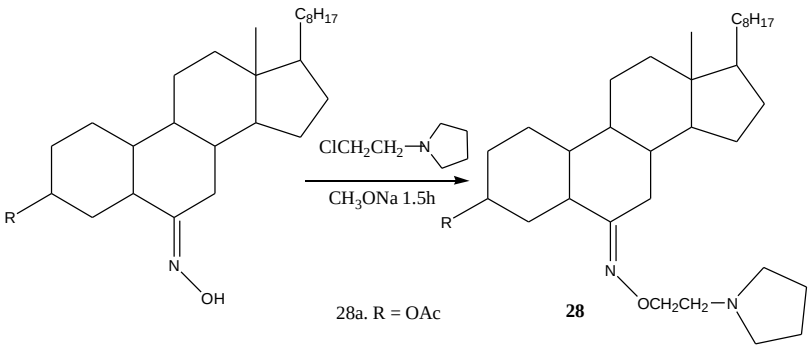
Olofsson *et al.* (2005) reported the use of oxime ethers such as 27 wherein R^1, R^2, R^3, and R^4 are substituents and pharmaceutically-acceptable salts of it for the



27

manufacture of medicaments for the treatment of a disease in which the inhibition of the activity of a lipoxygenase (e.g. 15-lipoxygenase) was desired and particularly in the treatment of inflammation.

khan (Ph.D. thesis, 2006) carried out the synthesis, characterization and *in vitro* antibacterial activity of new steroidal oxime-ether derivatives (eqn. 2.29). The *in vitro* antibacterial activity of these steroidal Oxime-Ether derivatives were evaluated by disk diffusion method against culture of *E. coli* and the results were compared with the standard drug, Amoxicillin. The results showed that all three compounds (28a-c, eqn. 2.29) have better antibacterial activity compared to Amoxicillin.



28a. R = OAc

28b. R = Cl

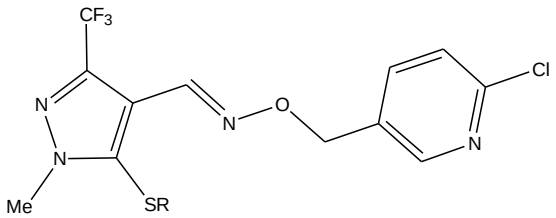
28c. R = H

28

Eqn. 2.29

The structures of the synthesized compounds were confirmed by the elemental analysis, IR, H NMR and FAB mass spectral analysis.

The pyridyl ring is a prominent heterocyclic scaffold in a lot of bioactive molecules. Numerous pyridine-based compounds have been reported to display versatile bioactivity, such as insecticidal, fungicidal, plant growth regulatory, anticancer, and antibacterial activity Fang *et al*, 2009). Likewise, pyrazoles constitute an important class of compounds in the field of agricultural and medicinal chemistry because of their broad spectrum biological activities. It is known that introducing a CF_3 group into heterocyclic molecules mostly results in the improvement of physical, chemical and biological properties. Encouraged by these observations, Fang *et al.*, (2009) anticipated that introduction of the important pyridyl moiety and the CF_3 group to pyrazole **oxime ether** molecules might generate a new group of biologically active compounds. Fang *et al., 2009*, have indeed, reported the synthesis and bioactivity of some novel trifluoromethylated pyrazole oxime ether derivatives containing a pyridyl moiety such as **29**.



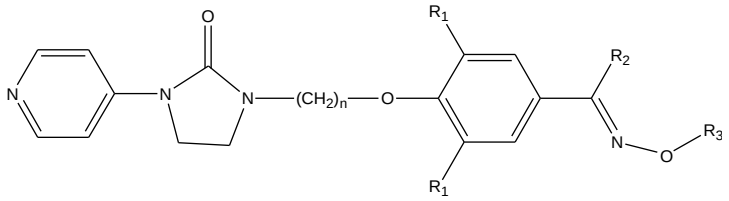
29

Fang *et al.*, 2009, reported that bioassays of some of these oxime ethers, 29, showed potential insecticidal activities against *Aphis craccivora*, and some compounds also displayed plant growth regulatory activities (Fang *et al.*, 2009).

A series of novel, oxime ether-containing pyridyl imidazolidinones were synthesized and their antiviral activity evaluated in a plaque reduction assay (Chern *et al.*, 2004). This class of compounds are specific for human enteroviruses, in particular. Some derivatives strongly inhibited enterovirus replication with activities higher or comparable to those of the compounds currently in use as anti-viral agents.

Preliminary SAR studies (structure-activity-relationship) revealed that the chain length of the alkyl linker and the alkyl substituent at the oxime ether group largely influenced the *in vitro* anti-viral activity of this new class of potent antiviral agents. Among this series of compounds synthesized, the pyridyl imidazolidinone with an ethyl oxime ether group located at the *para* position of the phenoxyl ring (**30**) was identified as the most potent enterovirus inhibitor with no apparent cytotoxic effect toward RD (rhabdomyosarcoma) cell lines.

Furthermore, this compound has shown broad-spectrum activity against most of the serotypes of enteroviruses tested in the nanomolar range (Chern *et al.*, 2004).

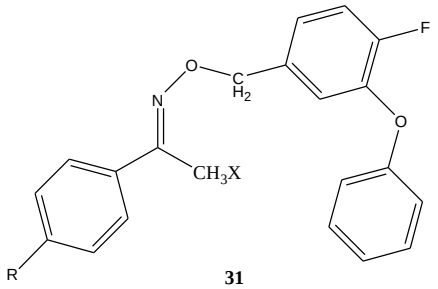


30

Sun and co-workers (2008) have also found that compounds of benzoylphenylureas containing oxime ether groups exhibited not only excellent insecticidal activities (excellent larvicidal activities against oriental army worms and mosquitoes) but also have good plant growth regulatory activities. Some of these compounds have larvicidal activities that were 5-10 times more powerful than commercial products like Flucycloxuron (Sun, *et al.*, 2008).

Karakurt *et al.*, 2006, studied the synthesis of some oxime ether derivatives of 1-(2-naphthyl)-2-(1, 2, 4-triazol-1-yl) ethanone and their potential anticonvulsant and antimicrobial activities. The oxime was synthesized by the reaction of ketone and hydroxylamine hydrochloride. O-Alkylation of the oxime by various alkyl halides gave the oxime ether derivatives. In addition to anticonvulsant tests, all the compounds were also evaluated against the following microorganisms: *S. aureus, E. coli, P. aeruginosa, E. faecalis, C. albicans, C. parapsilosis, and C. krusei* using microdilution broth method for possible antibacterial and antifungal activities. Although most of the O-alkyl substituted oxime ethers exhibited both anticonvulsant and antimicrobial activities, the O-arylalkyl substituted compounds were found to be inactive in both screening test processes.

In 1986, Holan *et al.*, synthesized 4-fluorophenσxy-benzyl ethers of oximes of substituted phenyl halomethyl ketones, **31**, and found that the active compounds are well tolerated by plants, have a favourable level of toxicity to warm-blooded animals, and can be used for combating arthropod pests, especially insects or acarids, which are encountered in agriculture, in veterinary practice, in forestry, in the protection of stored products and of materials, and in the hygiene field. They are active against normally sensitive and resistant species and against all or some stages of development. The pests tested for include *Lucilia cuprina*, *Blatella germanica*, and *Heliothis punctigera*. (Holan *et al.*, 1986).



31

Henry (1978) found that benzyl oxime ether compounds of the form, **15**, had useful insecticidal properties. The subgenus of this compound of which R is cyclopropyl appears to have a particularly attractive spectrum of insecticidal activity. The *E* form of **15** is significantly more active insecticidally than the *Z* form (Henry, 1978).

2.8.1 Evaluation of Antimicrobial Activity

Cukurovali *et al.*, 2005, tested their compounds, bisbenzofuran oxime ethers(**21a-j**, Scheme **2.5** and Table **5**) against two gram–positive (*Staphylococcus aureus*, *Bacillus megaterium*) and two gram–negative bacteria (*Klebsiella pneumonia*, *Escherichia coli*). The antifungal activities of compounds were evaluated *in vitro* against a yeast–like fungus such as *Candida albicans*. The test results obtained are listed in Table **5**. Antifungal and antibacterial data for streptomycin and nystatin are also included in this Table for comparison purposes. The data shows that these compounds generally exhibited moderate activity at the higher concentrations towards many of the bacteria and the fungus tested (Cukurovali *et al.*, 2005).

Table 5. Antimicrobial effect of Bisbenzofuran oxime ethers

Compound	*S. aureus*	*B. megaterium*	*K. pneumonia*	*E. coli*	*C. albicans*
21a	9	11	11	-	15
21b	-	-	-	-	-
21c	-	-	-		-
21d	-	-	-	-	-
21e	-	8	-	-	-
21f	13	15	13	11	-
21g	15	18	18	13	11
21h	-	11	-	-	-
21j	-	-	-	-	-
S.10	17	17	16	-	-
N.30	-	-	-	-	18

Compound concentrations = 50 μg/disc; including disc diameter (6 mm); S.10: Streptomycin sulfate 10 μg/disc, N.30: Nystatin: 30 μg/disc. The symbol (-) means that the compounds had no activity against the microorganisms. The figures are growth inhibition zones measured in millimetres. Larger inhibitory zones indicate higher strength of bioactivity.

2.8.2 Preparation of microbial cultures and biological assays

Microorganisms are usually nourished in appropriate broths before incubating for one or two days prior to preparing microbial cultures with them. Cukurovali *et al.*, 2005, nourished bacteria and yeast strains in nutrient broth and in malt extract broth and incubated for 24 and 48 h, respectively. Using the Disk Diffusion method, the sterile Agar for bacteria and Dextrose Agar for yeast were separately inoculated with the test microorganisms.

The compounds, dissolved in DMSO as 500 μg/disc solutions, were placed in 6 mm wells in the agar media and the plates were incubated at 32 °C for bacteria (18-24 h) and at 25° C for yeast (72 h). The resulting inhibition zones on the plates were measured (in mm) after 48 h. The control samples were only discs soaked in DMSO. The data obtained from the experiments was reported as the average of three experiments (Cukurovali *et al.*, 2005).

The antimicrobial activity technique used by Goker *et al.*, 2000, involved the use of a paper disc (8 mm in diameter) which was soaked in a 2000 mg/ml solution of the test compound in propylene glycol and placed on an agar plate containing fungi or bacteria cells, which was incubated at a temperature of 37°C for 24 h. Propylene glycol as a blank has no inhibition zone. The diameter of the growth inhibition zone around the paper disc was measured.

2.8.3 Drug delivery methods

There are several methods by which bioactive compounds may be delivered to their target organisms. Active oxime or oxime ether compounds are usually converted into such customary formulations as solutions, emulsions, wettable powders, suspensions, powders, dusting agents, foams, pastes, soluble powders, granules, aerosols, suspension-emulsion concentrates, seed-treatment powders, natural and synthetic materials impregnated with active compound, very fine capsules in polymeric substances, and coating compositions (Holan *et al*, 1985).

These formulations may be produced by mixing the active compounds with extenders, i.e., liquid or liquefied gaseous or solid diluents or carriers, optionally with the use of surface-active agents, i.e., emulsifying agents and/or dispersing agents and/or forming agents. Where water is used as an extender, auxiliary solvents, such as for example, organic solvents, can also be used (Holan *et al.*, 1985).

Examples of suitable liquid diluents or carriers, especially solvents, are aromatic hydrocarbons, such as xylene, toluene or alkyl naphthalenes, chlorinated aromatic or chlorinated aliphatic hydrocarbons, such as chlorobenzenes, chloroethylenes or methylene chloride; aliphatic or alicyclic hydrocarbons, such as cyclohexane or paraffins, for example mineral oil fractions; alcohols, such as butanol or glycol, as well as their ethers; and esters, ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone or cyclohexanone; and strongly polar solvents, such as dimethylformamide and dimethyl sulphoxide, as well as water (Holan *et al.*, 1985).

Chapter Three

Materials and Methods

3.1.0 Materials

3.1.1 Infrared spectra

The Infrared spectra were recorded on Perkin-Elmer Model 1310 spectrophotometer (32a and 32b oils were run neat at the chemistry laboratory of Abubakar Tafawa Balewa University, Bauchi) and Buck Scientific S 500 Infra-red spectrophotometer for 32c to 33d with oils run neat and the solids as films from $CHCl_3$ (Cukorovali *et al.*, 2005 and Fang *et al.*, 2009).

3.1.2. ^{1}H and ^{13}CNMR spectra

The ^{1}H and ^{13}CNMR spectra of 32a, 32b, 32c, 32d were run at 250 MHz (Bruker dpx 250 MHz, PROBHD 5 mm Dual 13, Solvent: $CDCl_3$) and 33a-33d at 89.56 MHz ($CDCl_3$) while ^{1}H, ^{13}C, ^{13}C-DEPT, ^{1}H-^{1}H coupling correlation, and ^{1}H- ^{13}C ^{1}J correlations were run at 400 MHz (Bruker dpx 400 MHz, Cardiff University of Wales, U.K.) for products 32**a** and 32**b,** the O-alkyl cinnamaldoxime and ethers, using deuterated chloroform and carbon tetrachloride as solvent and tetramethylsilane (Tms) as internal standard. The chemical shifts are given in **δ** (ppm) scale (Kabilan *et al.*, 2008 and Fang *et al.*, 2009).

3.1.3Reagents and Solvents

Cinnamaldehyde, crotonaldehyde, tetrahydrofuran (THF), pyridine, hydroxyl amine hydrochloride, methoxyamine hydrochloride, Oleoyl chloride and

palmitoyl chloride were purchased from Zayo-Sigma, representatives of Sigma-Aldrich in Nigeria. Column chromatography was performed using silica gel 60 (230–400 mesh, Merck). Solid reagent compounds were used with their melting points uncorrected. However, liquids were redistilled to remove stabilizers and other impurities. All liquid oxime ethers were purified by redistillation under reduced pressure (Kabilan *et al*., 2008).

3.1.4Testing for Antimicrobial Activity

Antimicrobial activities of the synthesised compounds were determined with the previously reported standard methods (Tuncbilek, *et al.,* 1999; Goker *et al.*, 2000; Cukurovali *et al*., 2005 and Elnima *et al.*, 1981).

3.2. Methods

3.2.1. General method for preparation of oximes:

A mixture of redistilled aldehyde, 9.43g(0.0714 mol); hydroxyl amine hydrochloride, 4.97g(0.0715mol); triethylamine, 7.24g, 11.0cm^3(0.0715mol) in methanol was heated and allowed to reflux for 1 hour (scheme 41). Methanol was removed by distillation and the cooled residue washed once with water and recrystallized with dilute ethanol (Fang *et al*., 2009)

3.2.2 Typical procedure for preparation of oximes

Preparation of Cinnamaldoxime

A mixture of cinnamaldehyde, 9.43g (0.0714); hydroxyl amine hydrochloride, 4.97g (0.0715 mol); triethyl amine, 7.24g, 11.0 mL(0.0715mol) in methanol was heated and refluxed for 1 hour. Methanol was removed by distillation and the cooled residue washed once with water and recrystallized with dilute ethanol (50%). Yield: 5.0g (56%), white crystalline solid, m.p.134-136°C

3.2.3 Preparation of Crotonaldoxime

A mixture of hydroxylamine hydrochloride (4.97g, 0.0715 mol) and triethyl amine, 7.24g (11.0mL, 0.0715mol) in methanol was stirred for 30 minutes at room temperature. The mixture was filtered cold and the residue (Triethyl ammonium chloride) was washed once with 10 mL of cold methanol and then discarded. Crotonaldehyde, 5.004g (0.0714 mol) was dissolved in methanol (10 mL) and added from a dropping funnel to the filtrate (Hydroxylamine) in a round bottom flask in ten minutes. The resulting mixture was stirred for 30 minutes and then refluxed for another 1hour. Methanol was removed by distillation and the cooled residue washed once with water and then recrystallised with dilute ethanol (50%).Yield: 5.0g (82.4%), white crystalline solid, m.p.118-121°C.

3.2.4 General method for the preparation of oxime ethers:

0.011mol (0.9g) of alkoxyamine hydrochloride and 1.5 mL of triethylamine was dissolved in 8 mL of methanol. After stirring the mixture for 5 minutes it was added over 20 minutes to a stirred solution of 0.011 mol of redistilled aldehyde in 5mls of methanol maintained at room temperature. The resulting

mixture was stirred for another 30 minutes and then heated and allowed to reflux for 30 more minutes, allowed to cool to room temperature and then quenched with 10 mL of cold water. The product was extracted with 2 x 5 mL of chloroform. The combined extracts were washed once with 5mL of cold water and dried over anhydrous sodium sulphate. The chloroform was evaporated off and the imine vacuum distilled.

3.2.5. Alkylation of oxime with silver oxide as catalyst and base

Silver oxide (0.017mol) is added in small portions to a cooled solution of aldoxime (0.016mol) in alkyl bromide, 50 mL. The mixture was refluxed for 24 hours. The resulting solution was filtered hot and the residue washed 3 times with 10 mL of chloroform each time. The filtrate was concentrated by distillation. The residue was vacuum-distilled to give the oxime ether (Agho *et al.,* 2003)

3.2.6. Alkylation or acylation of Oximes with Potassium carbonate as base

The oxime (3.6 mmol), K_2CO_3 (0.55 g, 4 mmol) and an appropriate alkyl halide or acid chloride (3.6 mmol) are mixed in absolute acetone or DMF (Cukurovali *et al.*, 2005, Fang *et al.*, 2009). The mixture is refluxed at 90^{o}C for 12 hours to complete the reaction. After cooling to room temperature, the mixture was poured into water. Solids were filtered off, washed with copious water and recrystallised from 95% ethanol (Cukurovali *et al.*, 2005). Liquid products were extracted from the mixture trice with about 5mL of chloroform, washed once

with water and the chloroform evaporated off under vacuum and the oxime ether was purified by vacuum distillation.

3.2.7 Preparation of Silver Oxide

Dilute sodium hydroxide solution (0.2 mol/dm^3) was added gradually to 10% aqueous silver nitrate solution until the silver nitrate solution was alkaline. The residue was filtered and washed thoroughly with distilled water (Agho *et al.*, 2003).

