"N-cyclohexyl, N-phenyl nitrones and their potentiality in isoxazolidine and isoxazoline syntheses"

THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY (SCIENCE)

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SGC/PhD/CM/2010 **01/02/2010**

To whom it may concern

This is to certify that Shri Manjit Singh Chhetri, research fellow in Chemistry, Sikkim Govt. College, Gangtok and Lecturer in Chemistry of Surendra Institute of Engineering & Management, Siliguri at present has duly completed research work leading to *Ph.D degree* under my supervision at the *Organic Chemistry Laboratory* of our institution and is now ready to submit *Ph.D thesis* entitled "*N-cyclohexyl,N-phenyl nitrones and their potentiality in isoxazolidine and isoxazoline syntheses*".

This is also to certify that the research work is original and completely new. Shri Chhetri had joined as *research scholar* in my laboratory on *June 2006* and since then he was actively engaged in research and was *registered* for *Ph.D degree* at the University of North Bengal on *26/11/2007*.

I wish him all the success in completion of his *Ph.D* work.

Bhaskar Chakraborty

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Date : 15/12/07

To
Sri Manjit Singh Chhetri
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Your name has been registered for the Ph.D. degree of this University for five years with effect from 26.11.07 the title of the thesis being "N-cyclohexyl, N-phenyl nitrones and their potentiality in isoxazolidine and isoxazoline syntheses".

Sd/-
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3. Dr.B.Chakraborty, Sikkim Govt. College

REGISTRAR

Preface

The nitrone moiety can be regarded as a 3 centered dipolar 4π system, which enables 1,3-dipolar cycloaddition reactions with different dipolarophilic reagent to occur. 1,3-dipolar cycloadditions are susceptible to both electronic and steric influences. 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophiles is an efficient method for the synthesis of isoxazolidine systems.

The question of reactivity and substituent effects in 1,3-dipolar cycloaddition reaction has been rationalized successfully using frontier molecular orbital theory which provides relative interaction energies of frontier orbitals between 1,3-dipole and dipolarophiles. The electron attracting or electron releasing moiety influences the atomic orbital co-efficience and have a significant influence on the regiselectivity of the reaction.

Further more, the cycloadducts have found numerous applications in synthesis through reductive cleavage of the $N - O$ bond to give γ-amino alcohols. Asymmetric induction in nitrone olefin cycloaddition has been achieved through the incorporation of chirality in both the dipole and the dipolarophiles. More recently advances have been made in the use of water as the solvent to influence the rate, regioselectivity and stereoselectivity of cycloaddition reactions. The present work entitled ***"N-cyclohexyl, N-phenyl nitrones & their potentiality in isoxazolidine & isoxazoline syntheses"*** reports newly discovered α-chloro nitrone from chlorohydrin and α-amino nitrone from *N,N*-dimethyl formamide and their cycloaddition reactions with different olefins and alkynes leading to the formation of regio and stereoselective products. An important application of the nitrones and the cycloadducts are aldehyde synthesis and antimicrobial activities.

The following chapters fulfill these ideas:-

Chapter I This chapter deals with the general theoretical approach of different 1,3-dipoles and their stabilities and general nature of intra and inter molecular 1,3-dipolar cycloaddition reactions of nitrones. Special emphasis has been given on HOMO – LUMO approach in this regard. Attempts have been made in this chapter to cover a complete review

of the literature and latest developments up to February, 2010 in a rather comprehensive manner.

Chapter II It deals with the most important experimental section. In this section, the method of formation of different nitrones (*N*-cyclohexyl-α-chloro nitrone, *N*-cyclohexyl-α-amino nitrone, *N*-phenyl-α-amino nitrone), cycloaddition reaction with different olefins and alkynes are studied along with their reaction conditions in solvent less condition and in aqueous phase.

Chapter III This chapter deals with results and discussion and achievements of the work done. Spectral interpretation *viz.* ^{1}H NMR, ^{13}C NMR, MS, IR, HRMS and elemental analysis have been discussed in detail.

Chapter IV This chapter is focused on the future perspective of the work done and is referred to as scope and objectives of the present work.

Acknowledgement

I would like to express deep gratitude towards my supervisor ***Dr. Bhaskar Chakraborty****, Reader in Chemistry, Sikkim Government College, Gangtok, who has been integral in shaping these four years in research into a unique and rewarding experience for me. Throughout the research work I have received expert criticism, valuable comment and above all his best loving care. His creativity has had a significant impact on my research, and his passion for his work has in turn provided me with a wealth of opportunities and for which I am truly grateful.*

I have also had the good fortune to interact with faculty members at both Department of Chemistry, University of North Bengal and Indian Association for the Cultivation of Science, Jadavpur over the course of my PhD career. Heartfelt thanks goes to ***Prof. B. Basu, Dr. A.K Nanda, Dr. P. Ghosh*** *and the Department of Chemistry, University of North Bengal for their constructive ideas and for providing NMR spectra of some of the vital compounds related to my present work. I would also take this opportunity to thank* ***Prof. B. C. Ranu and Prof. A. Dey*** *of Indian Association for the Cultivation of Science, Jadavpur for their valuable suggestion relating to the research work. Thanks are also due to* ***Dr. M. P. Kharel****, Principal, Sikkim Government College,* ***Dr. S. K. Pradhan****, former Principal, Sikkim Government College,* ***Dr. C. B. Sunwar,*** *former Principal, Sikkim Government College for their enthusiastic support, constant co-operation and for providing research facilities. I am equally grateful to* ***scientist in-charge****, SAIF, CDRI, Lucknow for providing IR, NMR, MS Spectral data.*

I express my personal appreciation of the assistance given by ***Shri Saurav Kafley,*** *Lecturer, Department of Chemistry, Sikkim Government College in this work. I am equally thankful to* ***Dr. A. Samanta*** *of Jadavpur University for helping in finding out the biological aspects of the entire work. I would also take this opportunity to place on record my appreciation of the assistance rendered to me by* ***Dr. Sajal Das****, Lecturer, Deptt. of Chemistry, University of North Bengal and* ***Mr. Achintesh Bishwas****, Lecturer, Deptt. of Chemistry, Siliguri College without their support my review work would not have been completed. I would like to express my thanks to* ***Mr. Arun Rai****, staff member of Chemistry department, Sikkim Government College for his*

continuous support. I would like to express my heartfelt thanks to ***Mrs. M. Chakraborty*** *and* ***Ms. M. Bhattacharjee*** *for their continuous encouragement. Finally, I would like to express my deep gratitude towards my* ***parents****. Their affection ever encouraged me for the entire work. Lastly, all the people who rendered valuable help and support in direct and indirect ways in bringing this research work to completion are sincerely acknowledged.*

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"The Ph.D dissertation is dedicated to Late Dr. A.R Ghosh, senior lecturer, Department of Chemistry Sikkim Government College, Gangtok".

Contents

CHAPTER I

Theoretical approach and Review work

General

The term "1,3-dipole", $a^{+}-b-c^{-}$ may be defined such that atom "a" possesses an electron sextet, that is an incomplete valence shell combined with a formal positive charge and the atom c, the negatively charged center, has an unshared pair of electrons and undergoes 1,3- dipolar cycloaddition to a multiple bond system called "dipolarophile".

Since compounds with 6 electrons in the outer shell of an atom are usually not stable, the a-b-c system is actually canonical form of a resonance hybrid for which at least one other structure may be drawn e.g.

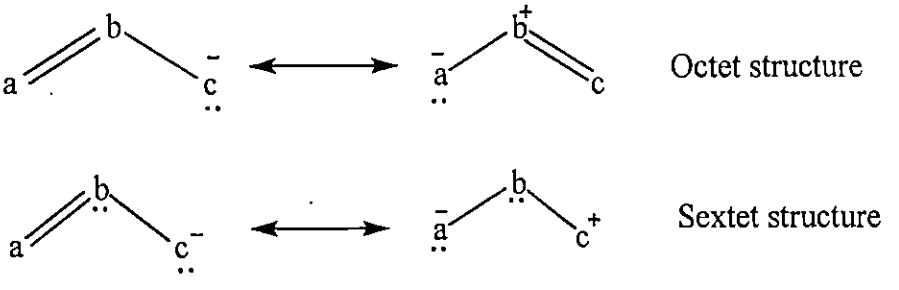


Fig 1

1,3-dipoles can be further stabilized by internal octet stabilization. 1,3-dipolar compounds can be divided into two main types:

(1) Propagyl - Allenyl type

Those in which the dipolar canonical form has a double bond on the sextet atom and other canonical form a triple bond on that atom.

Fig 2

(2) Allyl type

Those in which the dipolar canonical form has a single bond on the sextet atom other form a double bond.

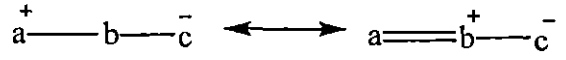
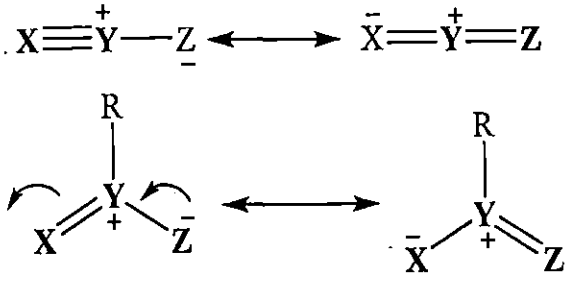


Fig 3

1,3-dipoles can be represented as depicted in Fig III. In this 1,3-dipoles, the central atom is never a carbon atom. If the central atom be a carbon function then internal octet stabilization is prevented by lack of an available free electron pair. Such systems are therefore extremely reactive and short lived. Examples of this type are unsaturated carbenes and azenes.

1, 3-dipole

1,3-dipole participates in the [3+2] cycloaddition reactions which form 5-membered ring systems, in an analogous way to the Diels-Alder process which forms 6 membered rings. The reactive partners in this reaction are 1,3-dipoles and dipolarophiles (c.f. diene and dienophile in the Diels-Alder reaction). It is a $4\pi+2\pi$ process as well.



X, Y, Z = C, N, O, S, P.....

Fig 4

1,3-dipoles vary in stability greatly. Some can be isolated and stored, others are relatively stable, but are usually made the same day as their use.

In order to compare the stability of nitrones the secular determinant could be set up using the suggested parameter values[1] for hetero atoms for the use of simple LCAO (Linear combination of atomic orbitals) treatment viz.

$h_N^+ = 2$; $h_O^- = 2$; $K_{C-N} = 1.1$; $K_{N-O} = 0.7$ etc.

$$\begin{vmatrix} \alpha_0-\varepsilon & \beta_{12} & \beta_{13} \\ \beta_{21} & \alpha_0-h_N+\beta_0-\varepsilon & \beta_{23} \\ \beta_{31} & \beta_{32} & \alpha_0+h_0+\beta_0-\varepsilon \end{vmatrix} = 0$$

Putting the above values and $\alpha_0 - \varepsilon / \beta_o = x$

$$\begin{vmatrix} x & 1.1 & 0 \\ 1.1 & x+2 & 0.7 \\ 0 & 0.7 & x+2 \end{vmatrix} = 0$$

The secular polynomial of the system was

$X^3 + 4X^2 + 2.3X - 2.4 = 0$

i.e. X = 0.5175, -1.58775 & 2.9297

Therefore the energy levels were

$\varepsilon_1 = \alpha_0 + 0.5175\ \beta_0$

$\varepsilon_2 = \alpha_0 - 1.58775\ \beta_0$

$\varepsilon_3 = \alpha_0 - 2.9297\ \beta_0$

and the total Π energy of system was

$E_\Pi = 4\alpha_0 + 5.03495\ \beta_0$

Approximate HMO calculation of nitrone 1

In order to verify the stability of *N*-phenyl-*α*-chloro nitrone (I), *N*-cyclohexyl-α-chloro nitrone[2] was taken as an example for the approximate HMO calculation.

The secular determinant for Nitrone 1 (*N*-phenyl-α-chloro nitrone) could be studied in two ways.

$$\begin{vmatrix} \alpha_0+2\beta_0-\varepsilon & \beta_{12} & \beta_{13} & \beta_{14} \\ \beta_{21} & \alpha_0-\varepsilon & \beta_{23} & \beta_{24} \\ \beta_{31} & \beta_{32} & \alpha_0+2\beta_0-\varepsilon & \beta_{34} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_0+2\beta_0-\varepsilon \end{vmatrix} = 0$$

$$\begin{vmatrix} x+2 & 0.4 & 0 & 0 \\ 0.4 & x & 1.1 & 0 \\ 0 & 1.1 & x+2 & 0.69 \\ 0 & 0 & 0.69 & x+2 \end{vmatrix} = 0$$

Thus solving x = 0.578; –1.5607; –2.9436; –2.0656.

The energy levels were

$\varepsilon_1 = \alpha_0 - 0.578\ \beta_0$

$\varepsilon_2 = \alpha_0 - 1.5607\ \beta_0$

$\varepsilon_3 = \alpha_0 - 2.9436\ \beta_0$

$\varepsilon_4 = \alpha_0 - 2.0656\ \beta_0$

the total Π energy of the system was

$E_\Pi = 4\alpha_0 + 7.1479\ \beta_0$

$$\begin{vmatrix} \alpha_0+2\beta_0-\varepsilon & \beta_{12} & \beta_{13} & \beta_{14} & \beta_{15} \\ \beta_{21} & \alpha_0-\varepsilon & \beta_{23} & \beta_{24} & \beta_{25} \\ \beta_{31} & \beta_{32} & \alpha_0+2\beta_0-\varepsilon & \beta_{34} & \beta_{35} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_0+2\beta_0-\varepsilon & \beta_{45} \\ \beta_{51} & \beta_{52} & \beta_{53} & \beta_{54} & \alpha_0+2\beta_0-\varepsilon \end{vmatrix} = 0$$

$$\begin{vmatrix} x+2 & 0.4 & 0 & 0 & 0 \\ 0.4 & x & 0.9 & 0 & 0 \\ 0 & 0.9 & x & 1.1 & 0 \\ 0 & 0 & 1.1 & x+2 & 0.69 \\ 0 & 0 & 0 & 0.69 & x+2 \end{vmatrix} = 0$$

The energy levels were

$\varepsilon_1 = \alpha_0 - 1.129\ \beta_0$

$\varepsilon_2 = \alpha_0 - 1.20\ \beta_0$

$\varepsilon_3 = \alpha_0 - 0.555\ \beta_0$

$\varepsilon_4 = \alpha_0 - 2.954\ \beta_0$

$\varepsilon_5 = \alpha_0 - 2.4195\ \beta_0$

Total Π energy of the system was

$E_\Pi = 5\alpha_0 + 8.2575\ \beta_0$

Considering the calculated energy levels, associated with nitrone **1** it was expected to be moderately stable. The above assumption also could be rationalized on the basis of Fukui's Frontier Orbital Theory (FMO)[3]. Recently reported DFT study on the stability

of *C*-aryl-*N*-methyl nitrones basing upon Gaussian–2003 series computational programs[4,5,6] along with their graphical user interface Gauss view 2003 inspired us to use the program to study the stability of the reported nitrone **1**. Although we could not use series of computational program but elementary application of this methodology suggests that *N*-phenyl-α-chloro nitrone (**1**) is moderately stable & hence the nitrone is used in-situ for the 1,3-dipolar cycloaddition reactions.

The molecular orbital calculations performed by DFT study using B3LYP theory for *N*-phenyl-α-chloro nitrone shows -0.154 & -0.032 for HOMO & LUMO energies in Hartrees (1 Hartree = 27.21 eV). *N*-phenyl-α-chloro nitrone has a chlorine group at *β*-position of the nitrone which has a strong electron withdrawing nature & therefore the nitrone should be electrophilic in nature. The high reactivity of *N*-phenyl-α-chloro nitrone could also be explained on the basis of perturbation theory where the HOMO level of parent nitrone is raised in energy by the introduction of chlorine group on the *β*-carbon atom & the stabilization of the dipole LUMO level thereby providing the stabilization to the transition state for the cycloaddition & consequently increasing the rate of the reactions.

