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Synthesis Towards Fulminic Acid and Its Derivatives in 1, 3-Dipolar Cycloaddition Reactions.

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Synthesis Towards Fulminic Acid and Its Derivatives in 1,3-Dipolar Cycloaddition Reactions

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by

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ABSTRACT

Synthesis Towards Fulminic Acid and Its Derivatives in 1,3-Dipolar Cycloaddition Reactions

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A new approach to fulminic acid cycloadditions has been developed. At reduced temperatures, fulminic acid is generated *in situ* and undergoes 1, 3-diploar cycloaddition reactions with dipolarophiles to form isoxazolines and/or its dimers. This procedure represents a novel, safe general method for the one-step generation of fulminic acid, which complements existing potentially explosive protocols.

DEDICATION

This work is dedicated to my late father; Peter TOH, my mom Helen AFOR

ACKNOWLEDGMENTS

I owe a lot to ETSU (Faculty and Staff) for the knowledge impacted on me during the master's degree program through their friendliness, collaboration, and willingness to help at any time.
My sincere thanks go to my supervisor, Dr. David G.Young, who is always there to explain some of the basic concepts underlying the research and as a result I was able to differentiate between theory and practical. Also, many thanks to Dr. Yu Lin Jiang and Dr. Jeff G. Wardeska for being members of my thesis committee. My brothers and sisters; Dr. Toh Ephraim and wife, Mr/Mrs Ngangyet Clement, Mr/Mrs Toh Hans, Mr/Mrs Otengong Helaria, Mr/Mrs Chick Stella, and Mr Toh Oswin for their relentless support and prayers.

My cousin; Mr/Dr Wini Akam for the relentless support, thanks and may God richly bless you. Classmates/friends who have contributed to this journey and the hope to light each of mile: Arrey B. Enyong, Nadine K. Njoya, Mark-Henry Kamga, Jennifer Ashie, Laude A. Bannerman, William E. Ghann, Charles Odame-Ankra, Aaron Apawu, Ernest Jum, etc. May the spirit of togetherness continue to abide in us wherever we may happen to find ourselves. Our mother of the department, Mrs Susan Campbell is not left out. Your encouragements, gentleness, kindness, and pretty smiles and above all love has contributed immensely to my success. Thank you all.

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ABBREVIATIONS

ppm	parts per million
δ	delta
R_f	retention factor
NMR	nuclear magnetic resonance
$CDCl_3$	Chloroform-D
d	doublet
dd	doublet of doublet
s	singlet
m	multiplet
t	triplet
br s	broad singlet
q	quartet
^1H	proton
^{13}C	Carbon-13
$NOBF_4$	nitrosonium tetrafluoroborate
$NOSbF_6$	nitrosonium hexafluoro antimonite
TMS	trimethyl silane
$MgSO_4$	magnesium sulfate
UV	ultraviolet
DCA	dipolar cycloaddition
GABA	gamma amino butyric acid

HOMO highest occupied molecular orbital

LUMO lowest unoccupied molecular orbital

ED_{50} effective dose

NOC nitrile oxide cycloaddition

INOC intramolecular nitrile oxide cycloaddition

BF_3 boron trifluoride

NaOAc sodium acetate

EtOAc Ethylacetate

Hz hertz

SAR structure activity relationship

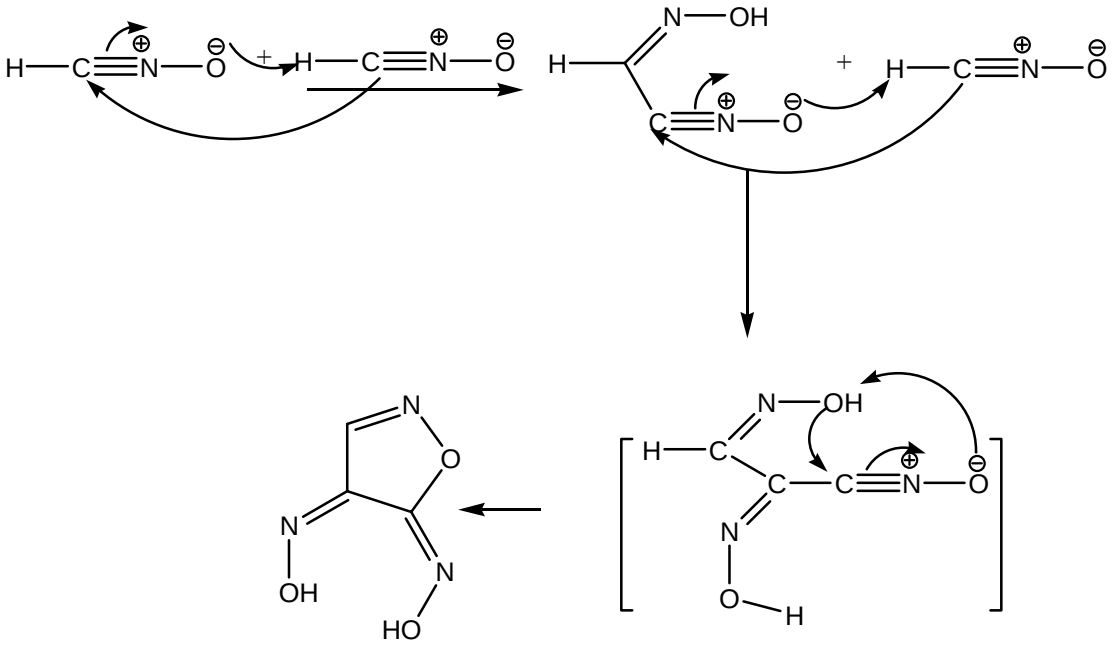
GP glycoprotein

TEA triethyl amine

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry due to the diversity of its synthetic procedures and applications. The chemistry of fulminic acid still attracts the attention of many theoreticians and has been the the subject of many experimental and theoretical studies over the past years. Fulminic acid is an unstable, poisonous, and volatile liquid with the empirical formula HCNO. It is a non-isolable compound that is usually generated *in situ* and readily undergoes a spontaneous polymerization at 15^{o}C to form the trimer (metafulminuric acid, scheme 1)[1].



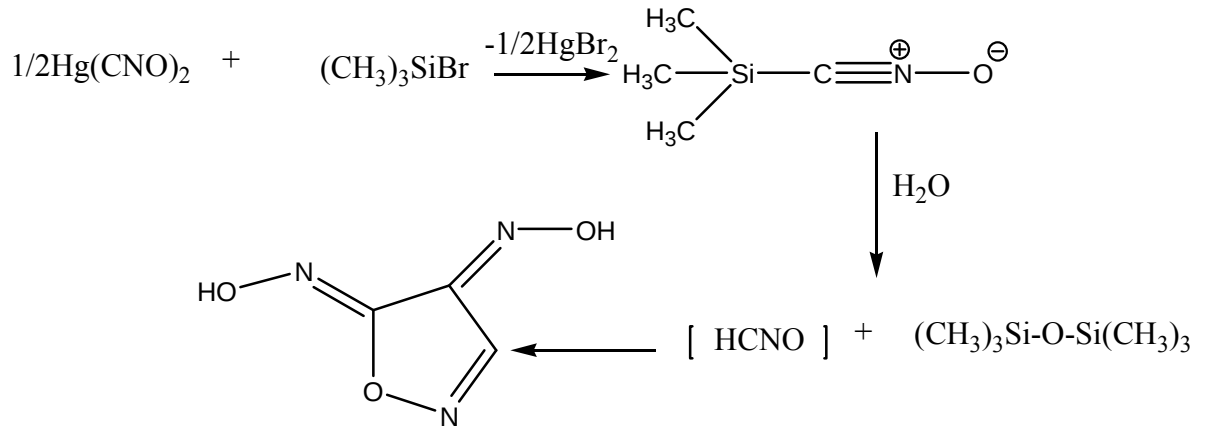
Scheme 1: Polymerization of Fulminic Acid

Discovery of Fulminic Acid

Fulminic acid was discovered in the 17th century (1630-1703) by Prof. Rolf Johannes Kunckel in which he dissolved silver and mercury in "aqua fortis"(nitric acid), then "spiritus vini" (alcoholic spirit) was added to the reaction mixture and allowed to react for a day. This led to an explosion [2]. Fulminic acid is an organic acid isomeric with cyanic and cyanuric acids; its salts, termed fulminates, are very explosive and are much employed as detonators.

Previous Method of Fulminic Acid Synthesis

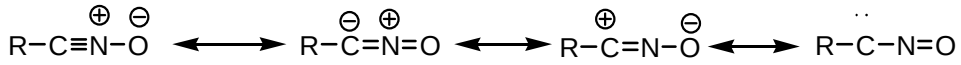
Fulminic acid was synthesized previously by the reaction between mercury fulminate and trimethylsilyl bromide followed by hydrolysis of the resulting trimethylsilyl carbonitrile oxide [3] (Scheme 2).



Metafulminuric acid hexamethyldisiloxane

Scheme 2: Previous Synthesis of Fulminic Acid

The chemistry of nitrile oxides has been well documented over the past years. They are widely used in 1,3-dipolar cycloaddition reactions to generate five membered ring isoxazolines. Nitrile oxides are generally unstable at room temperature (XCNO, X= ONC, NC, Cl, Br, Me) [4] and stable when stored at 0°C and lower.



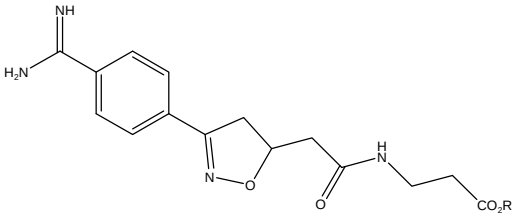
Scheme 3: Mesomeric Structure of Nitrile Oxides

Nitrile oxides undergo self dimerization to produce furoxans at ambient temperatures in the absence of a dipolarophile. Several methods for the generation of nitrile oxides *in situ* have been reported and are outlined in section 1.3. Nitrile oxides undergo 1,3-dipolar cycloaddition reactions with olefins and acetylenes to provide isoxazolines and isoxazoles respectively [5]. Stable nitrile oxides that have been reported are those of 4-substituted-2,6-dimethylbenzonitrile oxides and methylsulphonylthiophene carbonitrile oxide which are stable in the solid state and reactive in solution. These oxides can be obtained as a result of the steric shielding of the nitrile oxide moiety but easily decompose at temperatures > -20^{o}C.

The addition of unsaturated compounds to 1,3-dipoles yields five-membered ring heterocyclic compounds. In particular, cycloaddition of nitrile oxides to olefins provide versatile intermediates in the synthesis of a variety of natural products [6, 7]. Over the past years, some nitrile oxide compounds have been reported to show a wide spectrum of biological activities like anti-tubercular [8], antibacterial [8, 9], anticonvulsant [10], antiviral, 4**,** [11], analgesic, anti-inflammatory [9], and antidepressant [11]. Most of the activities reported are due to the presence of the isoxazoline moiety [8, 9, 10,11].

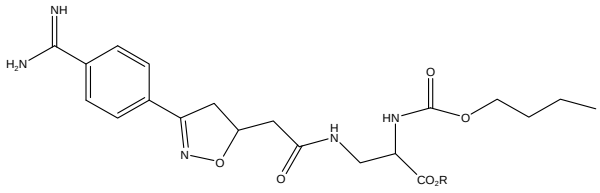
Recently, synthesis involving isoxazoline/isoxazole derivatives using nitrile oxides has been an attractive approach to biologically active molecules. Aspirin was used as a standard therapy for long-term oral treatment of platelet hyperactivity but was later abandoned due to its non selectivity and its inability to interfere to a greater extent with thrombogenic activity [11]. Ticlopidine as well as clopidogrel were later approved in the US as first-line therapy with improved efficacy and tolerability

versus aspirin. Due to the urgent need for antiplatelet/antithrombotic drugs that are more effective than aspirin, ticlopidine or clopidogrel for the prevention and treatment of cardiovascular and cerebrovascular thromboembolic disorders in humans and in animals, GP11b/111a antagonists having isoxazolinylacetates, 1 & 2 were reported [12]. The structure-activity relationship (SAR) of these 3, 5-disubstitued isoxazolines is due to the isoxazoline moiety. Roxifiban, 3, is another oral prodrug, potent and highly selective platelet GP11b/111a receptor antagonist which has been reported to provide prolonged antiplatelet effects in dogs and guinea pigs [13].



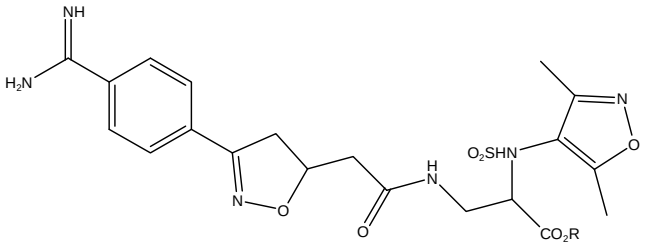
R = H, Et

1



R = H, Me

Roxifiban, 3



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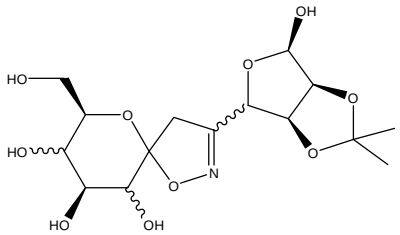

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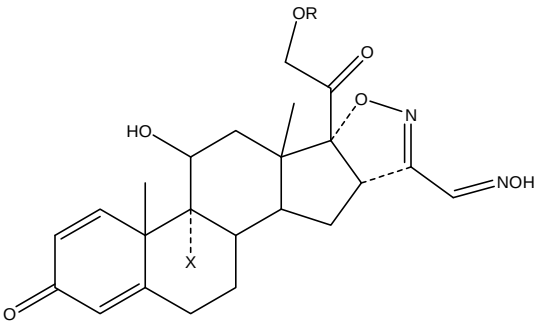
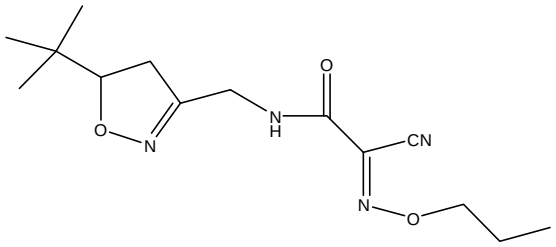
Figure 1: (continued on next page)



R	X	
$COCH_3$	F	5
OH	F	
$COCH_3$	H	
OH	H	



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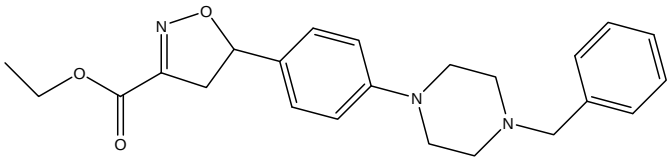


7

MIC_{90} of 1.56 μg/mL against *M. tuberculosis*

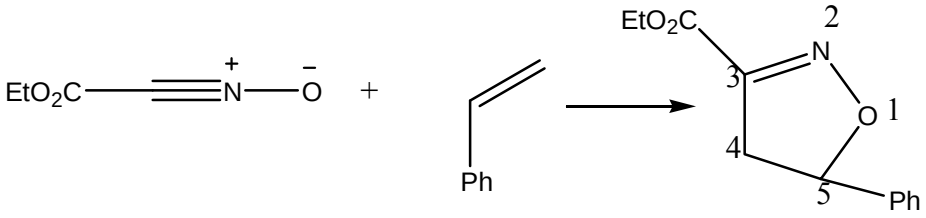
Figure 1: Biologically Active Isoxazolines

A series of new in vitro anti-inflammatory steroidal antedrugs, 5, with C-16,17-isoxazoline ring systems have been evaluated by the Kwan group. They investigated the high binding affinity to steroid receptors by fluorinated isoxazoline and oxime derivatives, and their ED_{50} values (concentrations that displace 50% of [^{3}H] dexamethasone binding) in rats were reported [14].

An "antedrug" is a designed compound that exerts desirable effects at the application site but is rapidly biotransformed to an inactive metabolite by a predictable enzymatic reaction upon entry into the circulation, thus resulting in reduction of adverse systemic effects [15].

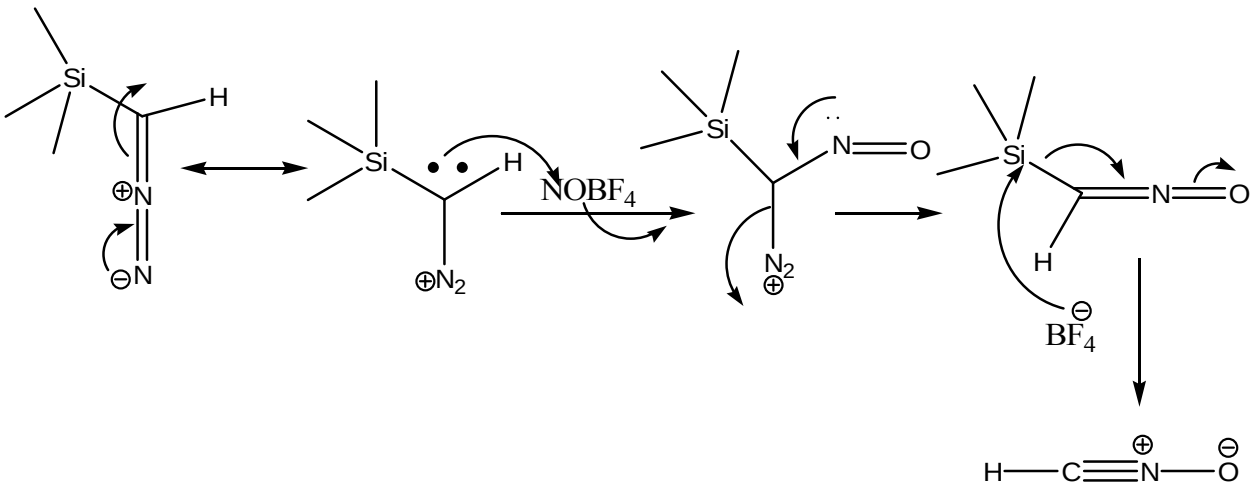
Over the past years, many isoxazoline/isoxazolidine derivatives have been introduced into the skeleton of a large number of natural products for the generation of natural product based libraries [15]. Nitrile oxides cycloadditions to terminal alkenes proceeds regioselectively to give 5-substituted

2-isoxazolines as the only product while disubstituted alkenes results in a mixture of regioisomeric 2-isoxazolines [16]. For example:



Scheme 4: Isoxazoline from Substituted Nitrile Oxide

In the studies reported here, a new route to nitrile oxides has been developed in the synthesis of a number of isoxazolines/isoxazoles. This new approach uses nitrosonium tetrafluoroborate ($NOBF_4$) or $NOSbF_6$ in acetonitrile (CH_3CN) with trimethylsilyl diazomethane ($C_4H_{10}SiN_2$) as common reagents that can be used to access complex networks. During the reaction, fulminic acid is generated *in situ* as trimethylsilyl diazomethane is slowly added to $NOBF_4$ or $NOSbF_6/CH_3CN$ at reduced temperatures (-35 to -45^oC).