3.3.0 Typical procedures:

3-Phenylpropenal o-ethyl oxime (**32a**)

Silver oxide (3.94 g, 0.017mol) was added in small portions to a cooled solution of cinnamaldoxime (5.00g, 0.016 mol) in ethyl bromide (50 mL). The mixture was heated and allowed to reflux for 12 h. The resulting mixture was filtered while still hot and the residue washed thrice with chloroform (10 mL), the filtrate was concentrated by distillation and the residue distilled under vacuum. Clear to yellowish Oil, b.p. 100-102 ºC (10 mmHg) 5.55 cm^3 (78%), d 0.994g/mL; IR(cm-1 , neat): 2820-2920, 1613 (C=N), 1030 (N-O); 1H-nmr (CDCl3): δ 1.25 (t, J = 12.5Hz, 3H, Me), 4.05-4.20(q, J = 12.5Hz, 2H, CH2O), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.4 (m, 5H, ArH), 7.8 (d, J = 12.5Hz, 1H, N=CH). 13C-nmr (CDCl3):δ 150.5,138.0, 136.0,129.0, 127.5,127.0,122.0, 70.0,

16.0. Anal. Calc. (%) for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99; O, 9.13. Found: C, 75.60; H, 7.20, N, 7.54; O, 9.20. (See Figs 6, 7,9, 10, 11, 12 and 14).

3-Phenylpropenal O-methyl oxime ether (32b)

Methoxyamine hydrochloride, 0.9g (0.11 mol) and triethylamine, 1.5mL, were dissolved methanol, 8.0 mL. The mixture was stirred for 5 minutes and added over 20 minutes to a stirred solution of of redistilled cinnamaldehyde, 0.011 mol (1.403g, 1.5mL) in methanol, 5.0mL, maintained at room temperature. The resulting mixture was stirred for another 30 minutes and then heated at reflux for further 30 more minutes; allowed to cool to room temperature and quenched with 10 mL of cold water. The product was extracted with 2 x 5 mL of chloroform. The combined extracts was washed once with 5mL of cold water and dried over anhydrous sodium sulphate. The chloroform was evaporated off and the imine vacuum distilled. Yield, 1.75g. (**32b**). Clear to yellowish Oil, b.p. 103 ºC (10 mmHg), Yield: 1.75g (70%), *d* 0.994g/mL. IR (cm-1 , neat): 2820-2920, 1613, 1030; 1H-nmr (CDCl3): δ 4.1 (s, 3H, MeO), 6.8-6.9 (m, 2H, CH=CH), 7.3-7.5(m, 5H, Ar-H), 7.9 (d, J = 10.0Hz, 1H, N=CH),. 13C-nmr (CDCl3): δ 150.5,140.0,138.5,129.0, 128.0, 127.0, 122.0, 63.0. Anal Calc. (%) for C10H11NO: C, 74.51; H, 6.88; N, 8.69; O, 9.93. Found: C, 74.20; H, 6.99; N, 8.88; O, 9.61.

But-2-enal O-methyl oxime (32c).

Methoxyamine hydrochloride 3.04g (0.0364mol) and triethyl amine, 5.1mL, were dissolved in methanol, 50mL. The mixture was stirred for 10 minutes and added over 20 minutes to a stirred solution of crotonaldehyde, 0.0364mol (2.55g) in methanol (10mL) at room temperature. The resulting mixture was stirred for 10 min and then refluxed for a further one hour; cooled to room temperature, and quenched with 40mL of cold water. The product was extracted from the mixture with 3 x 25mL of chloroform. The combined extracts was washed once with 15mL of water and dried over anhydrous sodium sulphate. After distilling of the chloroform, the imine was vacuum distilled to obtain 2.8mL of the imine. Yellow Oil, b. p. 103 ºC (10 mmHg), d 0.894g/mL, Yield: 2.8mL (77.8%); IR (cm-1 , neat): 2820-2920, 1613 (C=N), 1030; 1H-NMR (CDCl3): δ 1.4 (dd, J1 = 7Hz, J2 = 1Hz, 3H, Me); 4.0 (s, 3H, MeO-) 5.4-5.9 (m, 2H, CH=CH); 7.9 (d, J = 7sHz, 1H, N=CH); 13C-NMR (CDCl3) δ 163.0, 137.0, 124.0, 55.0, 17.0; Anal. Calc (%) for C5H9NO: C, 60.58; H, 9.15; N, 14.13, O, 16.14. Found: C, 60.42; H, 9.11; N, 14.08; O, 16.50.

But-2-enal O-ethyl oxime (32d).

The procedure is similar to the procedure for 32a. Silver oxide (3.48 g, 0.0147mol) was added in small portions to a cooled solution of crotonaldoxime (1.25g, 0.0147 mol) in ethyl bromide (50 mL). The mixture was refluxed for 12 hours. The resulting mixture was filtered while still hot and the residue washed thrice with chloroform (10 mL), the filtrate was concentrated by distillation and the residue distilled under vacuum. Yellow Oil, b.p. 107-110 ºC (12 mmHg);

Yield: 1.30 mL (78%), d 0.901g/mL; IR (cm-1): 2820-2920, 1613, 1030; 1H-NMR (CDCl3): δ 1.4 (m, 6H, Me); 4.1, (q, J = 8Hz, 2H, CH2O); 5.5-5.8 (m, 2H, CH=CH); 7.9 (d, J = 7Hz, 1H, N=CH); 13C-NMR (CDCl3) δ164.0, 137.0, 124.0, 64.0, 17.0, 12.0. Anal. Calc. (%) for C6H11NO: C, 63.68; H, 9.80; N, 12.38; O, 14.14. Found: C, 63.40; H, 9.30; N, 12.20; O, 14.10.

O-Palmitoyl cinnamaldoxime ether(33a)

Cinnamaldoxime, 5.0g (0.034mol), Palmitoyl chloride, 10.32mL (0.034mol), potassium carbonate, 4.62g (0.034mol) were mixed together in acetone, 100mL. The mixture was stirred for 10 mins and refluxed for 1 hour. After cooling to room temperature, the mixture was poured into cold water and stirred. The resulting mixture was suction filtered to obtain a white solid. Yield: 78%. m.p. 110-112^{o}C. IR (cm-1, film, CHCl3):3010-3020(Ar & olefinic C-H str.), 2820-2920(methyl & methylene str. C-H), 1740(C=O str.). 1H-nmr (CDCl3): δ 0.90(t, 3H, CH3),1.40 (sextet, 2H, CH2), 1.35(quintet, 22H, CH2), 1.65(quintet, 2H, CH2), 2.02(t, 2H, O-CH2), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.4 (m, 5H, ArH), 7.8 (d, J = 12.5Hz, 1H, N=CH); 13C-NMR (CDCl3) δ172.0, 33.3, 32.5, 30.3, 30.3, 30.3, 30.3, 30.3, 30.3, 30.3, 30.0, 30.0,29.7, 25.4, 23.1,14.0.

O-oleoyl cinnamaldoxime ether (33b)

The procedure was the same as in 33a above except cinnamaldoxime, 5.0g (0.034mol), oleoyl chloride, 10.234g or 11.25mL (0.034mol) and potassium carbonate, 4.62g (0.034mol) were mixed together in acetone, 100mL. Yield:

12g, 85%; white solid, m.p., 118-121^{o}C. IR (cm-1, film, CHCl3):3010-3020(Ar & olefinic C-H str.), 2820-2920(methyl & methylene str. C-H), 1740(C=O str.). 1H-nmr (CDCl3): δ 0.9(t, 3H, CH3),1.35(quintet, 14H, CH2), 1.40(m, 6H, CH2), 1.65(quintet,3H, CH2), 2.2(2q, 4H, allylic H),2.35(t, 2H, CH2), 5.3(q, 1H, CH), 5.7(q, 1H, CH), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.4 (m, 5H, ArH), 7.8 (d, J = 12.5Hz, 1H, N=CH). 13C-NMR (CDCl3): δ 177.0, 163.7,131.7, 140.1, 134.9, 130.2, 128.4, 127.7,126.2,120.6, 33.6, 33.4, 32.5, 31.2, 30.8, 30.6, 30.5, 30.4, 30.3, 30.1, 30.0, 29.7, 25.1, 23.1, 14.

Crotonaldoximyl palmitate or O-palmitoyl crotonaldoxime ether (33c)

Procedure was the same as for 33a except that crotonaldoxime, 2.89g (0.034mol), palmitoyl chloride, 10.32mL(0.034mol) and potassium carbonate, 4.62g(0.034mol) were dissolved in acetone, 100mL. Yield: 8.10g (74%); white solid, m.p. 101^{o}C. ^{1}H-nmr (CCl4): δ0.9 (t, 3H, Me); 1.30(quintet, 24H, CH2), 1.65(quintet, 2H, CH2), 1.90(Dd, J=7Hz and J=1Hz,3H, CH3), 2.4(t, 2H, OC-CH2); 5.0(m, 1H, =CH-), 5.8 (m, 1H, CH=); 7.9 (d, 1H, N=CH). 13C-nmr (CDCl3) δ174.0, 163.7, 137.0, 124.2, 34.16, 32.12, 29.90, 29.88, 29.82, 29.78, 29.70, 29.68, 29.66, 29.56, 29.47, 29.37, 25.13, 22.84, 17.50, 14.13.

Crotonaldoximyl oleate (33d)

The procedure was the same as in 33a except that crotonaldoxime, 2.89g (0.034mol), oleoyl chloride, 11.25mL (0.034mol) and potassium carbonate, 4.62g (0.034mol) were dissolved in acetone, 100mL. After work-up, Yield: 9.8g (82%),yellowish solid, m.p. 112^{o}C. 1H-nmr (CCl4): δ0.9 (t, 3H, CH_3);

1.35(quintet or m, 20H, CH_2), 1.60(quintet, 2H, CH_2), 2.18(Dd, J=7Hz and J=1Hz,3H, CH3), 2.25(m, 4H, allylic H) 2.35(t, 2H, OC-CH2); 5.0(m, 1H, =CH-), 5.3(m, 2H, CH=CH), 5.8 (m, 1H, CH=); 7.9 (d, 1H, N=CH). 13C-nmr (CDCl3) δ:173.2, 163.7, 143.0, 130.5, 130.2, 34.10, 32.64, 32.0, 31.94, 29.69, 29.61, 29.53,29.35, 29.22, 29.16, 29.09, 28.99, 24.88, 22.71, 17.5, 14.13.

3.4.0. Antimicrobial activity evaluation technique

Antimicrobial activities of the synthesised compounds were determined with the previously reported standard methods (Tuncbilek, *et al.,* 1999; Goker *et al.*, 2000; Cukurovali *et al.,* 2005 and Elnima *et al.*, 1981). The compounds were tested against gram-positive bacteria, *Staphylococcus aurreus*, and gram-negative bacteria, *Escherichia coli*; and yeast strains of *Candidas albicans* and *Sacharomyces cerevisiae*.

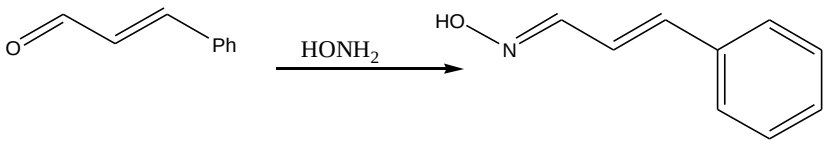
The bacteria and yeast strains were nourished in nutrient broth and in malt extract broth, and incubated for 24hrs and 48hrs, respectively (Cukurovali *et al.*, 2005). The sterile Mueller Hinton Agar for bacteria and Saburoud Dextrose Agar for yeast were separately inoculated with the test microorganisms. The compounds, dissolved in ethylene glycol or propylene glycol as 500 or 2000 μg/mL solutions of the test compounds. A paper disc (8mm in diameter) soaked in each solutions was placed in the agar media containing fungi or bacteria cells, which has been incubated at a temperature of 37°C for 24 hrs for bacteria and at 28° C for yeast (72 hrs). Propylene glycol, or ethylene glycol were used as

blanks and had no inhibition zones. The diameter of the growth inhibition zone around the paper discs were measured (in mm) after 48 h. The data reported is the average of three experiments as presented in Tables **6** and **7** in chapter 4.

Chapter Four
Results and Discussion

4.1. Formation of aldoximes

The oximes were prepared from *trans* crotonaldehyde and *trans* cinnamaldehyde because they contained the α, β-unsaturation desired in the oxime ether products. Cinnamaldoxime is easier to prepare because it is much more stable than crotonaldoxime (eqn. 4.1). This is the result of the presence of the phenyl group. Infact attempts to prepare crotonaldoxime in the same way as cinnamaldoxime is prepared resulted in instant polymerization of the reaction mixture and formation of a hard clear mass that was difficult to remove from the reaction vessel. This problem was solved by freeing the hydroxyl amine from the hydrochloride before reacting it with crotonaldehyde in the absence of any base.

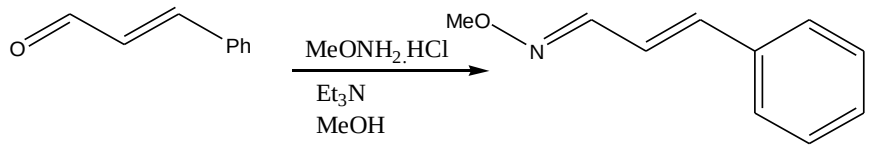


Eqn. 4.1

Cinnamaldoxime and crotonaldoxime are both white crystals that appear from the mixture as soon as most of the solvent is distilled off. The absence of C=O band of the carbonyl compounds (Cinnamaldehyde and crotonaldehyde) and the existence of a broad band in the i.r. spectrum of the oximes is the evidence that the aldehydes have been transformed into the oximes.

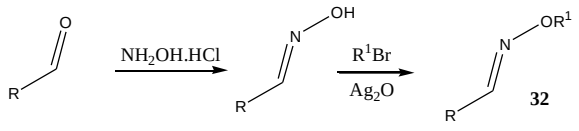
4.2 Methods and mechanisms of reactions

The oxime ethers in this series were synthesised via three methods: The first method is by direct alkoxymation of the corresponding oxime. O-methyl cinnamaldoxime ether, 32b and 32c, were obtained in excellent yield (70% and 78% repectively) by this method. This method (eqn. 4.2) is convenient because all possible alkylating agents: methyl chloride and methyl bromide and even iodomethane are fairly volatile compounds and would have required that the reaction be carried out under pressure higher than atmospheric pressure if any of the other methods available were used.



Eqn. 4.2

In the second method, silver (I) oxide is used as a base, oxidising agent or as a catalyst to give excellent yields of oxime ethers without the usual accompanying formation of nitrones and also without the use of a separate solvent since the alkyl or acyl halide also served as the solvent (scheme 4.1).



R	**R^1**
32a. PhCH=CH	CH_2CH_3
32b. PhCH=CH	CH_3
32c. CH_3CH=CH	CH_2CH_3
32d. CH_3CH=CH	CH_3

Scheme 4.1

All products obtained from the silver oxide catalysed reaction were in good yields comparable to the yields of conventional procedures. Olofsson *et al.* (2005) used silver(I)oxide as base in the synthesis of 3-Chloro-N'-(2-(methoxyimino)-1-phenylethylidene)benzohydrazide…but they used MeOH/CH_2Cl_2 mixed solvent as reaction medium and after stirring for 4 days obtained only 37% yield of the product. The Olofsson *et al.* (2005) reaction was carried out at room temperature.

We believe that the reaction involves silver (I) ion complex formation between silver and the oxime nitrogen. Like in the silver mirror test reaction, conversion occurs without attacking any double bonds (scheme 4.3).

In this case, the C=N double bond is not attacked, thereby preventing the alkylation of nitrogen that results in nitrone formation.

Although more studies are required to confirm the mechanism of the reaction; the reaction, like in the silver mirror test, leaves a deposit of pure silver in the form of tiny pellets of silver metal and silver halide in the product mixture (scheme 4.3).

An approach to formulating a mechanism for the reaction is to identify which of the reagents is the reducing agent since clearly, the silver (I) oxide has been reduced. In the silver mirror reaction (scheme 4.2), a diamine silver (I) ion complex (which is an oxidising agent that is itself reduced to silver metal during the cause of the reaction, scheme 4.2) is formed when the silver oxide reacts

with aqueous ammonia. The oxidising agent oxidises the aldehydes to carboxylic acids and leaves a silver mirror on the reaction vessel (scheme 4.2).

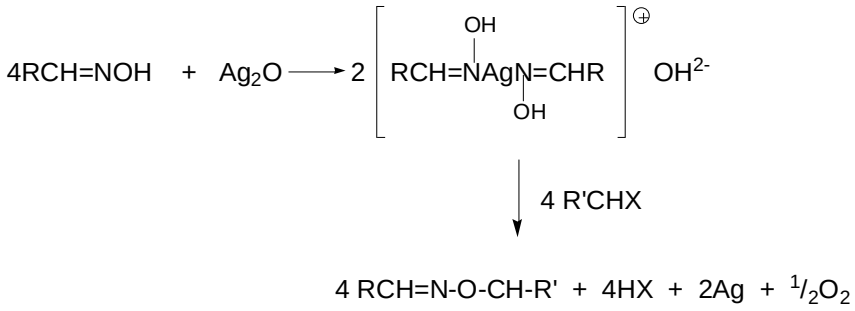
$$2AgNO_3(aq) + 2NaOH(aq) \longrightarrow Ag_2O(s) + 2NaNO_3(aq) + H_2O(l)$$

$$Ag_2O(s) + 4NH_3(aq) + 2NaNO_3(aq) + H_2O(l) \longrightarrow 2\ Ag(NH_3)_2NO_3(aq) + 2NaOH(aq)$$

$$[Ag(NH_3)_2]^+(aq) + e^- \longrightarrow Ag(s) + 2NH_3(aq)$$

Scheme 4.2

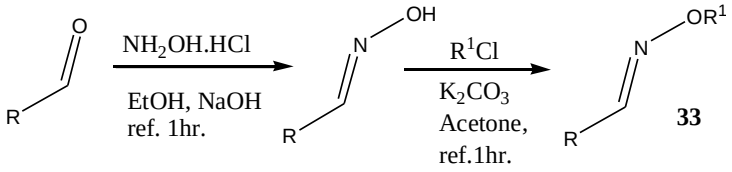
The mechanism in scheme 4.3 is proposed if the oxime which contains a nitrogen atom possessing an unshared electron pair is seen as playing the role of aqueous concentrated ammonia solution. That is, the oxime forms a complex with the silver ion and this complex serves as the oxidising agent that is then reduced by electrons from the reaction mixture.



Scheme 4.3

The only drawback to the procedure is the use of the expensive silver oxide. But it can be recovered from the silver metal or silver halides which are the end products of silver oxide in the reaction. The other disadvantage is that a solvent that is not one of the reagents will be required if the alkyl or aryl halide is not a liquid. This method was used to prepare compounds 32a and 32d.