There are two general classes of dipole sometimes referred to as sp^2 and sp hybridized dipoles.

sp-dipolarophile (linear dipoles like the propagyl anion)

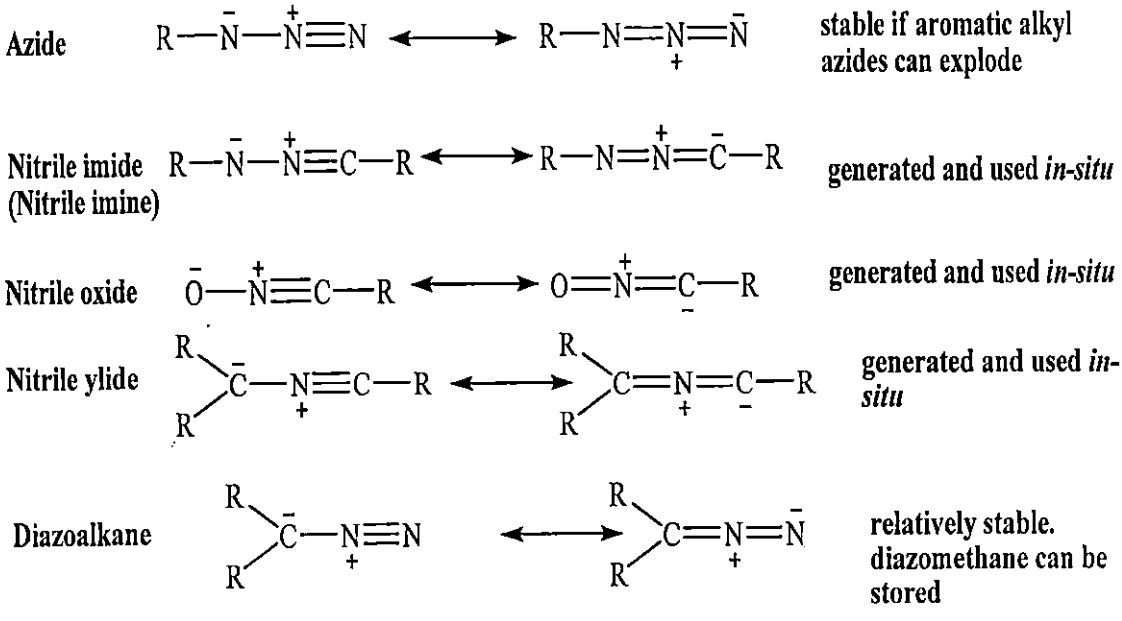


Fig 5

sp² hybridised (bent dipoles like the allyl anion)

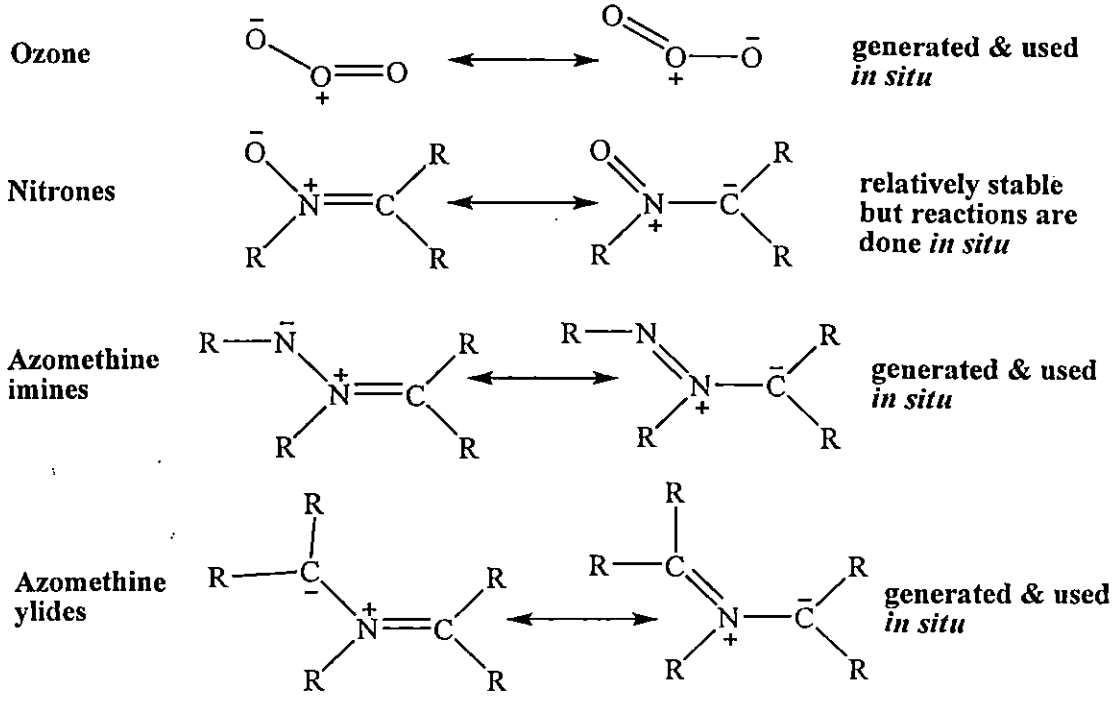


Fig 6

Reactivity profile of 1, 3-dipoles

The reaction between dipoles and dipolarophiles fit the following general profile:

(a) It is currently accepted that cycloadditions are concerted processes *i.e.* they have no distinct intermediates but the bond formation may be asynchronous.

(b) The reaction rates are not influenced much by solvent polarity indicating little change in polarity between reactants and transition state.

The rate of reaction between dipoles and dipolarophiles vary considerably. This can be explained by Fukui's Frontier Molecular Orbital Theory (FMO approach) which considers the interaction between molecular orbitals of the dipole and dipolarophiles.

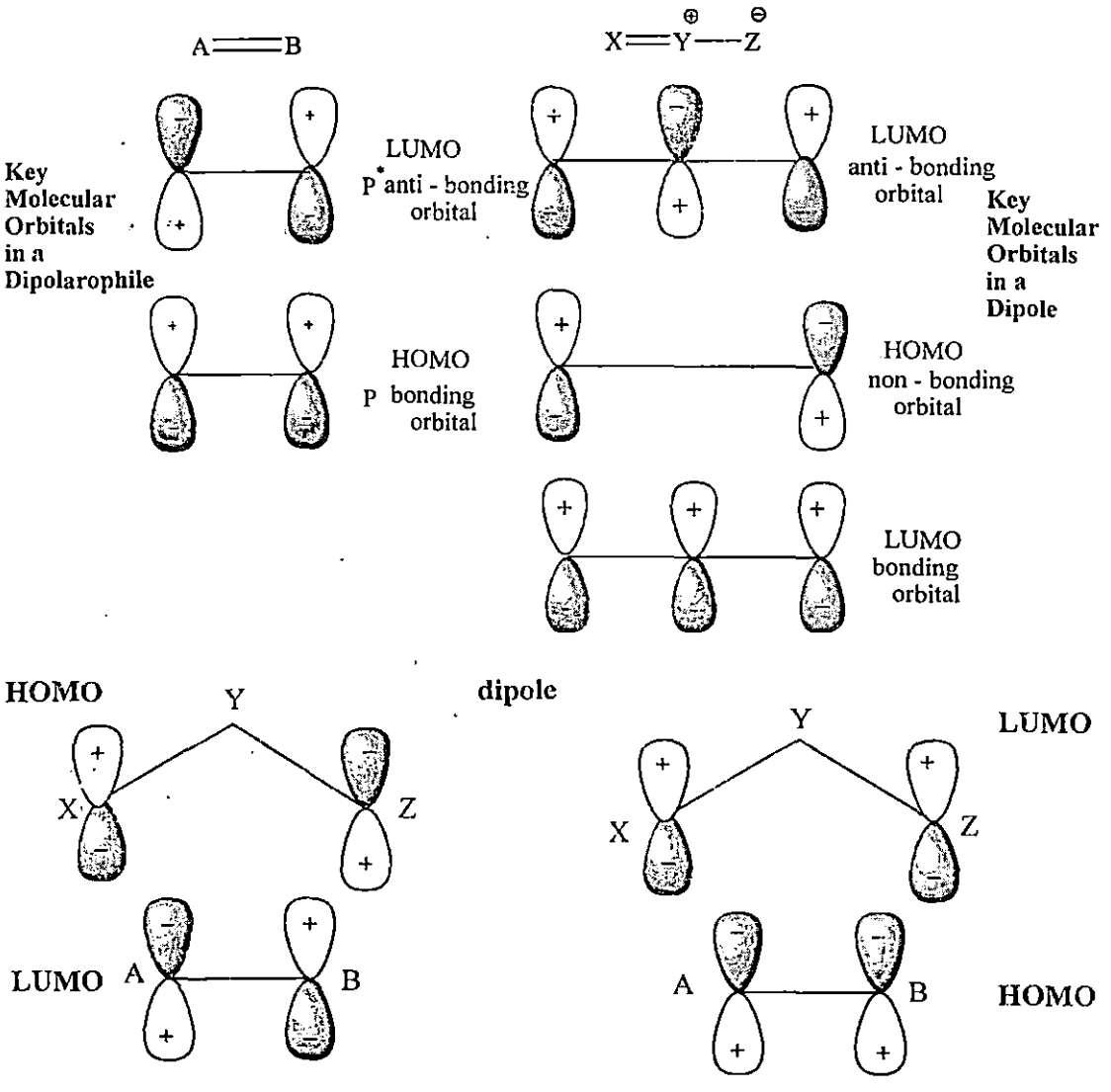


Fig 7

The term "nitrone" was coined from nitrogen ketone (azomethine oxide) in order to keep its resemblance to the carbonyl group in its several reactions[7].

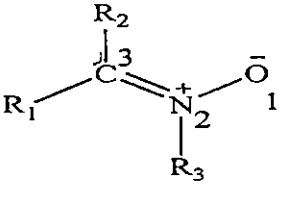


Fig 8

Nomenclature

The nitrones were known since 1887. The nomenclature employed by chemical abstract is as follows.

α-*N*-diphenyl nitrone

α-phenyl-α-(*p* –tolyl)-*N*-methyl nitrone.

The cyclic nitrones are named accordingly to the parent heterocyclic structures e.g. 2,4–dimethyl–Δ^1-pyrolidine-*N*-oxide, Δ^1–tetrahydropyridine-*N*-oxide etc. later, nitrones were named as *C*-cyclopropyl-*N*-methyl ketone, *C*-dicyclopropyl-*N*-methyl nitrone etc. The general term aldonitrones and ketonitrones have been employed occasionally. Aldonitrones contain a proton on the α-carbon atom.

$$\mathbf{RCH = N^{+}(O^{-})\ R^{1}}$$

While the ketonitrones contain the α-carbon fully substituted with alkyl or aryl group.

$$\mathbf{R, R^{1}\ C = N^{+}(O^{-})\ R^{2}}$$

Geometrical isomerism

Nitrones may exhibit geometrical isomerism because of the double bond in nitrone molecule.

Fig 9

The existing geometrical isomerism was first demonstrated in 1918 for α-phenyl-α-(*p* -tolyl)-*N*-methyl nitrone[8] . The configuration of the isomers was established by dipole moment studies. The *cis* and *trans* forms were readily converted into the *trans* form by heating. Generally aldonitrones exist in stable *trans* form and this has been established by UV, IR, ^{1}H NMR studies[9]. The only example of geometrical isomerism is known for α-phenyl-*N*-tertiary butyl nitrone[10]. Therefore in such cases where geometrical isomerism is possible, *E* / *Z* notation may be employed for naming.

A nitrone is a 1, 3-dipole in 1, 3-dipolar cycloadditions. It reacts with alkenes to form ***Isoxazolidines*** and the scheme has been shown as follows.

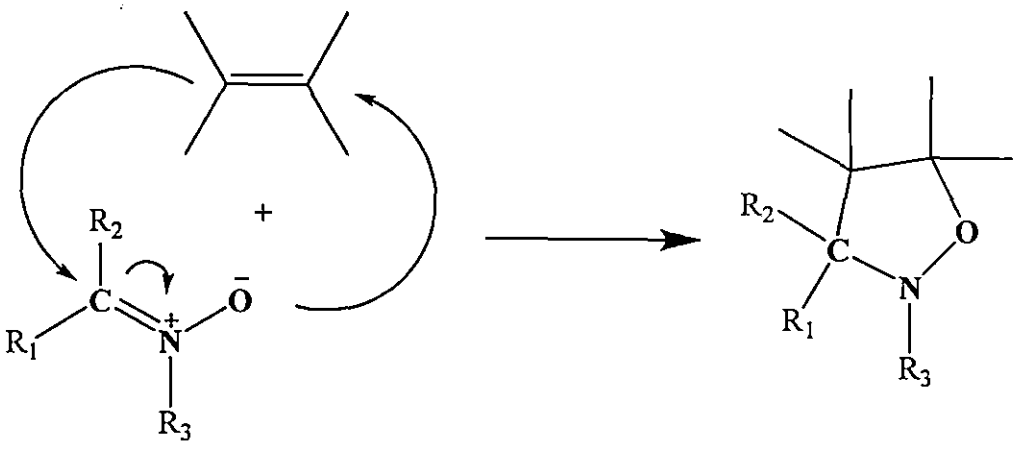


Fig 10

Similarly the nitrone can react as 1,3-dipole with alkynes in a in 1,3-dipolar cycloaddition reactions to form ***Isoxazolines***.

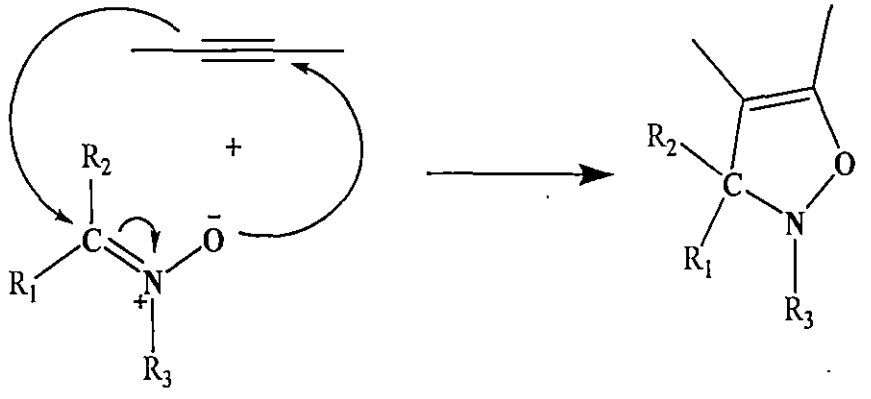


Fig 11

In allyl type of 1,3-dipole, if we restrict the atom a,b,c to carbon, nitrogen and oxygen, the nitrone results.

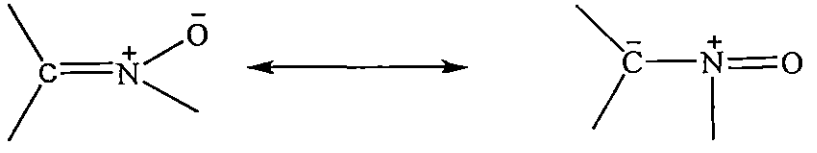


Fig 12

N-phenyl-α-chloro nitrone (**1**) has a chlorine group at β- position of the nitrone which has a strong electron withdrawing nature and therefore this nitrone is electrophilic in nature. In general, nitrones are HOMO-LUMO controlled 1,3-dipoles skewing towards LUMO controlled side.

Synthesis of nitrones

The chemistry and the synthesis of the nitrones have been reviewed several times. The general methods of synthesis of the nitrones are briefly discussed here.

a) By the oxidation of *N*, *N*-substituted hydroxylamines

$$R-N(OH)-CHR^1R^2 \longrightarrow R-N^+(O^-)=CR^1R^2$$

Both cyclic and acyclic nitrones were prepared by this method. Different oxidizing agents are used viz, yellow mercuric oxide[11], active lead oxide[12], potassium ferricyanide[13], hydrogen peroxide[14], potassium permanganate[15], diammine silver nitrate[16].

The formation of the nitrone salt was reported from the reaction between *p*-benzoquinone and 1-hydroxyl piperidine[17].

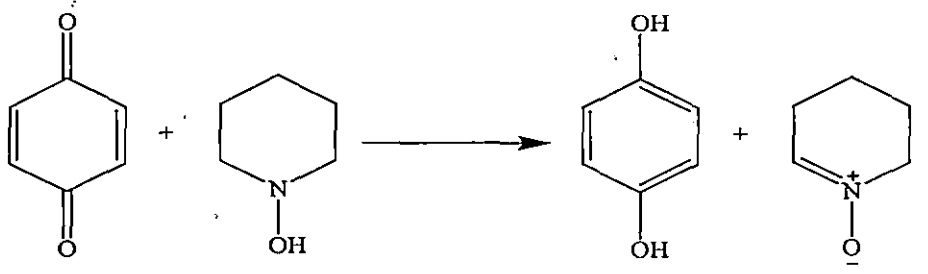


Fig 13

The formation of nitrone from *N,N*-disubstituted and *N*-substituted hydroxylamines using palladium catalyst were also reported[18]. Recently a four membered cyclic nitrone was also reported by the oxidation of 1-OH-azetidines with PbO_2[19].

Some other oxidative methods are also known e. g. diammino silver nitrate was used as the reagent for the preparation of α-styryl-α-benzyl-*N*-phenyl nitrone from corresponding hydroxylamine[20]. Photolysis of *N*-hydroxylamines in presence of 1, 4 – dicyano naphthalene (DCN) as an electron acceptor gave high yields of nitrone[21].

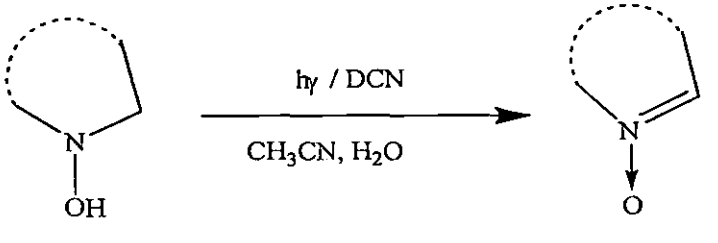


Fig 14

From oximes

The alkylation of the oximes was reviewed in 1938[22]. Disadvantage of this method was that nitrones were produced along with oxime ether.

$$R^1R^2C=N-OH + XR \longrightarrow R^1R^2C=NOR + R^1R^2C=N^+(O^-)$$

Li, Na, K or tetramethyl ammonium oxime salts did not alter the product ratio of oxime ether to nitrone significantly. Electron withdrawing group in the *para*, *ortho*-disubstituted benzophenone oxime salts markedly promoted the formation of nitrones while electron donating group favours nitrone formation whereas longer side chain favours oxime – ether formation.

Heptanal oximes when treated with benzyl chloride in solution of ethanol and sodium ethoxide yielded 77% of α-hexyl-*N*-benzyl nitrone[23]. DMSO was employed in the various keto-oxime alkylations. *C,C*-dicyclopropyl-*N*-methyl nitrone has been prepared by this method[24].