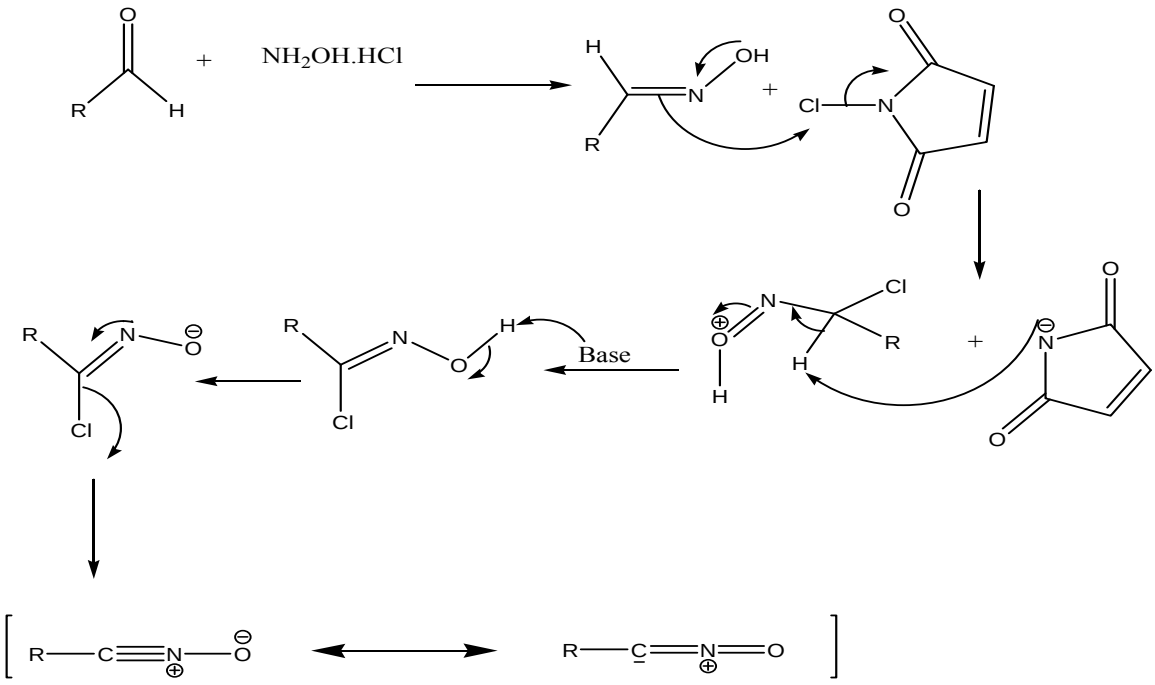
Scheme 5: Proposed Route to Fulminic Acid Synthesis

Quilico and Speroni first generated fulminic acid *in situ* and this idea was later supported by Francis and his research group[1].They emphasized the important role played by nitrile oxides in the synthesis of isoxazoline derivatives and since then, the cycloaddition of nitrile oxides to unsaturated compounds has become standard organic chemistry [17].

Methods of Nitrile Oxide Generation

Classical Method

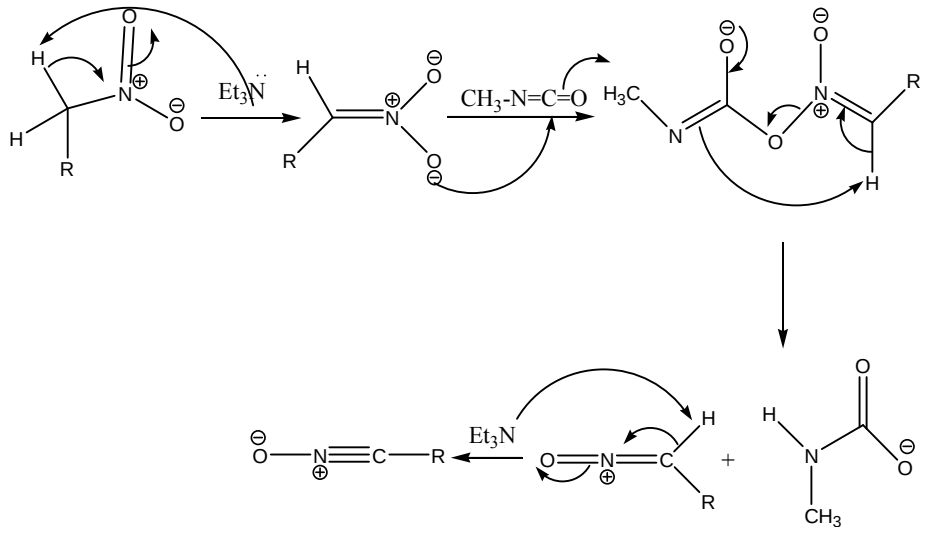
Nitrile Oxides are generally not isolable but are prepared *in situ* in the presence of a dipolarophile [16]. A common source of nitrile oxides are α-halo oximes that are readily available from aldehydes after treatment with NH_2OH/NaOAc. Further treatment of the resulting oxime with N-chlorosuccinimide and triethylamine yields nitrile oxides in excellent yields [17].



Scheme 6: Two-Step Generation of a Nitrile oxide from an Aldehyde

Mukaiyama-Hoshino Method [18, 19]

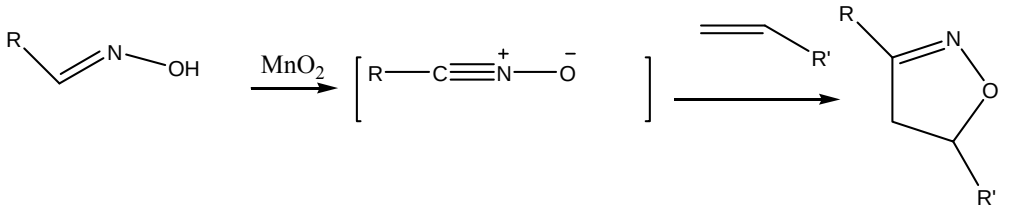
This method involves the dehydration of primary nitroalkanes using isocyanate in the presence of a base (scheme 7) and is most effective in the preparation of aliphatic or aromatic nitrile oxides.



Scheme 7: Generation of a Nitrile Oxide From a Primary Nitroalkane

Oxidation With Catalyst

Aldoximes bearing an electron withdrawing group are easily oxidized to nitrile oxides in the presence of manganese (1V) oxides (scheme 8) [19]. This reaction can be performed under mild conditions using (E) or (Z) isomers of aldoximes. On the contrary, oximes bearing a primary stannyl group close to the iminoxyl moiety appear to react by the cyclization not involving nitrile oxide [20].

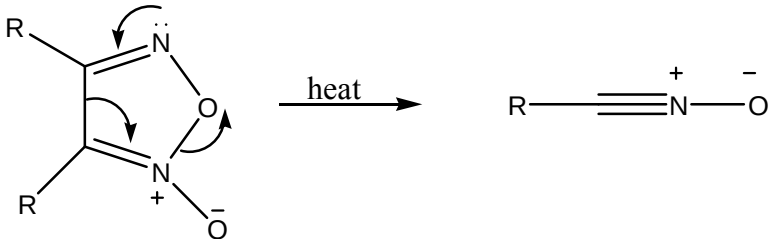


Scheme 8: Nitrile Oxide Generation Using Oxidation

Thermolysis of Furoxans[19]

Nitrile oxides can be regenerated from furoxans by thermolytic cycloreversion. This appears to be ideal for application to the nitrile oxide cycloaddition because dimerization is no longer a problem. Setbacks to this approach include;

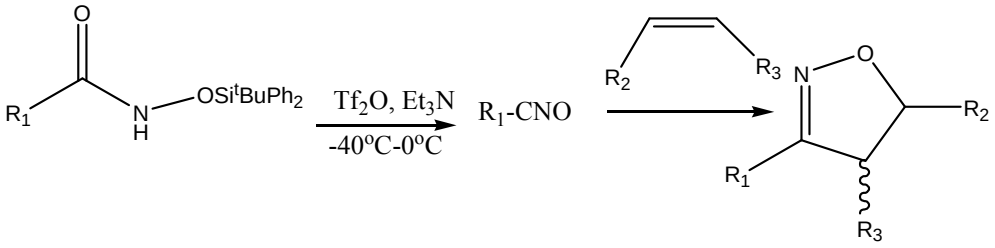
- Rearrangement of the nitrile oxide to isocyanates at high temperatures
- Limited types of functional groups



Scheme 9: Thermolysis of Furoxan

Nitrile Oxide From O-silylhydroxamates [20]

Another method that has been used to generate nitrile oxides is from enol triflate in the presence of a base at reduced temperatures.



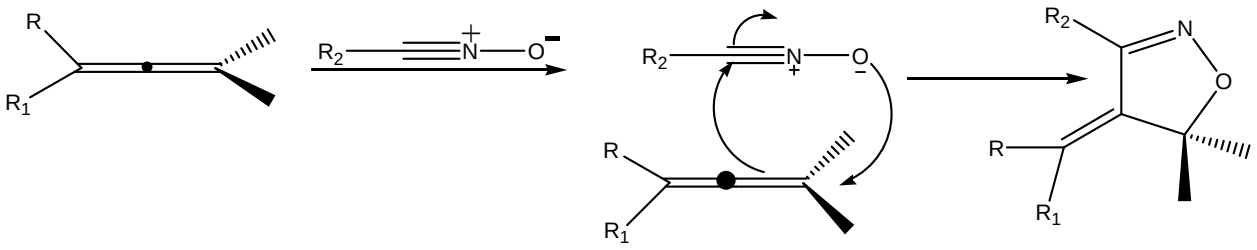
Scheme 10: Nitrile Oxides From Triflates

Methods of Nitrile Oxide Cycloaddition (NOC)

Allene-Nitrile Oxide Cycloaddition[21]

These are [3+2] cycloaddition of nitrile oxides to a pi bond(dipolarophile).This method is useful in the synthesis of cycloadducts that gives rise to site selectivity as well as regioselectivity

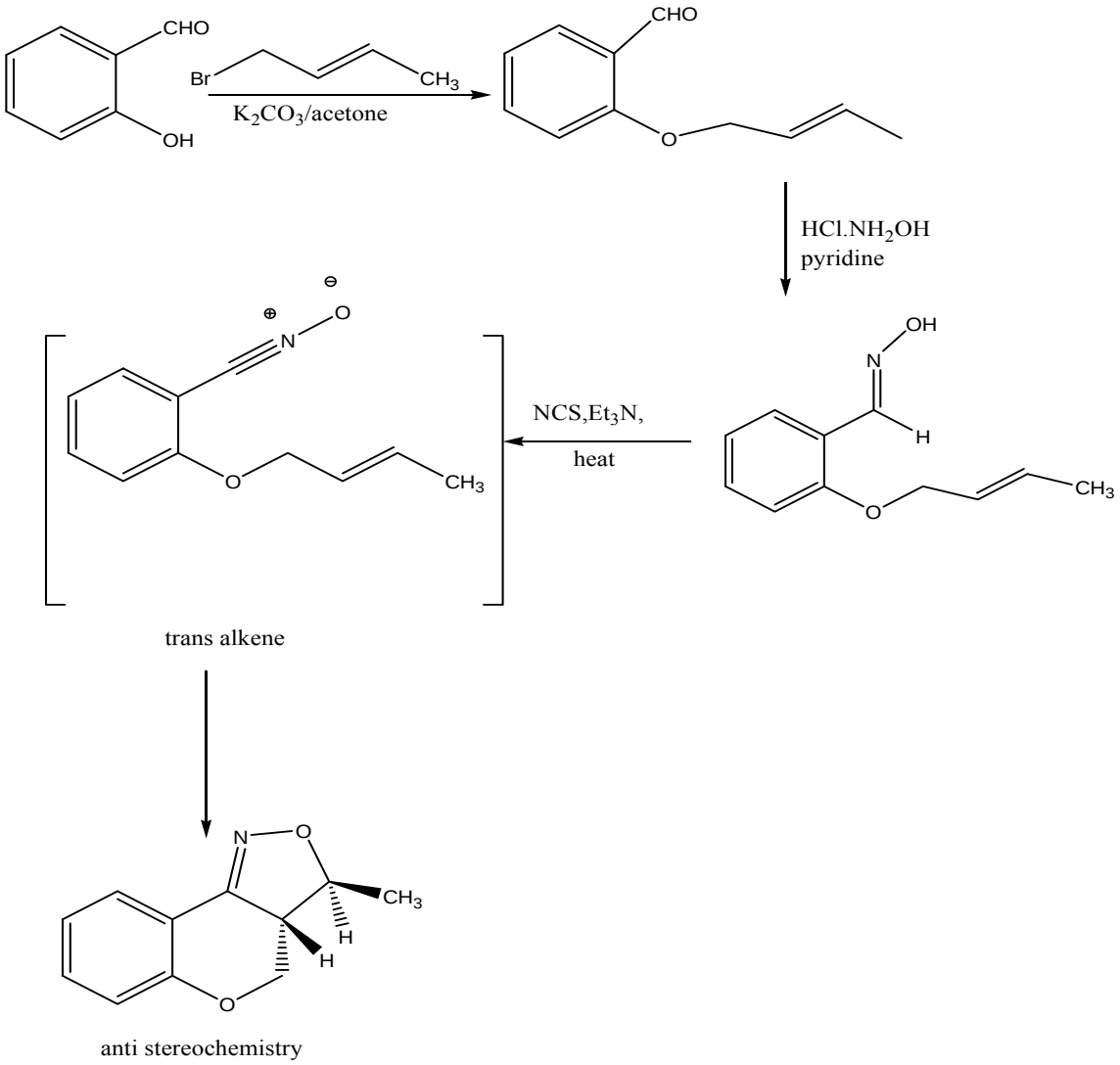
leading to a mixture of compounds both of which still contain an ethylenic bond suitable for further transformations[20]. Intramolecular and intermolecular cycloadditions of this type have been reported.



Scheme 11: Allene Nitrile Oxide Cycloaddition Reaction

Intramolecular Nitrile Oxide Cycloaddion [21]

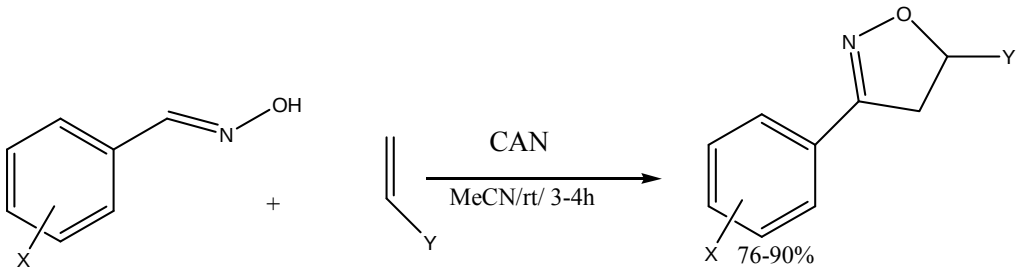
Chemoselectivity in INOC reactions has been observed in compounds with activated double bonds resulting in appreciable yields of a single product. Substituent effects on the rate and stereoselectivity of INOC reactions has been reported.



Scheme 12: Intramolecular Nitrile Oxide Cycloaddition(INOC) Reaction

Intermolecular Nitrile Oxide Cycloaddition

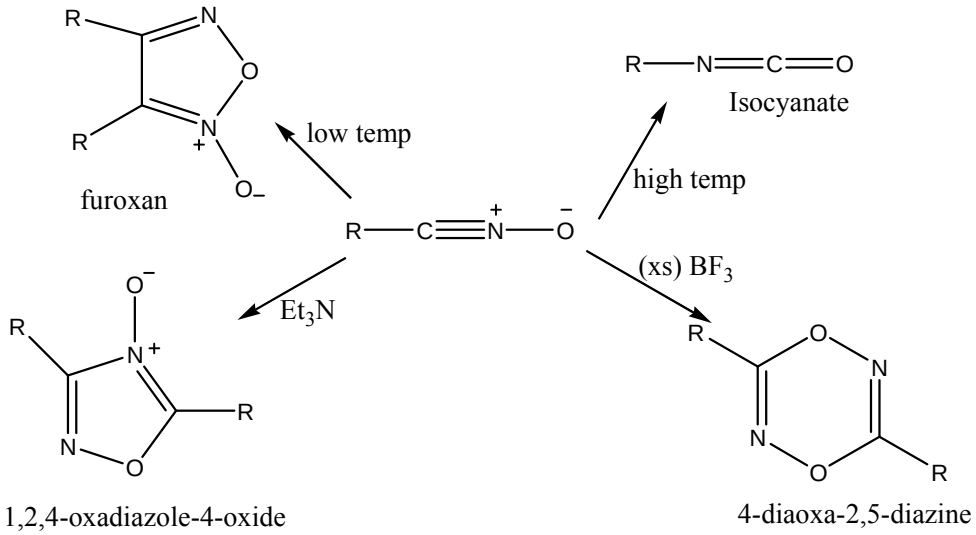
Most intermolecular nitrile oxide cycloadditions are similar to INOC reactions. HOMO-LUMO interactions and steric effects direct intermolecular nitrile oxide cycloaddition to 1-alkenes to produce 5-substituted isoxazolines. An example of this is the reaction of aldoximes (with an electron withdrawing/electron donating groups) with vinyl acetates in the presence of ceric ammonium nitrate (CAN) and acetonitrile as solvent to form isoxazolines (scheme 11) [21].



Scheme 13: Intermolecular Cycloaddition Reaction

Dimerization of Nitrile Oxide

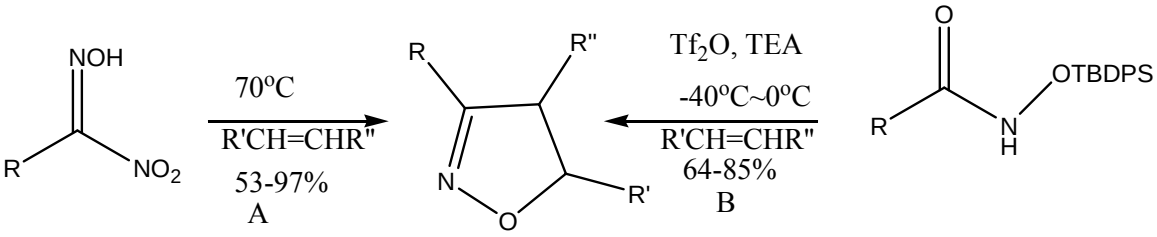
Nitrile oxides are reactive species and often dimerize on standing, to produce furoxans in the absence of a suitable dipolarophile (scheme 12)[22, 23]. Dimerization to furoxan proceeds at ambient and lower temperatures, while isomerization to isocyanates at elevated temperatures is the only reported reaction of sterically stabilized nitrile oxides. Dimerization to 1,2,4-oxadiazole 4-oxides proceeds in the presence of trimethylamine or BF_3 and to 1,4-dioxadiazines in excess BF_3 .



Scheme 14: Dimerization of Nitrile Oxides

Other Method of Isoxazoline Synthesis

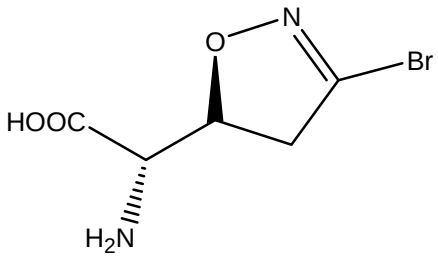
Isoxazolines can be synthesized by thermal fragmentation of nitrolic acids with alkenes (scheme13)[24,25].



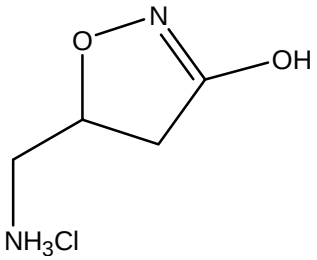
Scheme 15: Isoxazoline Synthesis Using Nitrolic Acid Fragmentation (method A) and Carreira Method (method B).

Uses of Isoxazoline in the Synthesis of Natural Products

Acivicin (AT-125) is an amino acid possessing a 3-chloroisoxazoline moiety isolated from broths of *Streptomycetes sviceus* and has been reported to display significant activity against tumors [19]. Acivicin can be synthesized either from the reaction of dibromoformaldoxime with vinylglycinates or from phosgene oxime addition to phthalimide-protected vinyl glycine. Dihydromucimol is a neurotransmitter of gamma amino butyric acid synthesized by the cycloaddition of dibromoformaldoxime to N-Boc- allylamine followed by hydrolysis of the bromide [20].