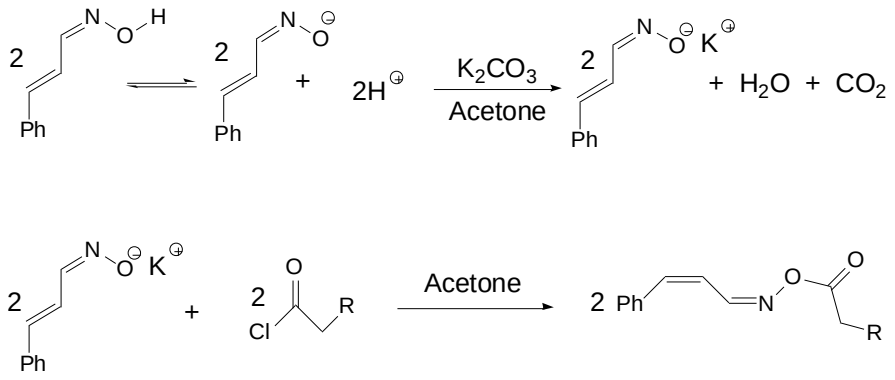
The third method of oxime ether or ester formation involved the use of potassium carbonate as base and acetone as solvent (scheme 4.4 and scheme 4.5).



	R	R^1
33a.	PhCH=CH	$CH_3(CH_2)_{14}CO$
33b.	PhCH=CH	$CH_3(CH_2)_7CH=CH(CH)_7CO$
33c.	$CH_3CH=CH$	$CH_3(CH_2)_{14}CO$
33d.	$CH_3CH=CH$	$CH_3(CH_2)_7CH=CH(CH)_7CO$
33e.	PhCH=CH	PhCO

Scheme 4.4

Compounds 33a, 33b, 33c, and 33d in which the acylating agents were acyl chlorides derivable from fatty acids of palm oil: palmitoyl chloride and oleoyl chloride were synthesized according to the methods used by Fang *et al*., 2009, with potassium carbonate as base and acetone as solvent providing the mild temperature required by the products (scheme 4.4). They were prepared using this method because the alkyl or acyl halides involved have relatively high boiling points and cannot be easily distilled off without decomposing the products. The products 33a-33d were passed through a column of silica gel with ethyl acetate/hexane (1:2) mixture to eliminate traces of nitrone.



Scheme 4.5

4.3 Spectral Characterization

It is easy to monitor and confirm the transformations as the reaction proceeds from the aldehydes through the oximes to the corresponding oxime ethers. The absence of the C=O band of the carbonyl compounds (Cinnamaldehyde and crotonaldehyde) and the existence of a broad =N-OH band centred around 3166 cm^{-1} in the IR spectrum of the oximes is the evidence that the aldehydes were transformed into the corresponding oximes.

The –OH proton appears as a broad singlet at around 13.0 ppm in the ^{1}H-NMR spectrum. This peak disappears upon alkylation of the oxime.

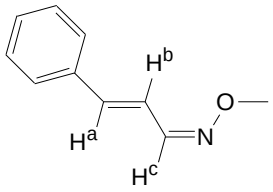
All the compounds are derived from cinnamaldehyde and crotonaldehyde, the α, β-unsaturation of these aldehydes, which are repeated in all the products, as well as the N-alkoxy substituents have characteristic ^{1}H-nmr and ^{13}C-nmr that can easily be identified. The ^{1}H-nmr of N-methoxy cinnamaldoxime ether, 32b is a typical example (**Appendix 3 and Table 6**). The phenyl protons occur at between δ (ppm) 7.3-7.45. This is the usual position of five aromatic protons aromatic peaks.

Table 6: Summary of Spectral characterization of 32a-d

Product	IR(cm^{-1})	^{1}H-NMR	^{13}C-NMR
32a	neat film:3020 (CH Ar.str), 2820-2920 (CH al. str.), 1613 (C=N str.), 1030 (N-O)	δ 1.25(t,3H, CH_3), 4.05-4.20(q, 2H, CH_2O), 6.7-6.8 (m,2H, CH=CH), 7.1-7.4(m, 5H, ArH), 7.8 (d, 1H,N=CH)	δ 150.5, 138.0, 129.0, 127.5, 127.0, 122.0, 70, 16.
32b	Film: 3020 (CH= Ar.str.),2820-2920 (CH Al. str.), 1613 C=N, 1030 (N-O str.)	δ 4.1 (s, 3H, MeO), 6.8-6.9 (m, 2H, CH=CH), 7.3-7.5 (m, 5H, Ar-H), 7.9 (d, 1H, N=CH)	δ 150.5, 140.0, 138.5, 129.0, 128.0, 127.0, 122.0, 63.0
32c	Film: 3020 (CH= Ar.str.),2820-2920 (CH al str.), 1613, 1030 (N-O str.)	δ 1.4 (dd, 3H, Me), 4.0 (s, 3H, MeO-), 5.4-5.9 (m, 2H. CH=CH), 7.9 (d, 1H,N=CH).	δ 163.0, 137.0, 124.0, 55.0, 17.0
32d	Film: 3020 (CH= Ar.str.),2820-2920 (CH Al. str.), 1613 C=N, 1030 (N-O str.)	δ 1.4 (m, 6H, Me), 4.1 (q, 2H, CH_2O), 5.5-5.8 (m, 2H, CH=CH), 7.9 (d, 1H,N=CH)	δ 164.0, 137.0, 124.0, 64.0, 17.0, 12.0.

The methoxy protons are also not difficult to identify at 4.0 ppm; compared to methoxy protons in mthyl acetate which occur at δ3.6 ppm, it is clear that the downfield shift of the CH_3O- protons in the case of 32b is due to the deshielding effect of the two electronegative atoms, oxygen and nitrogen, as well as the conjugated double bonds.

However, the three alkenic protons are not so easily assigned. The vinylic proton H^a, being *β*-placed on the *α*, *β*-unsaturated system is deshielded from the normal alkenic region. It is also further deshielded by virtue of being placed next to the aromatic ring. Its signal at δ7.6 is split into a doublet by H^b with J = 6.5Hz. The methyl protons of the methoxy group occur as a singlet at δ 4.0 ppm.



trans-methylcinnamaldoxime ether

The alkenic proton H^b at δ 6.8-6.9 gives four lines since it is coupled to two non-equivalent protons H^a and H^c and the coupling constants $J_{ab} \neq J_{bc}$ (**Appendices 3** and **4, Table 6**). The iminic proton H^c occurs as a doublet at 7.8(J = 10 Hz) being split by H^b (**Appendices 3** and **4, Table 6**). This iminic proton was the former aldehydic proton that appeared at δ9.6 ppm in both crotonaldehyde and cinnamaldehyde. Its signal has shifted further upfield to 7.9ppm in 32b (methyl crotonaldoxime) and 7.8 ppm in ethyl cinnamaldoxime ether, 32a, because of the electron releasing effects of the methoxy and ethoxy groups respectively.

The H-nmr spectra of *trans*-ethyl cinnamaldoxime ether, 32a, is similar to that of 32b except that the methyl protons occur as a triplet at δ 1.3-1.4 ppm (the dowmfield shift is due to the deshielding effect of the electronegative oxygen as well as nitrogen, the usual position is between 0.9-1.22 in ethanol) while the methylenic $–CH_2-$ protons occur as a quartet at δ 4.10 (**Appendix 4**).

The ^1H-^1H shift correlated spectra (COSY) of 32a, (**Appendix 5**) identifies pairs of protons which are coupled to each other. Again the CH_3- and $-CH_2-$ are clearly shown to be coupled to each other and the coupling associations of H^a,

H^b, and H^c indicate that assignment of peaks for these protons are correct, i.e. H^b is coupled to H^a while H^c is also coupled to H^b (See section 2.6.2).

Although the ^{13}C NMR spectra of 32a and 32b (**Appendices 6** and **13** respectively) are those of the *cis*- and *trans*-isomers they are still very useful for confirmation of the assignment of signals. The signals for the *cis*-isomer are the weaker signals and they occur in the same place for methoxy and ethoxy protons, 70.0 ($-CH_2-O-$), 15.0 (CH_3-) and 70.0 (CH_3-O-).

^{13}C-NMR-DEPT (Distortionless Enhancement by Polarisation Transfer) allows the determination of the number of hydrogens attached to each carbon. In **Appendix 7**, DEPT-NMR for 32a, three spectra are obtained. One is a normal broadband decoupled spectrum which shows the expected number of nine lines, although, in this spectrum, separate lines are showing for *cis*-isomer as weak signals. The second spectrum is DEPT-135^o spectrum in which only CH_3 and CH signals are showing, while a negative signal is displayed for the CH_2 group. The third spectrum is DEPT-90^o which displays only CH signals of the aromatic protons, iminic proton and alkelinic protons while no signals are displayed for CH_3 and CH_2 protons. **Appendix 8** is the DEPT-NMR spectra for 32b.

In the HETCOR (Hetero corelational spectroscopy) 2D-NMR spectra of 32a (**Appendix 9**) that displays ^{13}C-^1H shift correlations showing coupling between protons and carbon to which they are attached, the cross peaks show the relationship of a carbon with its directly bonded proton.

Again, CH_3 and CH_2 protons are easily traced to the ^{13}C-NMR lines of the carbon atoms bearing them (15.0 and 70.0 respectively). The alkelinic proton H^b at δ 6.8 ppm can be traced to the carbon atom at δ 122.0, H^a is from the carbon atom in the aromatic region while H^c peak is traced to δ150.35 ppm in the ^{13}C spectra axis.

Oxime ethers are theoretically able to exist as *E* or *Z* isomers. Studies have shown that the configuration may have been determined during the process of oxime formation (Pliego Jr. *et al*, 1999 and Johnson *et al*, 2001) depending on the pathway followed as there are several available (still disputed pathways(Pliego *et al*, 1999)) during this reaction. In thermodynamic terms, either *E*- or *Z*-isomers can be the more stable, depending on the substituent groups. For aldimines, *E*-isomers in general present lower free energy.

Experimental and theoretical data have been combined to obtain the heat of formation of (*E*)- and (*Z*)-N-methyl-acetaldimine, and it was found that the *E*-isomer is more stable by 4.4 kcal/mol (Pliego Jr. *et al*, 1999).

1, 3-dienes are generally known to prefer the *anti* co-planar geometry, though a minor component believed to be nearly *syn* but slightly twisted appears to be always present (Isaacs, 1987).

The Ph-CH=CH and CH_3-CH=CH fragments of the oxime ethers (32a-d and 33a-f) are assigned the *E* configurations because the transformations did not occur at this part of the starting reagents and it is assumed that their configuration around this double bond would most likely remain unchanged.

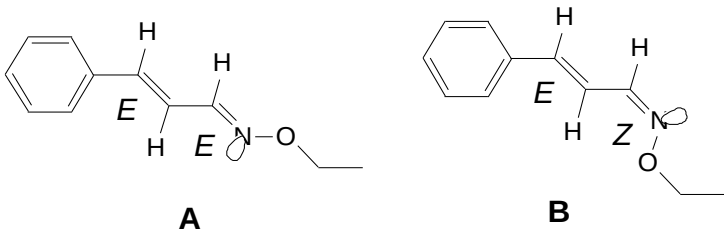
The starting cinnamaldehyde is 100% *trans*-cinnamaldehyde while the crotonaldehyde used is a mixture of *cis, trans*-crotonaldehyde in the ratio 1: 20.

However, the compounds 32a-32d are mixtures of *trans* and *syn* isomers with the *syn* isomer a very small proportion of the mixture. From literature (Karabatos and His, 1967; Boschmann, and Winter, 1980) transformation of aldehydes can result in either *trans* or *syn* oximes or oxime ether with the *trans* isomer usually the more stable. The ^{1}H-NMR peak of C=N-OCH_2 protons occurred at 4.25ppm for 32a and the protons of C=N-OCH_3 occur at 4.0ppm for 32b. No other peaks were found for these protons in each of the ^{1}H-NMR spectra. Both isomers are theoretically able to exist and have two different signals of 4.35-4.40 for the *E* isomer and 4.2-4.35ppm for the *Z* isomer (Karabatos and Hsi, 1967, Harney *et al*, 1977, Boschmann and Winter, 1980). However, in the ^{13}C-NMR of both compounds, signals of the smaller *syn* fraction can be detected as additional minor signals. This is the only reason we are assuming their presence in the samples. Calculations at the semi-empirical level (Mopac Version 6.0, AM1 Hamiltonian (Hunt *et al*, 1999)) support the fact that (in the gas phase) the *trans*-orientation about the N–O bond is the more stable, and that there is a high barrier to rotation about the N–O bond - ≈32 kJ mol^{-1} for the oxime ether MeCH=NO-CH_2Ph.

In conclusion, 32a-d consists of mixture of *E, E* and *E, Z* isomers with the *E, Z* fraction being considerably smaller. It seems that as the R group in the pendant N-OR fragment gets bulkier, the fraction of molecules that is of *E*

configuration about the imine double bond increases until only the *E* forms exist (Hunt *et al*, 1999, Fang *et al*, 2009, Pliego *et al*, 1999). Therefore 33a-d are *E*, *E* isomers only because of the bulky R fragments in N-OR.

That is, of the two possible configurations shown below (A and B), configuration A is the most likely configuration for compounds 32a -32d with minor fractions of B. Compounds 33a-d will be all A.



A **B**

4.4 Antimicrobial Activities

The title compounds 32a-d and 33a-d were screened for their biological activities *in vitro* against four selected microogarnisms including *S. aureus, S. cervicea, E. coli and C. albicans* at concentrations of 500 and 2000 μg/mL solutions according to procedures described previously.

Compounds 32a, 32b, 33a, and 33b were found to have some inhibitory antifungal effect against *C. albicans* and *S. cerevicea* with 32a having the activity at 500μg/mL and 2000μg/mL. 32b also has some inhibitory activity against *S. aureus* and *E. coli*, while 33b also has some inhibitory activity against *S. aureus*. The inhibitory activities were higher at the higher concentration of

2000μg/mL. 33d only showed antimicrobial activity at the higher concentration of 2000μg/mL against *S. cerevicea* and *C. albicans*.

Table7. Antimicrobial effect of 500μg/mL of α, β-Unsaturated oxime ethers

Compound	*S. aureus*	*S. cerevicea*	*E. coli*	*C. albicans*
32a	-	15	-	12
32b	11	17	13	10
32c	-	-	-	-
32d	-	-	-	-
33a	-	11	-	10
33b	-	-	-	-
33c	-	-	-	-
33d	-	-	-	-

Compound concentrations = 500 μg/mL; the symbol (-) means that the compounds had no activity against the microorganisms. The figures are growth inhibition zones measured in millimetres including disc diameter (8 mm). Larger inhibitory zones indicate higher strength of bioactivity.

Table8. Antimicrobial effect of 2000μg/mL of α, β-Unsaturated oxime ethers

Compound	*S. aureus*	*S. cerevicea*	*E. coli*	*C. albicans*
32a	-	18	-	14
32b	11	21	14	13
32c	-	-	-	-
32d	-	-	-	-
33a	-	16	14	13
33b	10	11	-	12
33c	-	-	-	-
33d	-	10	-	13

Compound concentrations = 2000 μg/mL; the symbol (-) means that the compounds had no activity against the microorganisms. The figures are growth inhibition zones measured in millimetres including disc diameter (8 mm). Larger inhibitory zones indicate higher strength of bioactivity.

Chapter Five
Summary, Conclusion and Recomendations

5.1. Summary

The following compounds were synthesized**:** *3-Phenylpropenal o-ethyl oxime (32a), 3-Phenylpropenal O-methyl oxime ether (32b), But-2-enal O-methyl oxime (32c), But-2-enal O-ethyl oxime (32d), O-Palmitoyl cinnamaldoxime ether(33a), O-Oleoyl cinnamaldoxime ether (33b), O-palmitoyl crotonaldoxime ether (33c), Crotonaldoximyl oleate (33d).*

The synthesis of O-alkylated and O-acylated α, β-unsaturated oxime ethers derived from cinnamaldehyde and crotonaldehyde were carried out through three different pathways:

1. Direct alkoxy amination of the aldehydes. 3-Phenylpropenal O-methyl oxime ether (32b) was prepared by this method.
2. Silver oxide mediated alkylation of oximes with the alkylating agent as solvent. 32a, 32c, and 32d were prepared using this method.
3. Potassium carbonate mediated alkylation or acylation of oximes with acetone as solvent. Compounds 33a-33d were prepared using this method.

The products were obtained in good to quantitative yields while the structures and configurations of the synthesized compounds were confirmed with the aid of IR, ^{1}H-NMR and ^{13}C-NMR. Detailed ^{1}H-NMR, ^{13}C-NMR, COSY-NMR and ^{13}C-DEPT-NMR spectral analysis of ethyl cinnamaldoxime ether and methyl cinnamaldoxime ether was done to establish the structures and most likely

configuration to be *E*, about the C=C bond in all the products obtained; *E* (*anti*) and *Z* (*syn*) about the C=N bond. 32a-d are a mixture of *E, E* and *E, Z* about the two double bonds with the *E, E* form predominating, while 33a-d being all *E, E* about the two double bonds because of the bulkier (N-OR) R fragment.

Compounds synthesized were tested for bioactivity against *C. albicans, S. cerevicea, E. coli* and *S. aureus* using methods previously described in literature.

5.2 Conclusion

The following compounds were synthesized in good to quantitative yield and their structural and molecular formulae confirmed wth the aid of of IR, ^{1}H-NMR and ^{13}C-NMR. Detailed ^{1}H-NMR, ^{13}C-NMR, COSY-NMR and ^{13}C-DEPT-NMR spectral analysis**:** *3-Phenylpropenal o-ethyl oxime (32a), 3-Phenylpropenal O-methyl oxime ether (32b), But-2-enal O-methyl oxime (32c), But-2-enal O-ethyl oxime (32d), O-Palmitoyl cinnamaldoxime ether(33a), O-Oleoyl cinnamaldoxime ether (33b), O-palmitoyl crotonaldoxime ether (33c), Crotonaldoximyl oleate (33d).*

Direct addition of hydroxylamine to the carbonyl carbon of α, β-unsaturated aldehydes, (cinnamaldehyde and crotonaldehyde) to yield the corresponding oximes exclusively (without any conjugate addition products) in good to quantitative yields is achieved without using any organometallic reagents (Organolithiums or Grignard reagents).