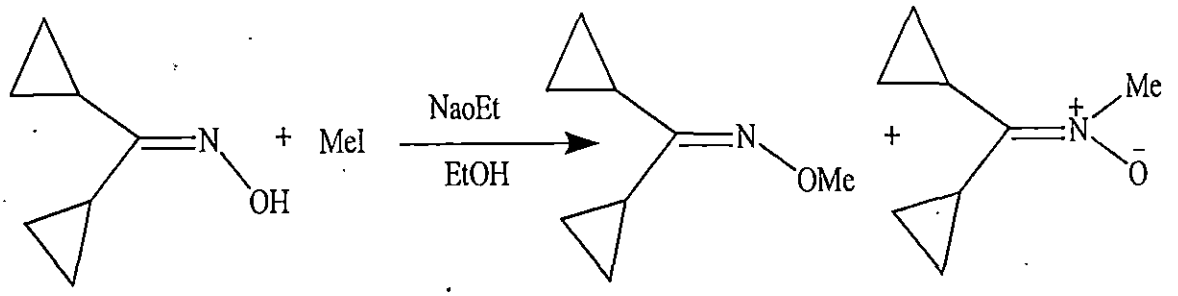


Fig 15

Formation of nitrones was also reported by the intramolecular Michael addition of aldoximes and ketoximes to electronegative olefins[25].

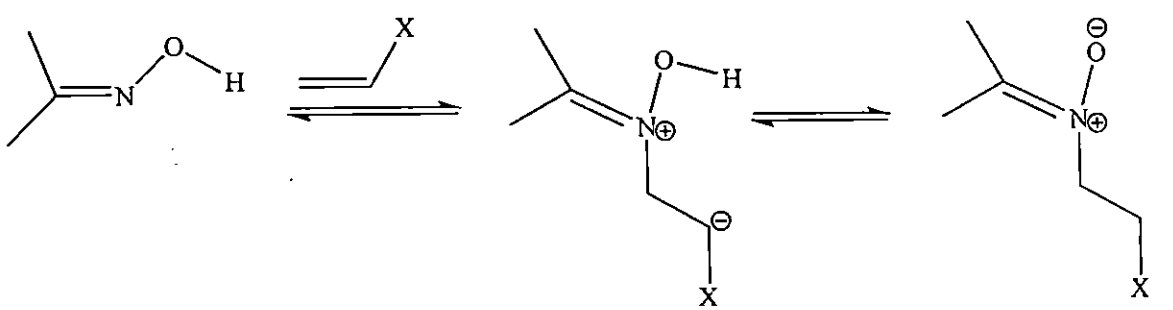


Figure 16

Recently oxime-*O*-allyl ether were converted to the corresponding *N*-allyl nitrones on treatment with 10 mole % of $PdCl_2$ ($MeCN_2$) by a formal [2+3] sigmatropic shift[26].

Formation of cyclic *N*–vinyl nitrones were also reported from δ-alkenyl oximes by a concerted 2n + 2π + 2δ 1, 3 – azprotio cyclotransfer reaction[27].Both the reaction proceeds smoothly and high yields were reported. This is one of the best methods for the preparation of aldonitrones. *N*-phenylhydroxylamine has been treated with a variety of aldehydes and ketones. *N*-cyclohexyl methylene nitrone[28] similar to *N*-phenyl methylene nitrone[29] can be prepared by passing formaldehyde gas through *N*-cyclohexylhydroxylamine in methylene chloride and anhydrous $MgSO_4$.

From aromatic nitroso compounds

Aromatic nitroso compounds react with a variety of compounds to form nitrones. 2, 4, 6-trinitro toluene, 9-methyl acrydine with sufficiently active methylene group react with aromatic nitroso compound to form nitrones[30,31]. The reaction is usually catalysed by trace amount of base (e.g. pyridine). One of the example of this type of reaction is shown in the following way.

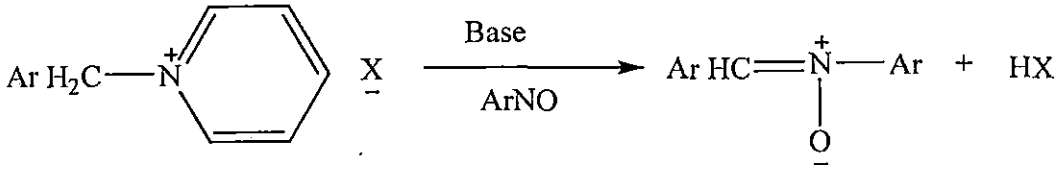


Fig 17

Aromatic nitroso compounds react with benzyl derivatives such as benzyl chloride in presence of some suitable base to yield nitrones[32,33].

Some other miscellaneous methods

Quinones yielded dinitrones upon treatment with nitrosobenzene[34].

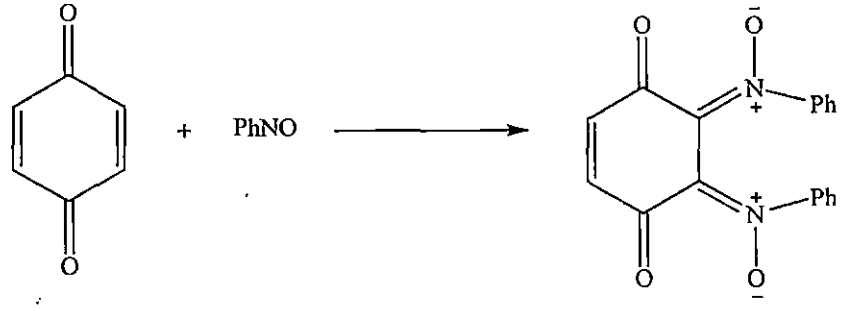


Fig 18

N–methyl nitrones can be generated in good to excellent yields from aldehyde and ketone with stoichiometric amount of *N*-Me, *N-bis* (trimethyl silyl) hydroxylamine[35]. Nitrones can also be isolated in pure state from D – glucose oximes and benzaldehyde without employing any protection of hydroxyl group[36].

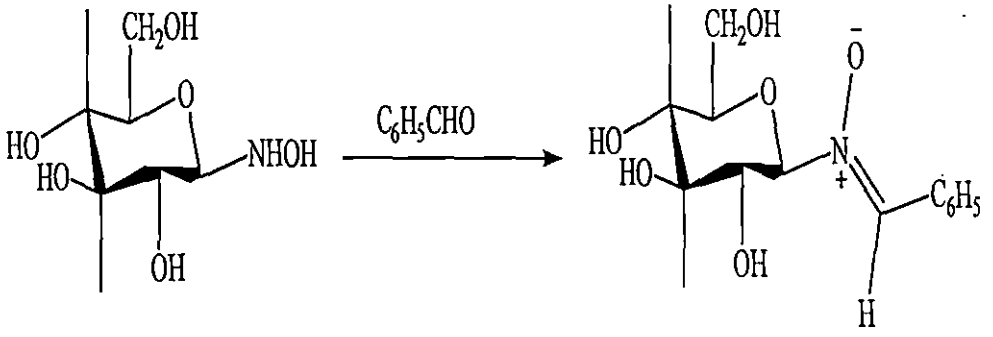


Fig 19

Nitrones can be obtained by the treatment of trimethyl silyl chloride and triethyl amine on nitroalkanes also[37].

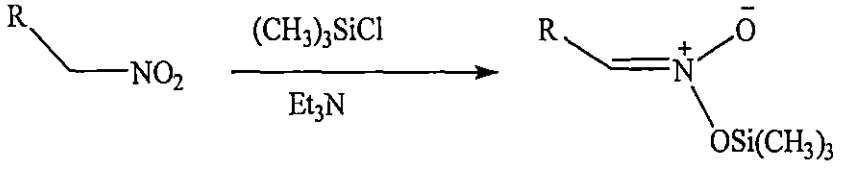
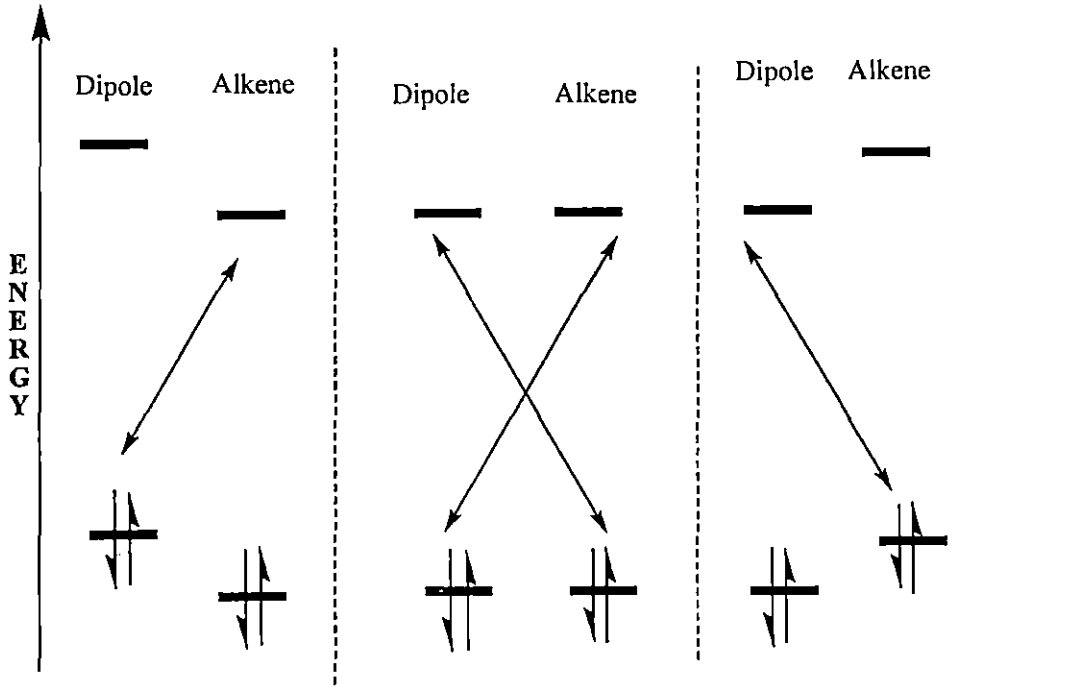


Fig 20

1,3 dipolar cycloaddition reaction

K. N. Houk et al[38] pointed out that mechanistic investigations have shown cycloadditions of 1,3-dipole to alkenes are stereospecifically suprafacial, solvent polarity have a little effect on reaction rates and small activation enthalpies. These facts along with reactivity and regioselectivity have been considered totally compatible with concerted five centered mechanism. Orbital symmetry consideration have provided permissive though not obligatory, theoretical evidence for the concerted mechanism and the observation of [4 π's and 6 π's] cycloaddition but not [4 π's + 4 π's] cycloaddition of 1,3-dipoles to diene has provided further evidence for the concerted mechanism. But the experimentally observed regioselectivity of most of the 1,3-dipolar cycloaddition has been the most difficult phenomenon to explain.

Houk et al solved this problem with the use of generalized frontier orbitals of 1,3-dipoles and dipolarophiles within the frame work of frontier molecular orbital theory. Whether 1,3-dipolar cycloaddition reaction to be allowed or forbidden may be judged according to the symmetry properties of the HOMO and LUMO orbitals of the dienes and the dipolarophiles as proposed by Sustman[39].



	Type I	*Type II*	*Type III*
	HOMO$_{dipole}$ — LUMO$_{alkene}$	HOMO$_{dipole}$ — LUMO$_{alkene}$ + HOMO$_{alkene}$ — LUMO$_{dipole}$	HOMO$_{alkene}$ — LUMO$_{dipole}$
Types of Dipoles	**azomethine ylides, azomethine imines, nitrile ylides**	**nitrones, nitrile oxides**	**ozone, nitrous oxide**

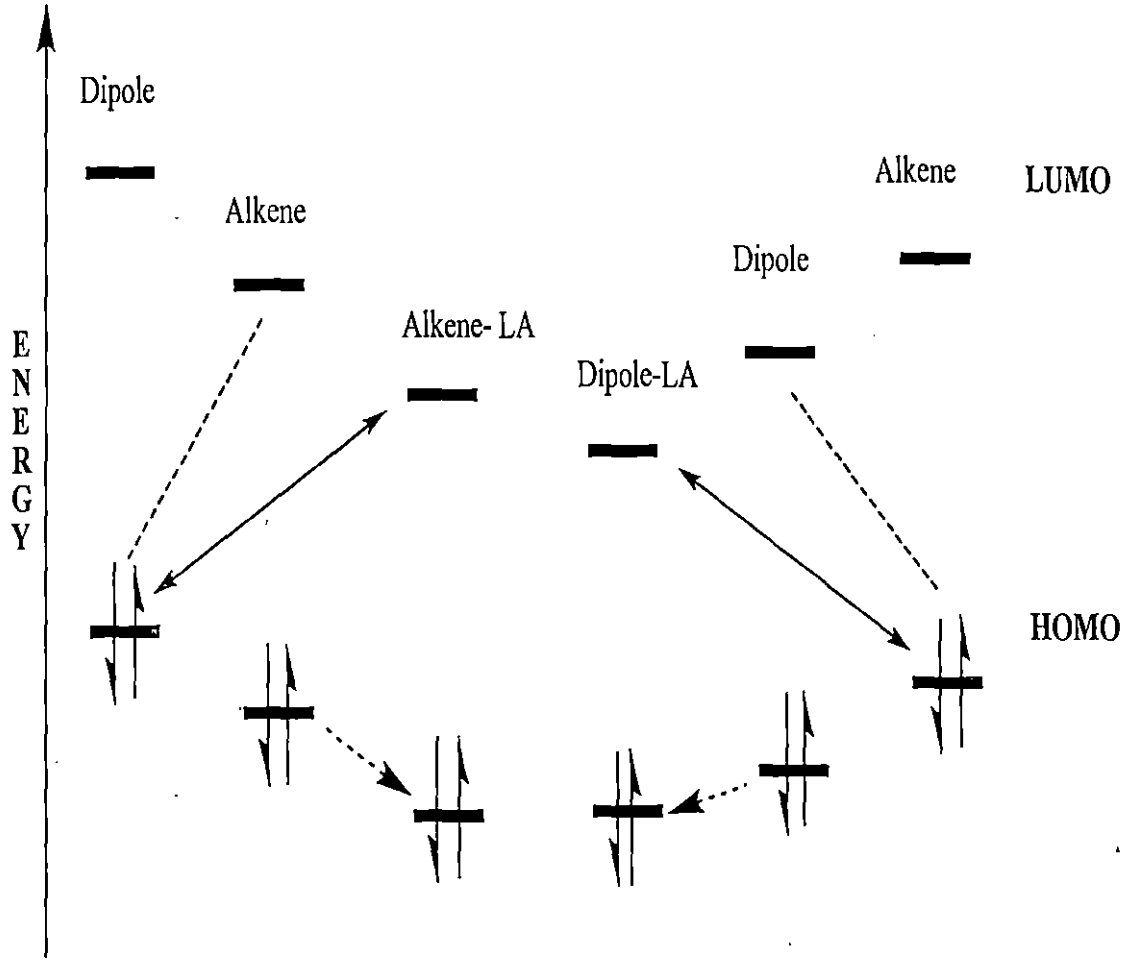
Type I: It involves dominant interaction between LUMO (dipole)–HOMO (dipolarophiles).

Type II: It involves LUMO (dipole)-HOMO (dipolarophiles). But in type II, both the LUMO (dipole)-HOMO (dipolarophiles) and HOMO (dipole)-LUMO (dipolarophiles) are important in determining reactivity and regioselectivity. Type *I* dipoles are those having high lying HOMO's and LUMO's and referred to as HOMO controlled or nucleophilic 1,3-dipoles. It is referred to as HUMO-LUMO controlled dipoles.

Type III: It has low lying FMO's and referred to as LUMO controlled or electophilic dipoles.

Molecular orbital theory behind 1,3-dipolar cycloadditions

Lewis acid activation



Coordination of LA to either the dipole or the alkene results in LUMO lowering and a faster reaction rate

Hauk et al have treated all common 1,3-dipoles according to this simple model and have shown that the prediction satisfactorily explains all the experimental results. The nitrile ylides, diazoalkanes and azomethine ylides are HOMO controlled 1,3 dipoles, reacting readily with alkenes having one or more electron withdrawing substituents. The nitrile imines, azides and azomethyne imines are HOMO-LUMO controlled dipoles which react rapidly with both electron rich as well as electron deficient dipolarophiles. The nitrile oxides and nitrones are also HOMO-LUMO controlled dipoles, but these species are skewed towards the LUMO controlled side. Finally,

species with several electro negative atoms are LUMO controlled 1,3 dipoles. *e.g.* – nitrous oxide and ozone.

The interaction of the dipole LUMO with dipolarophiles HOMO favours the formation of the product with the substituent on carbon adjacent to z while the opposite frontier orbital interaction favours opposite regioisomers. The HOMO's of the 1,3 dipolar system generally have larger terminal co-efficient on the group z while the LUMO's have larger co-efficient at the opposite terminus. The HOMO's and LUMO's of 1,3 dipoles are quantitatively similar to those of allyl anion. The greater differences in terminal co-efficient occur when the two terminal differ greatly in electronegativity.