Acivicin (8)



Dihydromucimol (9)

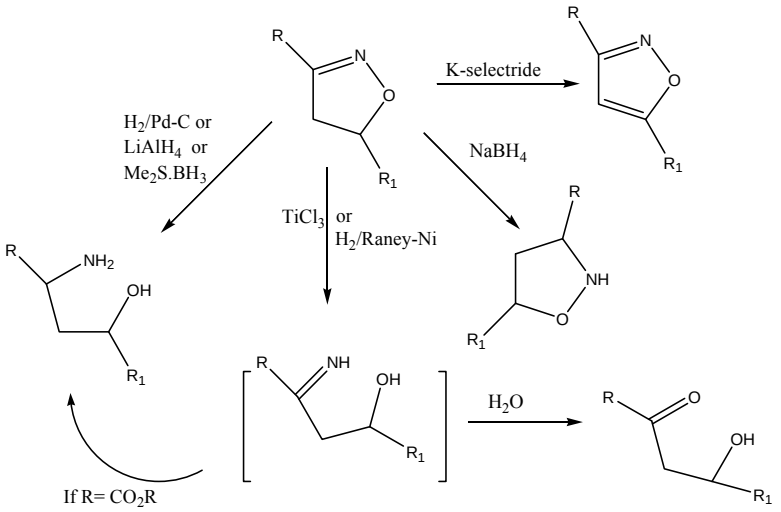
Figure 2: Natural Products Isoxazolines

Reactions of Isoxazoline

The N-O bond of nitrile oxides is weak and can easily be cleaved with a variety of reducing agents to yield different products. In protic solvents, the N-O cleavage is observed followed by the reduction of the intermediate azomethine, giving β-hydroxylamines as the principal products, while aprotic solvents give rise to β-hydroxyketones (scheme 14) [26].Conjugated isoxazolines can be converted to the corresponding alpha, beta-unsaturated hydroxyl ketones by reacting with SmI_2 and $B(OH)_3$[21].

Reduction

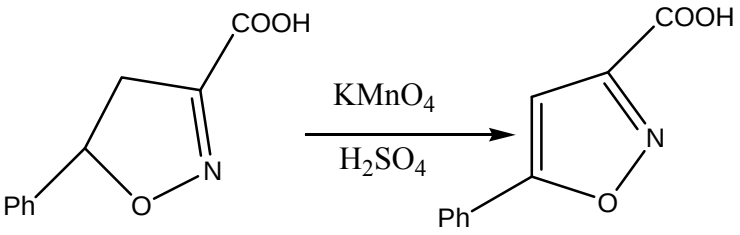
Reduction of isoxazolines can be achieved with a variety of reducing agents leading to different products. In the presence of K-selectride, isoxazolines are reduced to the aromatic isoxazoles.



Scheme 16: Reduction and Hydrolysis of Isoxazolines

Oxidation

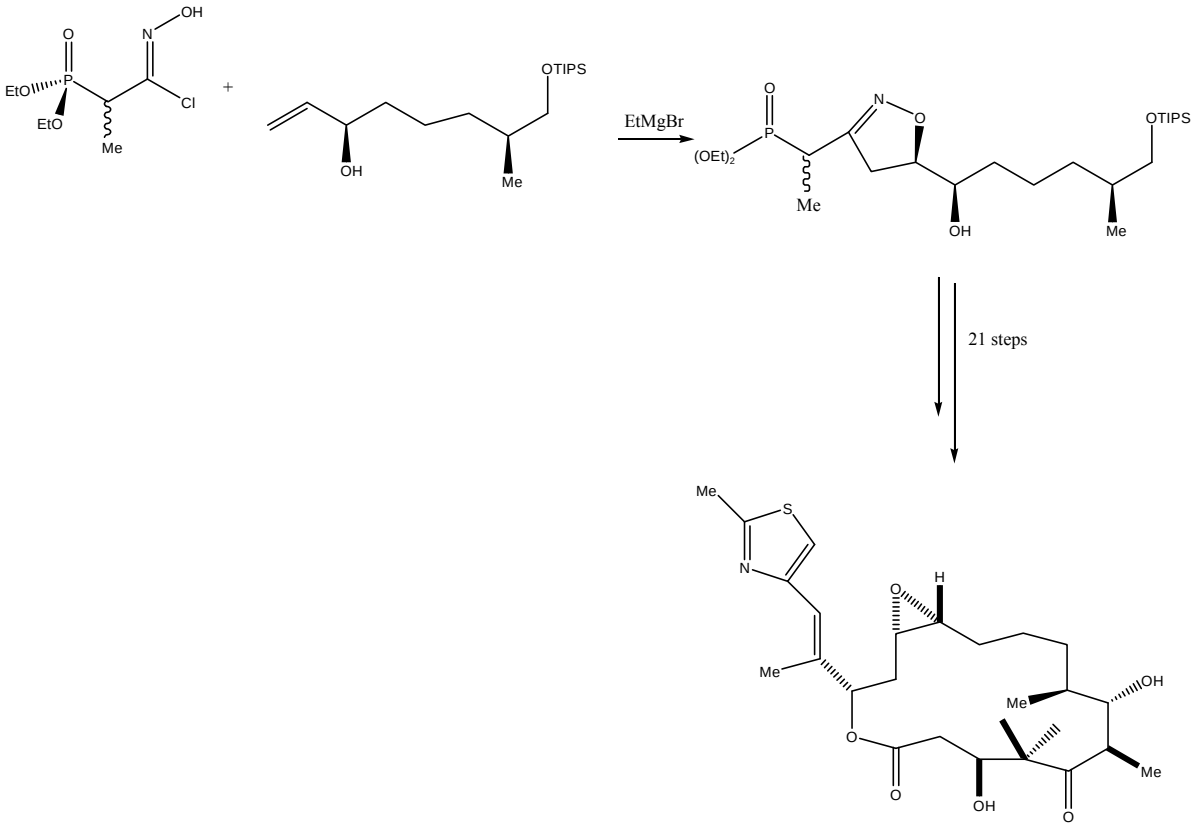
Oxidizing agents often react with isoxazoline derivatives to dehydrogenate the ring forming an aromatic isoxazole system. For example, 2-isoxazolines are easily oxidized to the corresponding isoxazole in the presence of potassium permanganate in sulfuric acid.



Scheme 17: Oxidation of Isoxazoline

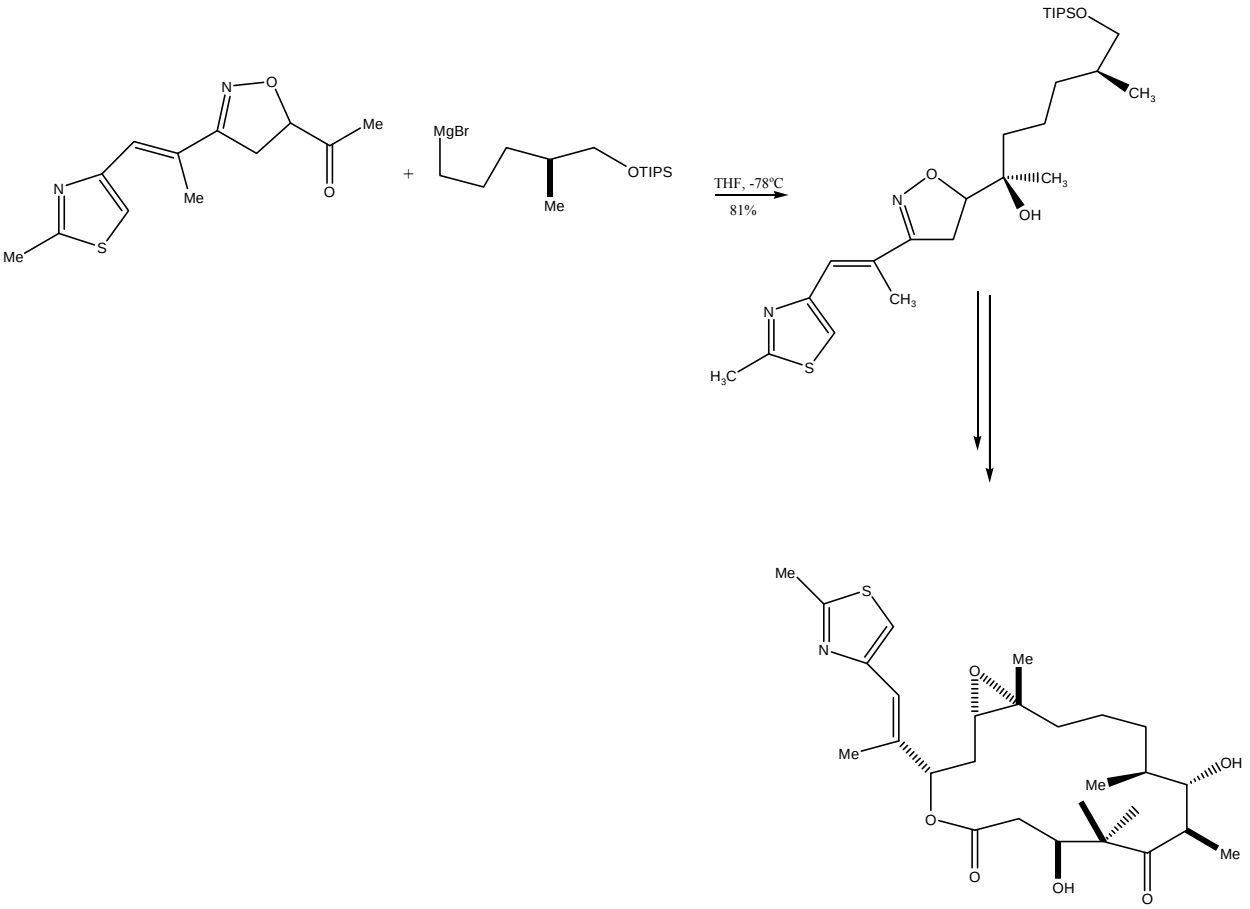
Applications of Nitrile Oxides

Nitrile oxides have been used in the total synthesis of some natural products and other substrates. For example, epothilone A was synthesized (21 steps) through the nitrile oxide cycloaddition as a diastereoselective aldol coupling reaction while epothilone B (11 steps) prepared by chemoselective Grignard coupling as a diastereoselective aldol reaction [18, 19, 27, 28].



Epothilone A, 10

Scheme 18: (continuation on next page)



Epothilone B, 11

Scheme 18: Application of Nitrile Oxides in Natural Product Synthesis

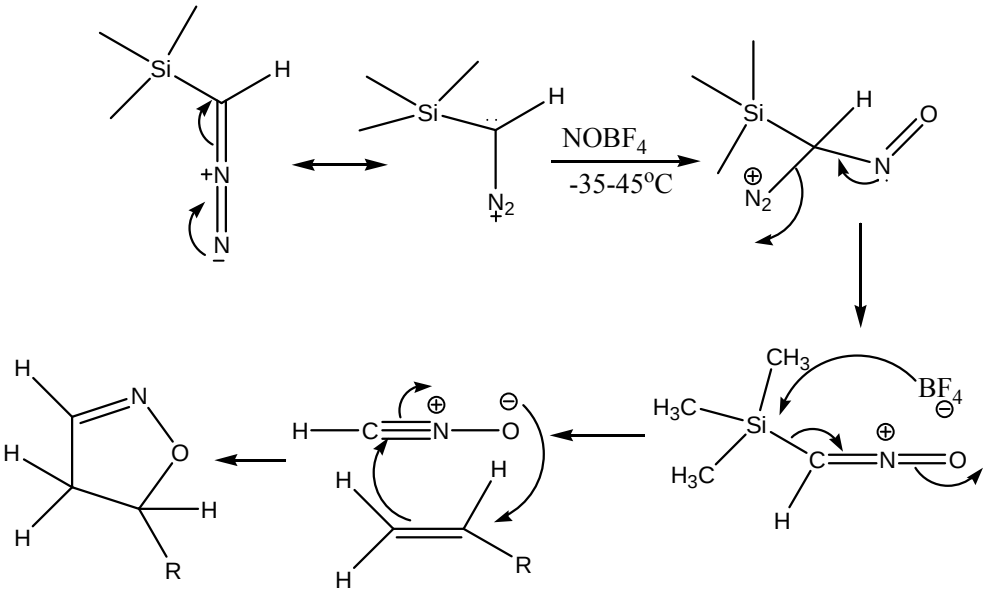
The success in the synthesis of epothilone A and B has been documented to be as a result of a hydroxyl-directed syn-selective nitrile oxide cycloaddition using phosphorus functionalized/ magnesium chelated nitrile oxides [18]. Nitrile oxides have been used in fullerene functionalization [29]. Reports have shown that nitrile oxides generated under different conditions add readily to [60] fullerene giving rise to fullerene-fused isoxazoline (isoxazolinylfullerenes). Table 1 outlines the existing methods for synthesizing 5-phenylisoxazoline. Method A is a new route that generates fulminic acid *in situ* developed in our laboratories.

Table 1: Comparison of Method A for 5-phenyl-4, 5-dihydroisoxazole synthesis with other methods

Compound	Reagents/conditions	%Yield	Ref
Method A	$NOBF_4$(1 mmol), CH_3CN, TMS-CHN_2, Styrene -41^oC	60	
Francesco et al	TMS-CNO (10 mmol), THF(10 mL), 5% H_2O	76	1
Kim and Kochi	Cyclopropylbenzene (2.86 mmol), $NOBF_4$(0.74 mmol),CH_3CN(40 mL), -40^oC	50	30
Francesco et al	TMS-CNO, H_2O, $(Me3Si)_2O$, Styrene	76	31
Khenkin and Neumann	Phenylcyclopropane, $NaNO_3$(0.3M), $H_5PV_2Mo_{10}O_{40}$/AcOH, 80^oC	59	32

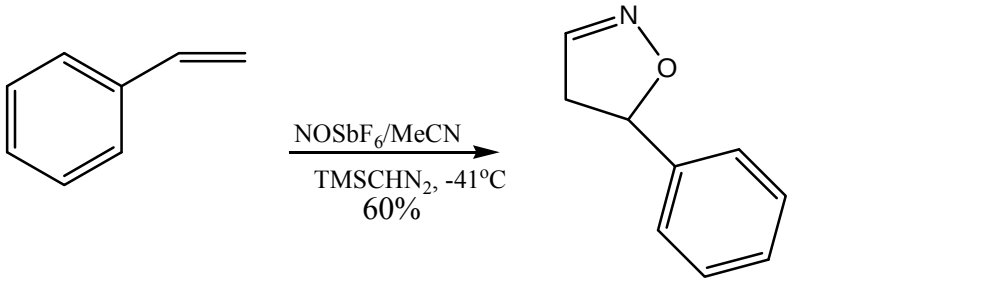
CHAPTER 2

RESULTS AND DISCUSSION



Scheme 19: Proposed Route to Isoxazolines

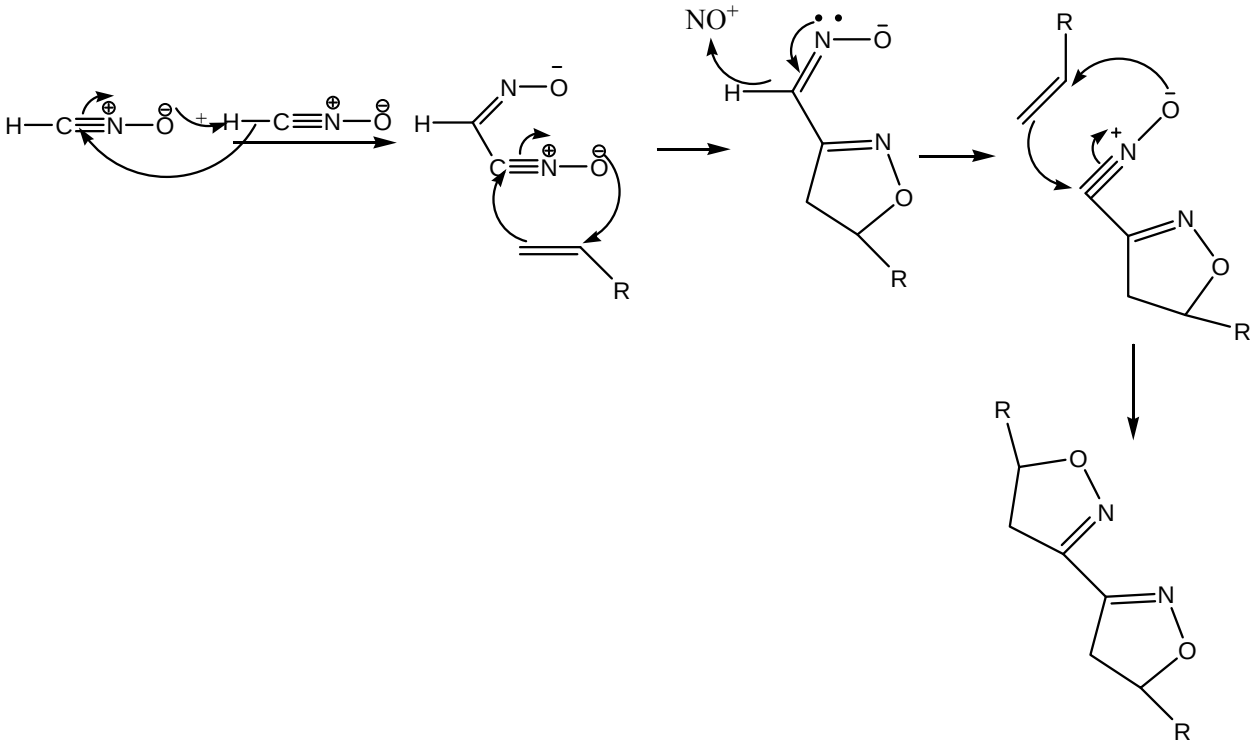
The chemistry in scheme 19 was proposed as a means for accessing fulminic acid from trimethylsilyl diazomethane.The method was expected to offer attractive advantages because other methods for fulminic acid required the use of explosive reagents. As a test substrate, styrene was selected as a dipolarophile.



5-phenyl-4,5-dihydroisoxazoline

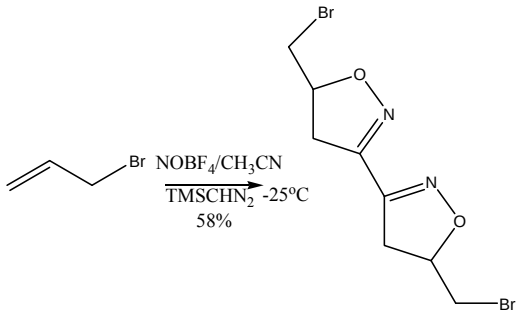
Scheme 20: Synthesis of 5-phenyl-4,5dihydroisoxazoline

In earlier publications, 5-phenyl-4,5-dihydroxyisoxazoline, 12 now prepared via [1, 30, 31,32]. Table 1 compares our route with the known methods. Although the reaction with styrene gave an appreciable yield of the fulminic acid cycloadduct, dimerization was observed in the other cases examined as shown below (scheme 18).



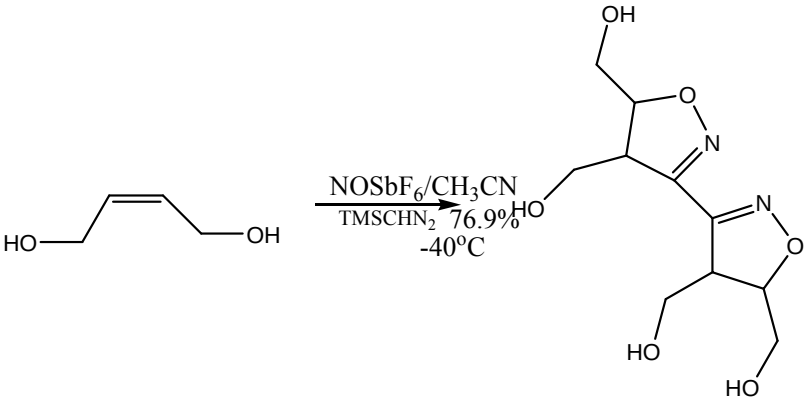
Scheme 21: Mechanism of Dimerization of Cycloadducts

For example, when allyl bromide was treated with $NOBF_4$ in acetonitrile and trimethylsilyl diazomethane, cycloadduct, 13, was obtained as pale yellow oil.



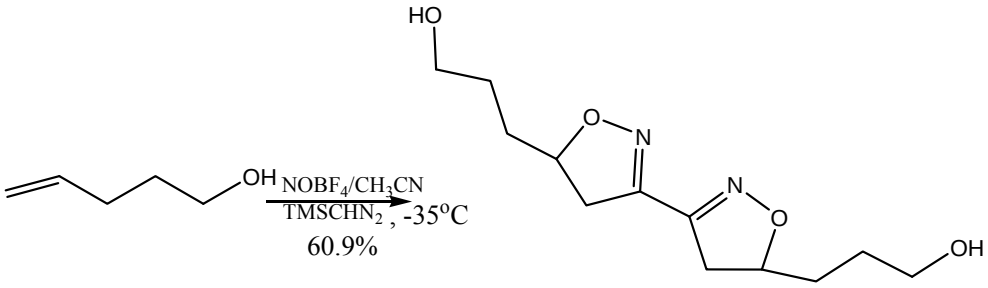
Scheme 22: Synthesis of 5,5'-Bis-bromomethyl-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl

Upon treatment of 2-Buten-1,4-diol with $NOSbF_6$ in acetonitrile and trimethylsilyl diazomethane at reduced temperatures, a pale yellow oil was obtained.