The mechanism of normal base mediated alkylation or acylation is fairly straightforward. The partial ionization of the oxime is a reversible reaction in which the forward reaction is enhanced or catalysed by the base. The resulting oximoxide ion (oxime anion) is a nucleophile that attacks the alkyl or acyl halide to give the oxime ether.

The few scattered reports of oxime ether formation using silver(I)oxide achieved very low yields, about 35%, in a reaction that was carried out for 4 days at room temperature (Olofsson *et al*, 2005,). In this work, upto 70% yield was achieved by heating the reaction mixture at the refluxing temperature of the alkylating halide which also served as the solvent.

No previously proposed mechanism for this reaction is available. A mechanism is proposed that is analogous to the mechanism of the silver mirror test reaction for aldehydes from the observation of the reaction products of this work. A complex is formed between silver ion and the oxime which is analogous to the complex formed between silver ion and concentrated ammonia solution in the silver mirror test. The complex is then attacked by the alkylating or acylating agent to form the oxime ether and in the process, it is reduced to silver metal by electron transfer.

Compounds 32a, 32b, 33a, and 33b were found to have some inhibitory antifungal effect against *C. albicans* and *S. cerevicea* with 32a having the activity at 500μg/mL and 2000μg/mL. 32b also has some inhibitory activity against *S. aureus* and *E. coli*, while 33b also has some inhibitory activity against

S. aureus. The inhibitory activities were higher at the higher concentration of 2000μg/mL.

5.3 Recommendations

The mechanism of reaction for the silver oxide mediated reaction is complicated and hence requirs further investigation. The mechanism proposed in this thesis is only a tentative mechanism. An investigation to device a method for reconverting the silver pellets in to reusable silver (I) oxide is worth pursuing. It is also suggested that research be conducted to investigate the feasibility of using Copper (I) oxide (Cu_2O) as base and oxidizing agent or catalyst in place of silver (I) oxide which is a more expensive reagent. This is because copper (I) ion has electronic similarities with silver (I) ion (copper (I) and silver (I) possess filled d^{10} shells of electrons; copper, silver and gold are also known to form unstable organo-derivatives (Powell, 1988).) and copper (I)oxide is easily obtained by reduction of an alkaline solution of copper(II)sulfate.

The result obtained after the compounds were tested for bioactivity showed that disappointingly, only 32a and 32b as well as 33a and 33b seem to have any significant inhibitory anti-fungal activity against *Candidas albicans* and *S. cerevicea.*

Further research is needed to find what the minimum and maximum Inhibitory Concentrations is for each of the compounds for these microorganisms. Considering the versatility of oximes and oxime ethers as

attested to by literature, it is worthwhile to investigate other potential biological activities such as herbicidal, anti-inflammatory, and plant and insect growth regulatory activities, antiviral, larvicidal, insecticide, anticonvulsant activities. All these other activities were not within the scope of this study.

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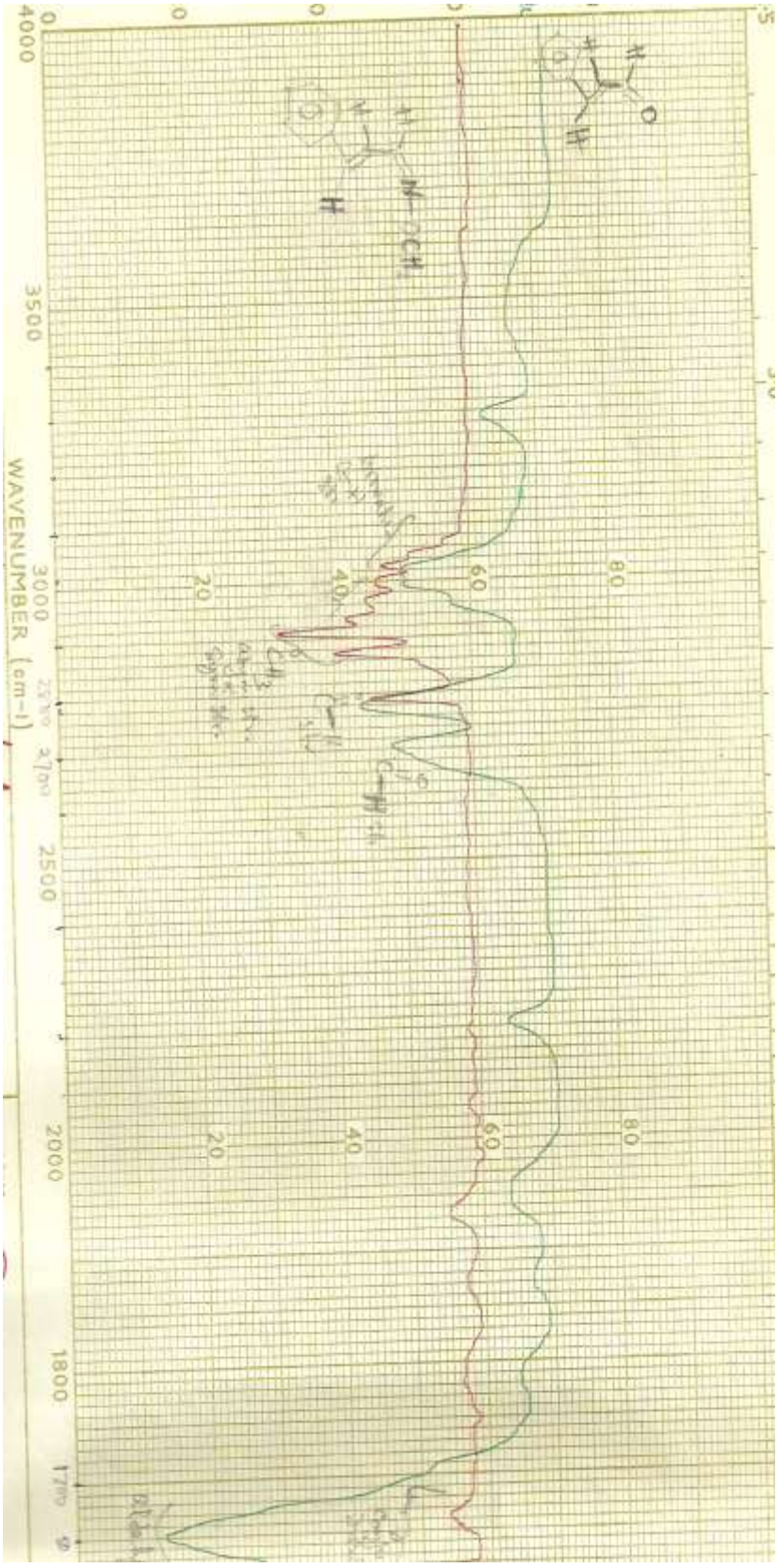
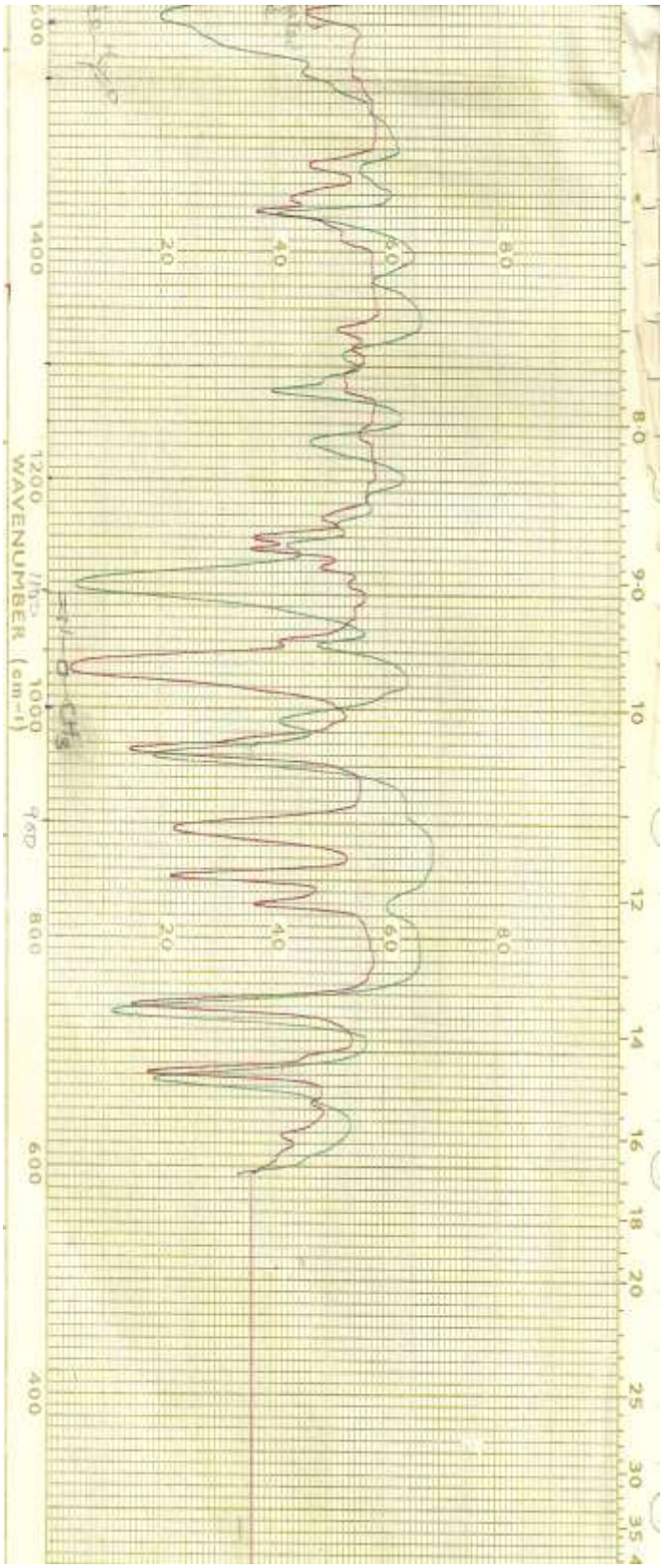
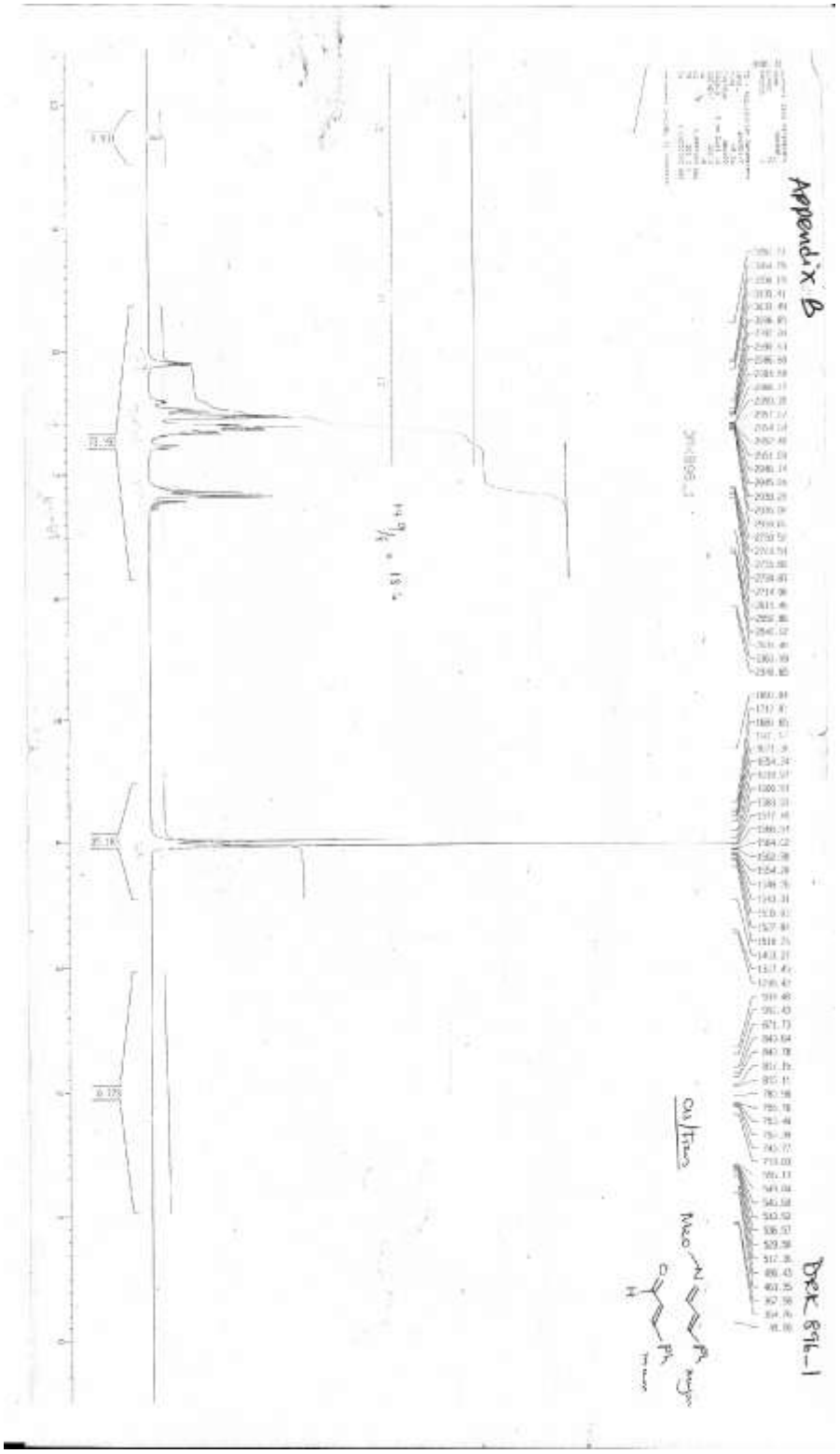
Appendix 1: Infrared spectrum of Cinnamaldehyde and Compound 32a



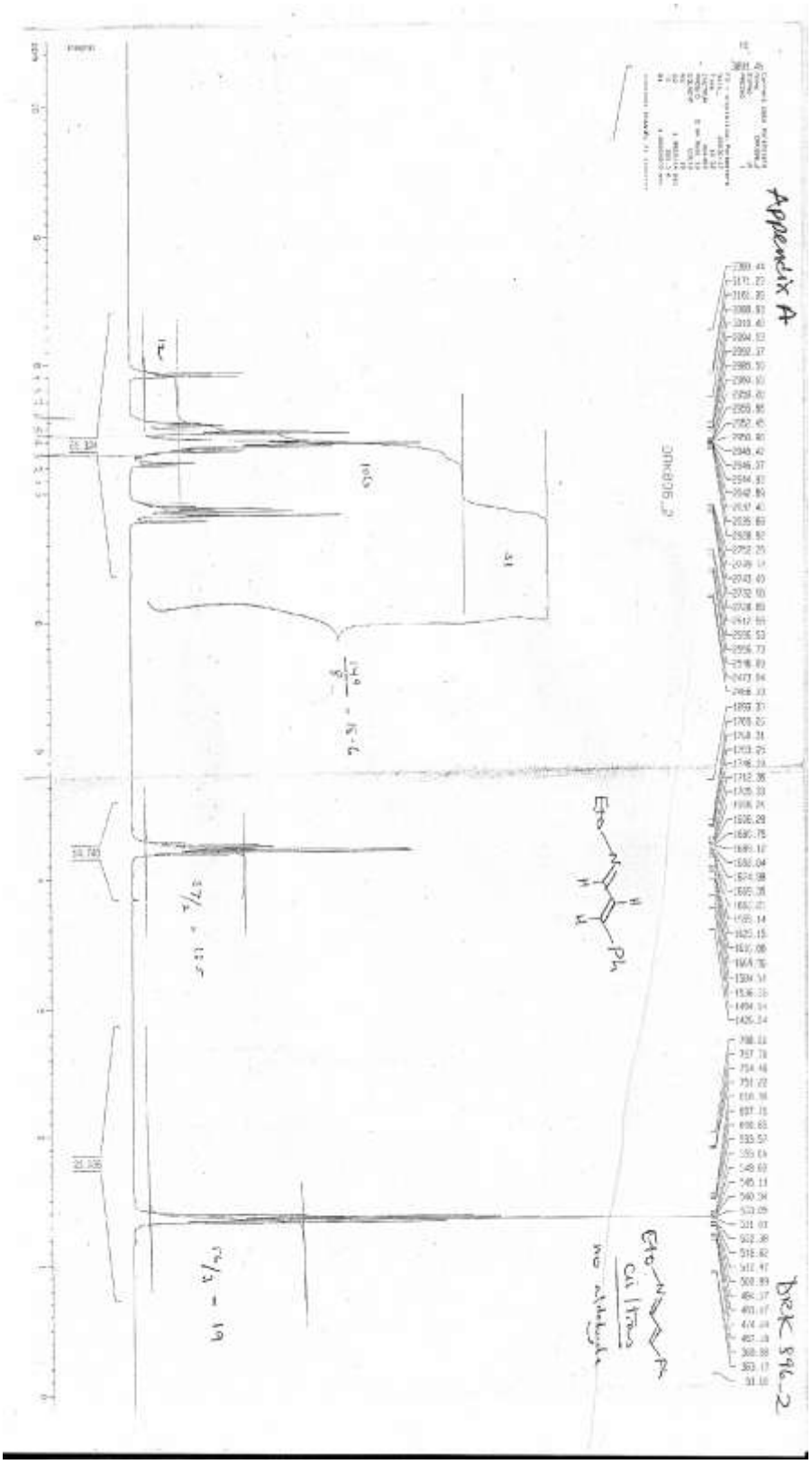
Appendix 2: Infrared spectrum of Cinnamaldehyde and 32a (1600-600 cm^{-1})