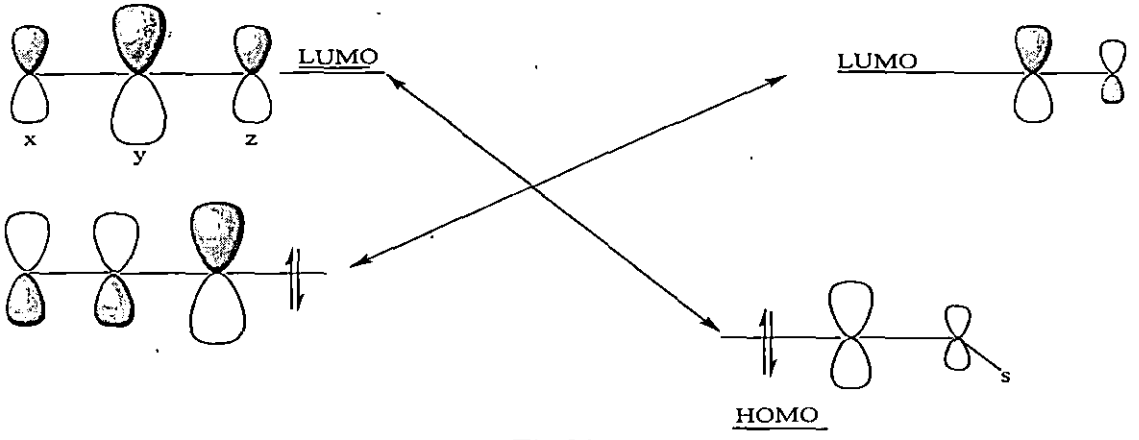


Fig 21

Nitrile oxides and nitrones react to give mainly the five substituted adduct with weakly electron deficient alkenes like acrylonitrile and ethyl acrylate. The HOMO's and LUMO's of these electron deficient alkenes both interact fairly with the LUMO's and HOMO's of the nitrile oxides and nitrones so that the orientation is influenced by both the interactions. The experimental results shows that the dipole LUMO – dipolarophile HOMO has more influence on regioselectivity. Huisgen[40] observed that acetylinic dipolarophiles are less reactive then expected on basis of their ionization potentials. Since alkynes have large HOMO – LUMO gap then alkenes, it is expected that during interactions with the alkyne, LUMO plays the most significant part and hence alkynes are less reactive then as expected. However, the reactivity of nitrones with both electron deficient alkynes and alkenes are actually determined by dipole (HOMO)-dipolarophiles (LUMO) interactions and the regiochemistry in former case is still controlled by dipole (LUMO)-dipolarophiles (HOMO) interaction therefore in

case of alkyne, the dipole (HOMO)-dipolarophiles (LUMO) interactions become very important and dominates the reaction for the formation of 4- substituted adducts.

Stereoselectivity in nitrone cycloaddition

Nitrone addition is always *cis* to dipolarophiles, so the relative stereochemistry at C_4 and C_5 is always determined by the geometric relationship of the substituents on the alkene. *Syn* and *anti* isomers of dipole (stability and therefore proportion of each depends on steric considerations and hydrogen bonding etc.) can lead to diastereoisomeric products depending on approach of dipole and dipolarophiles. *Exo / endo* approach of dipolarophiles needs to be considered. Secondary orbital interactions are not relevant, as in Diels-alder reactions, steric interactions are important. So the *exo* product is the more stable product.

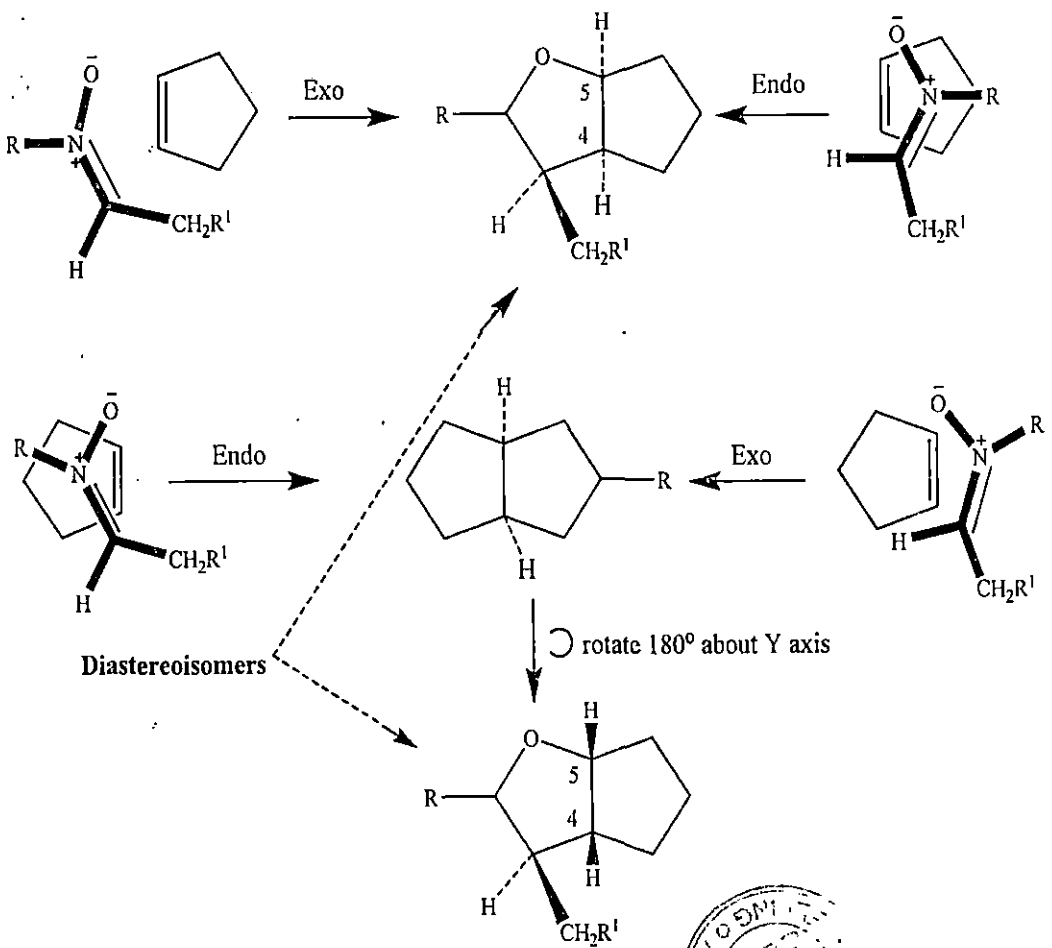
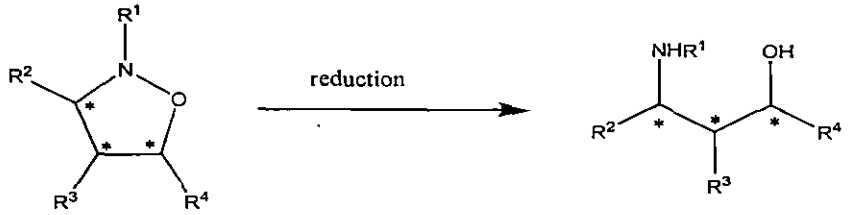


Fig. 22

Formation of biologically active amino alcohol from isoxazolidine formed by 1, 3 – dipolar cycloaddition reaction



Isoxazolidine **β - amino alcohol**

Fig. 23

1,3 – dipolar cycloaddition reaction can create up to three asymmetric centers (* = stereocenter).

A comprehensive review on the generation of different type of nitrones and their 1,3-dipolar cycloaddition reaction has been studied along with their biological properties *viz*; antimicrobial, antitumor, antifungal, antibacterial, activities. From the literature consultation it has been found that majority of the nitrones are generated in situ. Because of their instability, 1,3-dipolar cycloaddition reactions are carried out by trapping the nitrones at the time of their formation. This process avoids dimerization of the nitrone and the yield of the cycloadducts is also extremely high.

Current literature survey:

The recent reviews (from 2001 onwards) suggest that the greater emphasis has been given to the greener chemistry. Environment friendliness and sustainable development being the need of the hour, instead of using conventional solvents like benzene, dichloromethane, tetrahydrofuran etc, synthesis of the nitrone and their cycloaddition reactions nowadays are mainly performed in the following ways:

- Microwave assisted synthesis of nitrones and their cycloaddition reactions
- Solid phase synthesis of nitrones and their cycloaddition reaction
- Aqueous phase synthesis

In all the cases the reactions are mild, easy work up and the isolation of the compounds are not so difficult. Interestingly in these cases better yields, lesser required time are reported compared to conventional methods. Nowadays aqueous phase cycloaddition reaction is mostly applied to avoid hazardous solvents and also to get higher yields in a short reaction time and is completely a green approach of cycloaddition reaction of nitrones. Some research articles in this regard have been

already published in *Indian Journal of Heterocyclic Chemistry and Indian Journal of Chemistry, Section B* from our laboratory[41,42,43].

Microwave induced intramolecular 1,3-dipolar cycloaddition reactions of *N*-substituted oximes, nitrones etc. are highly stereoselective in nature[44]. These reactions are generally carried out on the surface of silica gel without adding a solvent and have been conducted under microwave irradiation to form functionalized tricyclic isoxazolidines fused with pyrolidine or piperidine ring in extremely good yield. From 2000 onwards it has been found that High Resolution Mass Spectra (HRMS),^{13}C NMR and X-ray crystallography of single crystal studies are commonly used for the characterization of nitrone and cycloadducts.In the present study, we have used HRMS, ^{13}C NMR techniques along with ^{1}H NMR and IR studies. The most important advantage of the microwave studies regarding the formation of cycloadducts is that within a very short period of time (3 to 8 min) generally 70 – 90 % and sometimes 100 % yield are found to be reported. It has been also suggested from the new works found in the literature that microwave irradiation is also potentially useful for the chiral synthesis of functionalized nitrogen heterocycles using suitable starting materials.

From the research article published by Q. Chang and his group[44], it has been found from the spectral analysis that the spectra of one of the oxime that gets converted to nitrone by microwave irradiation, gives HRMS authentic value in support of the structure of the nitrone.

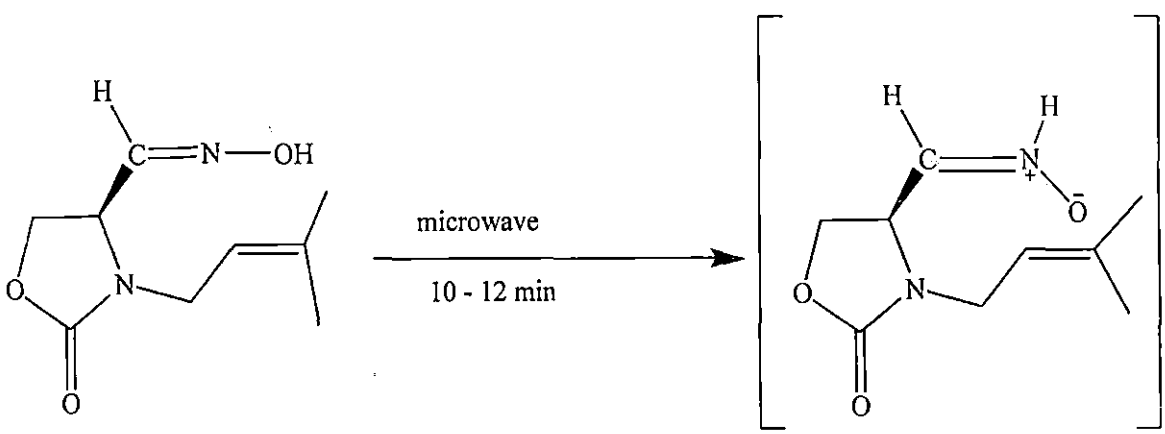
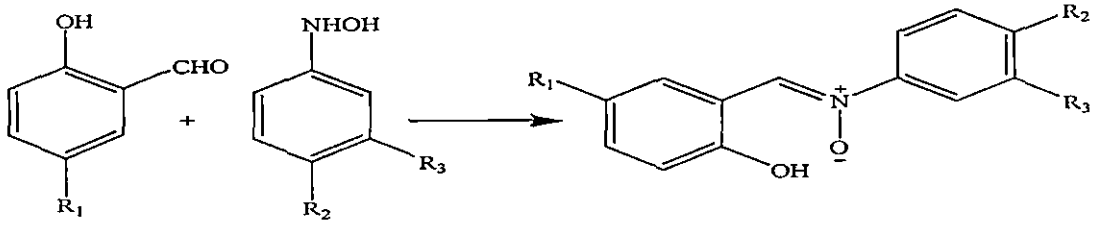


Figure 24

From the structure, calculated value for $C_9H_{14}N_2O_3$ (M) has been found to be 198.1003 while the experimental value is found to be 198.1006.

A good review[45] on microwave assisted 1,3-dipolar cycloaddition reaction was published on 2003 in *Indian Journal of chemistry Sec B* from Madurai Kamraj University by S. Muthusubramaniun and his co – workers. They synthesized α-(5-substituted-2-hydroxyaryl)-*N*-arylnitrones. They have shown that in microwave reaction the required time for the cycloaddition is much less and the yield is much higher than the conventional methods.



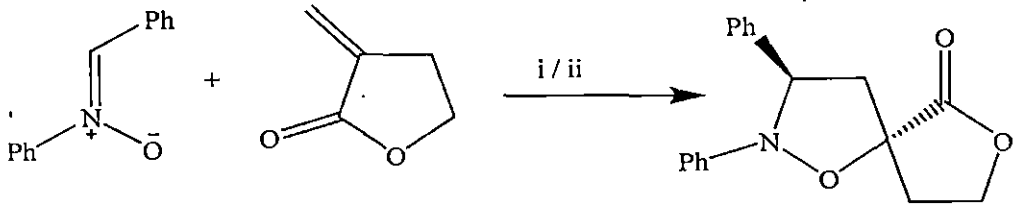
R_1 = t-Bu, i-Pr, Ph

R_2 = H, Me, Cl

R_3 = H, Me

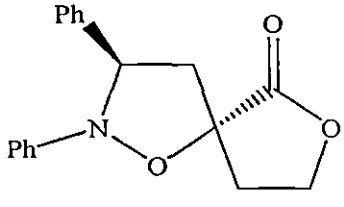
Figure 25

Another important work suggested by A. Goti and his co-workers[46] in Italy, working with *C*, *N*-diphenyl nitrone and the dipolarophiles were used are butyrolactones. The reactions are highly stereoselective in nature giving both the enantiomers having high yield. It has been found in the following scheme:



a

+



b

i Benzene, 80°C, 5 hr a : b = 90 : 10 (ee 82%)

ii Toluene, 110°C, 3 hr a : b = 80 : 20 (ee 89%)

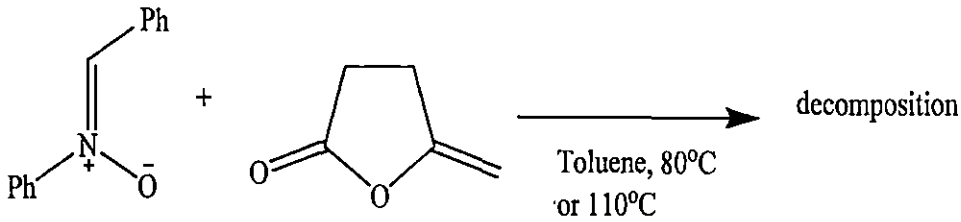


Figure 26

Another brilliant work was suggested by R. Shintani and Gregory C. Fu[47] suggest a copper catalysed [3+2] cycloaddition reaction which is a enantioselective coupling of terminal alkenes with azomethyne imines to generate five membered heterocycles.

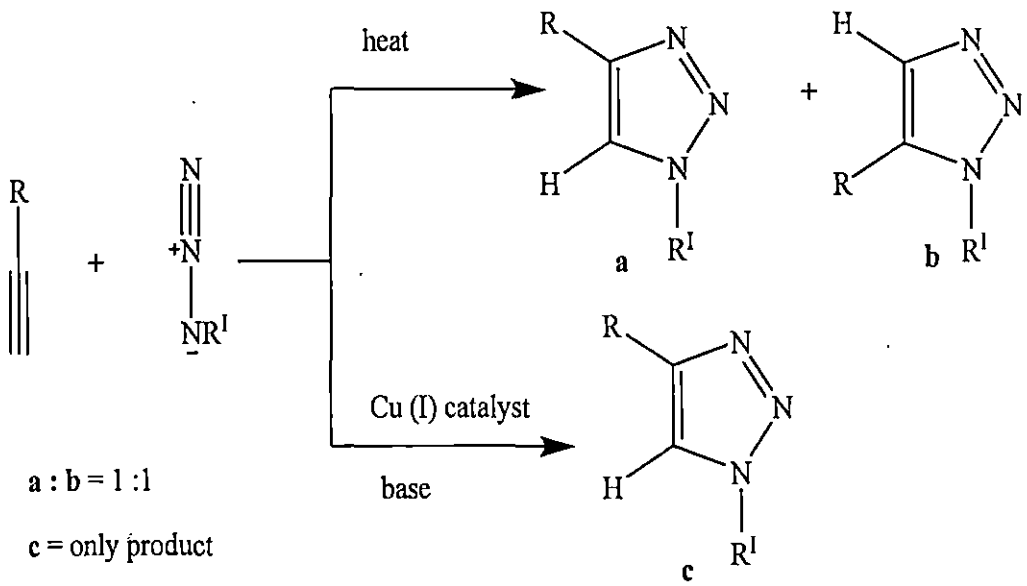


Figure 27

Some new works on nitrone cycloaddition reaction has been suggested by K. V. Kudryavtsev and V. Irkha[48] which suggest 1,3-dipolar cycloaddition reaction of homoprolein, involving protein chemistry using *N*-methyl maleimide. The most important feature of this reaction is the multicomponent raction.

Anup Bhattacharya et. al[49] suggests some remarkable work on glucose derivatives in the year 2005 which suggests intramolecular 1,3-dipolar nitrone and nitrile oxide cycloaddition of 2 and 4 allyl and propergyl glucose derivatives. This is the versatile approach to chiral cyclic ether fused isoxazolidines, isoxazolines, isoxazoles.

With the help of 1,3-dipolar cycloaddition reaction natural products also can be prepared and was shown by G. W. Gribble and his coworkers[50] in the year 1985 and has been published in *Journal of Organic Chemistry*. Later on A. Padwa in his latest

review has given emphasis on the synthetic application of nitrones towards natural products (Ref 54).