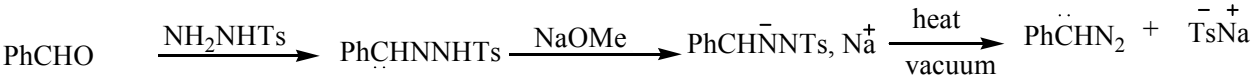
Scheme 23: Synthesis of 5,4',5',-Tris-hydromethyl-4,5,4',5'-tetrahydro-[3,3]biisoxazolyl-4-yl)-methanol.

3-[5'-(-Hydroxy-propyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propan-1-ol was synthesized by the reaction between, 4-penten-1-ol with nitrosonium tetrafluoroborate in acetonitrile, while slowly adding trimethylsilyl diazomethane to the reaction mixture.



Scheme 24: Synthesis of 3-[5'-(-Hydroxy-propyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propan-1-ol.

The precursor for the synthesis of benzocarbonitrile oxide was carried out in a three-step process. The red phenyldiazomethane is a stable compound at very low temperatures but easily decomposes to a yellow oil at temperatures > -20^{o}C. They are easily converted to benzonitrile oxide upon the addition of a solution of $NOBF_4/Me_3CN$ while nitrogen gas bubbles off immediately.



Scheme 25: Synthesis of Phenyldiazomethane

Metafulminic acid was obtained upon the addition of 2-buten-1,4-diol instead of (5-hydroxymethyl-4,5-dihydroisoxazol-4-yl) methanol which we expected. The ^{1}H NMR showed two protons. This suggested that polymerization reaction of fulminic acid as proposed by scheme 5, had occurred instead of 1,3-dipolar cycloaddition reaction.

CHAPTER 3

EXPERIMENTAL

General methods

All melting points were measured on Thomas Hoover capillary melting point apparatus. ^{1}H and ^{13}C-NMR were recorded on Oxford NMR AS 400 and are recorded in parts per million. The Splitting patterns of the ^{1}H NMR spectra were reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. FT- infrared spectra was obtained on Genesis II FTIR Matson instrument.

All commercial reagents were used unless further purification unless otherwise stated. All reactions were conducted under nitrogen atmosphere unless otherwise noted, and yields refer to isolated yields of material unless otherwise stated.

Analytical thin-layer chromatography (TLC) was conducted using Whatman K5F 150A 250 μm silica gel plates. Column chromatography was performed on ICN Silitech silica gel (63-200 mesh, 60Å).

Nomenclature of new compounds was generated using a ChemDraw Ultra program.

GC-MS analysis

The GC analysis was performed on a Shimadzu GCMS-QP2010 Plus instrument. The column (Shimadzu SHRX1-5MS) was 30 m long with 0.25 mm inside diameter. The GC-MS data were collected and processed on a Dell computer (Optiplex 755) using a GC-MS Solution software. The injection volume was 1 μL in the split mode. The carrier gas was high purity (Grade 5.0) He. The GC-MS parameters and temperature programming were as follows:

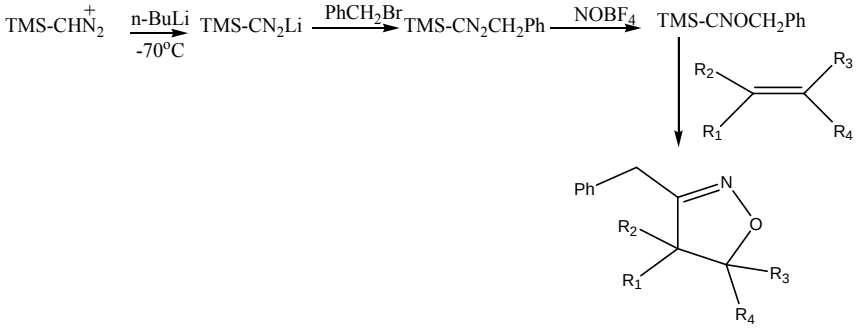
Initial column oven temperature, 50^{o}C held for 1 minute. Final column temperature was set at 250^{o}C at the rate of 20^{o}C/min, and held for 3 minutes. The injection temperature was 250^{o}C/ minute, the MS ion and interface temperature were 200^{o}C and 250^{o}C, respectively.

General experimental for method A

To a stirred solution of nitrosonium tetraborofluorate at -35°C to -45°C was added trimethylsilyl diazomethane drop wise. After stirring at this temperature for 10-20 minutes, the alkene was added slowly. The reaction was left to run overnight while following the reaction progress on TLC. Extraction was done with CH_2Cl_2/H_2O, dried with $MgSO_4$, concentrated in vacuo, and flash chromatographed over silica gel (230 X 400 mesh) after choosing the best eluting solvent.

General procedure for method B

To the corresponding weighted (1-diazo-2-phenylethyl) trimethylsilane was added (0.1168 g, 1 mmol) $NOBF_4/CH_3CN$. After stirring for 30 minutes, 114 μL of styrene was added by syringe and further stirred for 3hrs at 20°C, then extracted with ether/brine, dried, and concentrated in vacuo.



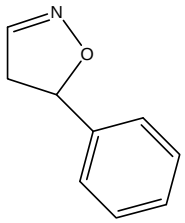
$R_1=R_2=R_3=H, R_4$ = Ph, CH_2OH, CH_2Br,

Scheme 20**:** Isoxazoline Synthesis from Trimethyl Lithium Diazomethane

General experimental for method C [34]

P-toluenesulfonylhydrazide (14.6 g, 0.07 mol) was placed in a 100 mL Erlenmeyer flask and methanol was added while swirling. To the slurry, was added pure benzaldehyde (7.50 g, 0.071 mol) and further swirled until dissolution was completed and tosylhydrazone began to crystallize. Crystallization was enhanced by placing the flask in an ice bath for 10 minutes. The white crystals

formed were collected, washed with methanol, dried between filter papers, and dried under reduced pressure to afford tosylhydrazone (18.39 g, 96.6%), mp 124-125^{o}C. The resulting crystals were treated with (51 mL, 0.051 mol) of 1.0 M solution of sodium methoxide followed by vacuum pyrolysis at 70^{o}C, to afford (5.10 g, 86.4%) red phenyldiazomethane distills out. ^{1}H NMR ($CDCL_3$ 400 MHz) δ 1.81 (br s, NH); 2.56 (s, 3H); 7.2-7.74 (aromatic); 7.87 (s, 1H). ^{13}C NMR($CDCl_3$ 100.9 MHz) δ 21.69, 127.49, 128.06, 128.76, 129.8, 130.6, 132.3, 143.2, 147.92.

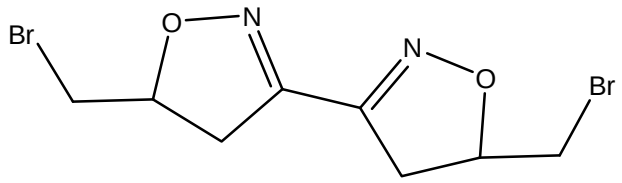


12

5-phenyl-4, 5-dihydroisoxazoline(12).

To a stirred solution of (0.1168 g, 1 mmol) nitrosonium tetrafluroborate in 1mL of acetonitrile at -41^{o}C was added (1 mmol, 0.5 mL) of a 2M solution of trimethylsilyl diazomethane in hexane dropwise. After stirring at this temperature for 10 minutes, (1 mmol, 114 μL) of styrene was added dropwise. The mixture was further stirred for an additional 20 minutes then diluted with 10 mL methylene chloride, washed with 10 mL of distilled water, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 20 g of florisil and eluted with hexane/ethyl acetate, 5:1 to afford (0.08 g, 60%) yellow oil.

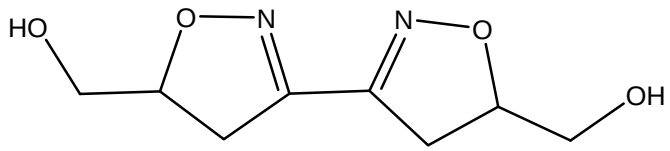
^{1}H NMR ($CDCl_3$, 400MHz): δ 3.13(dd, J = 8.8 Hz, 1H); 3.52(dd, *J* = 6.2 Hz, 11.36 Hz, 1H); 5.76(dd, *J* = 9.16 Hz, 11.36 Hz, 1H), 7.28-7.35 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.7 MHz); δ 29.8, 85.56, 125.85, 128.68, 129.08, 139.59, 157.95; mass spectrum, m/z 120



13

5,5'-Bisbromoethyl-4,5,4',5'tetrahydro-[3,3']biisoxazolyl(13).

To a stirred solution of (0.1168 g, 1 mmol) $NOBF_4$ in 1mL of CH_3CN was added (0.121g, 87μL) of allyl bromide and the resulting mixture was cooled to 0°C. After stirring for 15 minutes, (0.5 mL, 1 mmol) of a 2M solution of trimethylsilyl diazomethane in hexane was added dropwise over a 10 mins period. The reaction was stirred for 2 days, diluted with 10 mL of CH_2Cl_2, washed with 10 mL of H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with 20% ethylacetate/hexane) to afford (177 mg, 58%) pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.82 (d, 2H), 3.5-3.82(dd, 2H), 5.0 (br m, 1H). ^{13}C NMR ($CDCl_3$, 100.7 MHz); mass spectrum, m/z 326

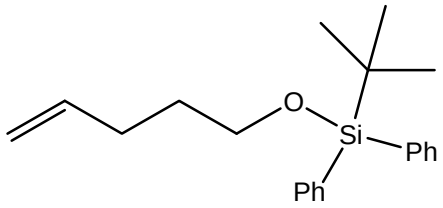


14

(5,4',5'-Hydroxymethyl-4,5,4',5'-tetra hydro-[3,3']biisoxazolyl-5-yl)-methanol (14)

To a cooled solution of (0.1168 g, 1 mmol, 1eq) $NOBF_4$ in 1ml of CH_3CN at -25°C was added (0.5mL, 1mmol, 1eq) of 2M solution of TMS-diazomethane and the reaction stirred for 10 min. Allyl alcohol (0.058 g, 1mmol, 68.2 μL) was added slowly over 30 minutes. The mixture was stirred

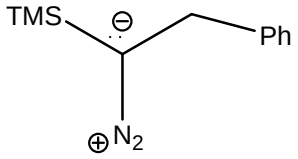
overnight diluted with 10 mL of CH_2Cl_2, washed with 10 mL of H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of florisil (eluted with hexane/ethylacetate, 1:3) to afford (108 mg, 54%) of yellow oil. ^{1}H NMR ($CDCl_3$ 400 MHz). δ 2.11 (d, 2H); 2.49 (t, OH); 3.06(dd 1H), 3.83(dd, 1H); 4.86 (br m, 1H). ^{13}C NMR ($CDCl_3$, 100.7 MHz);



15

1-(tert-butyldiphenylsiloxy) pent-4-ene (15)[35**]**

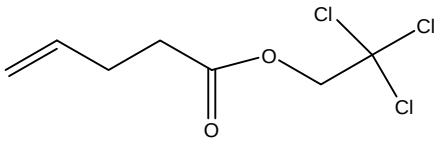
To a mixture of 4-penten-1-ol (300 mg, 3.4 mmol) and imidazole (694 mg, 10.21 mmol) in (5 mL) CH_2Cl_2 at 0^{o}C under nitrogen was added tert-butyldiphenylsilylchloride (1.4 g, 5.1 mmol). After 4 hrs at room temperature, the reaction mixture was filtered and the cake rinsed with 10 ml CH_2Cl_2.The filtrate was concentrated in vacuo then flashed chromatograhed over silica gel and eluted with 5% ethylacetate/hexane to afford **(**1.113 g, 98%) silyl ether and white crystals. ^{1}H NMR ($CDCl_3$ 400 MHz): δ 1.05 (s, 9H); 1.64(t, 2H), 2.12(q, 2H); 5.00 (m, 2H); 5.83 (m, 1H); 7.36 (m, 6H), 7.66 (m, 4H). ^{13}C NMR ($CDCl_3$); δ 19.31, 26.94, 30.14, 31.9, 63.36114.59, 127.67, 129.6, 134.15, 135.66, 138.65. The ^{1}H NMR ($CDCl_3$ 400 MHz): δ 1.04 (t, *J* = 2.2 Hz, 9H); 7.39 (d, *J* = 1.48 Hz, 2H); 7.71 (t, *J* = 1.48 Hz, 6.2 Hz, 1H).



16

(1-diazo-2-phenylethyl)trimethylsilane (16) [36]

To a stirred solution of $TMSCHN_2$ (6 mmol) in hexane and n-BuLi (6 mmol) 1.6M in hexane in 25 mL of THF at -70°C under nitrogen was added dropwise a solution of (5mmol) $PhCH_2Br$ in 5 mL of THF and mixture was allowed to react for 8 hrs. The mixture was diluted with10 mL ether, washed with 10 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 25 g of silica gel (eluted with 5:1 hexane/ethylacetate) to afford 0.37g, 63.2% yield, R_f = 0.57. ^{1}H NMR ($CDCl_3$ 400MHz) δ 0.09(s, 9H), 4.47(s, 2H), and at 7.33-7.38(m, 5H).

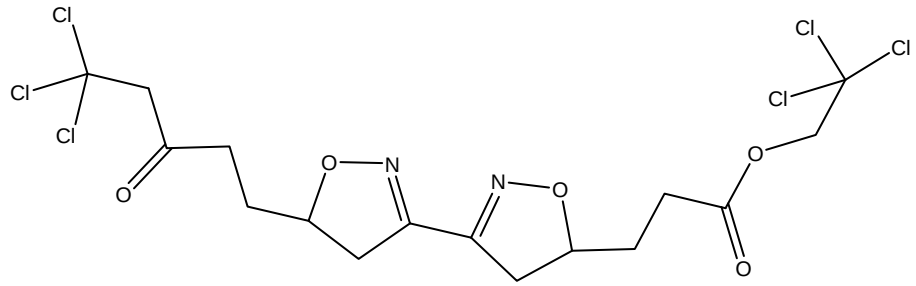


17

2, 2, 2-trichloroethyl-4-pentenoate (17)

To a solution of 4-pentenoic acid (4.008 g, 40 mmol), and 2 drops of catalytic DMF under nitrogen. Oxalyl chloride (5.0007 g, 3.44 ml) was added. The resulting solution was stirred for 15 minutes. To the mixture was added 2,2,2-trichloroethanol(3.86 mL, 5.976 g, 10 mmol) and triethylamine (3.78 g, 5.25 mL, 40 mmol) and the reaction mixture stirred for 1hr. The solid (cake) was dissolved in 10 mL of CH_2Cl_2 and 10 mL of brine. The filtrate was dried ($MgSO_4$), concentrated, and chromatographed over 250 g of silica gel (eluted with 20% ethylacetate:hexane) to afford colorless oil(7.53g, 96.6% yield). ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.44(dd, *J* = 6.24 Hz, 2H) 2.59(dd, *J* =

7.72 Hz, 2H), 4.74(s, 2H), 5.11(dd, *J* = 10.24 Hz, 27.12 Hz, 2H), 5.84 (br m, *J* = 6.96 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100.9) δ 28.67, 33.27, 74.03, 116.04, 136.16, 171.48.



18

3-[5'-(5,5,5-Trichroro-3-oxo-pentyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propionic acid 2,2,2-trichloro-ethyl ester (18)

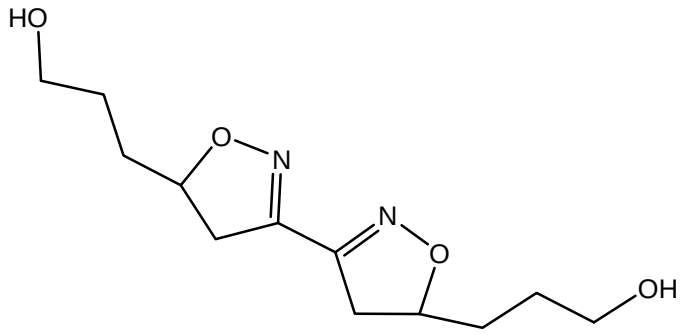
To a solution (0.265 g, 1 mmol) of $NOSbF_4$ in 1 mL of CH_3CN was added of a 2M solution 0.5 mL of $TMSCHN_2$ in hexane and the mixture was cooled to -35^{o}C. To the reaction mixture was added (0.216 g, 1 mmol) of 2, 2, 2-trichloroethyl-4-pentenoate and the resulting solution was stirred overnight. The reaction was diluted with 10 mL of CH_2Cl_2, washed with 10 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (eluted with hexane:ethylacetate) to afford a colorless oil (157 mg, 60.9 %). ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.04 (q, *J* = 2.16 Hz, 2H); 2.66 (t, *J* = 3.28 Hz, 1.84 Hz, 2H); 3.02 (dd, *J* = 10.6 Hz, 1H); 3.37 (dd, *J* = 10.6 Hz, 1H); 4.75 (s, 2H); 4.83 (br m, *J* = 30.4 Hz, 1H). ^{13}C NMR δ 29.84, 30.11, 38.81, 74.15, 81.26, 95.25, 151.12, 171.15

CH_2=$CHCH_2CH_2CH_2OTBDMS$

19

Tert-butyldimethylsiloxyl pent-1-ene (19) [37]

Sodium hydride (0.12 g, 1 mmol) was washed with three 5 mL of hexane and suspended in 50 mL of anhydrous THF. Hexane (0.4306 g, 5 mmol) was added and the reaction was stirred for 45 minutes at room temperature. Tert-butyl dimethylsilyl chloride (0.753 g, 5 mmol) in 5 mL THF was added and mixture stirred for further 45 minutes. The mixture was diluted with 10% K_2CO_3 (100 mL), followed by 100 mL of brine, 100 mL of ether, dried with ($MgSO_4$), and concentrated in vacuo to afford colorless oil. Purification of the resulting oil was accomplished by chromatography over 50 g of silica gel (eluted with 20% ethylacetate:hexane) to afford (0.84 g, 84 %) colorless oil. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 0.084(s, 6H); 0.89 (s, 9H); 1.58(m, 2H); 2.1(m, *J* = 7.32 Hz, 2H); 3.6(t, *J* = 6.2 Hz, 6.6 Hz, 2H); 4.93-5.03(dd, *J* = 30.04 Hz, 9.88 Hz, 2H); 5.77-5.82(m, *J* = 6.96 Hz, 9.88 Hz, 1H).