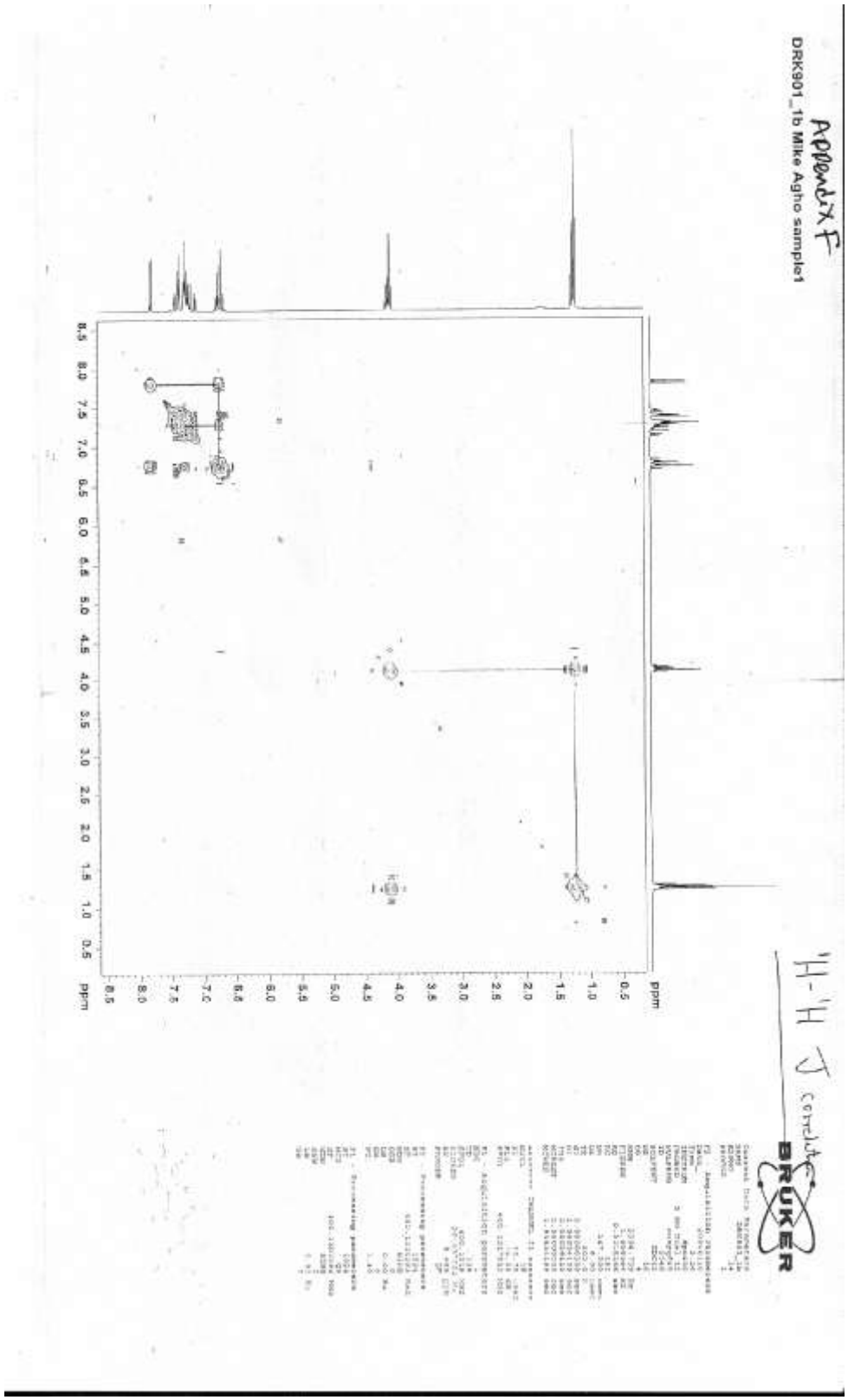
Appendix 3: ^{1}H-NMR spectrum of 3-Phenyl propenal O-ethyl oxime, 32b



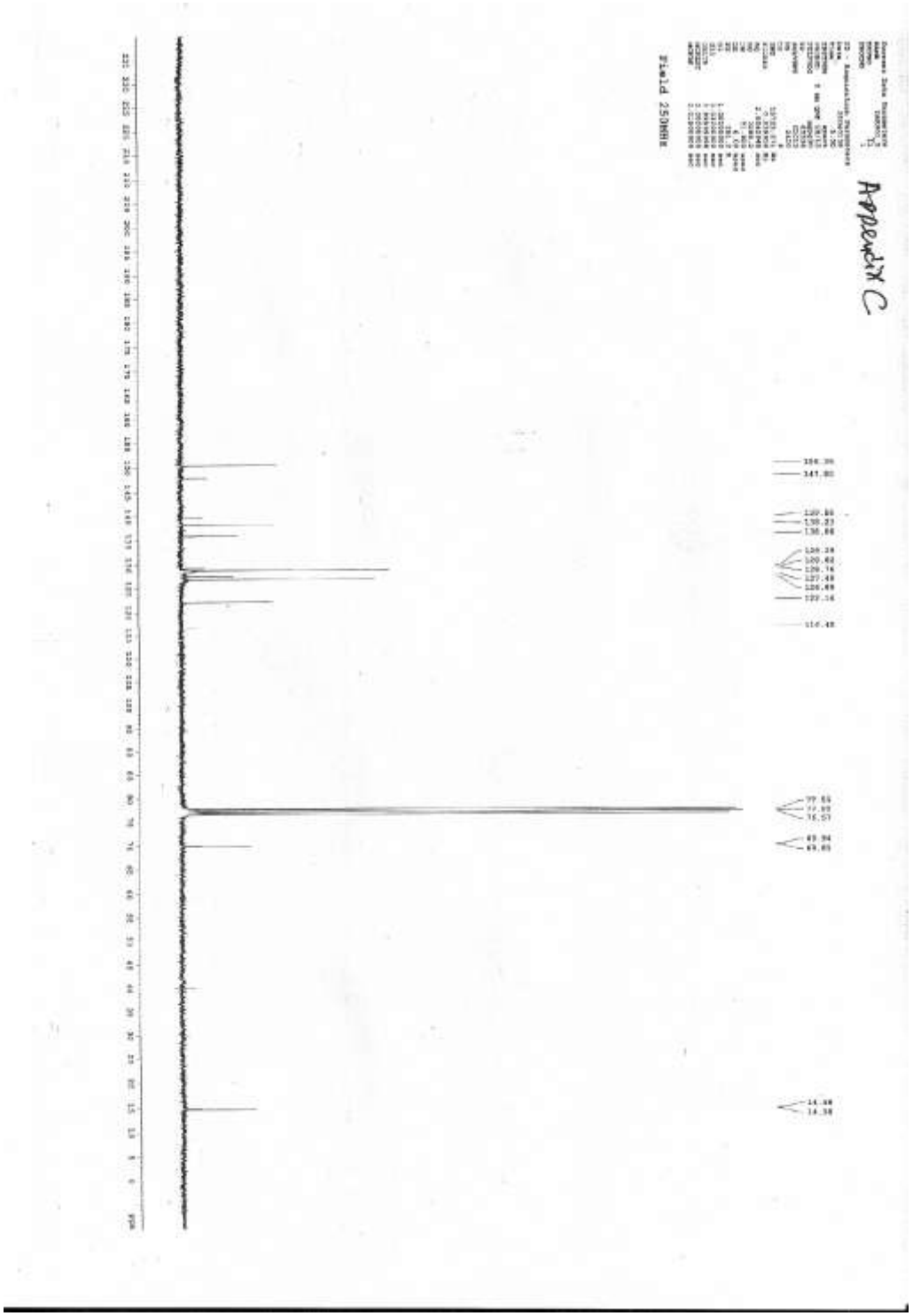
Appendix 4: ^{1}H-NMR spectrum of 3-Phenylpropenal O-ethyl oxime, 32a



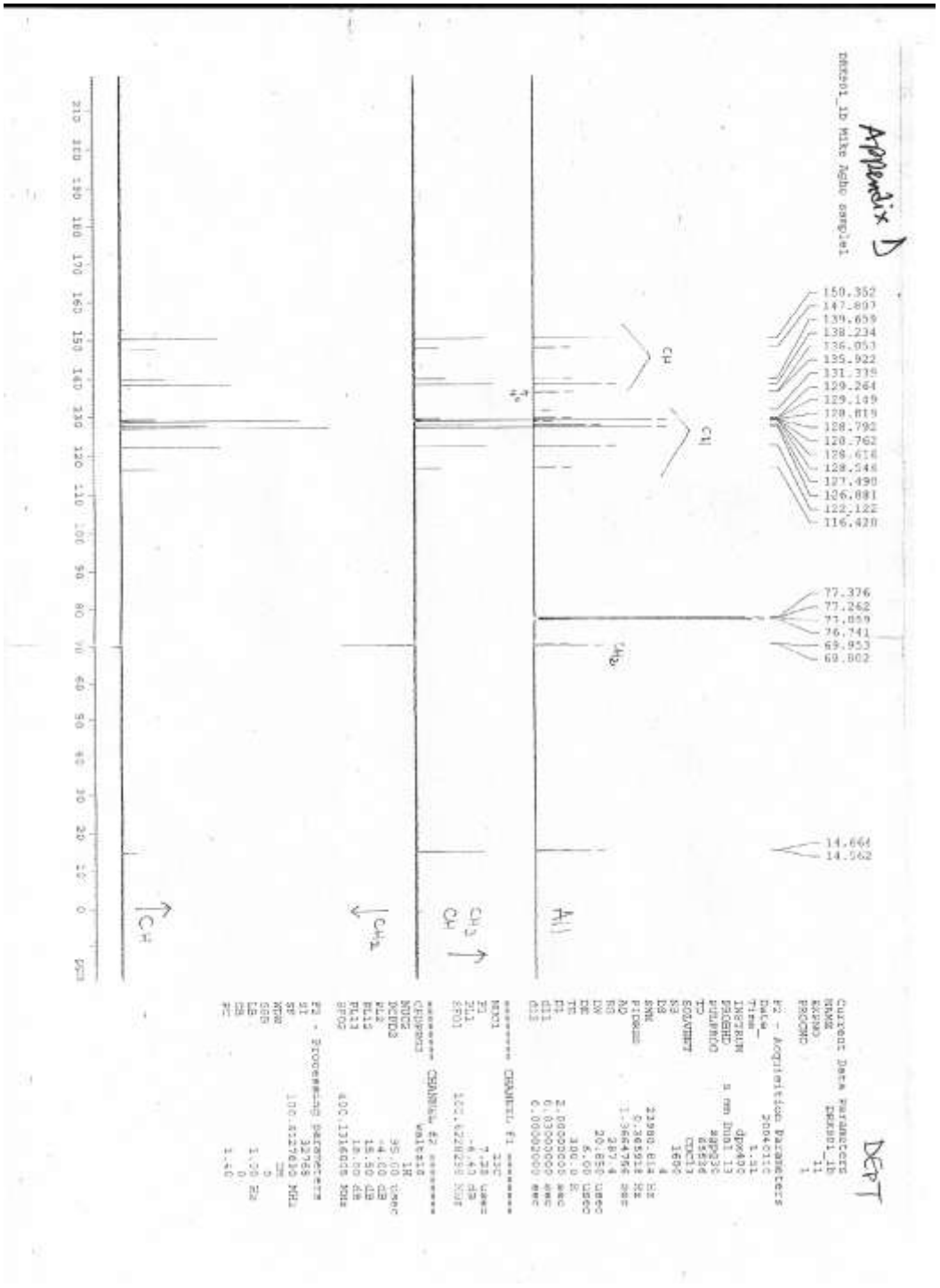
Appendix 5: ^{1}H-^{1}H-NMR COSY of 3-Phenylpropenal O-ethyl oxime, 32a



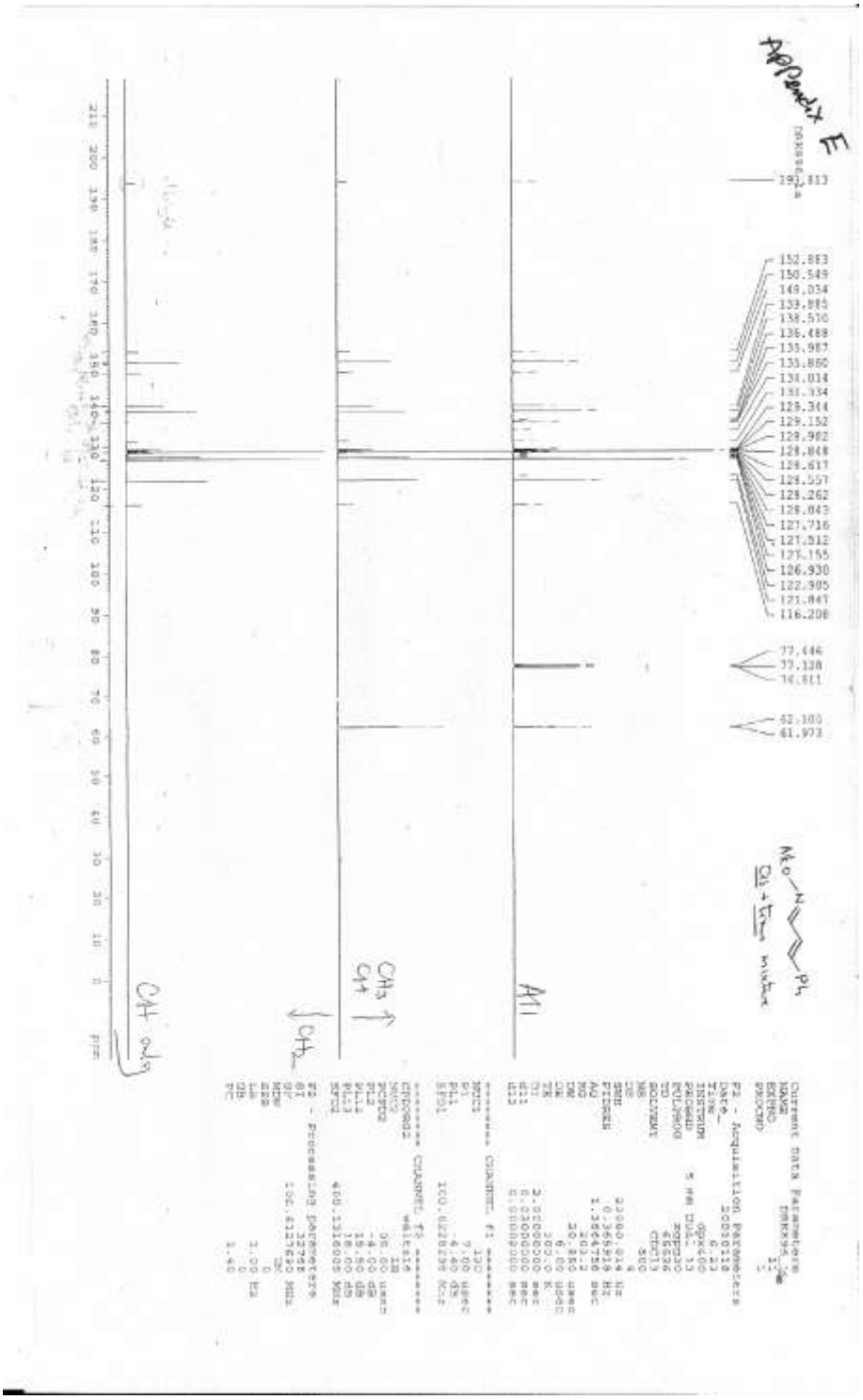
Appendix 6: ^{13}C-NMR of 3-Phenylpropenal O-ethyl oxime, 32a



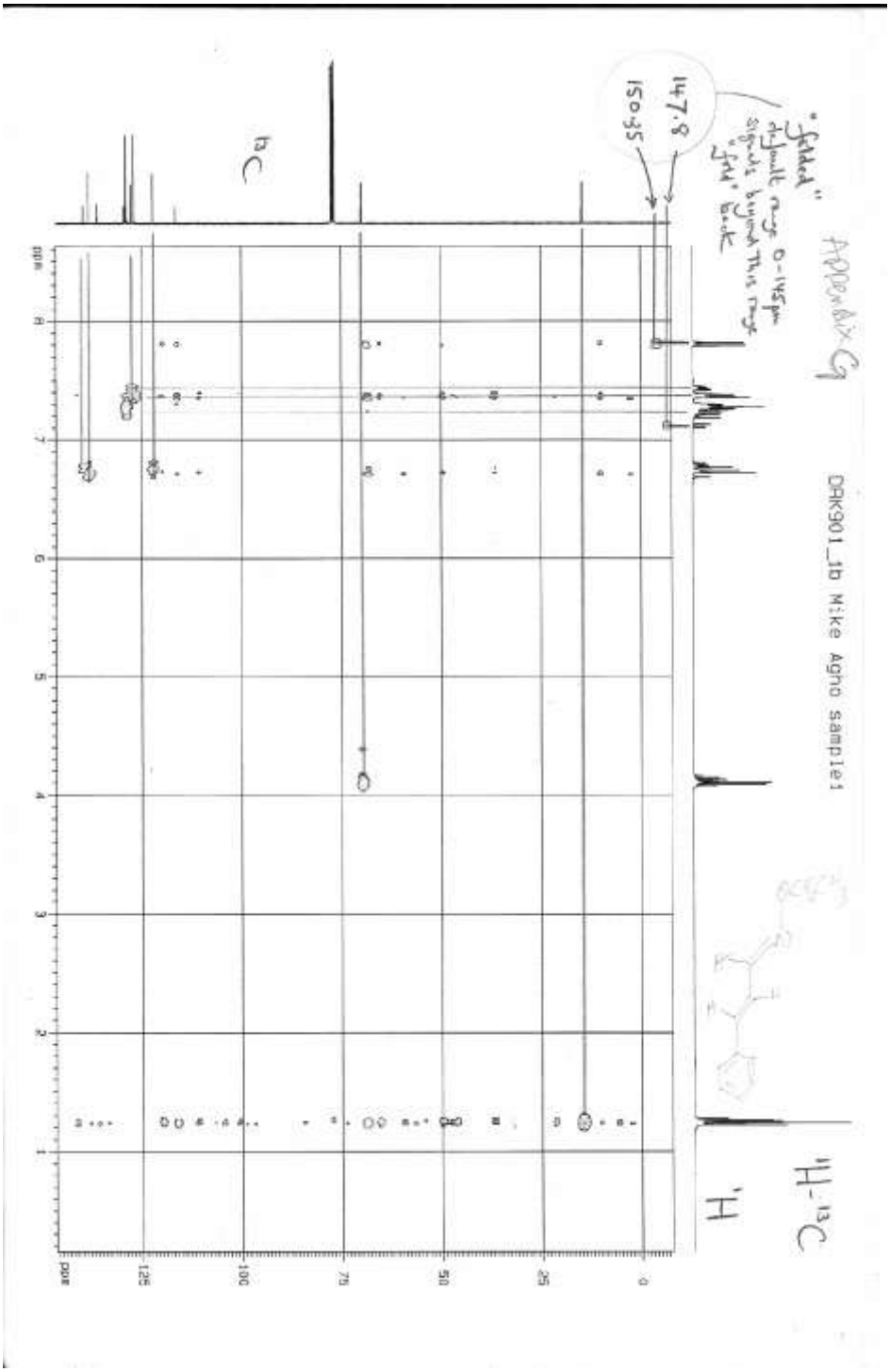
Appendix 7: ^{13}C-NMR DEPT of 3-Phenylpropenal O-ethyl oxime, 32a