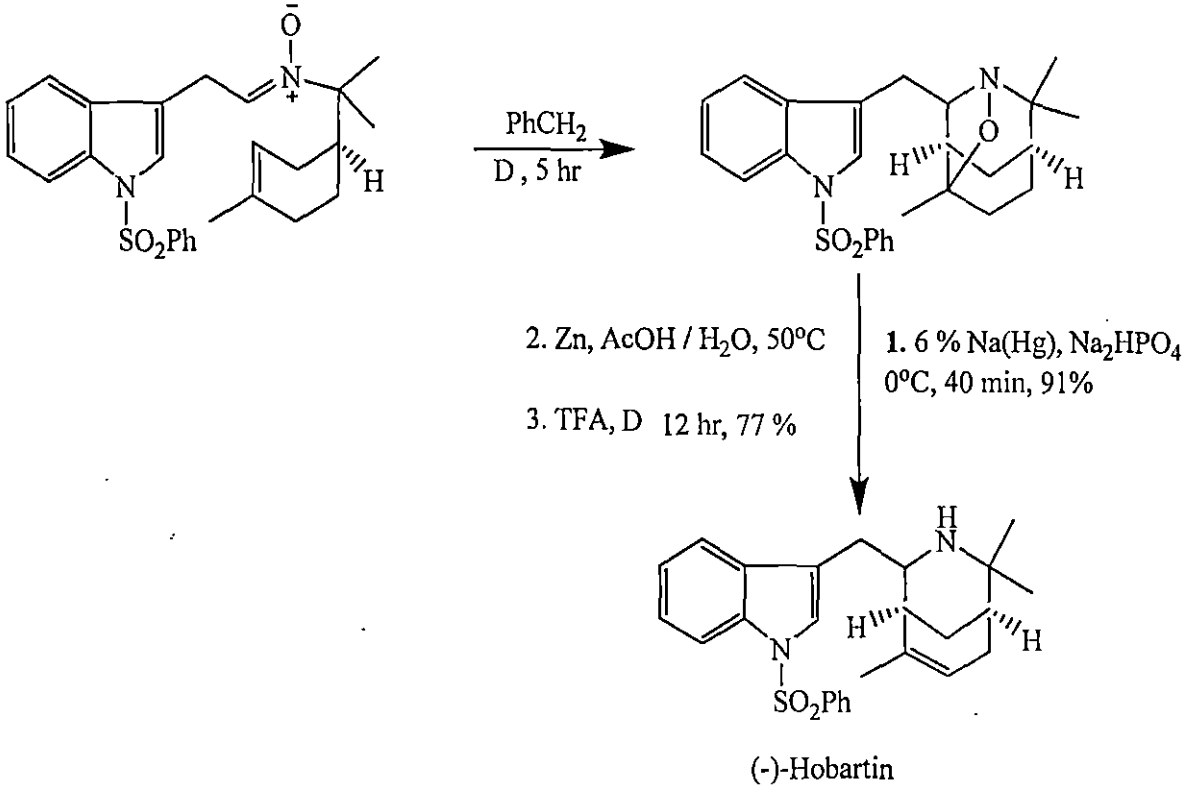


Figure 28

It has been found from various literature survey that newly formed cycloadducts as reported by different workers contain antifungal , antitumor activities but antitumor activities of the said cycloadducts are however not so common. The different workers suggest in various publications that the antitumor activities are characteristic properties of those five membered heterocycles containing oxygen and nitrogen forming the isoxazolidine and Isoxazoline or their derivatives.

Another new development in the field of antibacterial activity of isoxazolidines has been shown by Gurpinder Singh and his co – workers[51] from the intramolecular low temperature 1,3-dipolar cycloaddition reaction of nitrones where chromano heterocycles are synthesized.

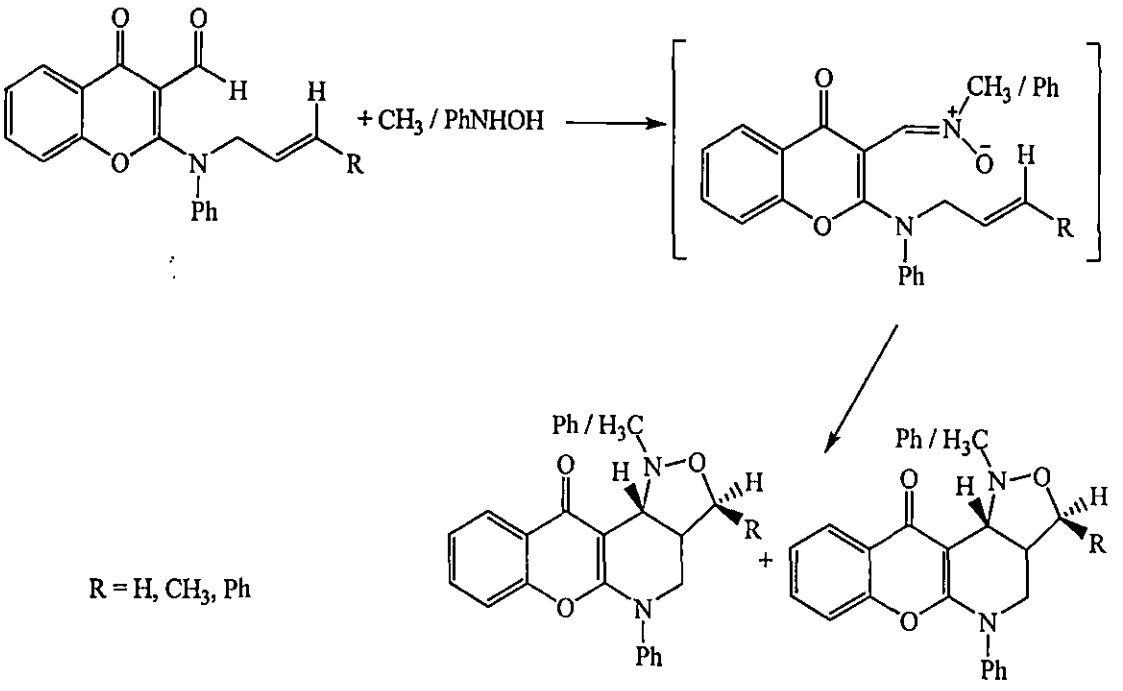
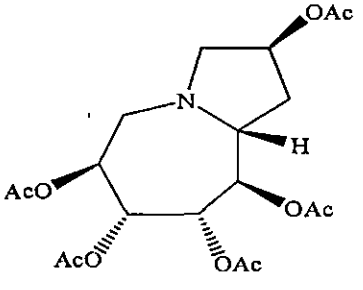


Figure 29

From the D – galactose derived nitrone 1, 3-dipolar cycloaddition reaction some per hydro aza azulene alkaloids has been synthesized. This compound has been found to have very good antimicrobial activities as reported.

During the synthesis of new amino cyclo-hexitols by the intramolecular nitrone, antifungal activities of the compounds are also reported. One of the synthesized compounds can be shown in the following way



Acetoxy-perhydroazazulene

Figure 30

Some stereoselective synthesis of pyrolidinyl glycines from nitrones also report moderate antifungal activities as reported by P. Merino and his co-workers[52].

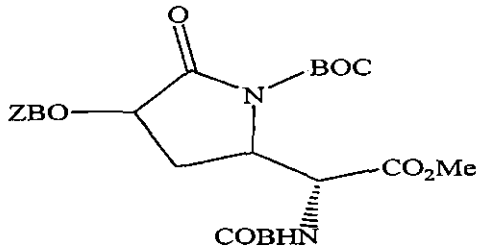


Figure 31

Penta substituted cyclopentanes have been prepared from monosaccharide. The reductive fragmentation of 5-bromo-5-deoxy hex-5-enones (a) which upon treatment with *N*-methylhydroxylamine followed by intramolecular cyclization afford chiral isoxazolidine (b) in very good yield [53].

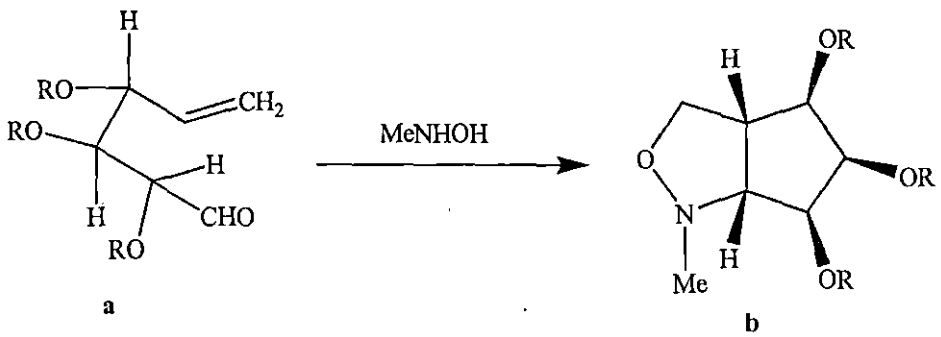


Figure 32

This compound is good antifungal agent as reported. Some of the antitumor activities shown by the cycloadducts formed between α-phenyl-*N*-methyl nitrone with *p*-methoxy styrene and *p*-methyl styrene. It has been found from the detailed survey work that isoxazolidines are more powerful antifungal, antibacterial agents compared to isoxazolines.

In addition to all literature survey shown above, we have also reported antitumor, antibacterial, antifungal activities of isoxazolidine derivatives (Ref 43) which are synthesized in our laboratory following the method which are represented earlier.

The recent reviews of A. Padwa[54] suggest some brilliant work regarding antimicrobial and antitumor activities of cycloadducts formed. The results are at par with the works we have completed in our laboratory to study antimicrobial, antifungal activities along with normal cycloaddition reactions.

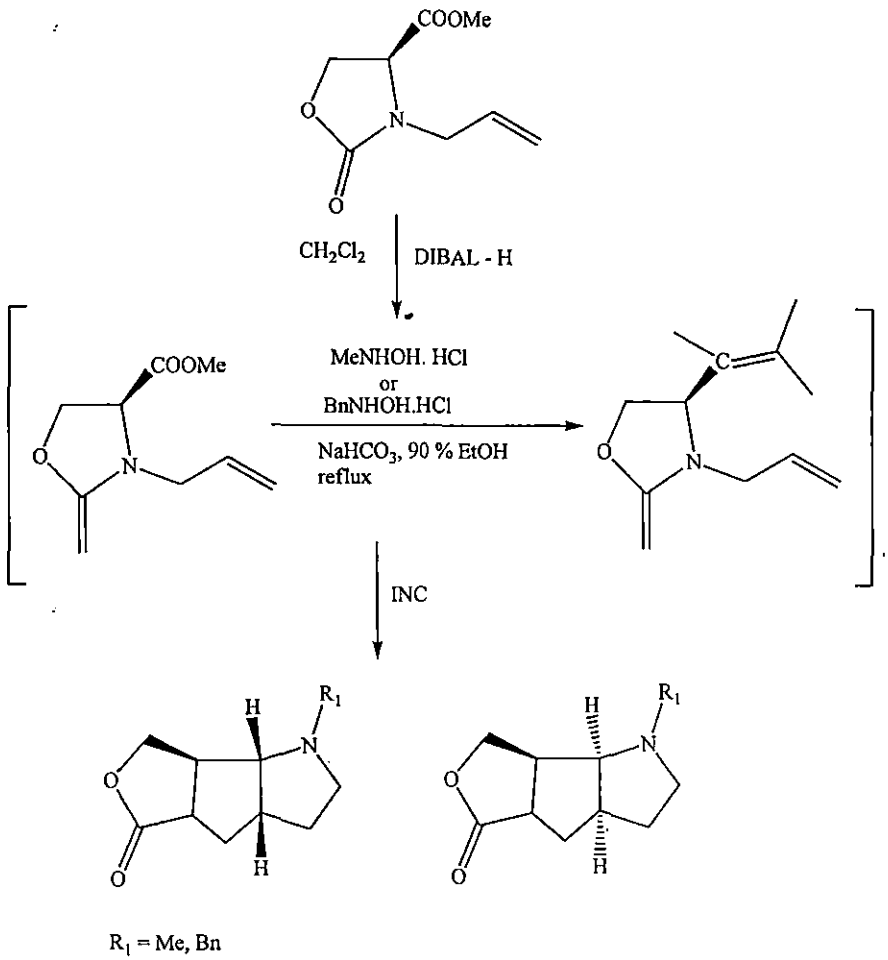
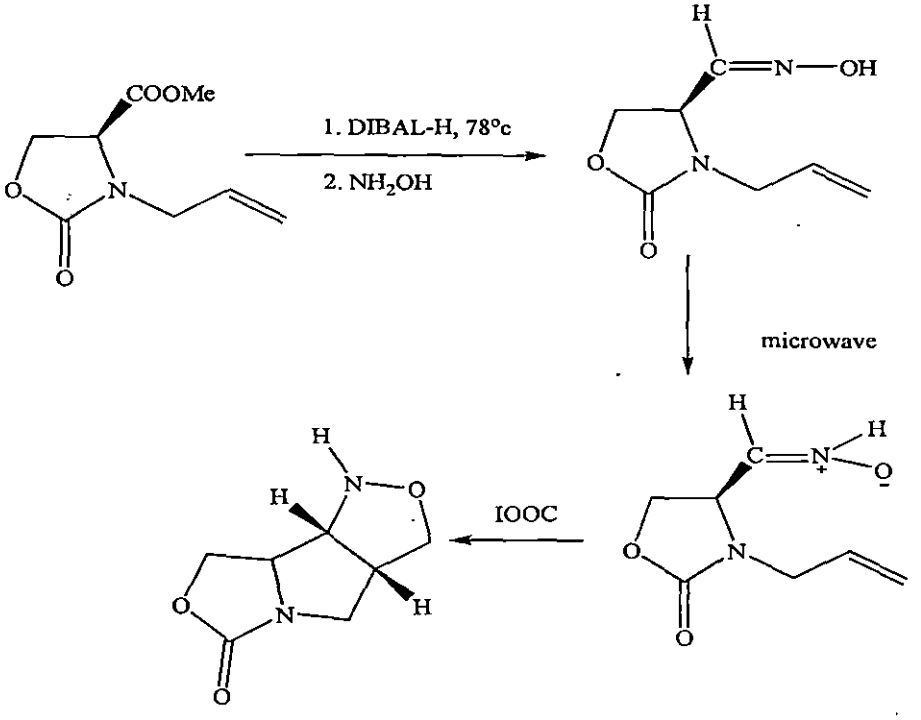


Figure 33

It has been found from the review work that the newly synthesized compounds were screened for antimicrobial activities in vitro using gram positive bacteria *E. Coli* and gram negative bacteria *Serrative Marcesens* by disc diffusion method[55]. T*etracycline* was employed as reference standard (10 microgram) to evaluate the potential of tested compounds. Among the selected compounds screened for antimicrobial activities, very few showed potential antibacterial activity.

Highly stereoselective intramolecular cycloaddition reactions of unsaturated *N*-substituted oximes, nitrones and azomethyne ylides on the surface of the silica gel without a solvent have been conducted under microwave irradiation to produce tricyclic isoxazolidines fused with pyroline or pipyridine ring in good yields were reported by Q. Chang, W. Zhang, Y. Tagan and their group in the year 2001[56].



IOOC = Intramolecular oxime-olefin cycloaddition

Fig 34

A series of unexpected cycloadducts along with normal cycloadducts have been reported by Abhijit Banerjee and his group[57] using 1,3-dipolar cycloaddition reaction of 3,4-dehydro morpholine *N*-oxide with pipyridine of cinnamic acid and *p*-substituted cinnamic acids. Since unexpected cycloadducts are quite rare therefore this work has immense interest for the workers of nitrone cycloaddition reactions.

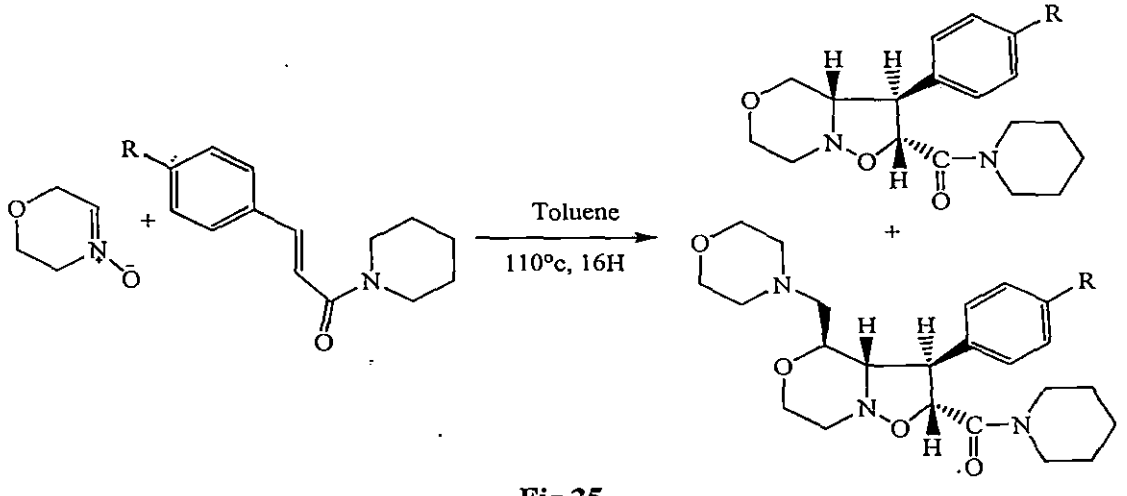


Fig 35

A brilliant work reported by Francis Heaney, Oliver Rooney in 2001[58] which reports the formation of *bis* isoxazolidines involving *bis* nitrones using *N*-methyl maleimide

as □dipolarophiles. The reaction as reported is highly diastereospecific in nature. This has the first reported case of bis isoxazolidines.