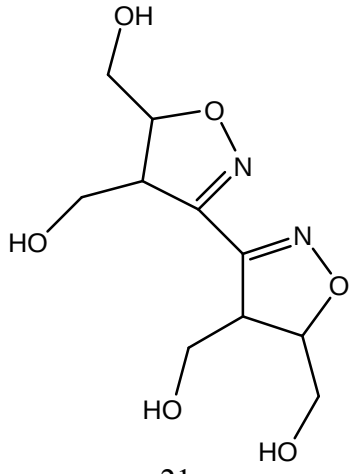


20

3-[5'-(-Hydroxy-propyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propan-1-ol (20)

To a (0.116 g, 1 mmol) of $NOBF_4$ in 1 mL of CH_3CN solution was added (0.5 mL) of 2M solution of $TMSCHN_2$ in hexane dropwise. At -55^{o}C, (0.086 g, 1 mmol) of 2-penten-1-ol was added slowly. The resulting mixture was diluted with 10 mL of CH_2Cl_2 and washed with 10 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 40 g of silica gel (eluted with hexane:ethylacetate, 3:1) to afford a pale yellow oil (100 mg, 76.9%). ^{1}H NMR ($CDCl_3$

400 MHz) δ 1.56 (t, 2H); 1.68 (m, 2H); 2.12 (br t, OH); 3.54 (m, 2H); 3.66-3.84 (dd, 2H); 5.04 (m, 1H); 5.8 (br m, 1H). ^{13}C NMR($CDCl_3$, 100.9 MHz) δ 25.93, 27.23, 29.16, 66.15, 67.31, 68.79, 78.98, 104.44, 114.8, 114.89, 138.30, 138.40; mass spectrum, m/z 259



21

5,4',5',-Tris-hydromethyl-4,5,4, '5'-tetrahydro-[3,3]biisoxazolyl-4-yl)-methanol (21)

To a solution of (265 mg, 1 mmol) of $NOSbF_6$ in 1 mL of CH_3CN at -40^oC was added 0.5 mL of 2M solution of TMS-diazomethane in hexane and (88 mg , 1 mmol) 2-Buten-1,4-diol. The mixture was stirred as it gradually warmed to room temperature. The mixture was diluted 10 mL of methylene chloride and washed with 10 mL of brine, dried ($MgSO_4$), and concentrated at reduced pressure. The pure product was obtained through chromatography of the resulting residue (eluted with hexane:ethylacetate, 3:1) to afford (100 mg, 76.9%) colorless oil. ^1H NMR ($CDCl_3$, 400 MHz); δ 0.8 (m, 1H); 1.22 (m, J = 2.92 Hz, 4H); 1.99 (t, J = 2.92 Hz, 4.04 Hz, OH); 4.07 (t, 1H, J = 4.00) ^{13}C NMR ($CDCl_3$, 100.9 MHz) δ 14.2, 21.02, 3.62, 60.41, 171.16; mass spectrum, m/z 259

CHAPTER 4

CONCLUSION

Both methods have proven to work well with terminal and mono-substituted alkenes only. Several attempts were carried out with substituted alkenes, alkynes have not been successful. Reasons for the observed discrepancy are yet to be established. It is worth mentioning that the low yields may be associated to the sticky nature of the compounds to grease and the incomplete dissolution of $NOBF_4$ in acetonotrile. Cycloaddition with $NOSbF_6$ has proven to be a better method. To some extent, the objectives of the study were attained.

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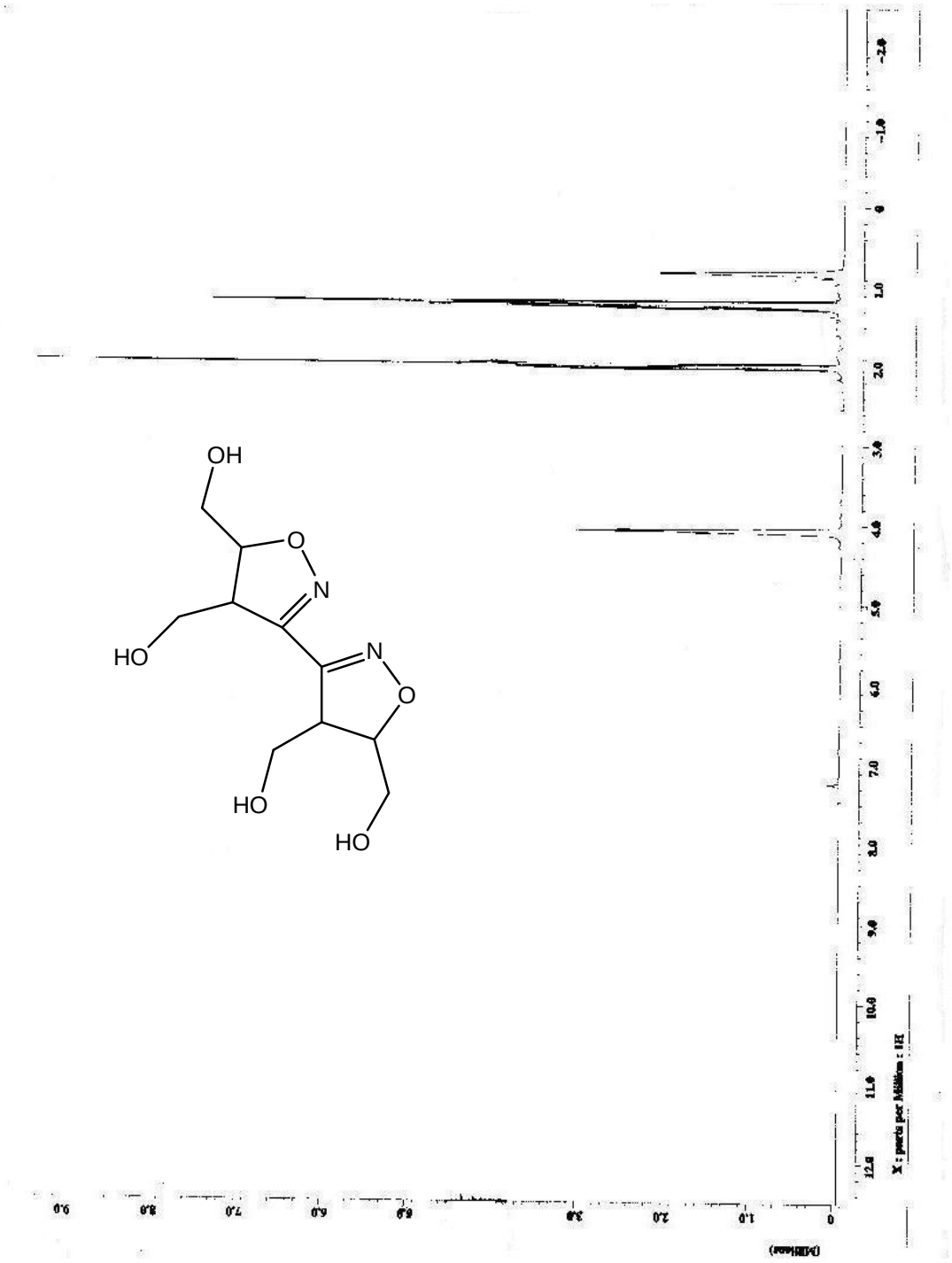
APPENDICES

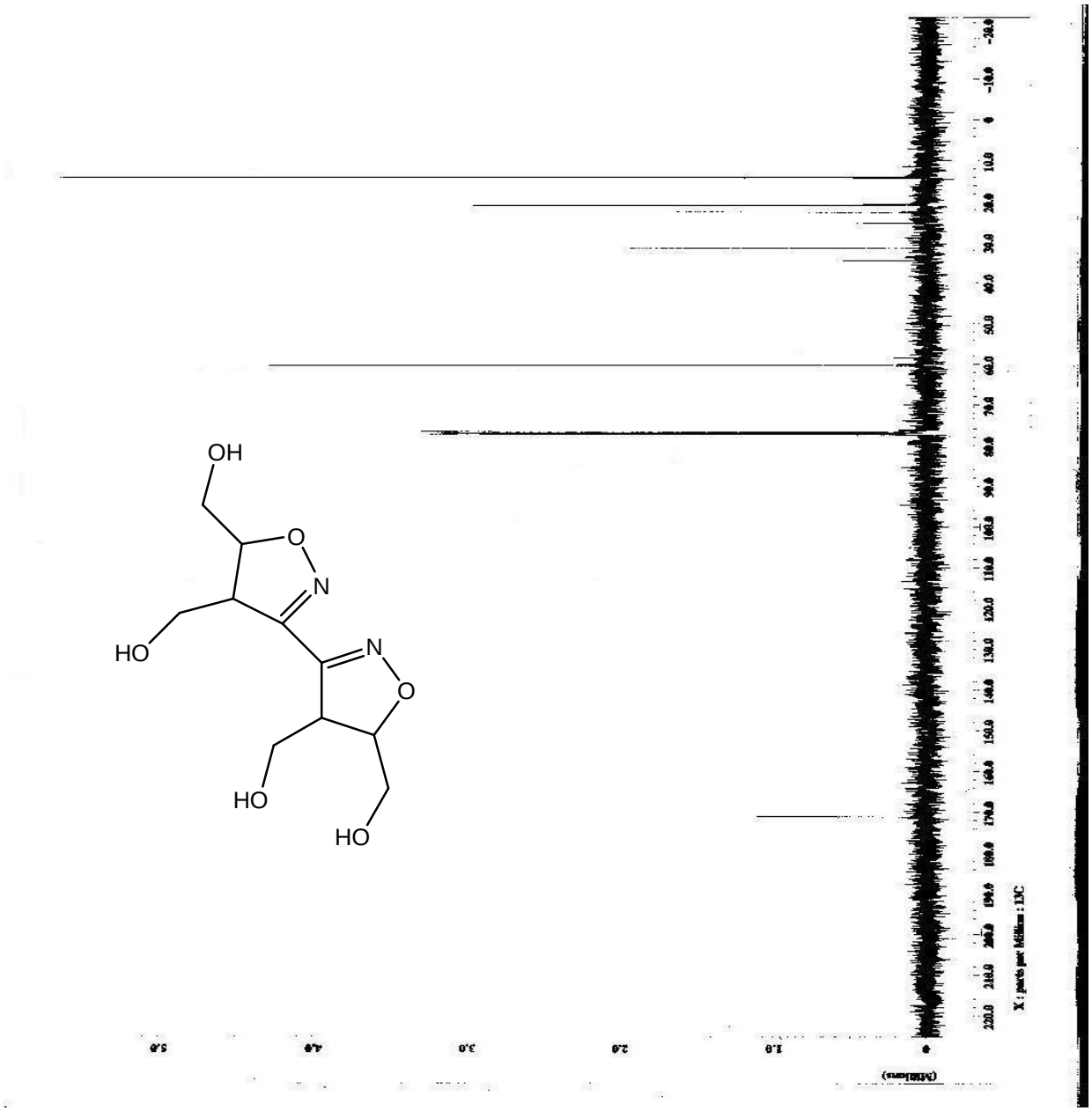
APPENDIX A

^{1}H-NMR for 5,4',5',-Tris-hydromethyl-4,5,4,'5''-tetrahydro-[3,3]biisoxazolyl-4-yl)- methanol



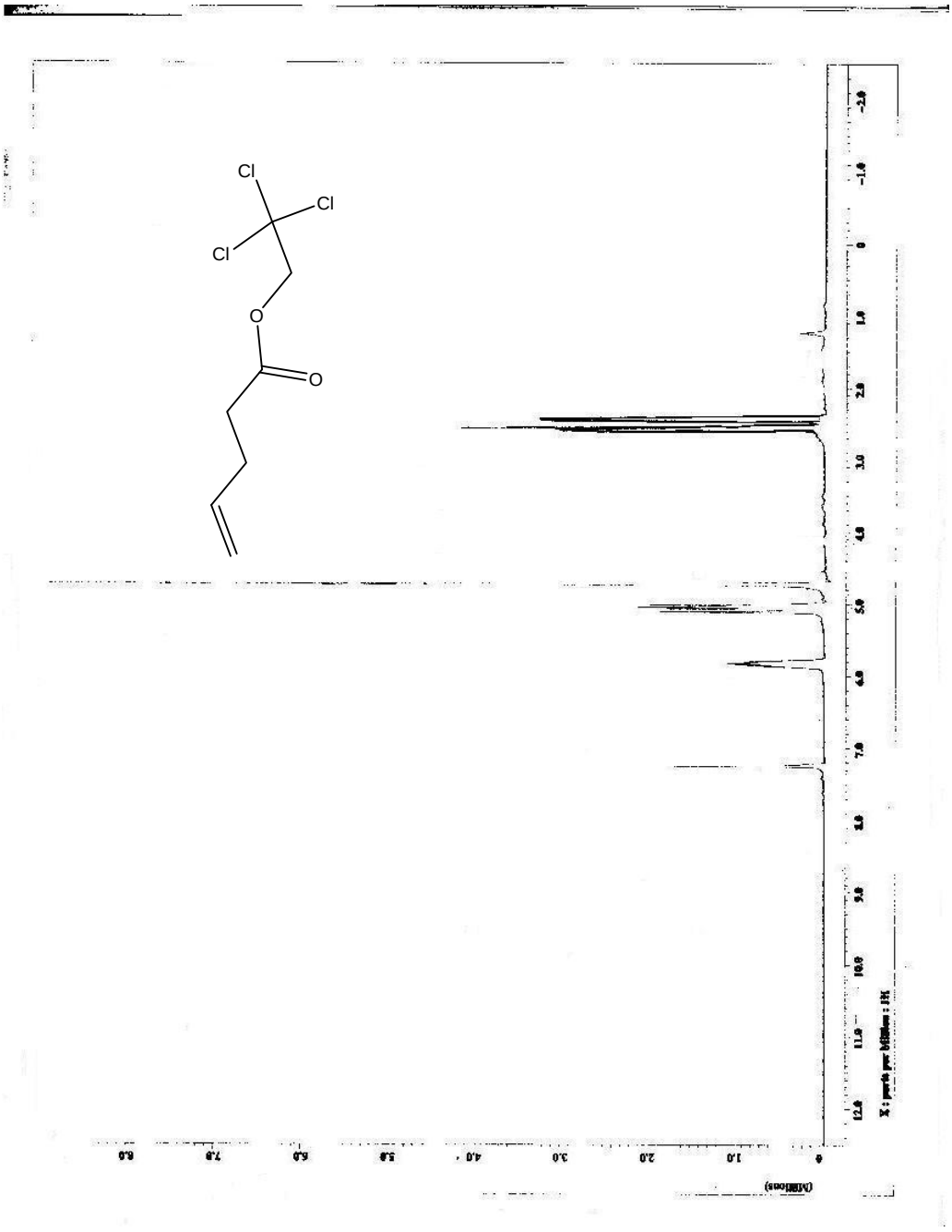
APPENDIX B

^{13}C-NMR for 5,4',5',-Tris-hydromethyl-4,5,4,'5'-tetrahydro-[3,3]biisoxazolyl-4-yl)- methanol