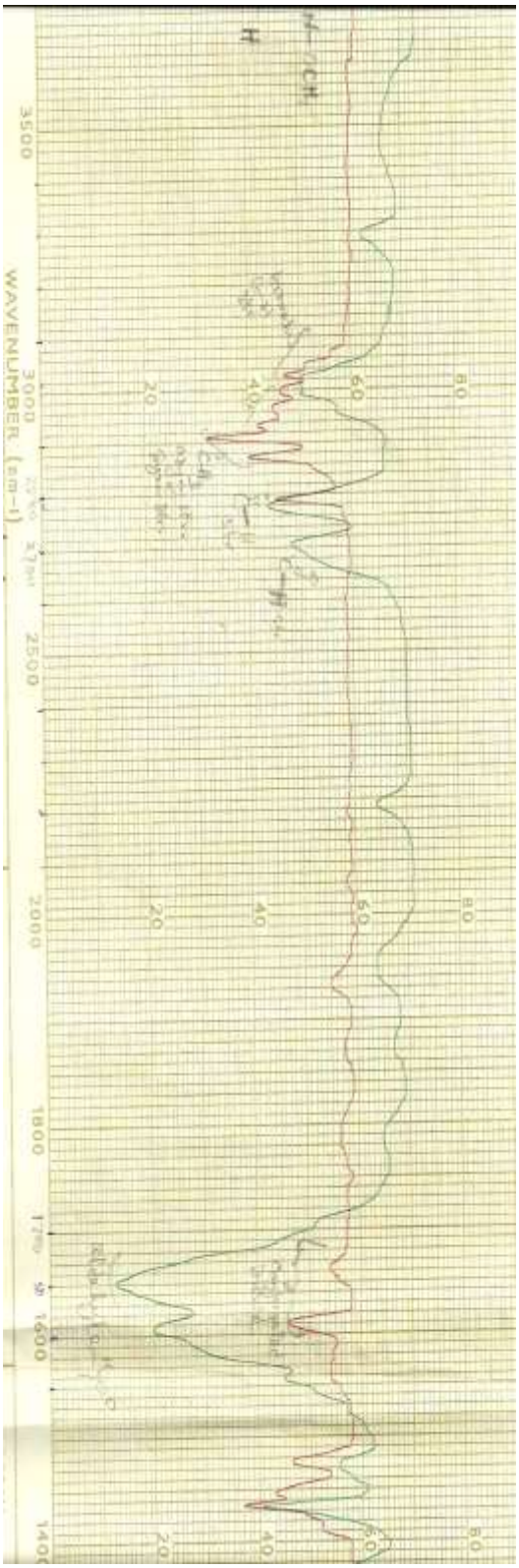
Appendix 8: ^{13}C-NMR of 3-Phenylpropenal O-methyl oxime, 32b



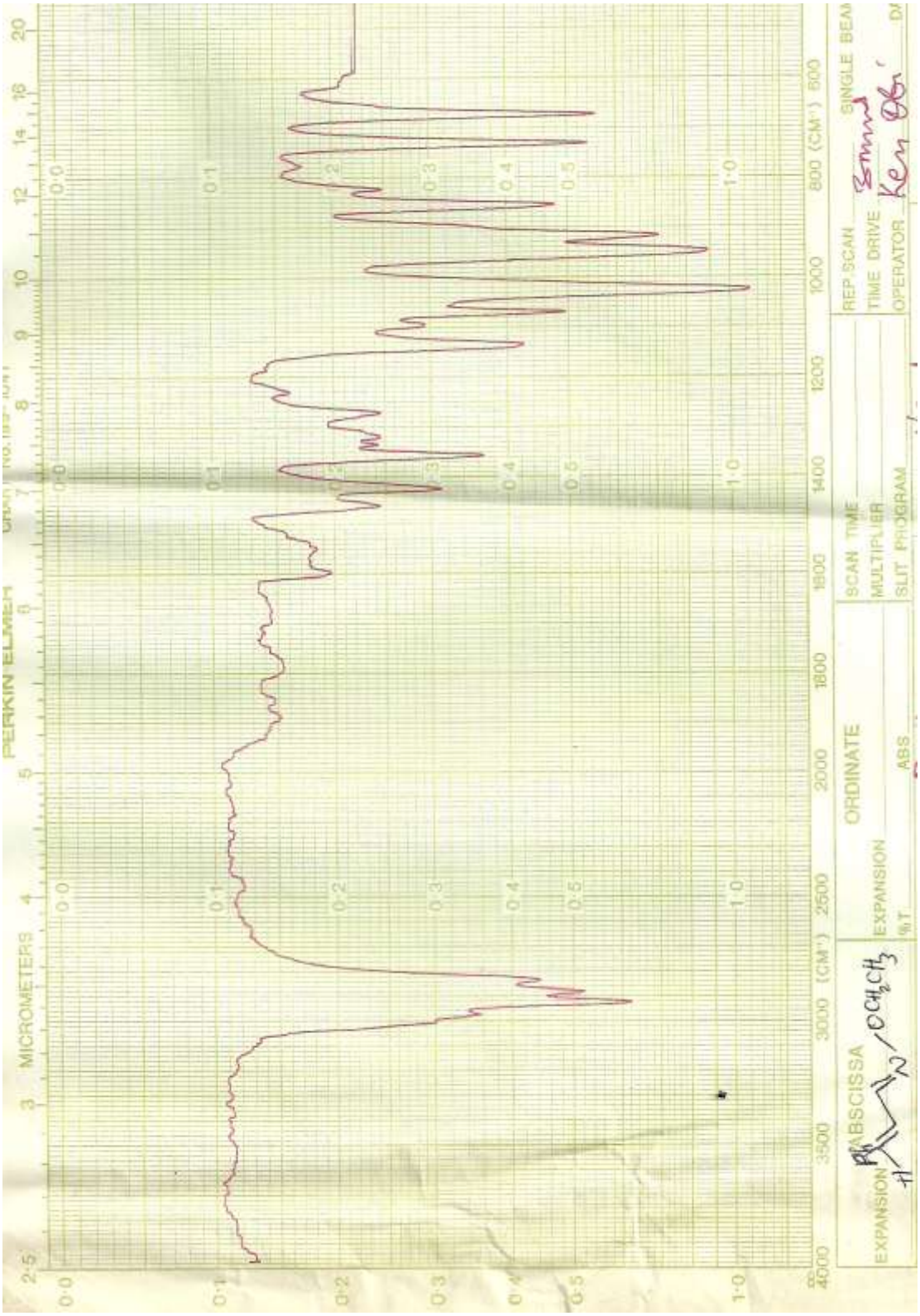
Appendix 9: ^{1}H-^{13}C HETCOR of 3-Phenylpropenal O-ethyl oxime 32a


DRK901_1b Mike Agno sample1
13C
1H
1H-13C
147.8
150.35
ppm

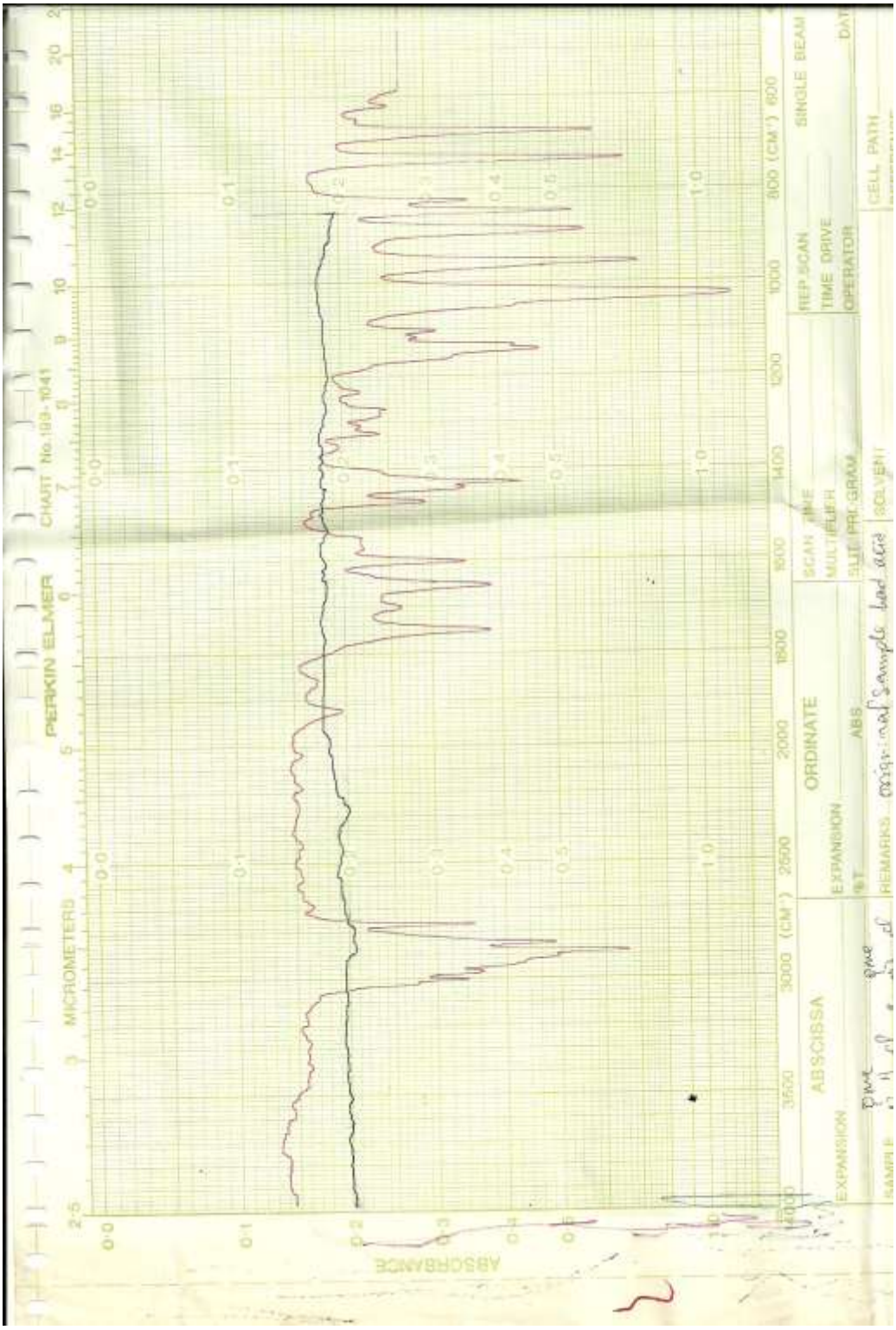
Appendix 10: Infrared spectrum of Cinamaldehyde and 3-Phenylpropenal O-methyl oxime, 32c



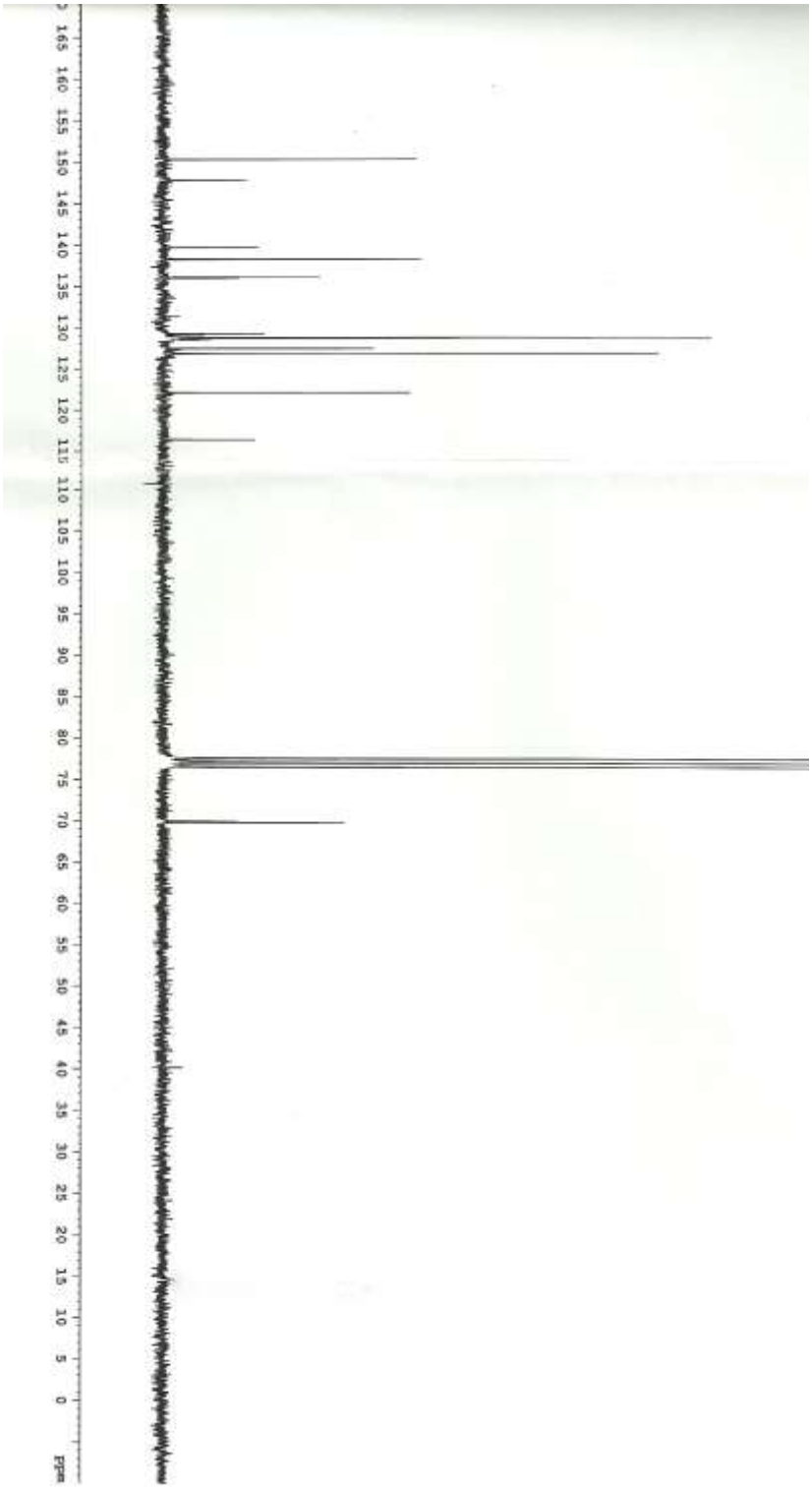
Appendix 11: Infrared spectrum of 3-Phenylpropenal O-ethyloxime, 32a



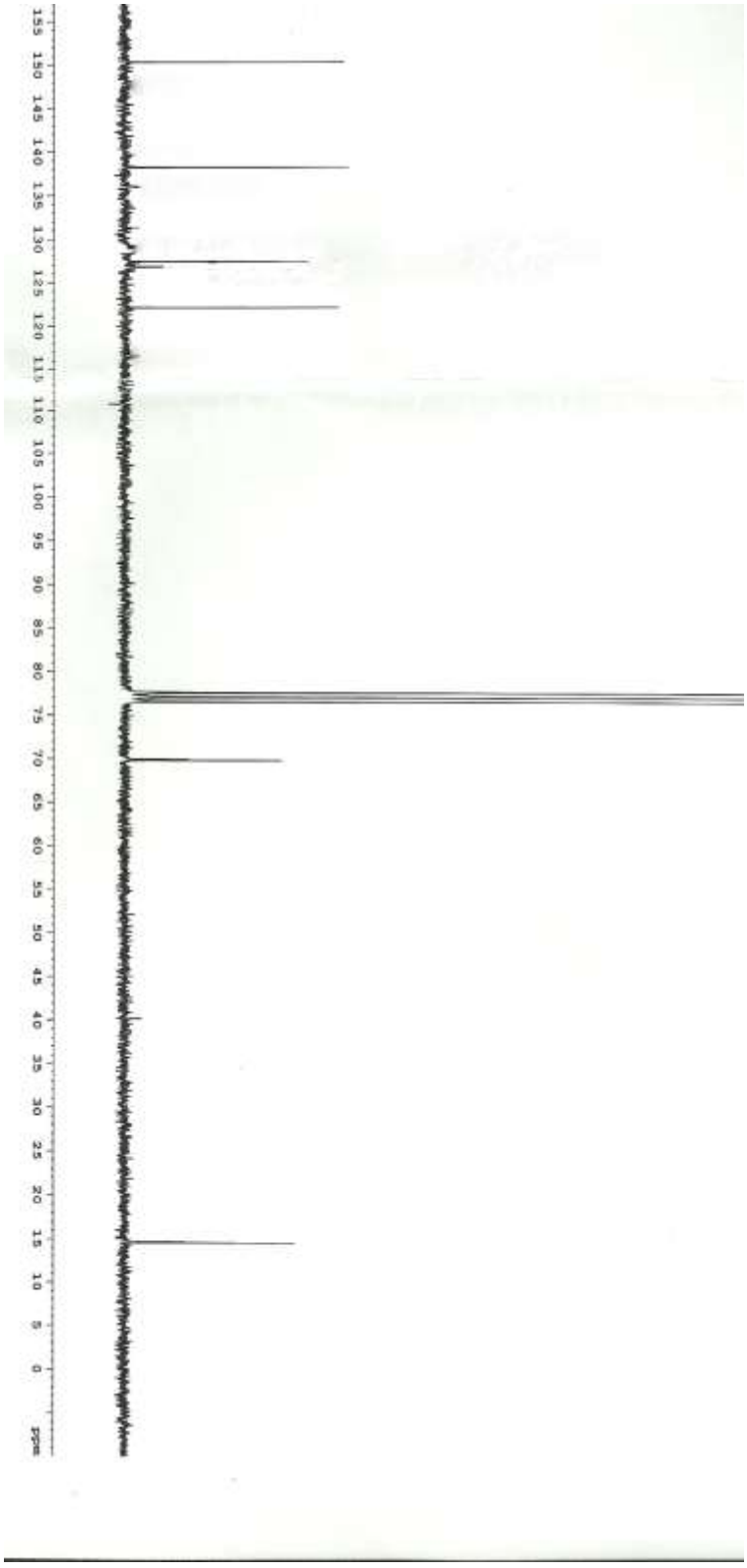
Appendix 12: Infrared spectrum of, 3-Phenylpropenal O-methyloxime, 32b