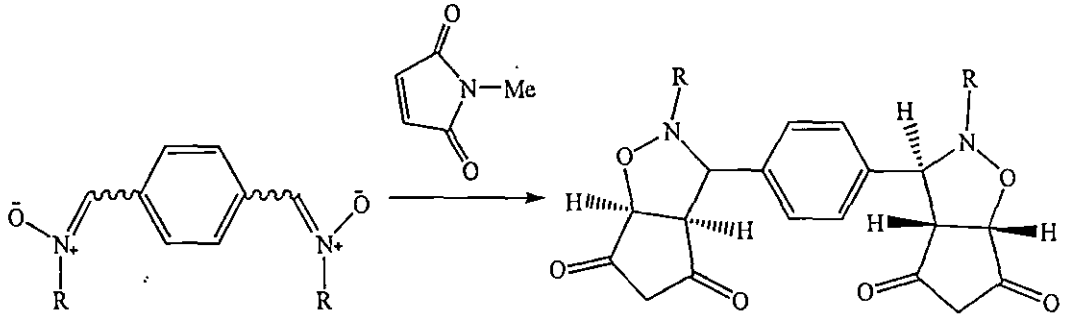
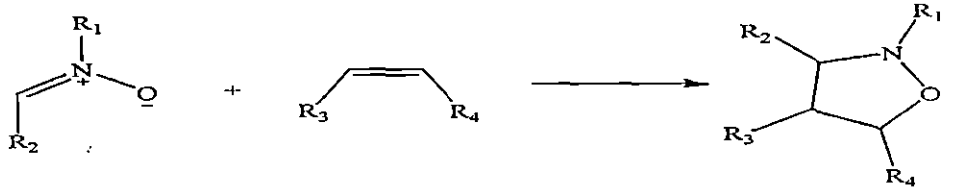


Fig 36

Reports of 1,3-dipolar cycloaddition reaction of nitrones in aqueous solution was first ever reported by O. Mersbergen and his group[59] in 1988 where the reaction rate and yield of the reactions were reported as much higher compared to usual or conventional cycloaddition reactions. The common dipolarophiles used were cyclohexene, methyl vinyl ketone, styrene and *N*-methyl maleimides respectively.



$R_1 = R_2 = Ph$ or $R_1 = Me$; $R_2 = Ph$

Fig 37

Development of nitrones and their cycloaddition reactions from oxaziridines involving *N*-sulphonyl nitrones were reported recently in 2008 by K. M. Patridge and their group[60]. This work is novel, as far the formation of nitrone is concerned.

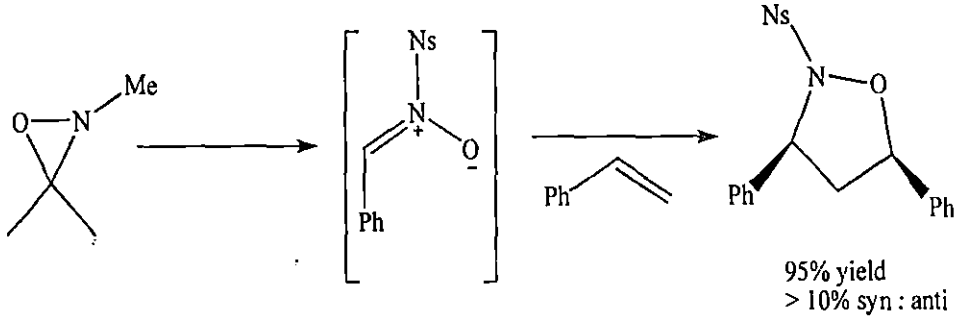
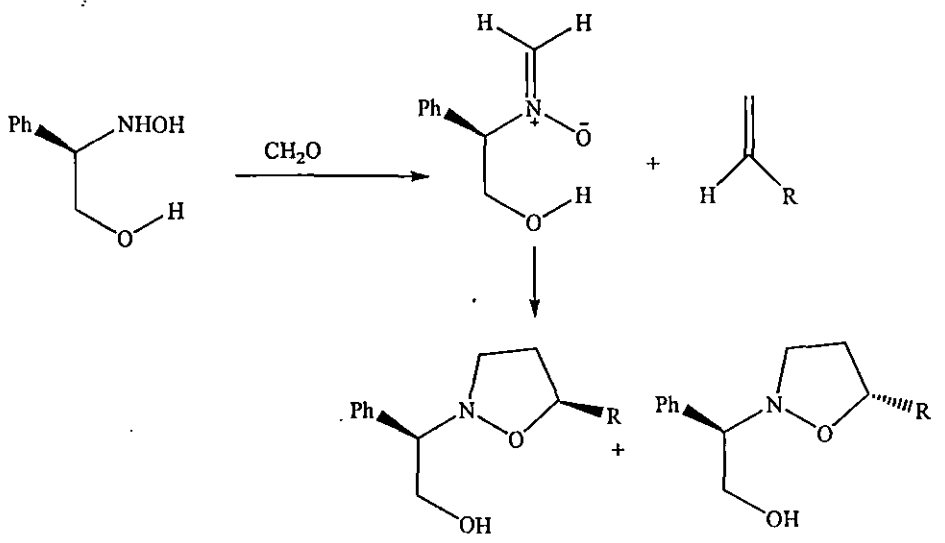


Fig 38

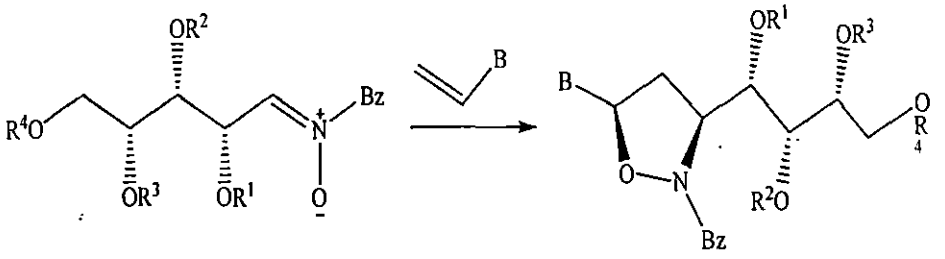
In the year 2007, Sheikh Ali and his group[61] reported a new stereochemical approach of 1,3-dipolar cycloaddition reaction of internally H-bonded chiral methylene nitrones.



R = $(CH_2)_3CH_3$, PHCHO, CO_2Me, CO_2Bu, CH_2OH, $CH_2OsiBuMe_2$, $CH_2CH_2OsiBuMe_2$, $CH_2CH_2CH_2OH$

Fig 39

Lubor Fisera and his group[62] reported some novel cycloaddition reactions in early 2009 where the nitrones are derived from sugars. The work is actually diastereoselective synthesis of isoxazolidinyle nucleosides by means of 1,3-dipolar cycloaddition reaction of chiral sugar derived nitrone as the key step.



R_1, $R_2 = R_3$, $R_4 = CMe_2$

R_1, $R_2 = CMe_2$, R_3 = Bz (Benzyl), R_4 = TBDPS

R_1, $R_2 = CMe_2$, R_3 = Bz (Benzyl), R_4 = TBDPS

Fig 40

An interesting example of the formation of nitrone in water exclusion reaction in aqueous media using surfactant and subsequent cycloaddition reactions in the same pot has been reported by P. K. Bhattacharya[63] as reported. This is a new example of green chemistry and it will not only lead to environmentally benign system but also provides a new aspect of reactions in water.

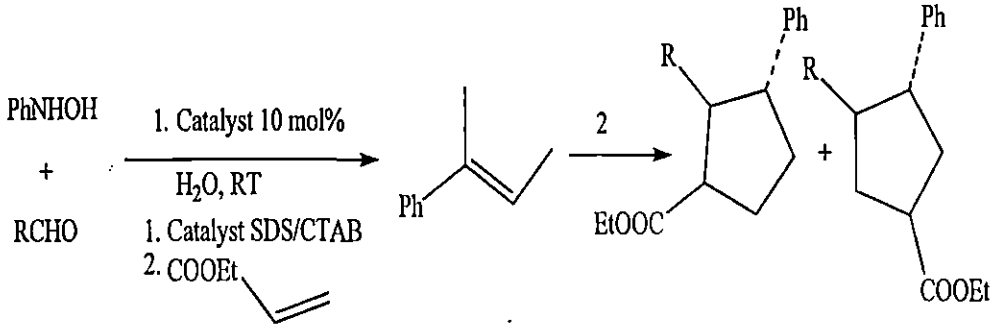


Fig. 41

An example of highly efficient solvent free 1,3-dipolar cycloaddition reaction of *N*-substituted dipolarophiles and nitrone was reported by T. B. Nguyen and his group[64]. New isoxazolidines were synthesized in good to excellent yields by 1,3-dipolar cycloaddition reactions of *N*-vinyl amide dipolarophiles and nitrones. Strikingly solvent free condition gave high conversion and yields, shortened reaction time and minimized degradation products.

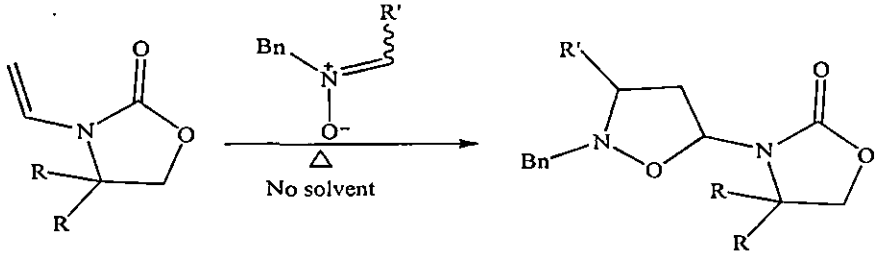
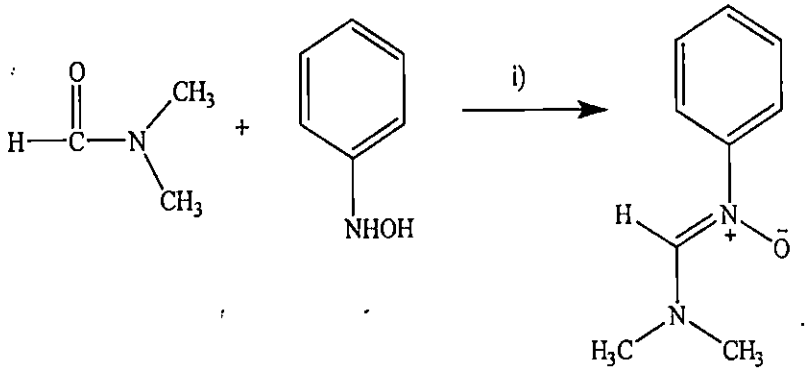
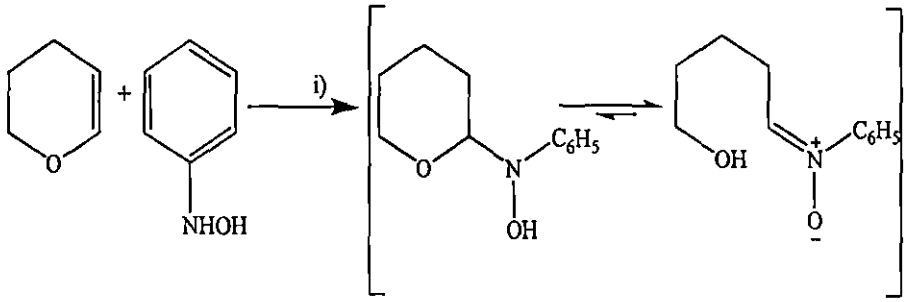


Fig 42

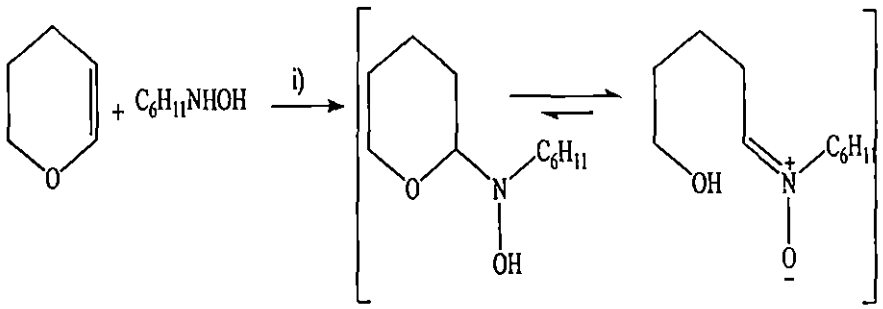
Synthesis of different *N*-cyclohexyl, *N*-phenyl-*α*-chloro nitrone along with other nitrones have also been reported from our laboratory[41- 43,65-78]. Few of the nitrones thus reported are prepared by the following way.



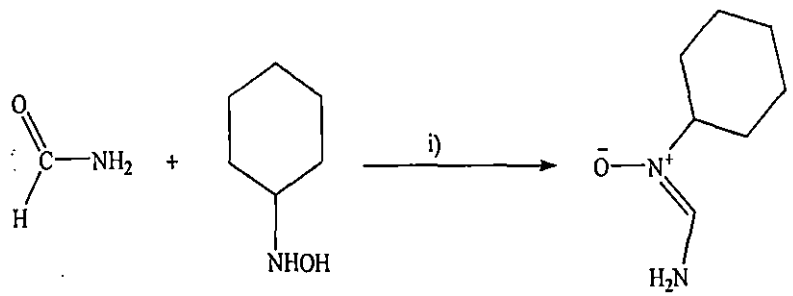
i) Anhydrous $MgSO_4$, N_2 atmosphere, RT, 12 hours



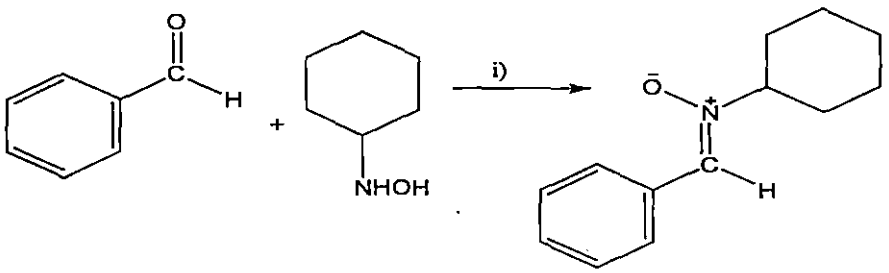
i) Anhydrous $MgSO_4$, N_2 atmosphere, Reflux, 24 hours



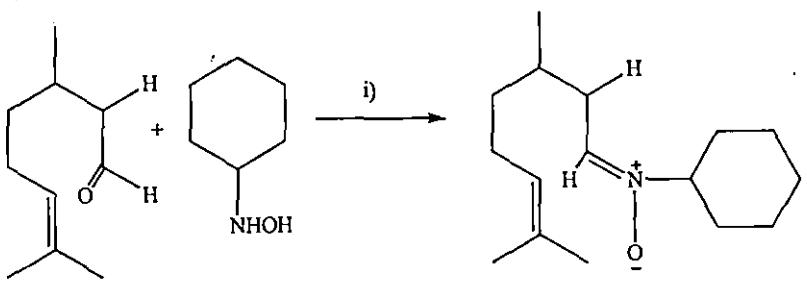
i) Anhydrous $MgSO_4$, N_2 atmosphere, Reflux, 20 hours



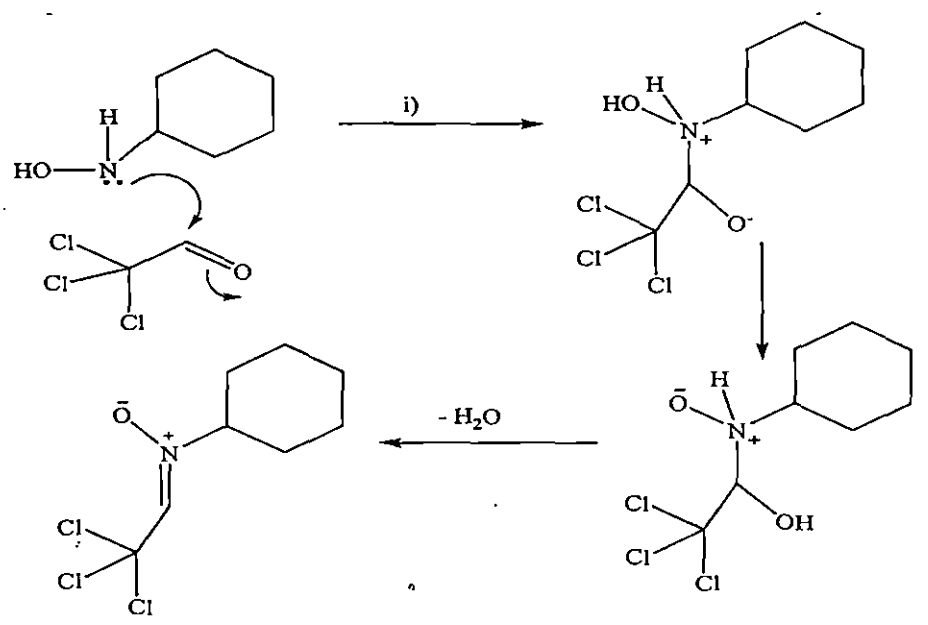
i) Dry benzene, N_2 atmosphere, RT,18 hours



i) Dry benzene, N_2 atmosphere, Reflux, 8-9 hours



i) Dry benzene, anhydrous $MgSO_4$, N_2 atmosphere, RT, 8 hr



i) Methylene chloride, N_2 atmosphere, 0-5^{0}C, anhydrous $MgSO_4$

Fig 43

REFERENCES

1. Streitwieser A, "*Molecular Orbital Theory for Organic Chemist*"; (Wiley Toppan), **1961**, 117.
2. a) Chakraborty B, Ghosh A R, *Indian J Chem* 33B, **1994**, 1113; b) Chakraborty B, *PhD dissertation*, University of North Bengal, **1996**.
3. Fukui K, Fortsch F, *ACC Chem Res*, 57, **1971**, 4.
4. Gaussian 03W program (Gaussian Inc. Pittsburg – PA), **2003**.
5. Becke D A, *J Chem Phys*, 98, **1993**, 5648.
6. Lee C, yang W, Parr R G, *Physical review (B)*, 37, **2008**, 785.
7. Smith J L, *Chem Rev*, 23, **1938**, 193.
8. Semper L and Lichtenstadt L, *Chem Rev*, 51, **1918**, 923.
9. Thesing J and Sirrenberg W, *Chem Rev*, 92, **1959**, 1748.
10. Emmons W D, *J Am Chem Soc*, 79, **1957**, 5739.
11. Exner O, *Chem Rev*, 49, **1955**, 603.
12. Thesing J, *Chem Rev*, 87, **1954**, 507.
13. Renner G, *Chem. Rev*, 92, **1953**, 193.
14. Utzinger J E, *Chem. Rev*, 50, **1944**, 550.
15. Brown C W, Roggers M A, *Chem Abst*, 55, **1961**, 6498.
16. Johnson D H, Roggers M A, *J Am Chem Soc*, 5, **1956**, 1093.
17. Brown C W and Roggers M A, *Chem Abst*, 55, **1961**, 6498.
18. Murahasi S I, Mitsui H, Watanabe T, Zenski T, *Tet Lett*, 24, **1983**, 1049.
19. Reinhaudt D N & Vanelburg P A, *Chem Rev*, 107, **1988**, 381.
20. Regenass F A, Utzing G.E, *Angew Chem*, (Intl. Ed. English), 37, **1954**, 1892.
21. Pandey G, Kumarswami G, Krishna A, *Tet Lett*, 28, **1987**, 2649.
22. Smith I L, *Chem Rev*, 23, **1938**, 193.
23. Nerdel F and Haldeshinsky I, *Chem Abst*, 86, **1953**, 1005.
24. Bimanand A Z and Houk K N, *Tet Lett*, 24, **1983**, 435.
25. Armstrong P, Grigg R, Surendrakumar S, *Tetrahedron*, 25, **1991**, 4495.
26. Grigg V, Markandu J, *Tet Lett*, 2, **1991**, 279.
27. Grigg R, Sexton J, Surendrakumar S, *J Chem. Soc*, **1993**, 372.
28. Nanda A, *Ph.D Dissertation*, University of North Bengal, Darjeeling, **1984**.
29. Heinzer F, *Ph.D Dissertation*, ETH, Zurich. Germany, **1977**.