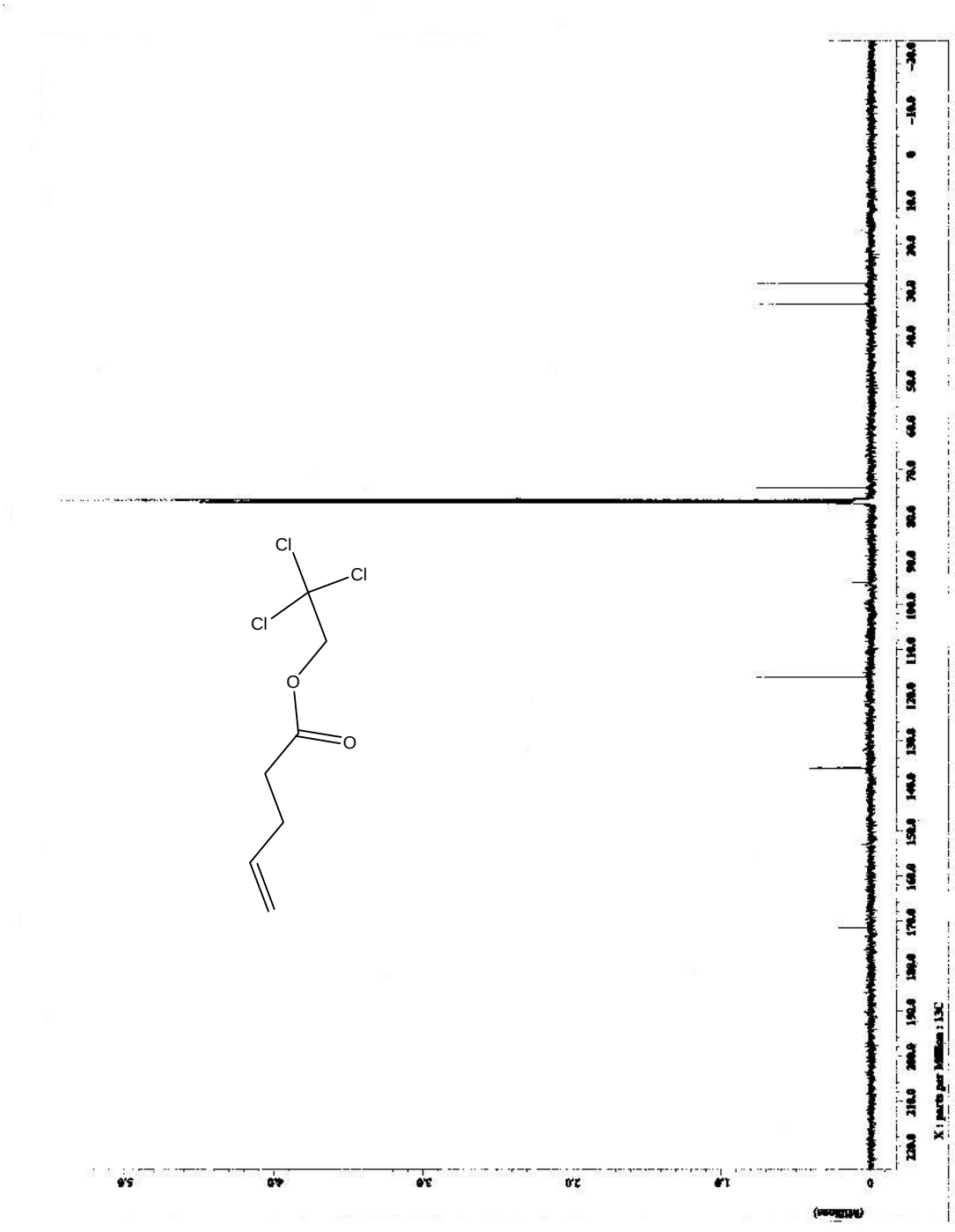
APPENDIX C

^{1}H-NMR for 2,2,2-trichloroethyl-4-pentanoate



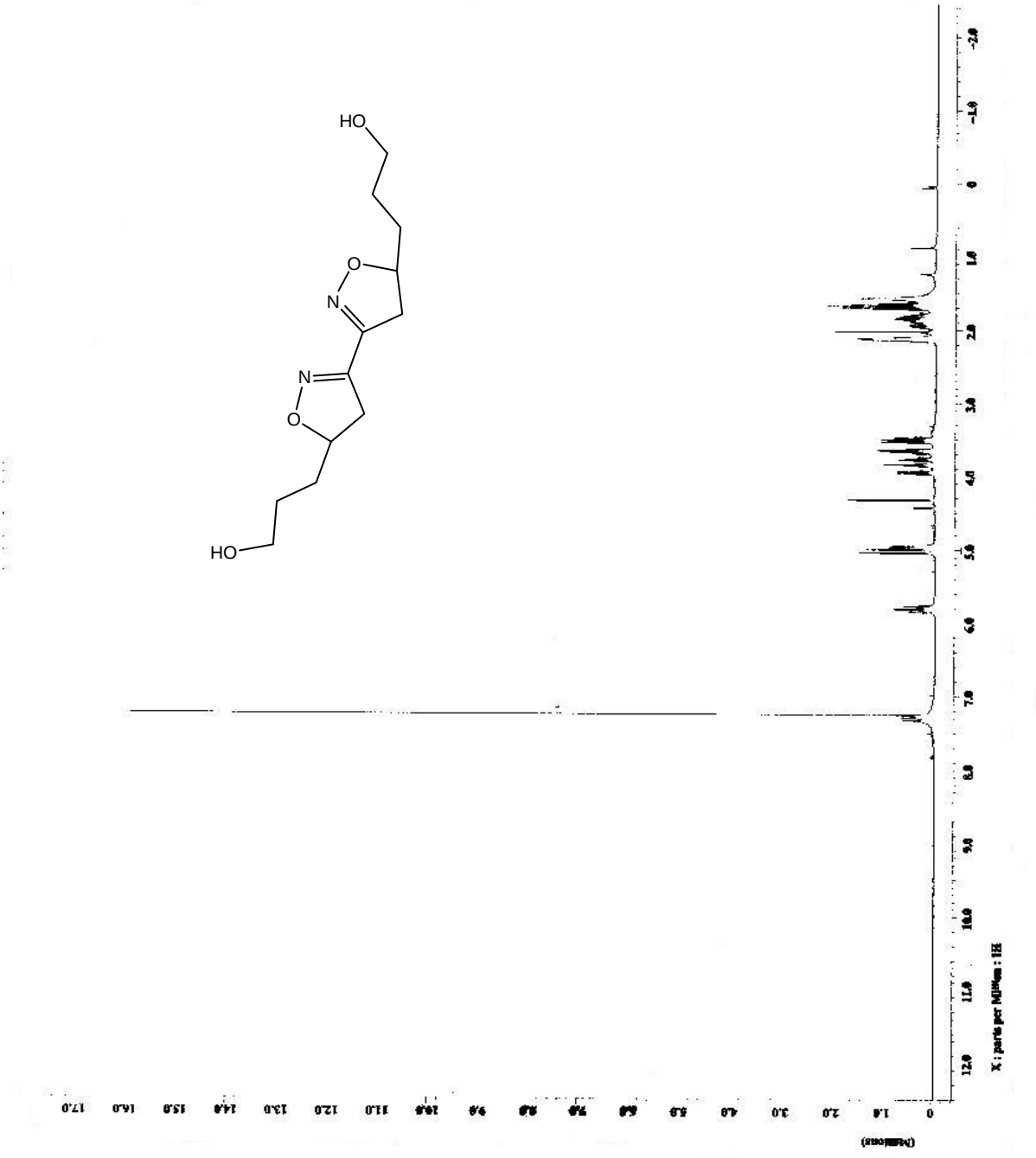
APPENDIX D

^{13}C-NMR for 2,2,2-trichloroethyl-4-pentanoate



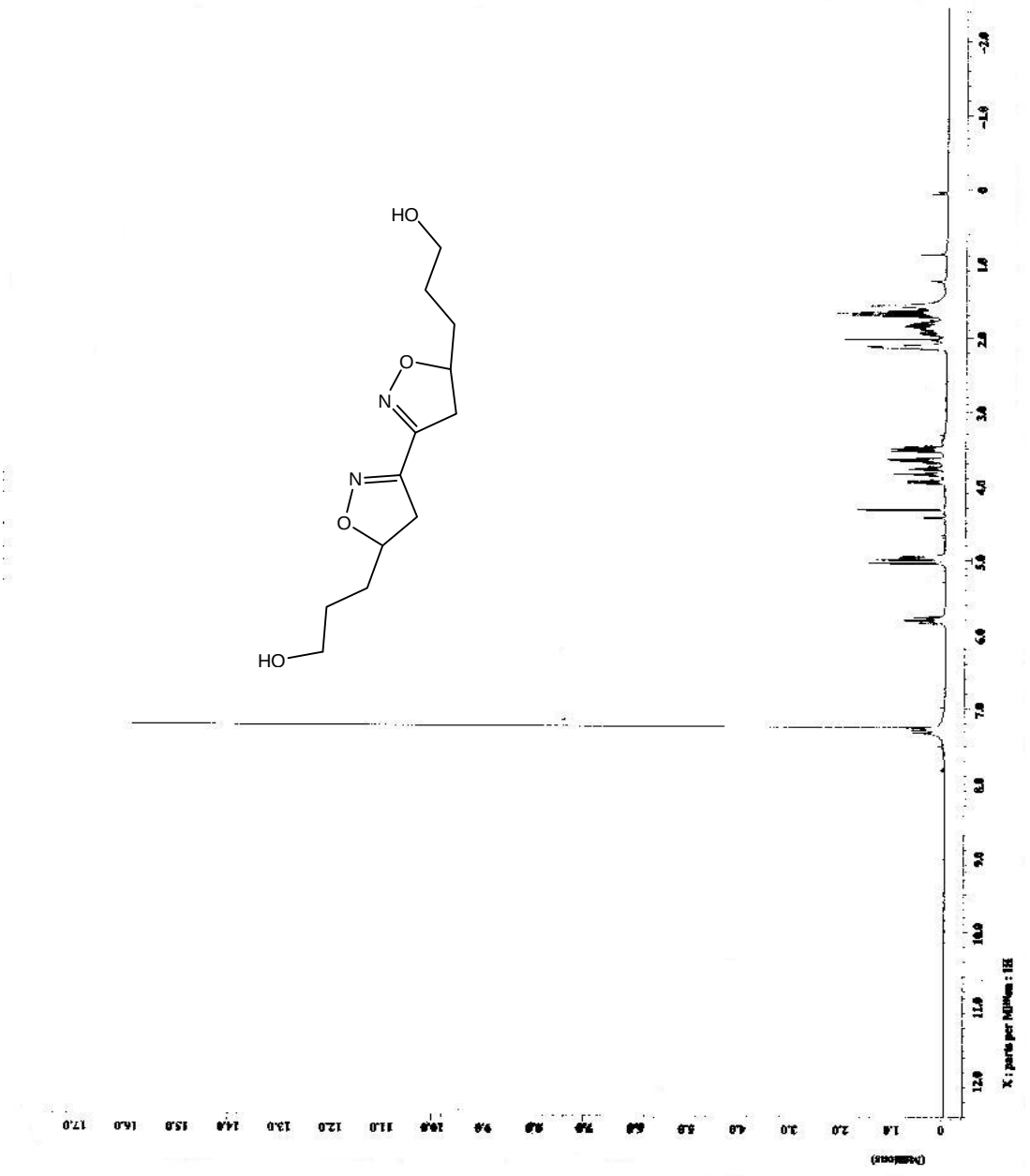
APPENDIX E

^{1}H-NMR for 3-[5'-(-Hydroxy-propyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propan-1- ol



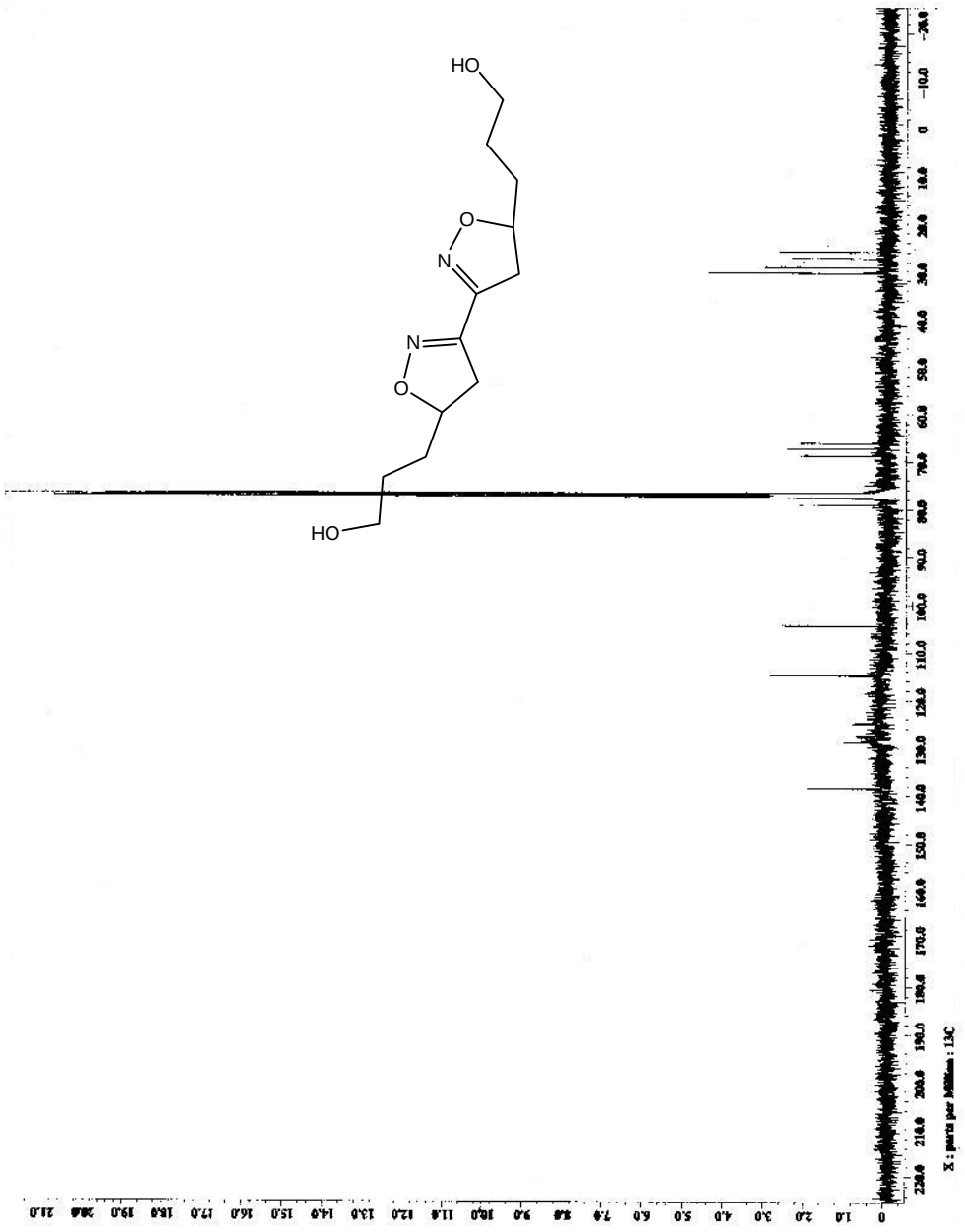
APPENDIX F

^{1}H NMR for 3-[5'-(-Hydroxy-propyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propan-1- ol



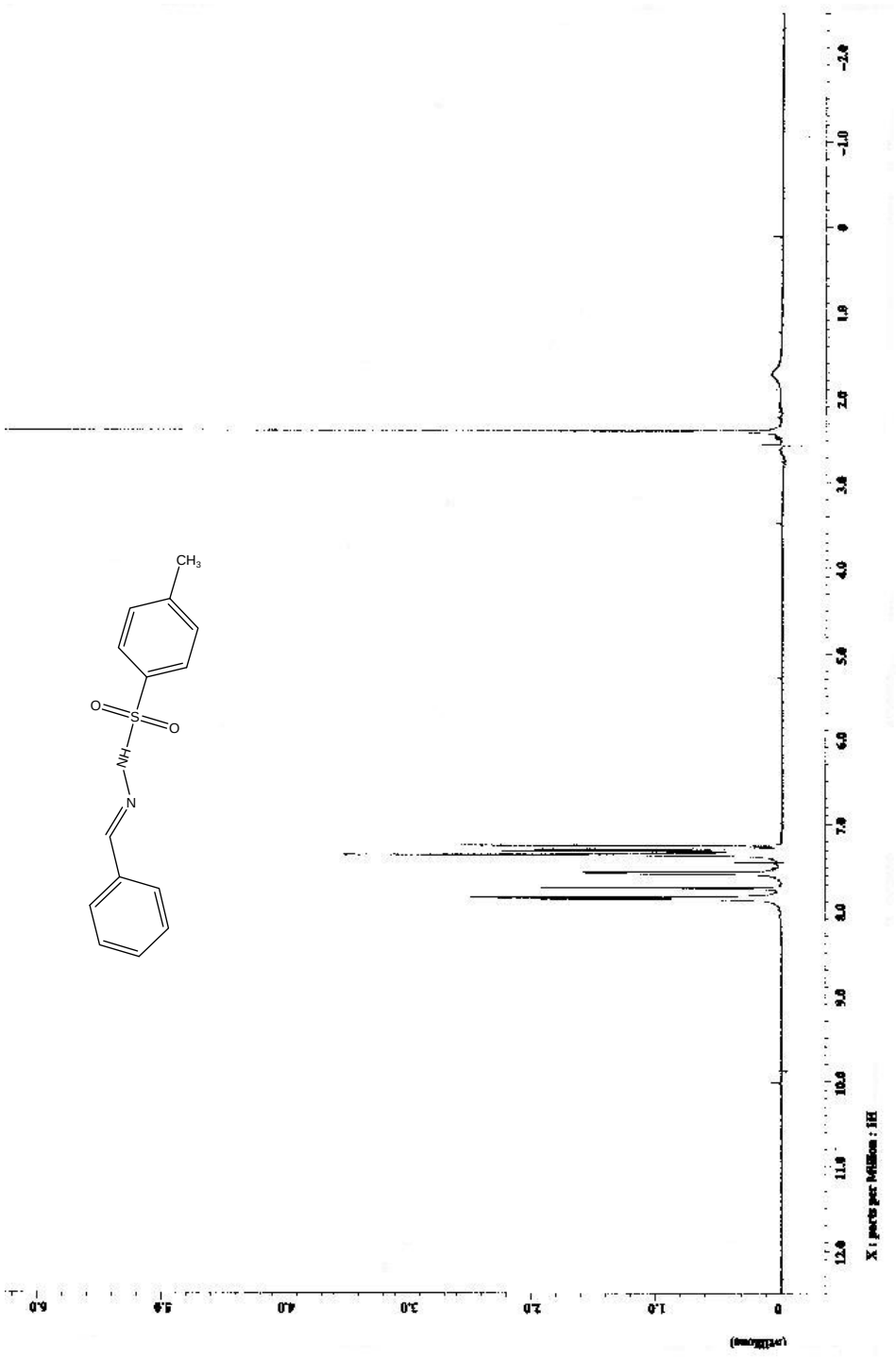
APPENDIX G

^{13}C-NMR for 3-[5'-(-Hydroxy-propyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propan-1- ol