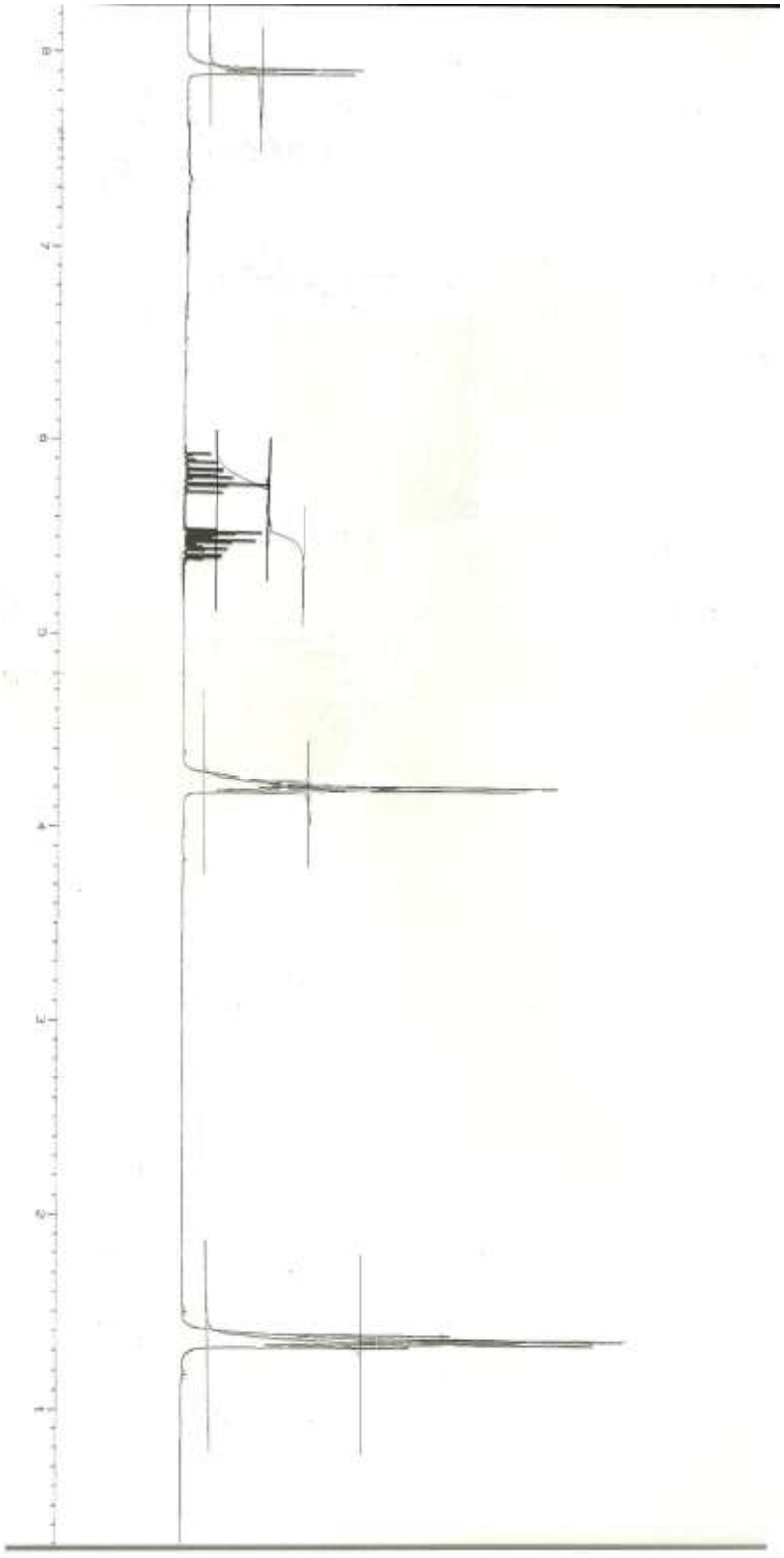
Appendix 13: ^{13}C-NMR of 3-Phenylpropenal O-methyl oxime, 32b



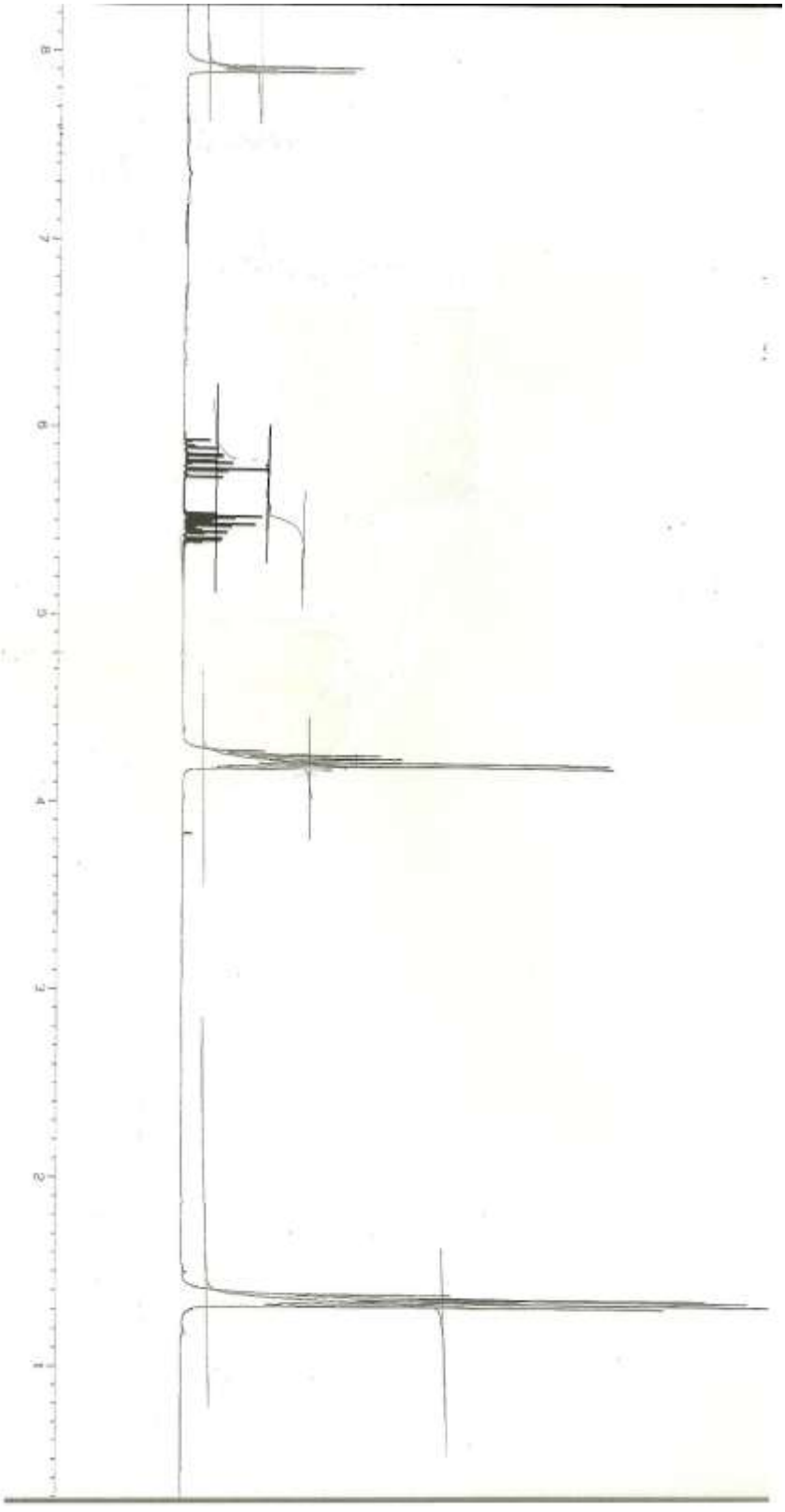
Appendix 14: ^{13}C-NMR of But-2-enal O-methyl oxime, 32c



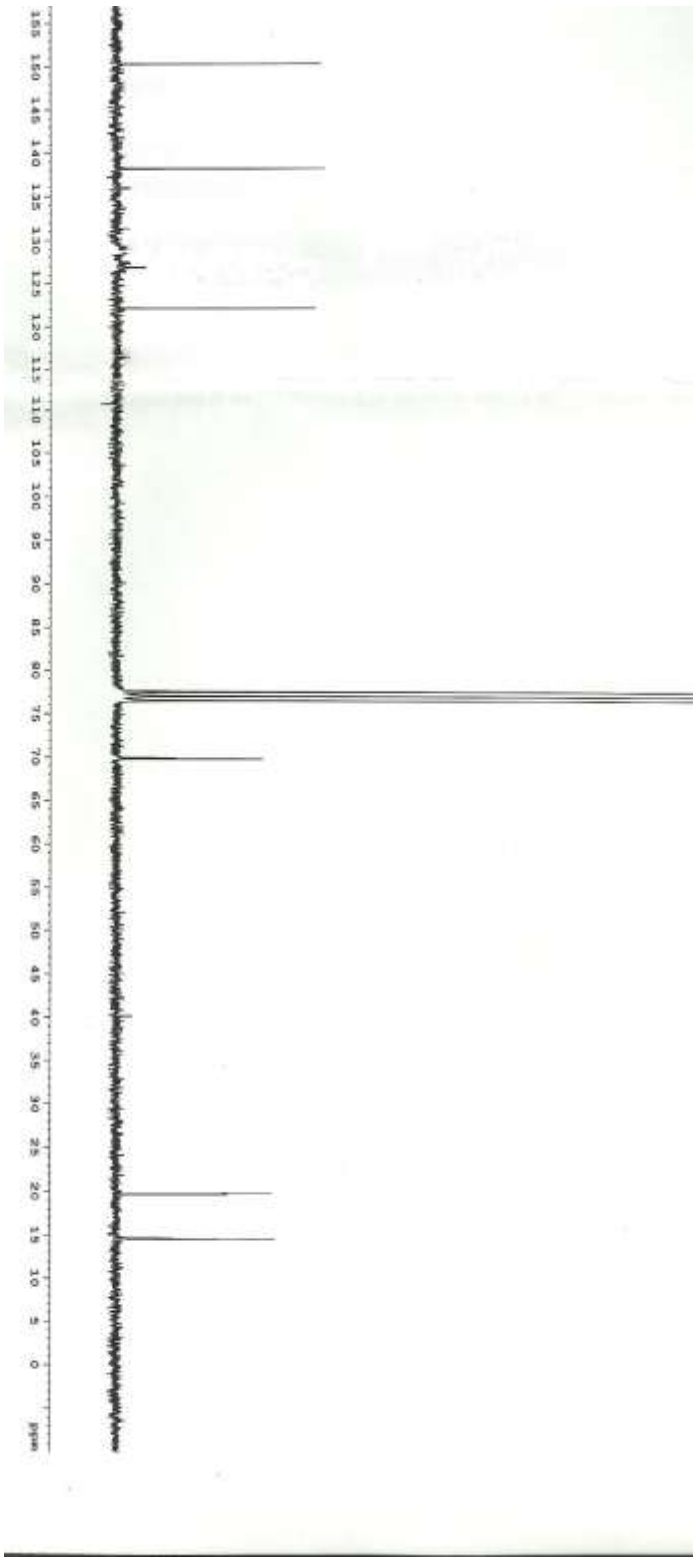
Appendix 15: ^{1}H-NMR of But-2-enal O-methyl oxime, 32c



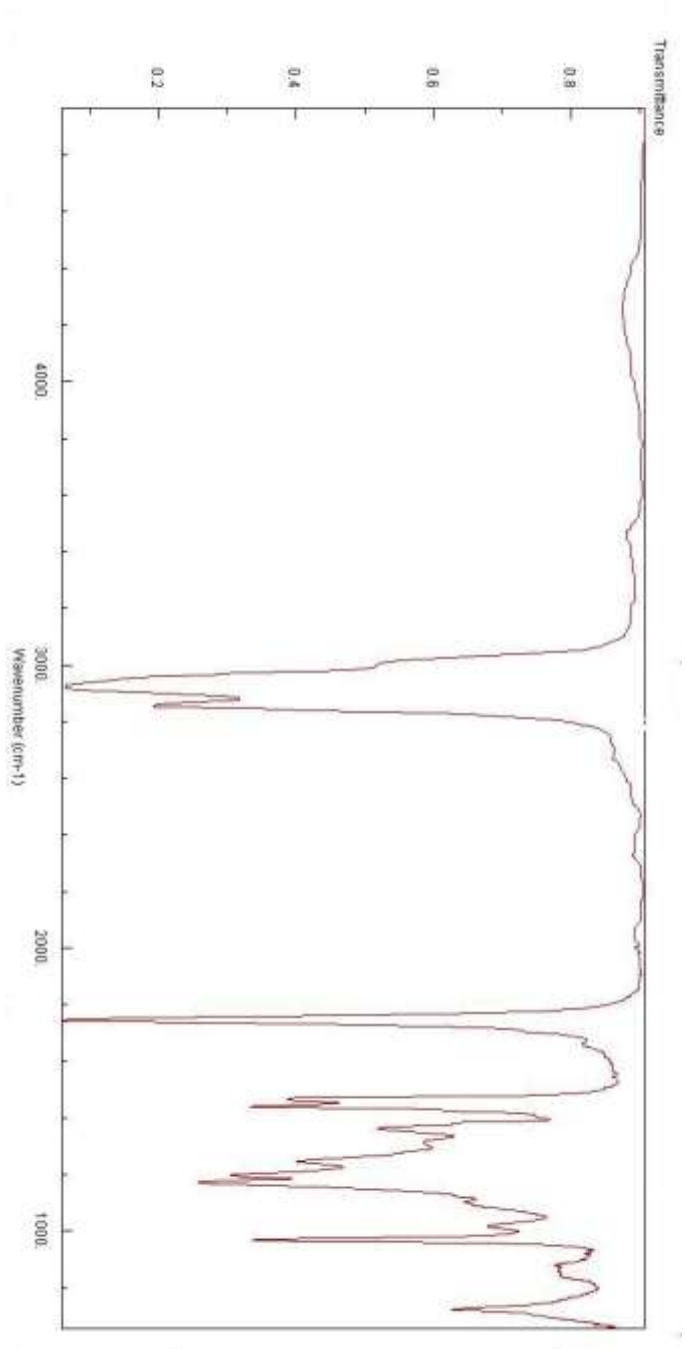
Appendix 16: ^{1}H-NMR of But-2-enal O-ethyl oxime, 32d



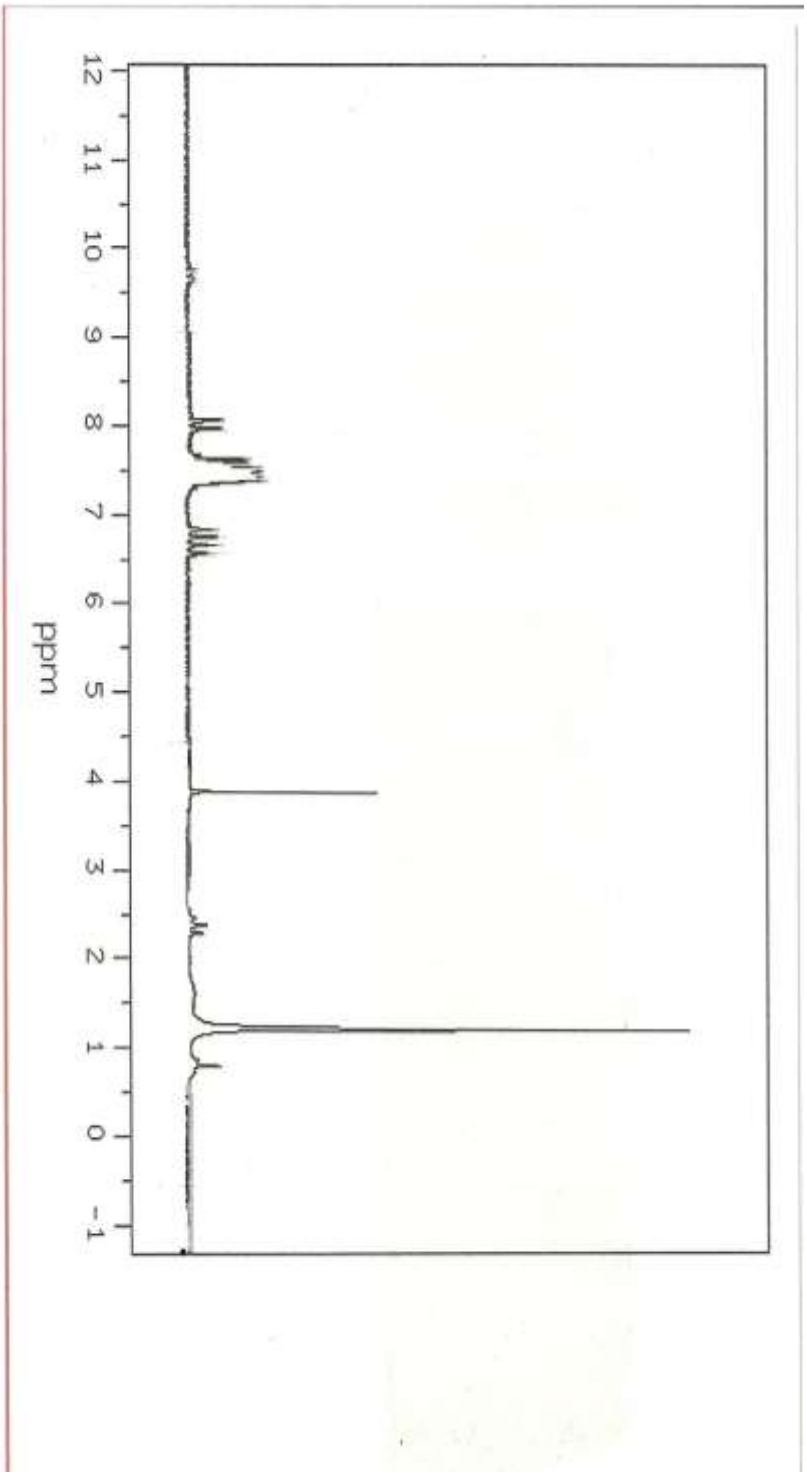
Appendix 17: ^{13}C-NMR of But-2-enal O-ethyl oxime, 32d