30. Woal H L and Brink C V, *Chem Rev*, 89, **1956**, 636.
31. Kroehnki F, Kroehnki G, *Chem Abst*, 91, **1958**, 1474.
32. Colona M & Monti A, *Chem Abst*, 56, **1962**, 1546.
33. Kroehnki F, Leister H, *Chem Abst*, 90, **1957**, 2792.
34. Guenda W & Pummerer R, *Chem Rev*, 529, **1937, 1068.**
35. Robl J A & Hui J R, *J Org Chem*, 50, **1985**, 5913.
36. Fisera L, Aei U A, Pronayova U A, *Monatshefte Fur Chemie*, 124, **1993**, 1019.
37. Kim B H, Lee J, Wang D, *Tet Asym*, 2, **1991**, 27.
38. Houk K N, Sims J, Lukas C R, *J Am Chem Soc*, 95, **1973**, 7301.
39. Sustman R, *Pure Appl Chem,* 40, **1974**, 569.
40. Huisgen R, *J. Org Chem*, 41, **1976**, 403.
41. Chakraborty B & Chhetri M S, *Indian J Heterocyclic Chem*, 18, **2008**, 201.
42. Chakraborty B, Kafley S & Chhetri M S, *Indian J Heterocyclic Chem*, 18, **2008**, 204.
43. Chakraborty B, Kafley S & Chhetri M S, *Indian J Chem, Sec B* (in press: paper no. **SCCB 1225**).
44. Chang Q, Zhang W, Tagami Y, *J Am Chem Soc, Perkin Trans I,* **2001**, 755.
45. Sridharan V, Muthusubramanian S & Shivasubramanian S, *Indian J Chem*, 43B, **2004**, 857.
46. Cacciarini M, Franca M, Faggi C & Goti A, Molecules, **2000**, 637.
47. Shintani R & Fu G C, *J Am Chem Soc,* 125, **2003**, 10778.
48. Kudryavtsev K V & Irkha V, *Molecules*, 10, **2005**, 755.
49. Ghorai S, Mukherjee, R, Kundu A, Bhattacharya A, *Tetrahedron*, 61, **2005**, 2999.
50. Gribble G W & Barden T C, *J Org Chem*, 50, **1985**, 5902.
51. Singh G, Ishar M P S et al, *Tetrahedron*, 63 (22), **2007**, 4773.
52. Carmona D, Lamata P M, Viguri F, Rodriguez R, Merino P, *J Am Chem, Soc*, 127, **2005**, 13386.
53. Renner G, *Chem Rev*, 92, **1953**, 193.
54. Padwa A, "*Synthetic applications of 1,3–dipolar cycloaddition chemistry toward heterocycles and natural products*", Pearson W H, Ed, (John Wiley & sons, New York), **2003**.

55. Grigg R, J Sexton, Surendrakumar S, *J Chem Soc*, **1993**, 372.
56. Cheng Q, Zhang W, Tagami Y & Oritani T, *J Chem Soc, Perkin Trans I*, **2001**, 452.
57. Bannerjee A, Bandyopadhyay D, Prange T & Neuman A, *Tet lett*, 46, **2005**, 2617.
58. Heaney F, Rooney O, Cunningham D, Mcarde P, *J Chem Soc, Perkin Trans II*, **2001**, 373.
59. Mersbergen D, Wijnen W J & Engberts B F N, *J Org Chem*, 63, **1998**, 8801.
60. Patridge K M, Mary E, Anzovino M R & Yoon T P, *J Am Chem Soc*, 130 (10), **2008**, 2920.
61. Ali S K, Iman M Z N, *Tetrahedron*, 63, **2007**, 9134.
62. Hyrosova E, Fisera L, Kozisek J, Fronc M, *Synthesis*, 8, **2008**, 1233.
63. Chatterjee A, Maiti K A and Bhattacharjee P K, *Org Lett*, 5 (21), **2003**, 3967.
64. Nguyen B T, Martel A, Dhal R, Dujardin G, *J Org Chem*, 73, **2008**, 2621.
65. Chakraborty B, Kafley S and Chhetri M S, *Indian J Chem, 48B*, **2009**, 447.
66. Chakraborty B, Chhetri M S & Kafley S, *Indian J Heterocyclic Chem*, 18, **2009**, 283.
67. Chakraborty B, Chhetri M S, *Indian J Chem, 47B*, **2008**, 485.
68. Chakraborty B, Chhetri M. S, *Indian J Heterocyclic Chem*, 17, **2008**, 213.
69. Chakraborty B, *Indian J Heterocyclic Chem*, 17, **2008**, 293.
70. Chakraborty B, *Indian J Heterocyclic Chem*, 9, **1999**, 79.
71. Chakraborty B, *Indian J Heterocyclic Chem*, 9, **1999**, 77.
72. Chakraborty B, *Indian J Heterocyclic Chem*, 8, **1999**, 243.
73. Chakraborty B, *Indian J Heterocyclic Chem*, 7, **1997**, 231.
74. Chakraborty B, *Indian J Heterocyclic Chem*, 6, **1997**, 233.
75. Chakraborty B, *Indian J Heterocyclic Chem*, 6, **1996**, 77.
76. Chakraborty B & Ghosh A R, *Indian J Heterocyclic Chem*, 5, **1996**, 317.
77. Chakraborty B, Ghosh A R, *Indian J Heterocyclic Chem*, 5, **1995**, 99.
78. Chakraborty B, Ghosh A R, *Indian J Chem, 33B*, **1994**, 1113.

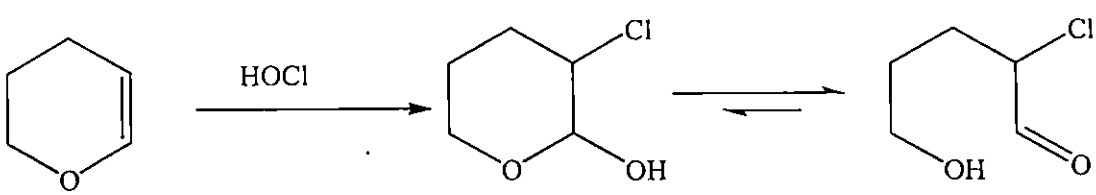
CHAPTER II

Experimental Section

All the melting points were determined in open capillary tube and were uncorrected. ^{1}H NMR spectra were recorded with a Bruker – Avans DPX 400 spectrometer (400MHz, FT NMR) using tetramethyl silane as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in hertz (Hz). Chemical shift values are given in δ ppm with tetramethyl silane as internal standard. IR spectra were obtained with a Perkin – Elmer RX 1881 machine as film for all the products. MS and HRMS spectra were recorded with a Jeol – SX 102 (FAB) instrument. Elemental analysis (C,H,N) were performed with a Perkin – Elmer 2400 series CHN analyzer. Analytical thin layer chromatography (TLC) was performed on both Fluka silica gel and Merk precoated silica gel plates (60 F_{254}). Visualization was done by exposing to iodine vapour. All the chemicals and reagents along with common solvents were purified after receiving from commercial suppliers using established procedures. *N*-cyclohexyl hydroxylamine was prepared following the methodology as already reported. *N*-phenyl hydroxylamine was prepared following the standard methods available in the literature.

Reaction type I

Preparation of Chlorohydrin



a **b**

2-Chloro-5-hydroxy pentanal

Scheme 1

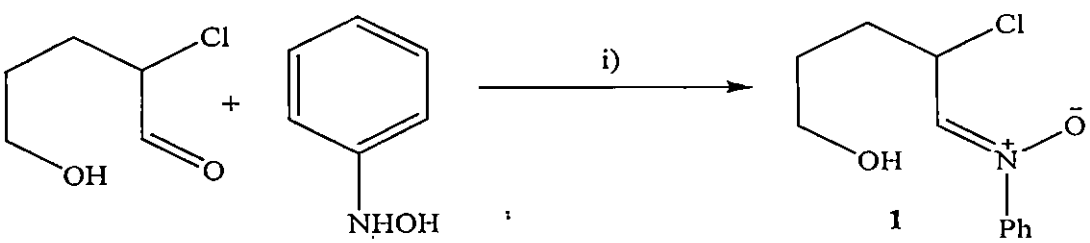
Hypochlorous acid was prepared following the standard methodology available in inorganic text books[1,2,3]. To a saturated solution of sodium bicarbonate, chlorine gas was passed till saturation. After the completion of reaction, the product was isolated by shaking with ether vigorously in a separatory funnel and finally collected by reduced pressure vacuum pump. Pure hypochlorous acid was obtained as greenish white liquid.

In a 100 mL conical flask, dihydropyran and hypochlorous acid (1 equivalent each) was taken in a required amount of DMSO as solvent and was stirred with a magnetic stirrer for 5 – 6 hour. The reaction was monitored by TLC (R_f = 0.76). After completion of the reaction the product (chlorohydrine) was isolated with ether and finally obtained under reduced pressure as a greenish gummy liquid[3].

Spectral data of 2-Chloro-5-hydroxy pentanal

Greenish gummy liquid, 74.6%; IR ($CHCl_3$): 3600 – 3200 (br), 2920 (s), 1720 (s), 1440 (m), 1380 (s), 1340 (m), 1284 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.75 (1H, CHO), 5.06 (d, 1H, J = 6 Hz, -OCH), 5.23 – 4.96 (br, 1H, -OH, exchanged in D_2O), 4.10 – 3.93 (dt~m, 1H, CHCl), 3.80 – 3.4 (m, 4H, CH_2); MS (*m/z*): 136 (M^+), 118, 108, 102, 78, 69.

Preparation of *N*-phenyl-α-chloronitrone (1)



i) anhydrous $MgSO_4$, RT, 12 hr, N_2 environment

Scheme 2

N-phenylhydroxylamine[4] (250 mg, 2.11 mmole) was added to chlorohydrin solution (1 equivalent) taken in diethyl ether (50 mL) and anhydrous $MgSO_4$. The solution was kept at room temperature for 12 hour with constant stirring with a magnetic stirrer under nitrogenous atmosphere. The formation of nitrone was monitored by TLC (R_f = 0.32). After completion of the reaction, the nitrone was isolated under reduced pressure as white needle shaped crystals, m.p, 58°C (uncorrected). The nitrone was unstable and decomposes at room temperature when kept for longer period.

Spectral data of (*Z*)-*N*-(2-chloro-5-hydroxypentylidene)aniline oxide:

White needle shape crystals, 93%, IR ($CHCl_3$): 3660 – 3520 (br), 1610 (s), 1440 (m), 1150 (s), 784 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.73 – 7.28 (m, 5H, C_6H_5), 6.45 (d, 1H, J = 6.06 Hz, $CH{=}N^+$), 5.12 (br, 1H, OH, exchanged in D_2O), 3.66 (dt~m, 1H, J = 6.06, 6.08 Hz, CHCl), 2.04 – 1.25 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 142.04 ($CH{=}N^+$), 134.80, 133.00, 131.60, 130.00 (aromatic carbons), 95.30 (CHCl), 31.45, 28.60, 25.40 (3 CH_2 carbons); HRMS – EI: Calcd. for $C_{11}H_{14}O_2NCl$, (M), 225.0864, Found M^+, 225.0852.

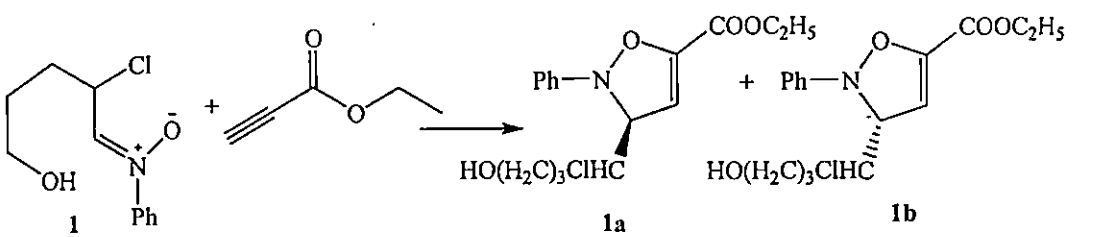
General Procedure for 1,3-dipolar cycloaddition reaction with alkynes at RT

Since *N*-phenyl-α-chloro nitrone may decompose at RT therefore the nitrone was used immediately after isolation for the cycloaddition reactions with dipolarophiles (alkynes) in a 1:1 ratio. In a 100 mL conical flask nitrone 1 (2.20 mmol), alkyne (1 equivalent) was added to 50 mL dry ether and stirred at RT with a magnetic stirrer under N_2 atmosphere for 10 - 12 hour. The progress of the reaction was monitored by TLC. After completion of the reaction the solvent was evaporated off and the products (all the cycloadducts were obtained as diastereomers) were purified and separated by column chromatography using ethyl acetate-hexane combinations to furnish pure cycloadducts. This procedure was followed for all the substrates listed in Table I.

Table 1

- Ethyl propiolate
- Dimethyl acetylene dicarboxylate
- Phenyl methyl propiolate
- Acetylene dicarboxylic acid

1. Ethyl propiolate cycloadducts



Scheme 3

In a 100 mL conical flask *N*-phenyl-α-chloro nitrone (2.20 mmol) and ethyl propiolate (1 equivalent) was added to a 50 mL dry ether and stirred at RT with a magnetic stirrer under nitrogenous atmosphere for 12 hour. The progress of the reaction was monitored by TLC (R_f = 0.42, 0.44). After completion of the reaction, the solvent was

evaporated under rotary evaporator and the mixture of diastereoisomers were purified and separated by column chromatography using ethyl acetate-hexane to furnish white viscous liquids. **1a**: 73 mg, 70 %; **1b**: 36 mg, 22 %.

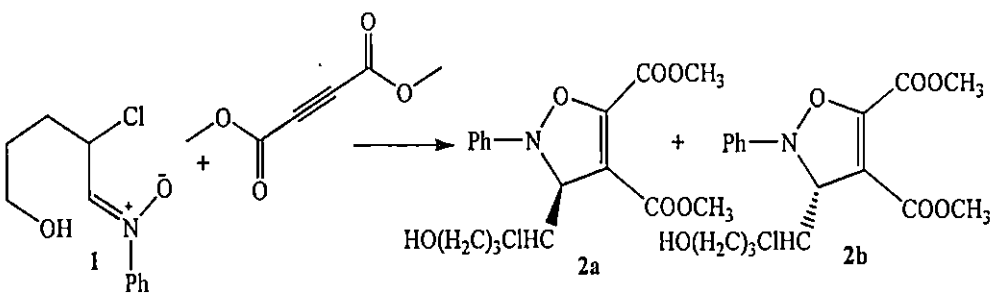
1a. Spectral data of (3*S*)-ethyl 3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-5-carboxylate

White viscous liquid, 70%; IR ($CHCl_3$): 3560 – 3490 (br), 2945 (s), 1770 (m), 1680 (s), 1430 (m), 1260 (m), 780 (s) cm^{-1} .^{1}H NMR ($CDCl_3$): δ 7.02 – 6.92 (m, 5H, C_6H_5), 5.10 - 5.02 (br, 1H, OH, exchanged in D_2O), 4.80 – 4.64 (t, 1H, J = 9.26 Hz, C_3H), 4.26 - 4.12 (dd, 2H, J = 6.24, 6.36 Hz, $COOCH_2CH_3$), 3.82 - 3.50 (dd, 1H, J = 6, 9.28 Hz, CHCl), 3.35 – 3.26 (d, 1H, J = 7.5 Hz, C_4H), 3.00 – 2.62 (m, 6H, CH_2 protons), 1.40 – 1.24 (t, 3H, J = 4.36 Hz, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 168.40 (carbonyl carbon), 133 – 126 (6 aromatic carbons), 93 (CHCl), 86 (C_5), 78 (C_3), 55 (C_4), 32, 30 ($COOCH_2CH_3$), 26, 25, 23 (3 CH_2 carbons); MS (*m/z*): 326 (M^+), 295, 253, 249, 219, 108, 77, 73; HRMS – EI: Calcd. for $C_{16}H_{20}O_4NCl$ (M) 325.5944, Found M^+, 325.5932.