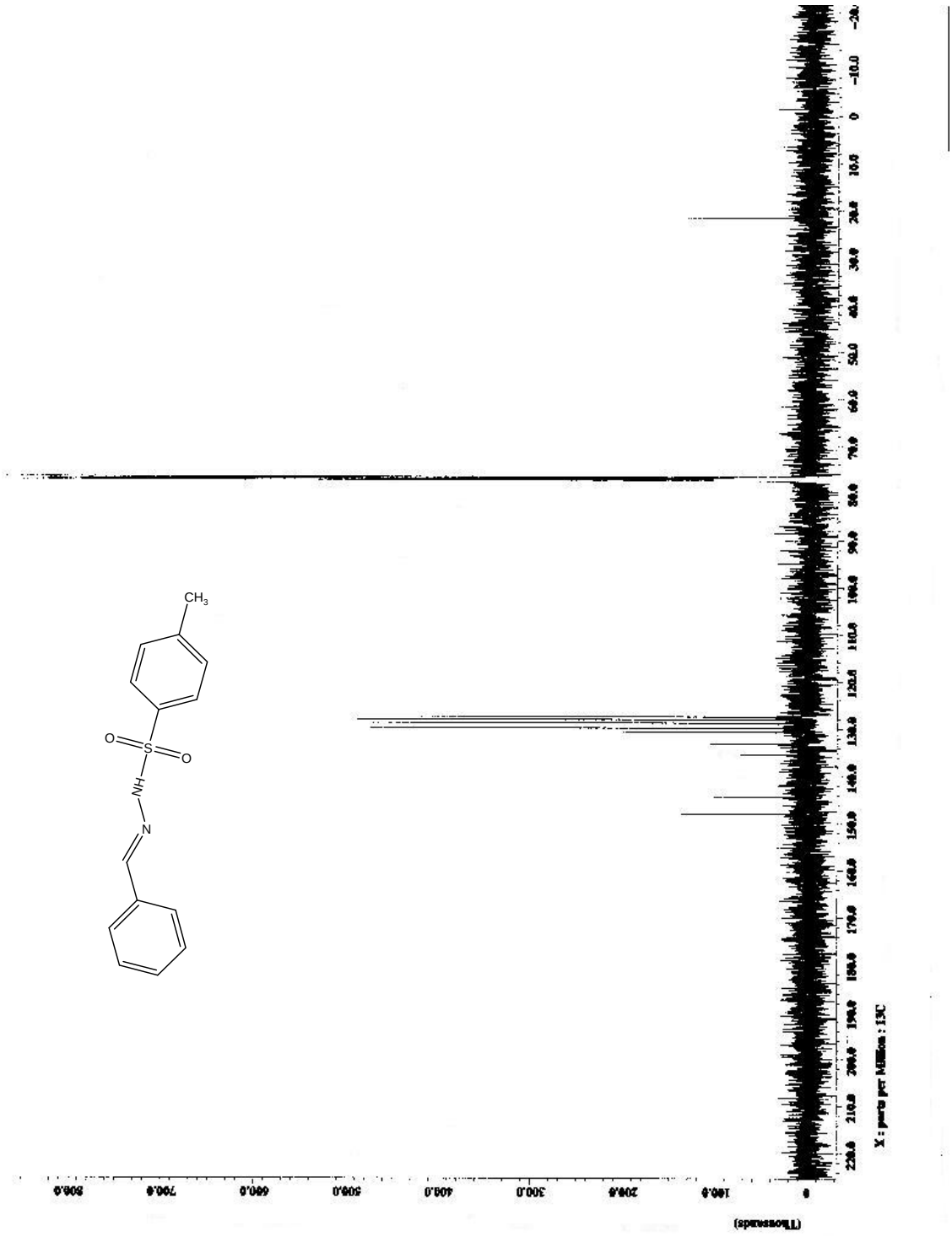
APPENDIX H

^{1}H-NMR for *P*-toluenesulfonulhydrazide



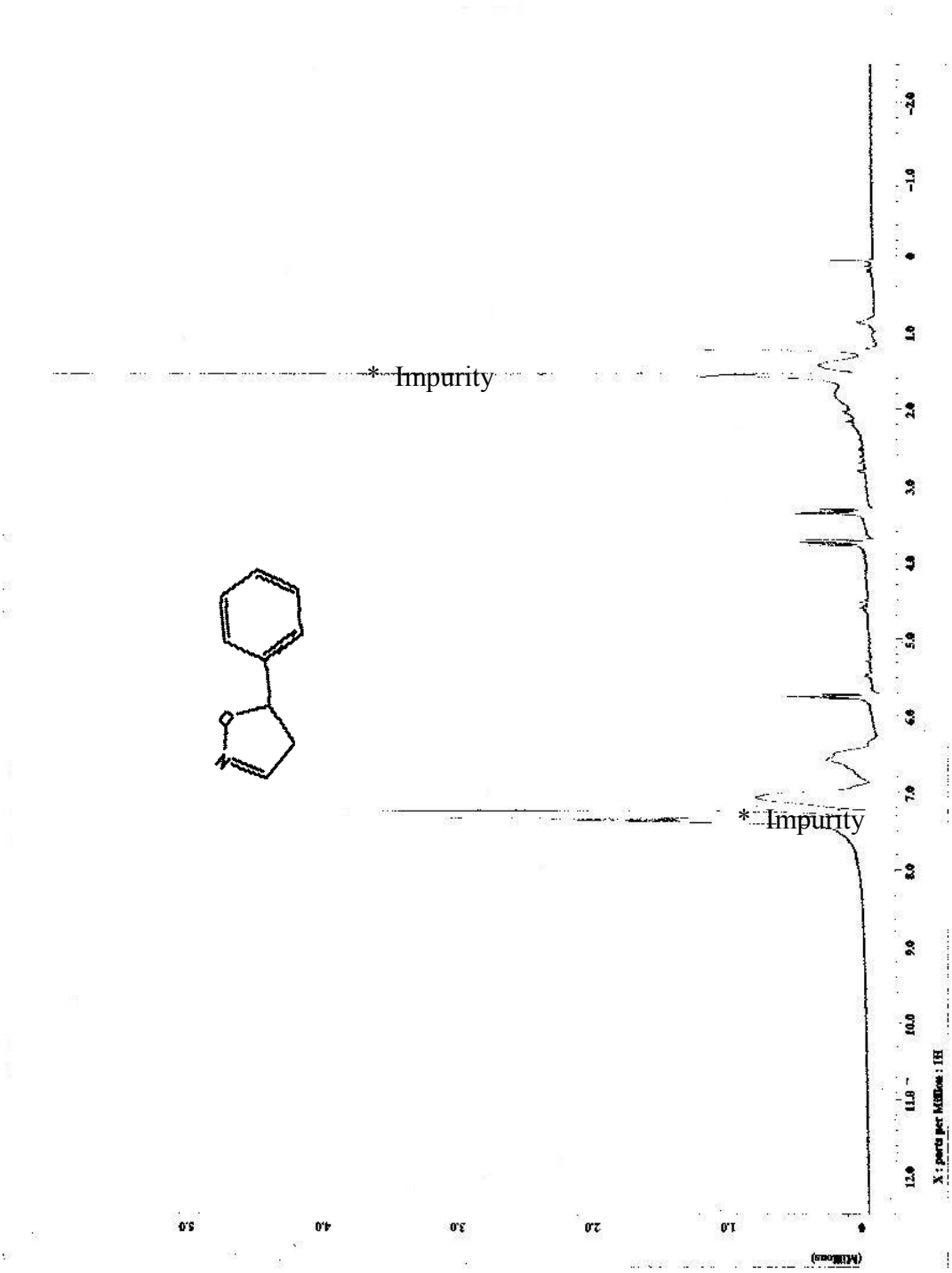
APPENDIX I

^{13}C-NMR for *P*-toluenesulfonulhydrazide



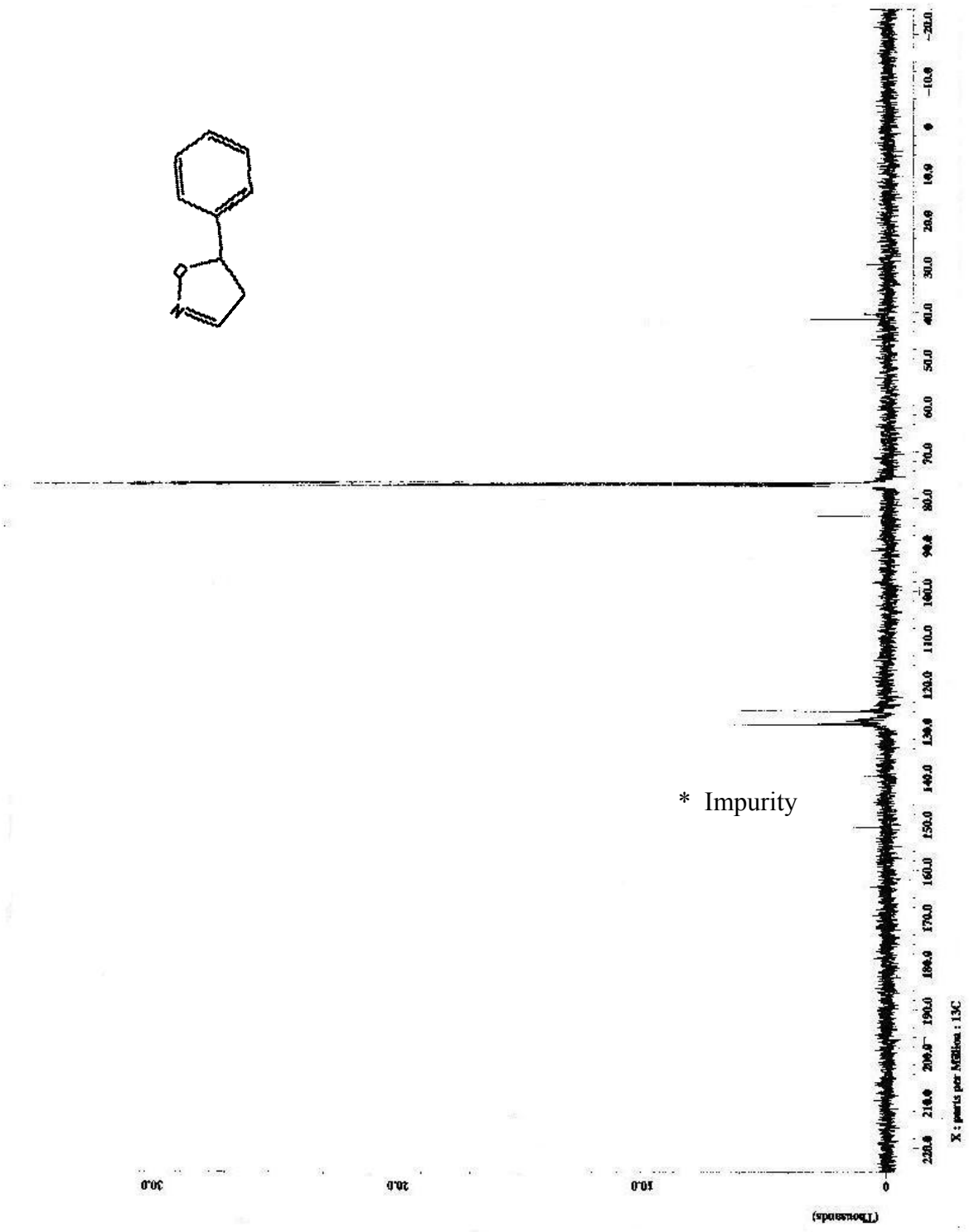
APPENDIX J

^{1}H-NMR for 5-phenyl-4,5-dihydroisoxazoline



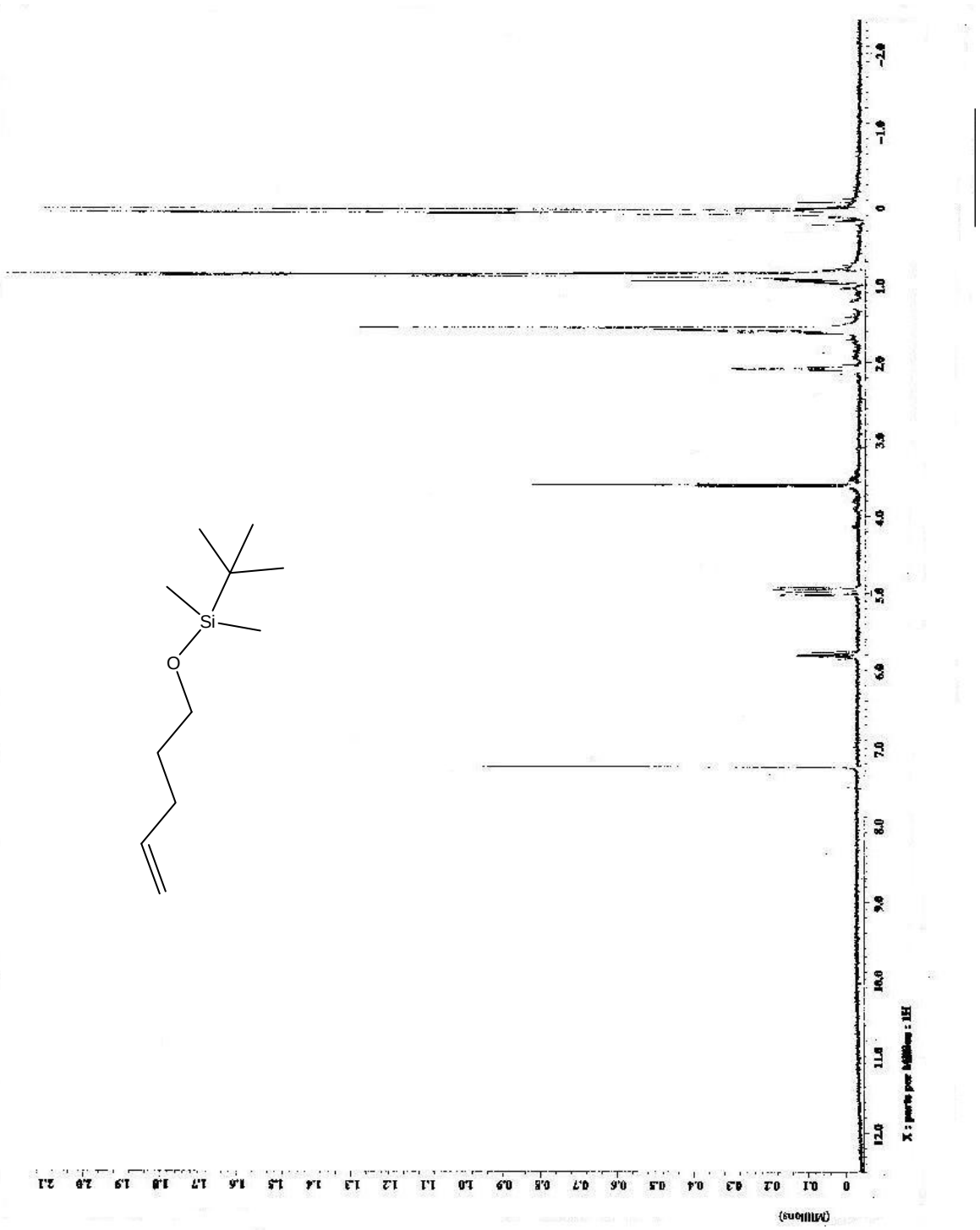
APPENDIX K

^{13}C-NMR for 5-phenyl-4,5-dihydroisoxazoline



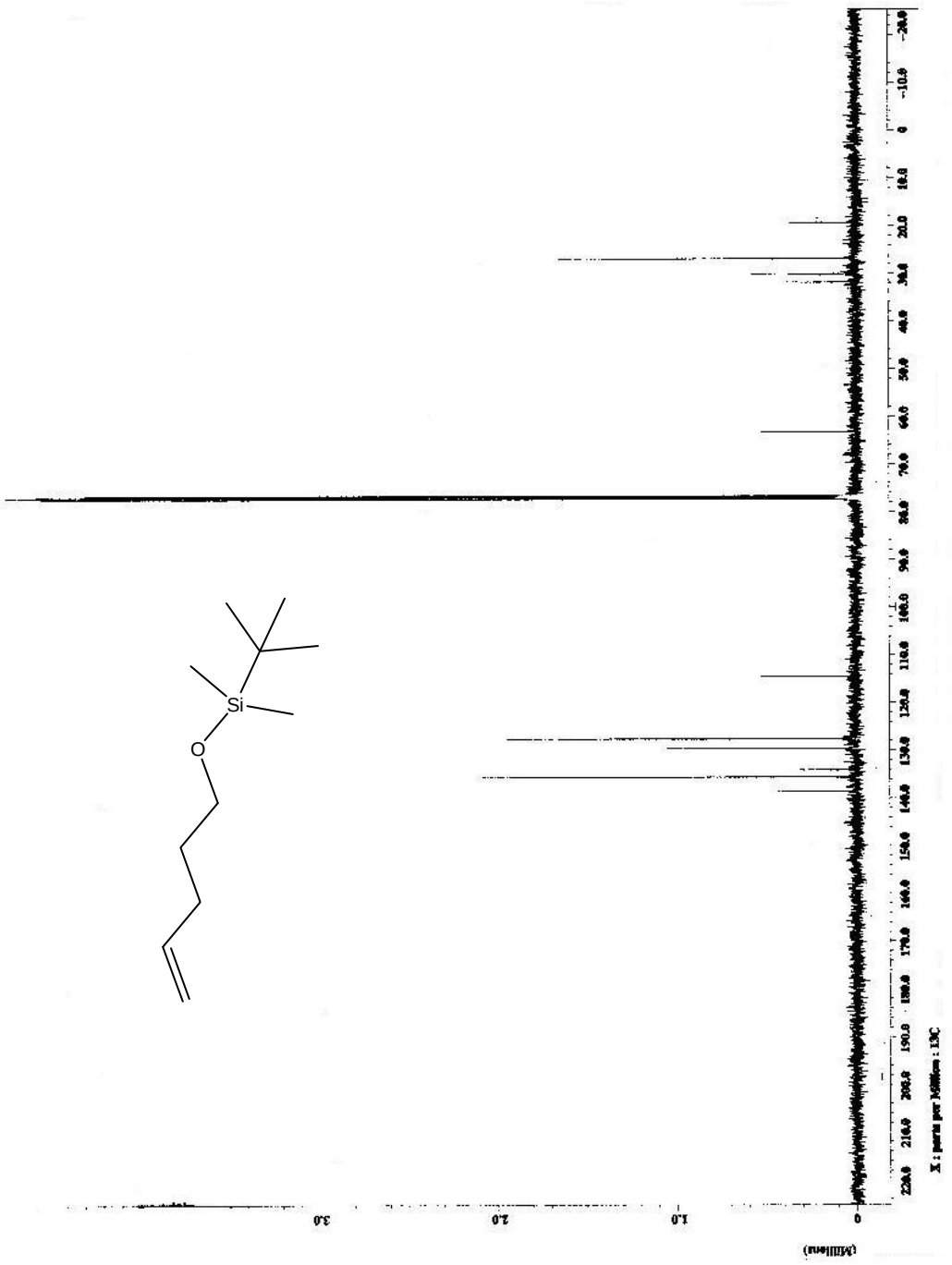
APPENDIX L

^{1}H-NMR for Tert-butyldimethylsiloxyl pent-1-ene



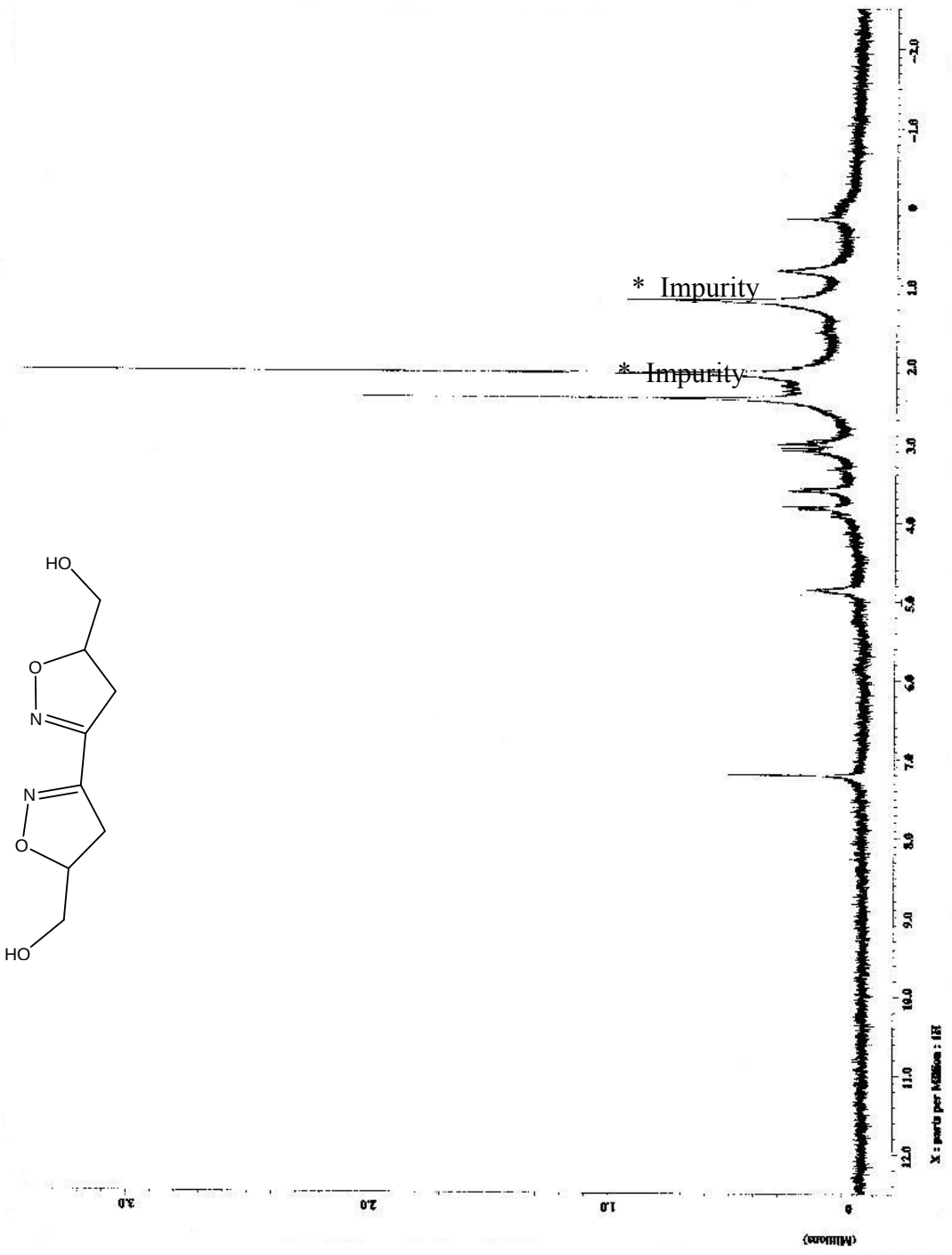
APPENDIX M

^{13}C-NMR for Tert-butyldimethylsiloxyl pent-1-ene



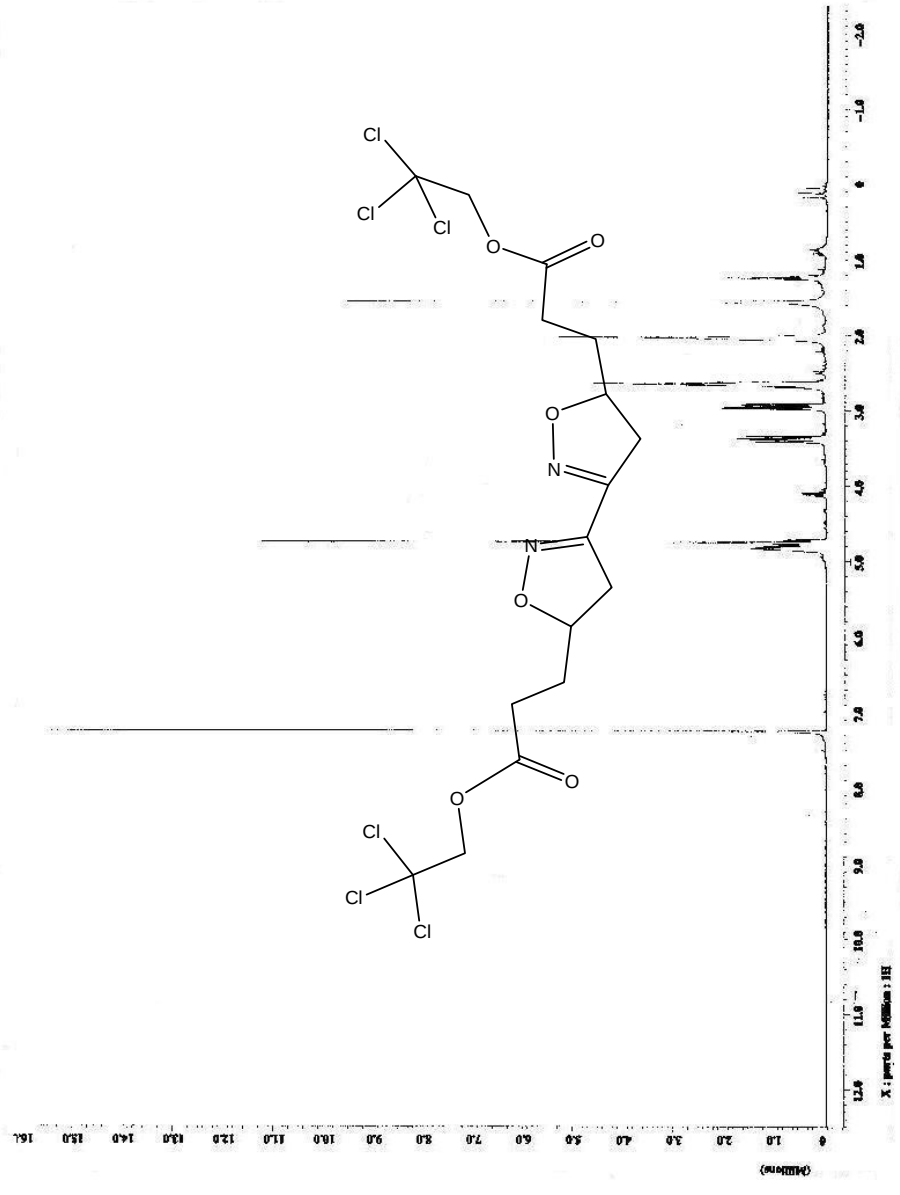
APPENDIX N

^{1}H-NMR for (5'-Hydroxymethyl-4,5,4',5'-tetrahydro-[3,3']biisoxasolyl-5-yl)-methanol