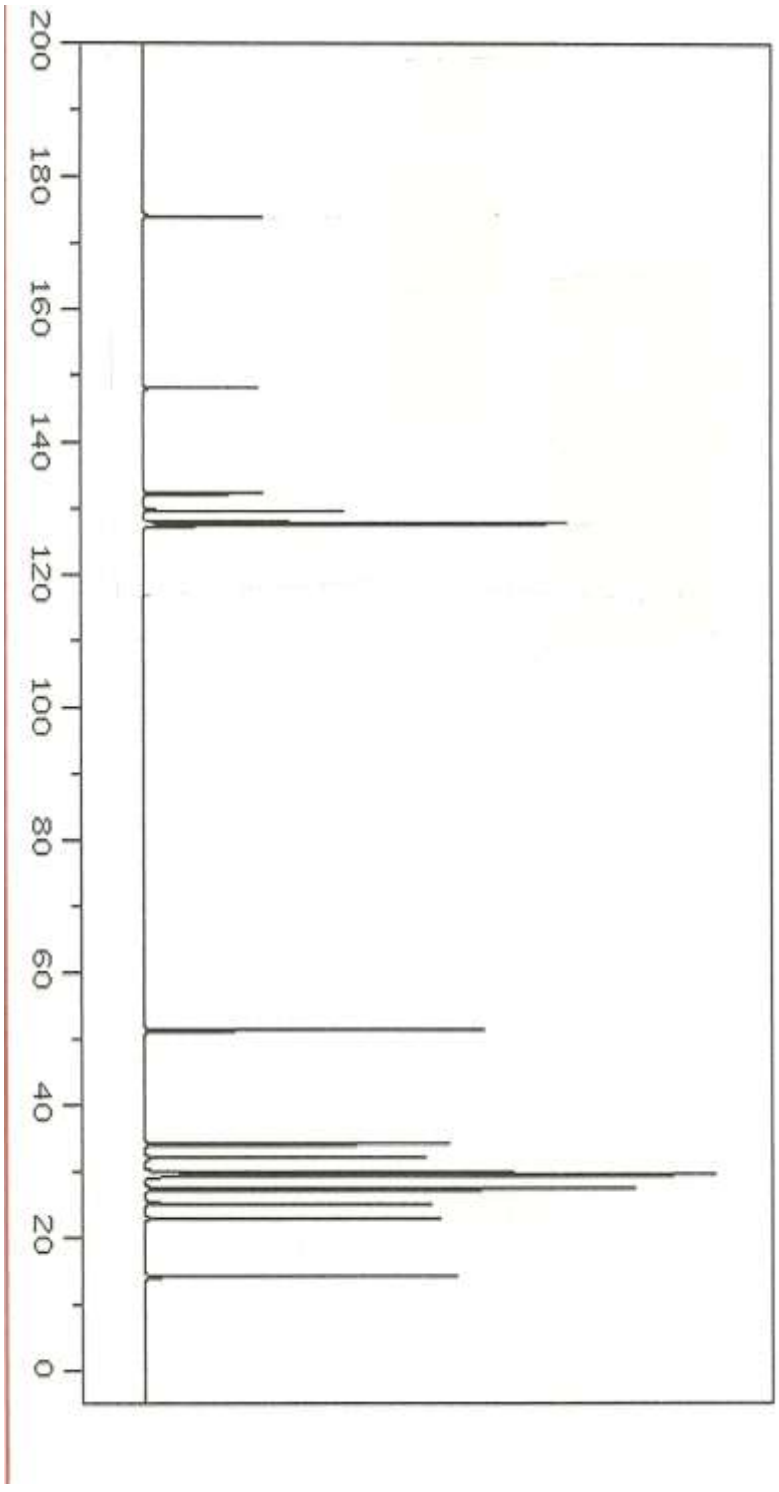
Appendix 18: Infrared spectrum of O-Palmitoyl cinnamaldoxime ether, 33a



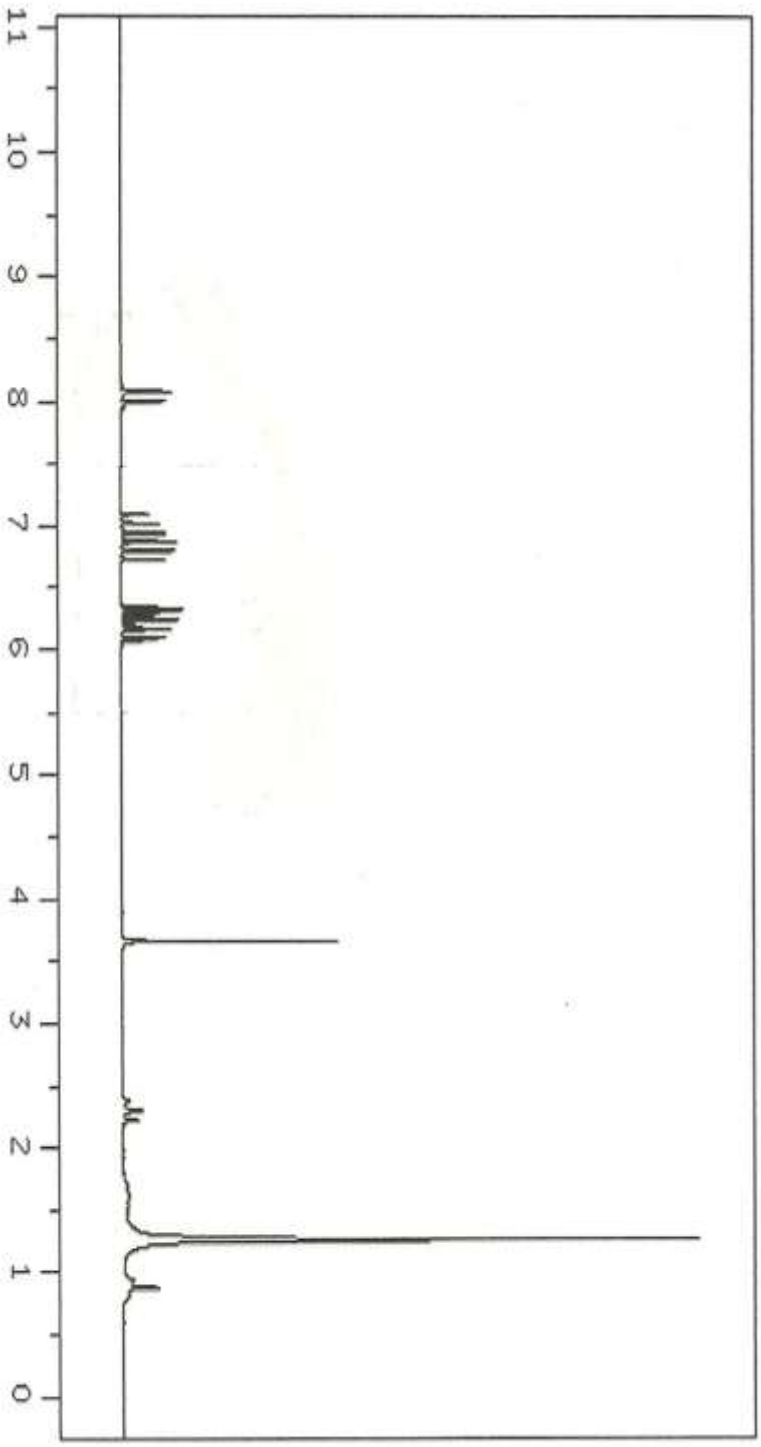
Appendix 19: ^{1}H-NMR of O-Palmitoyl cinnamaldoxime ether, 33a



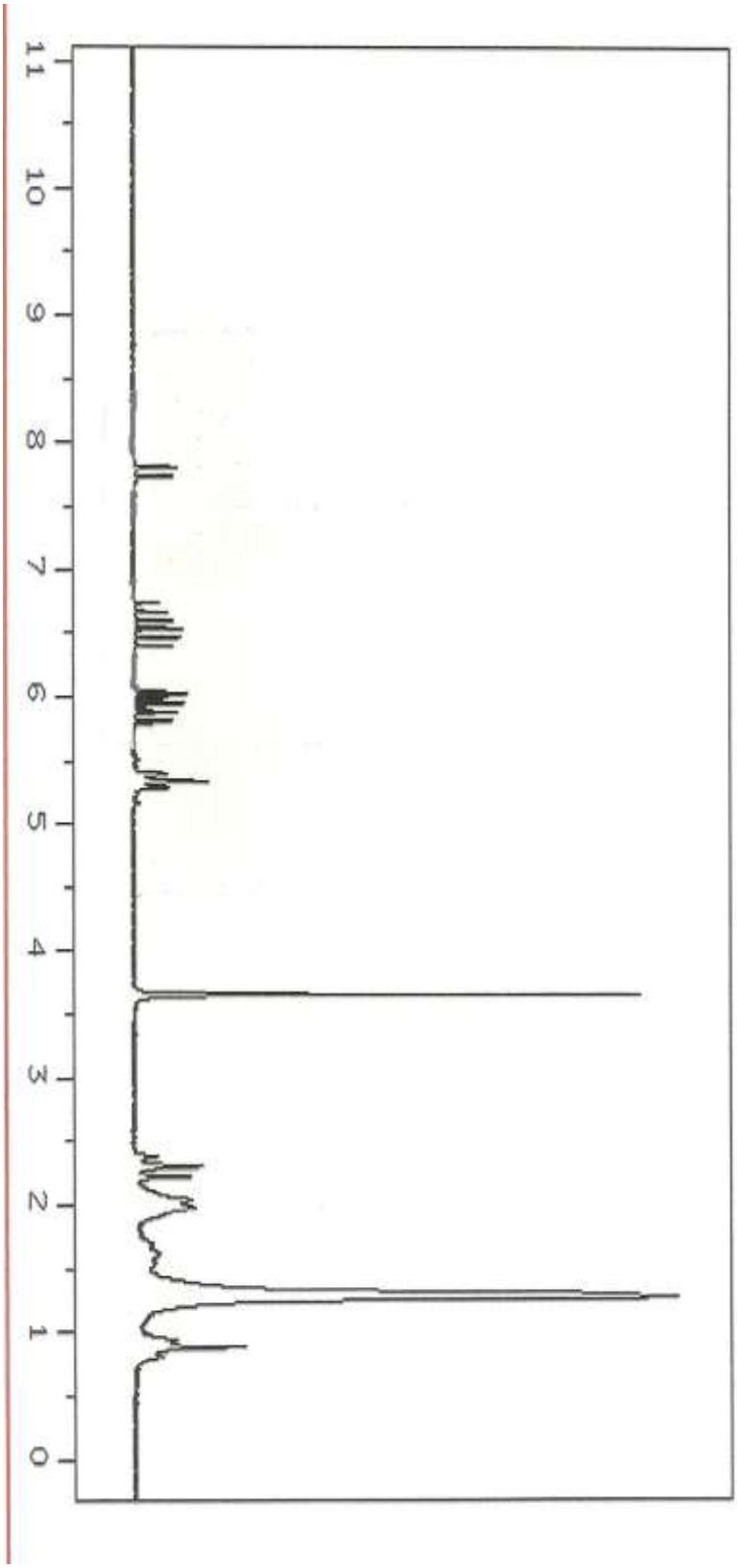
Appendix 20: ^{13}C-NMR spectrum of O-Oleoyl cinnamaldoxime ether, 33b



Appendix 21: ^{1}H-NMR of O-Palmitoyl crotonaldoxime, 33c



Appendix 22: ^{1}H-NMR of But-2-enal O-octadec-9-enoyl oxime, 33d



Appendix 23

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Synthesis and Antimicrobial Activities of Some N-Alkoxy α, β-Unsaturated Oxime Ethers

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Federal University of Technology, Yola

ABSTRACT

The synthesis, spectral characterization and microbial activity evaluation of a series of some N-alkoxy (and acyloxy) α, β-unsaturated oxime ethers were carried out. The products obtained were characterized and tested for bioactivity against Stapphylococcus aurreus, Escherichia coli, Candidas albicans and Sacharomyces cereviciae. Alkyl halides and a group of compounds comprising of acyl chlorides derived from fatty acids of palm oil (palmitic acid, oleic acid) were coupled with cinnamaldoxime and crotonaldoxime to form the ethers or esters.

Key words: oxime ethers, Synthesis, characterization, microbial activity.

INTRODUCTION

References to the potential of oxime ethers and their derivatives as anti-microbial drugs abound in literature [1-5]. Oxime ethers have also found many uses in recent years as non-steroidal anti inflammatory drugs, mold inhibitory active compounds in poultry science, anti-protozoan, insect growth regulator, and herbicides and as various materials with steroidal effects. Most of the work done so far on this class of compounds is on oxime ethers but very little on the α, β-unsaturated analogues.

Despite the growing list of antimicrobial agents, their clinical value has been limited by their relatively high risk of toxicity, the emergence of drug resistance, and insufficiencies in their antimicrobial activity. Since the environmental and economic requirements imposed on modern-day antibiotics are continually increasing, with regard to the spectrum of action, toxicity, selectivity, application rate, formation of residues, and favourable preparability, a constant task is to develop new antibiotics which in some areas at least have advantages over their known counterparts. This situation has led to an ongoing search for potent broad spectrum antimicrobial agents with low side effects, which can be administered both orally and parenterally.

Appendix 24

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IR, ^{1}H-NMR AND ^{13}C-NMR CHARACTERIZATION OF SOME O-ALKYL α, β-UNSATURATED OXIME ETHERS

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Chemistry Department, School of Pure and Applied Sciences,
Federal University of Technology, Yola, Nigeria

Abstract : The synthesis and spectral characterization of some selected N-alkoxy (and acyloxy) a, (3-unsaturated oxime ethers were carried out. The products obtained were characterized by ^{1}H-NMR, ^{13}C-nmr, COSY and HETCOR as well as IR spectroscopy. The ^{1}H and ^{13}C nmr spectra of ethyl cinnamaldoxime ether, methyl cinnamaldoxime ether, O-Palmitoyl cinnamaldoxime ether and O-Oleoyl cinnamaldoxime ether were run at 250 MHz while ^{1}H, ^{13}C, ^{13}C-DEPT, ^{1}H-^{1}H coupling correlation and ^{1}H-^{13}C ^{1}J correlations were run at 400 MHz for ethyl cinnamaldoxime ether and methyl cinnamaldoxime ether, the O-alkyl cinnamaldoxime ethers, using deuterated chloroform as solvent.

Introduction

References to the potential of oxime ethers and their derivatives as anti-microbial drugs abound in literature. (Djik and Davies, 1976; Bozdag-Dunder, 2003; Balsamo et al, 1990; Sun et al, 2008; Khan, 2006). Most of the work done so far is on oxime ethers but very little on α, β-unsatrated analogues. The products obtained from this synthesis were used to study the ^{1}H-NMR, ^{13}C-NMR, COSY and HETCOR as well as IR spectroscopic characteristics of this class of organic compounds which are currently not well documented.

The NMR technique is a versatile tool for the structural elucidation of most organic compounds and it is useful for the conformational analysis of compounds also. ^{1}H NMR and ^{13}C NMR techniques have been extensively applied in deriving stereodynamical information about a wide variety of systems. For example, the conversion of the carbonyl group into the oxime, C=N-OH, and oxime ether C=N-OR etc exhibit an abrupt change in the NMR chemical shifts and infra-red bands (Rani et al, 2008, Kabilan et al, 2008).

In a wide search for new and efficient antimicrobial agents, Kabilan et al, 2006, synthesized a series of substituted piperidin-4-one oxime ethers. The structures of these oxime ethers and their relative stereochemistries were investigated by nuclear magnetic resonance spectroscopy. In all the oxime ethers synthesized, the orientation of the N-O bond of the oxime ether moiety, the configuration, was deduced based on ^{1}H NMR and ^{13}C NMR spectra (Kabilan eral, 2006).

Many of the original (prior to 1921) assignments of configuration of the Z and E isomers were based on chemical reactions (the Beckman rearrangement) and were in error because of incorrect assumptions concerning the stereochemistry of these reactions (Johnson et al, 2001). The assignment of configurations of oximes, when both isomers are available, can be made from ^{1}H and ^{13}C nuclear magnetic resonance spectra by noting that, E and Z isomers of oxime ethers exhibit two signals for the C=N-O-CH_2-protons at 84.35-4.45 ppm (E-isomer) and 4.20-4.30 ppm (Z- isomer), O-CHa resonance for E isomer occurs at higher 8 ppm values than for the Z isomers (Karabatsos and Hsi, 1967; Haney et al, 1977; Boschmann and Winter, 1980).

Key words : Oxime ethers, IR, ^{1}H-NMR, ^{13}C-nmr, COSY and HETCOR spectroscopy.

Appendix 25

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Silver Oxide-Mediated Oxime Ether Synthesis

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ABSTRACT

A series of oxime ethers were prepared from (E, E)-cinnamaldoxime, crotonaldoxime, (syn)-benzaldoxime and p-methoxybenzaldoxime by reaction with methyl iodide, ethyl bromide and benzyl chloride with silver oxide as base and catalyst. Excellent yields of the corresponding (E, Z isomers) ethers were obtained without the formation of nitrones or the use of undesirable solvents.

Keywords: silver oxide; oxime ether; catalysis; reactive solvent

INTRODUCTION

The usual method for the preparation of oxime ethers is the reaction of aldehydes and ketones with alkyl halides in the presence of a base such as sodium alkoxides, NaH, K_2CO_3, KOH, $NaHCO_3$ etc [1, 3], in solvents like acetone, DMSO, DMF *etc*. These methods are usually complicated by the accompanying formation of nitrones as a side product [2-4]. We present a procedure in which the alkyl or aryl halide, aside from being the oximation agent, also serves as the solvent and the excess halide can be recovered from the reaction mixture by distillation and reused for further oxime alkylation/arylation or other uses. The silver oxide is also recoverable as silver metal which can be converted to silver nitrate. Another advantage of this procedure is that no nitrones are formed [2-4].

MATERIALS AND METHODS

3. Experimental

3.1. General

The infrared spectra were recorded on Perkin-Elmer Model 1310 spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra of **a, b, e, f** and **g** were run at 250 MHz while ^{1}H, ^{13}C, ^{13}C-DEPT, ^{1}H-^{1}H coupling correlation, ^{1}H- ^{13}C ^{1}J correlations were run at 400 MHz for products **c** and **d,** the *O*-alkyl cinnamaldoxime ethers, using deuterated chloroform (or carbontetrachloride) in some cases as solvent and tetramethylsilane (TMS) as internal standard and the chemical shifts are given on the δ (ppm) scale. Elemental analysis was determined on a Yanaco CHN Corder Elemental analyzer. Cinnamaldehyde, crotonaldehyde, benzaldehyde, p-methoxybenzaldehyde and