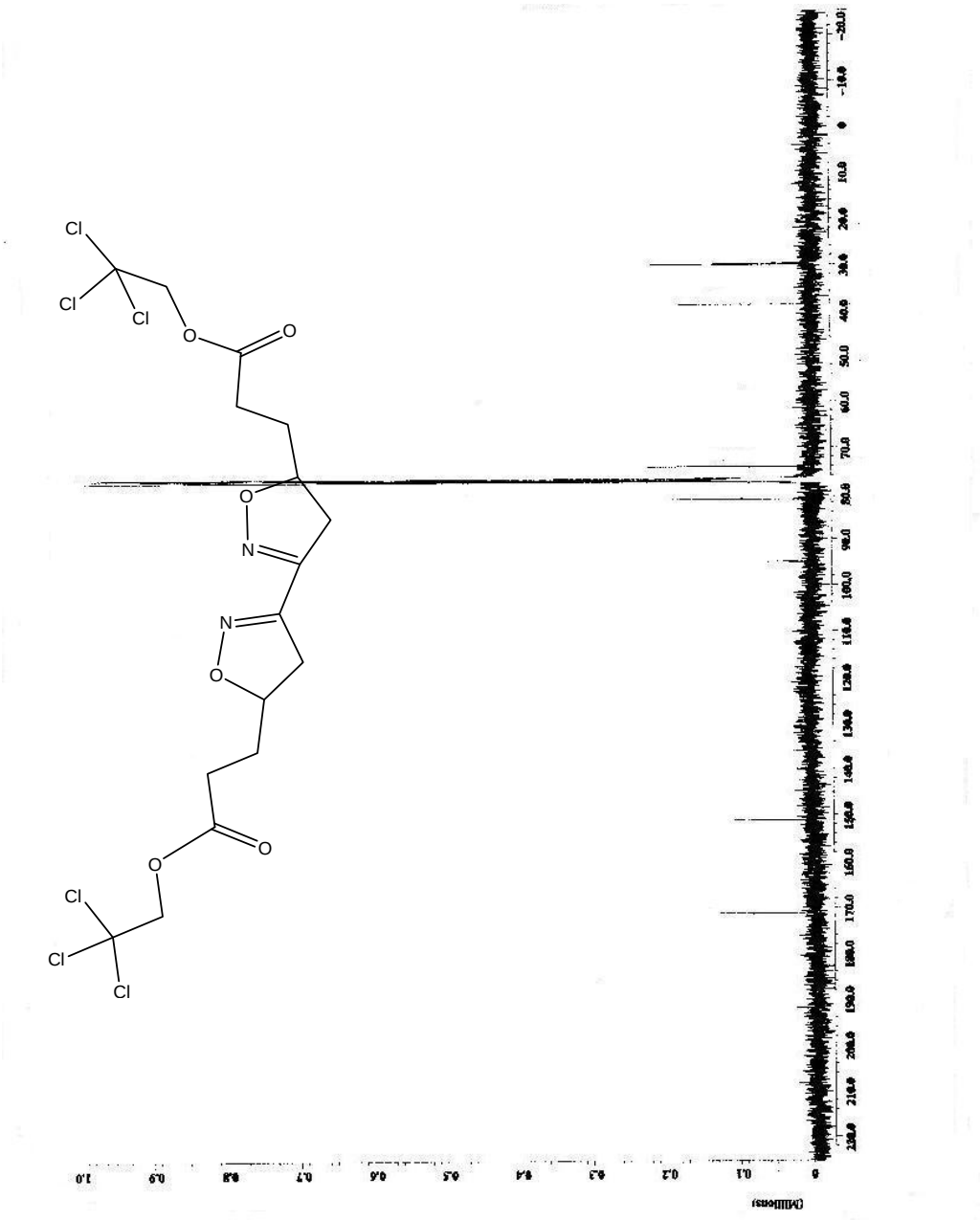
APPENDIX O

^{1}H-NMR for 3-[5'-(5,5,5-Trichroro-3-oxo-pentyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propionic acid-2,2,2-trichloro-ethyl ester



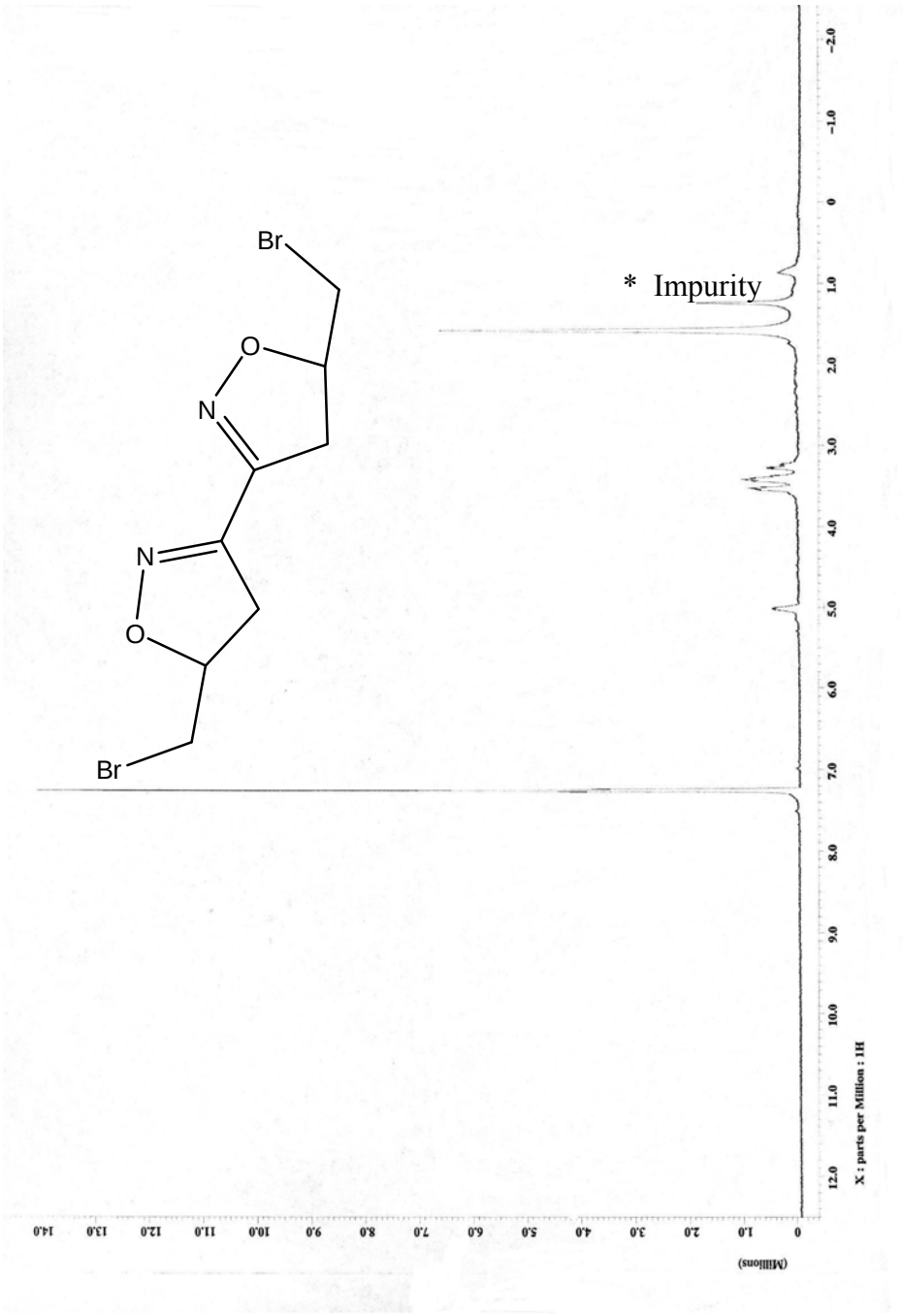
APPENDIX P

^{13}C-NMR for 3-[5'-(5,5,5-Trichroro-3-oxo-pentyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propionic acid-2,2,2-trichloro-ethyl ester



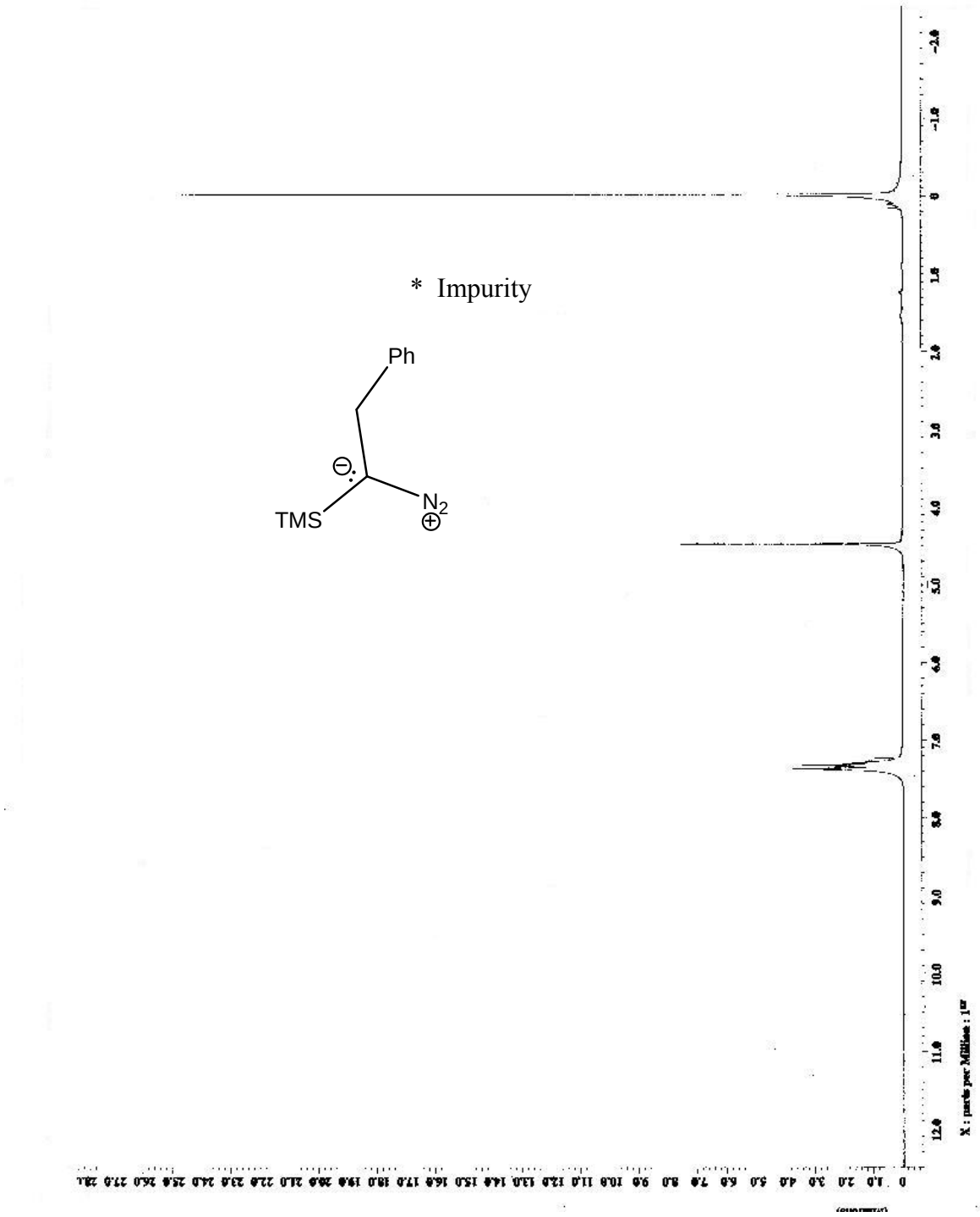
APPENEDIX Q

^{1}H-NMR for 5,5'-Bisbromoethyl-4,5,4,'5'-tetrahydro-[3,3']biisoxazolyl



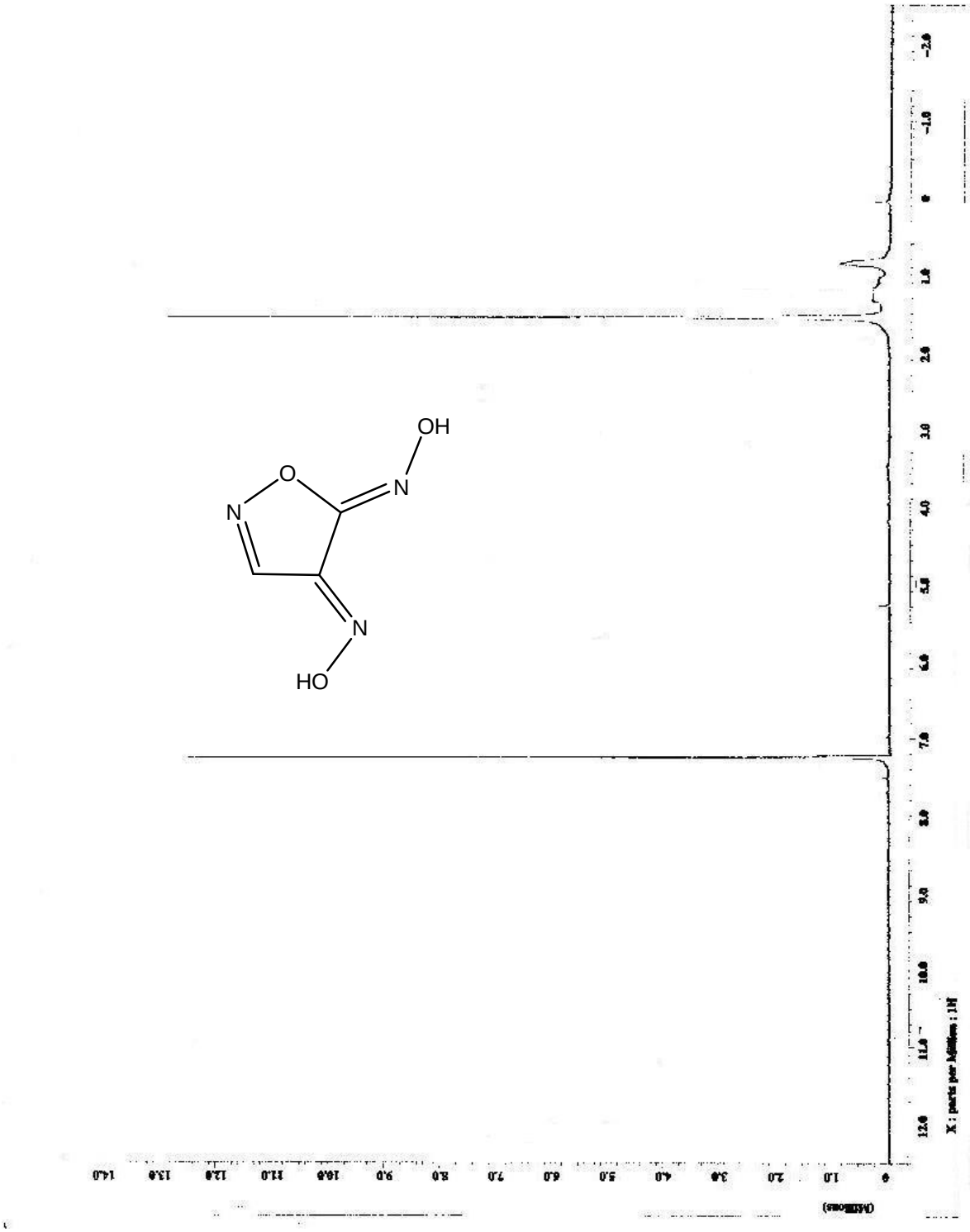
APPENDIX R

^{1}H-NMR for (1-diazo-2-phenylethyl)trimethylsilane



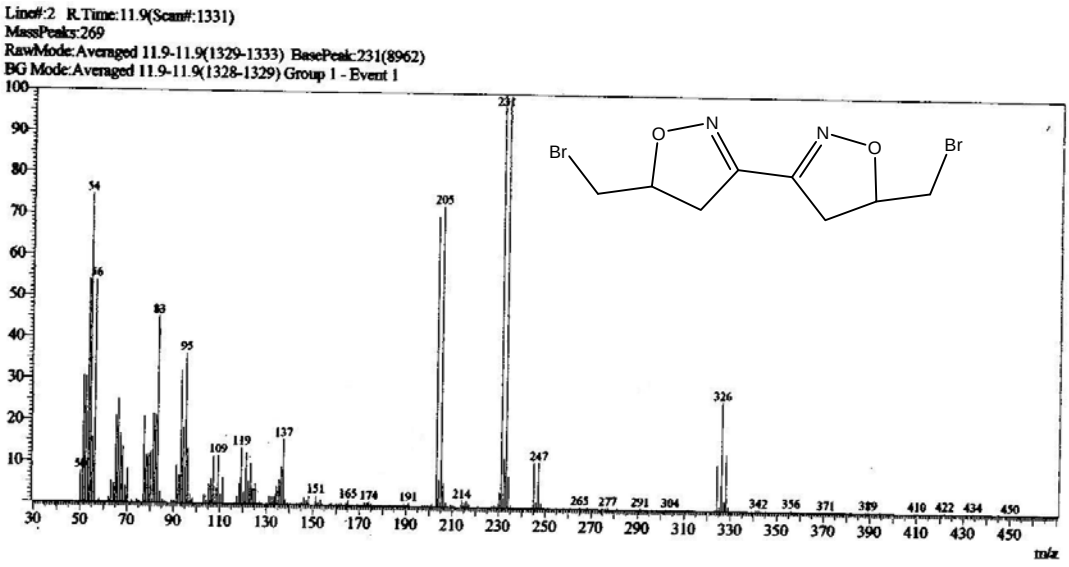
APPENDIX S

^{1}H-NMR for Metafulminic acid



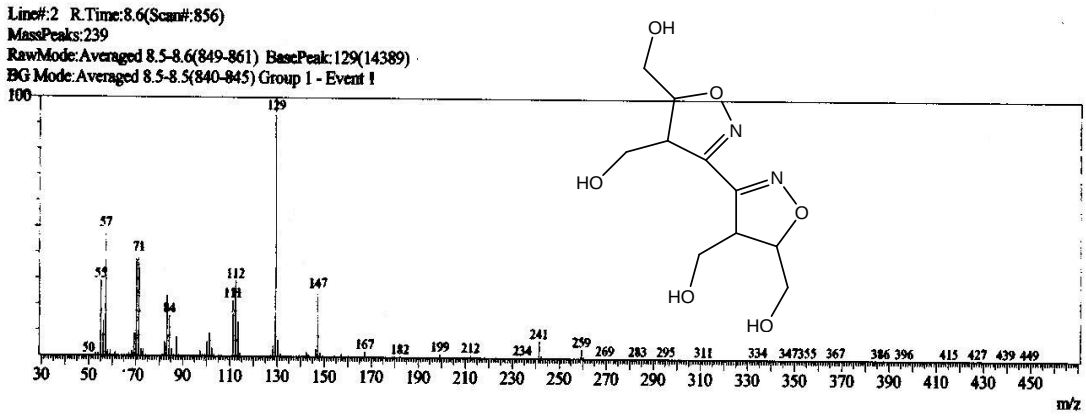
APPENDIX T

Mass Spectrum for 5,5'-Bisbromoethyl-4,5,4,'5'tetrahydro-[3,3']biisoxazolyl



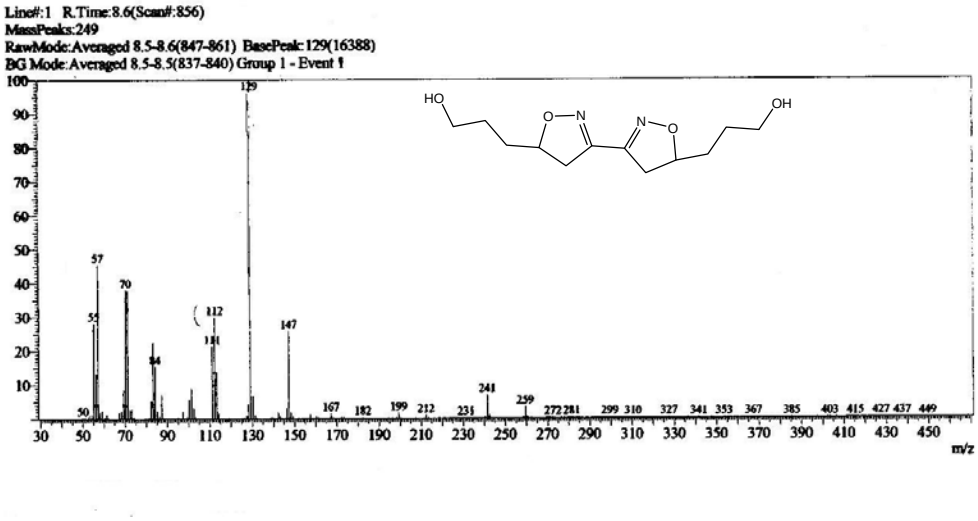
APPENDIX U

Mass Spectrum for 5,4',5'-Hydroxymethyl-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-4-yl)-methanol



APPENDIX V

Mass Spectrum for 3-[5'-(-Hydroxy-propyl)-4,5,4',5'-tetrahydro-[3,3']biisoxazolyl-5-yl]-propan-1- ol



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