1b. Spectral data of (3*R*)-ethyl 3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-5-carboxylate

White viscous liquid, 22 %; IR ($CHCl_3$): 3520 - 3440 (br), 2925 (s), 1755 (s), 1675 (m), 1440 (m), 1345 (m), 770 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.52 – 7.35 (m, 2 x 5H, C_6H_5 protons), 5.15 - 5.05 (br, 1H, -OH, exchangeable in D_2O), 4.54 - 4.43 (dd, 1H, J = 2.52, 4.18 Hz, CHCl), 4.08 - 3.92 (d, 1H, J = 2.54 Hz, C_3H), 3.62 (s, 3H, -$COOCH_3$), 1.95 - 1.50 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 168 (carbonyl carbon), 138 – 126 (6 x 2 aromatic carbons), 90 (CHCl), 87 (C_5), 76 (C_3), 54 (C_4), 45 (-$COOCH_3$), 39, 35, 33 (3 CH_2 carbons); MS (*m/z*): 326 (M^+), 295, 253, 219, 108, 77, 73; HRMS – EI: Calcd. for $C_{16}H_{20}O_4NCl$ (M) 325.5944, Found M^+, 325.5926.

2. Dimethyl acetylene dicarboxylate cycloadducts



Scheme 4

In a 100 mL conical flask, *N*-phenyl-α-chloro nitrone (2.20 mmol) and dimethyl acetylene dicarboxylate (1 equivalent) was added to a 50 mL dry ether and stirred at RT with a magnetic stirrer under nitrogenous atmosphere for 10 hr. The progress of the reaction was monitored by TLC (R_f = 0.46, 0.40). After completion of the reaction, the solvent was evaporated under rotary evaporator and the mixture of diastereoisomers were purified and separated by column chromatography using ethyl acetate-hexane to furnish white viscous liquids.

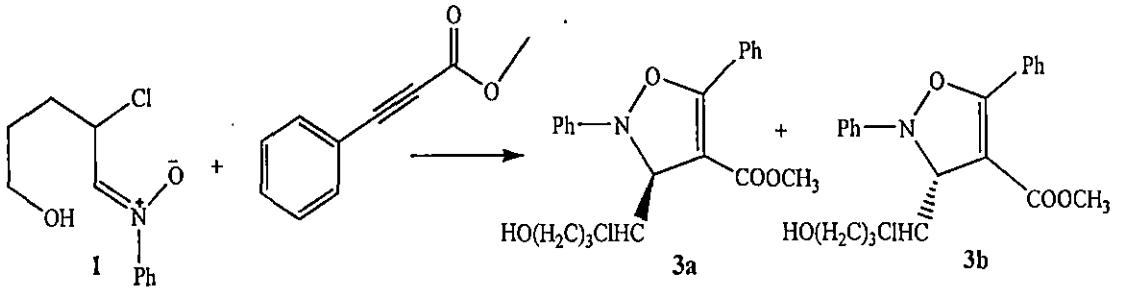
2a. Spectral data of (3*S*)-dimethyl 3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate

White viscous liquid, 69 %; IR ($CHCl_3$): 3545 – 3480 (br), 2820 (s), 1745 (s), 1700 (m), 1670 (m), 1420 (s), 1260 (m), 775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 - 7.54 (m, 5H, C_6H_5 protons), 5.22 - 5.05 (br, 1H, OH; exchanged in D_2O), 4.86 - 4.75 (d, 1H, J = 9.25 Hz, C_3H), 4.26 – 4.10 (dd, J = 6, 9.26 Hz, CHCl), 3.68 (s, 3H,- $COOCH_3$),3.56 (s, 3H,- $COOCH_3$), 2.20 - 2.05 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169, 168.4 (carbonyl carbons), 133 - 126 (6 aromatic carbons), 94 (CHCl), 87.50 (C_5), 76 (C_3), 59.45 (C_4), 44, 43 (OCH_3), 36, 34, 30 (3 CH_2 carbons); MS (*m/z*): 370 (M^+), 339, 311, 293, 283, 262, 252, 234, 204, 108, 77, 59, 31; HRMS – EI: Calcd. for $C_{17}H_{20}O_6NCl$, (M) 369.64240, Found M^+, 369.64128.

2b. Spectral data of (3*R*)-dimethyl 3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate

White viscous liquid, 27%; IR ($CHCl_3$): 3555 – 3485 (br), 2825 (s),1740 (s),1710 (m), 1660 (m), 1425 (s), 1260 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70 - 7.56 (m, 5H, C_6H_5 protons), 5.20 - 5.08 (br 1H, OH, exchanged in D_2O), 4.88 - 4.74 (d, 1H, J = 2.58 Hz, C_3H), 4.36 – 4.26 (dd, J = 4, 2.26 Hz, CHCl), 3.66 (s, 3H, - $COOCH_3$), 3.54 (s, 3H,- $COOCH_3$), 2.12 - 1.95 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169, 168 (carbonyl carbons), 134 - 126 (6 aromatic carbons), 95 (CHCl), 88.5 (C_5), 74 (C_3), 56 (C_4), 44, 42 (OCH_3), 36, 35, 30 (3 CH_2 carbons); MS (*m/z*): 370 (M^+), 311, 293, 262, 252, 234, 204, 108, 77, 59, 31; HRMS – EI: Calcd. for $C_{17}H_{20}O_6NCl$, (M), 369.6420, Found M^+, 369.6405.

3. Phenyl methyl propiolate cycloadducts



Scheme 5

In a 100 mL conical flask, *N*-phenyl-α-chloro nitrone (2.20 mmol) and phenyl methyl propiolate (1 equivalent) was added to a 50 mL dry ether and stirred at RT with a magnetic stirrer under nitrogenous atmosphere for 13 hour. The progress of the reaction was monitored by TLC (R_f = 0.46, 0.40). After completion of the reaction, the solvent was evaporated under reduced pressure and the mixture of diastereoisomers were purified and separated by column chromatography using ethyl acetate-hexane to furnish white viscous liquid.

3a. Spectral data of (3*S*)-methyl 3-(1-chloro-4-hydroxybutyl)-2,5-diphenyl-2,3-dihydroisoxazole-4-carboxylate

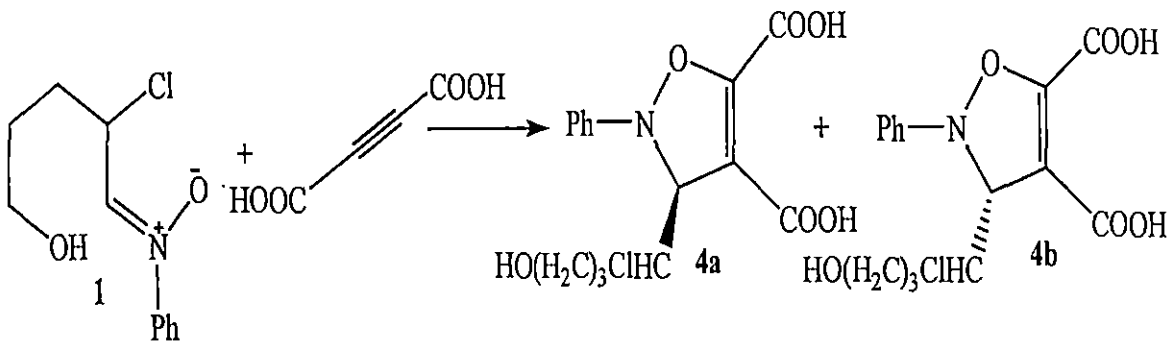
White viscous liquid, 75%; IR ($CHCl_3$): 3570 – 3420 (br), 2933 (s), 2246 (m), 1813 (m), 1662 (s), 1480 (s), 1324 (s), 1225 (s), 1105 (s), 993 (m), 779 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55 - 7.38 (m, 2x5H; C_6H_5 protons), 5.10 - 4.95 (br, 1H, -OH, exchangeable in D_2O), 4.55 - 4.40 (dd, 1H, J = 9.22, 6.18 Hz, CHCl), 4.05 - 3.90 (d, 1H, J = 9.2 Hz, C_3H), 3.60 (s, 3H, - $COOCH_3$), 1.95 - 1.72 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 168 (carbonyl carbon), 137 – 126 (6x2 aromatic carbons), 92 (CHCl), 88 (C_5), 73 (C_3), 58 (C_4), 45 (-$COOCH_3$), 36, 34, 33 (3 CH_2 carbons); MS (*m/z*): 388 (M^+), 357, 329, 311, 283, 280, 203, 105, 77; HRMS – EI: Calcd. for $C_{21}H_{22}O_4NCl$ (M), 387.7000, Found M^+, 387.6990.

3b. Spectral data of (3*R*)-methyl 3-(1-chloro-4-hydroxybutyl)-2,5-diphenyl-2,3-dihydroisoxazole-4-carboxylate

White viscous liquid, 24 %; IR ($CHCl_3$): 3520 - 3440 (br), 2925 (s), 1755 (s), 1675 (m), 1440 (m), 1345 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52 – 7.35 (m, 2x5H, C_6H_5 protons), 5.15 - 5.05 (br, 1H, - OH, exchangeable in D_2O), 4.54 - 4.43 (dd, 1H, J = 2.52, 4.18 Hz, CHCl), 4.08 - 3.92 (d, 1H, J = 2.54 Hz, C_3H), 3.62 (s, 3H, -

$COOCH_3$), 1.95 - 1.50 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 168 (carbonyl carbon), 138 - 126 (6x2 aromatic carbons), 90 (CHCl), 87 (C_5), 76(C_3), 54 (C_4), 45 (-$COOCH_3$), 39, 35, 33 (3 CH_2 carbons); MS (*m/z*): 388 (M^+), 357, 329, 311, 283, 280, 203, 105, 77; HRMS - EI: Calcd. for $C_{21}H_{22}O_4NCl$ (M) 387.7000, Found M^+ 387.6982.

4. Acetylene dicarboxylic acid cycloadducts



Scheme 6

In a 100 mL conical flask nitrone 1 (2.20 mmol), acetylene dicarboxylic acid (1 equivalent) was added to 50 mL dry ether and stirred at RT with a magnetic stirrer under N_2 atmosphere for 14 hour. The progress of the reaction was monitored by TLC (R_f = 0.38, 0.40). After completion of the reaction the crude products were concentrated on a rotary evaporator and finally the products were purified and separated by column chromatography using ethyl acetate-hexane to furnish colourless viscous liquids.

4a. Spectral data of (3*S*)-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid

Coluorless viscous liquid, 73%; IR ($CHCl_3$): 3545 – 3480 (br), 1760 (s), 1685 (m), 1420 (s), 1260 (m), 780 (s) cm^{-1}, ^1H NMR ($CDCl_3$): δ 10.12 (s, 1H, COOH), 10.04 (s, 1H, COOH), 7.75 - 7.54 (m, 5H, C_6H_5 protons), 5.22 - 5.05 (br, 1H, OH, exchanged in D_2O), 4.75 (d, 1H, J = 9.25 Hz, C_3H), 4.26 (q, 1H, J = 6, 9.26 Hz, CHCl), 2.20 - 1.75 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 180.60, 178.40 (carbonyl carbons of COOH), 133.90, 132.00, 130.50, 128.65 (aromatic carbons), 94.00 (CHCl), 87.50 (C_5), 76.00 (C_3), 59.40 (C_4), 36.00, 34.00, 32.00 (3 CH_2 carbons); MS (*m/z*): 341 (M^+), 310, 296, 268, 251, 236 ; HRMS – EI: Calcd. for $C_{15}H_{16}O_6NCl$, (M), 341.6080, Found M^+ , 341.6070.

4b. Spectral data of (3*R*)-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid

White viscous liquid, 24 %; IR ($CHCl_3$): 3560 – 3465 (br), 1765 (s), 1680 (m), 1430 (s), 1260 (m), 782 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.16 (s, 1H, COOH), 10.00 (s, 1H, COOH), 7.40 - 7.24 (m, 5H, C_6H_5 protons), 5.20 - 5.08 (br, 1H, OH, exchanged in D_2O), 4.60 (d, 1H, J = 2.50 Hz, C_3H), 4.20 (q, 1H, J = 2.20, 3.55 Hz, CHCl), 2.10 - 1.64 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 182.40, 177.60 (carbonyl carbons of COOH), 134.00, 132.70, 131.50, 129.60 (aromatic carbons), 92.40 (CHCl), 88.50 (C_5), 76.77 (C_3), 58.46 (C_4), 37.00, 36.00, 34.00 (3 CH_2 carbons); MS (*m/z*): 341 (M^+), 310, 296, 268, 251, 236; HRMS – EI: Calcd. for $C_{15}H_{16}O_6NCl$, (M), 341.6080, Found M^+ 341.6064.

General Procedure for 1,3-dipolar cycloaddition reaction of nitrone 1 in aqueous phase

To run a chemical reaction under an environment friendly condition is a challenge now-a-days. In touch with the recent developments we have also successfully carried out aqueous phase cycloaddition reaction of *N*-phenyl-α-chloronitrone[5,6]. Surprisingly aqueous phase condition gave high yield, greater selectivity in a much lesser time. Details are discussed in **results and discussion** chapter.

General procedure for cycloaddition (for diastereomers)

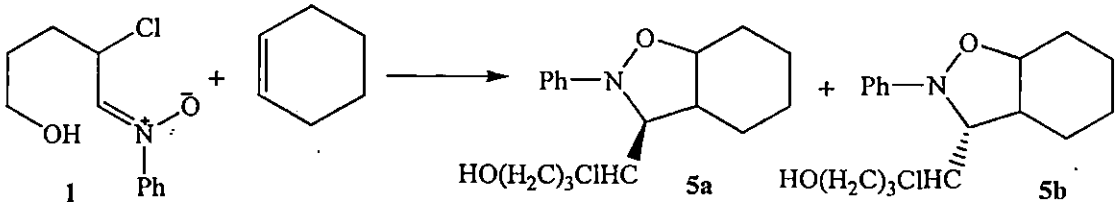
In a 50 mL conical flask, nitrone **1** (1 mmol), dipolarophile (1 mmol) and water (15 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 4-5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the products were extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate-hexane to afford cycloadducts. This procedure was followed for the substrates listed in **Table 2.**

Table 2. List of dipolarophiles used for cycloaddition reaction in aqueous phase

- Cyclohexene
- *N*-methyl maleimide
- *N*-phenyl maleimide

- *N*-cyclohexyl maleimide
- *p*-OMe-*N*-phenyl maleimide
- Acenapthylene
- Ethyl acrylate
- Methyl vinyl ketone

5. Synthesis of Cyclohexene cycloadducts



Scheme 7

To a stirred solution of nitrone **1** (1 mmol) in 15 mL water was added cyclohexene (1 equivalent) at RT under nitrogen atmosphere and the reaction mixture was stirred for 14 hr. The progress of the reaction was monitored by TLC (R_f = 0.36, 0.46). The products were extracted with ether (2 x 25 mL), the organic layers were washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as reddish gummy liquid.

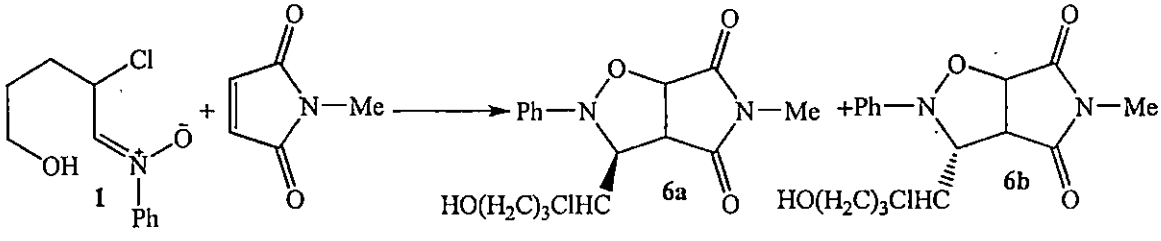
5a. Spectral data of 4-chloro-4-{(3*S*)-2-phenyl octahydrobenzo[*d*]isoxazol-3-yl}butan 1-ol

Reddish gummy liquid, Yield: 60%; IR($CHCl_3$): 3490 - 3370 (br), 2924 (s), 2850 (m), 2766 (m), 1542 (s), 1443 (m), 1250 (s), 774 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.28 - 7.14 (m, 5H, C_6H_5), 5.37 (d, 1H, J = 8.20 Hz, C_5H), 5.22 - 5.14 (br, 1H,exchanged in D_2O), 4.50 (dd, 1H, J = 9.2, 7.34 Hz, C_3H), 4.12 (dd, 1H, J = 9.40, 7.10 Hz, C_4H), 3.58 (q, 1H, J = 4.26, 6.20 Hz, CHCl), 1.80 - 1.14 (m, 14H); ^{13}C NMR ($CDCl_3$): δ 130.00, 129.00, 128.40, 127.30 (aromatic carbons), 88.50 (C_5), 78.00 (C_3), 66.20 (CH_2OH), 54.60 (C_4), 52.60 (CHCl), 33.00, 31.00, 29.00, 27.00, 25.00, 24.40 (6 CH_2 carbons); MS (*m/z*): 309 (M^+), 227, 226, 211, 148, 147, 107, 77, 59, 31; HRMS-EI: Calcd. for $C_{17}H_{24}O_2NCl$ (M) 309.6330, Found (M^+) 309.6318.

5b. Spectral data of 4-chloro-4-{(3*R*)-2-phenyl octahydrobenzo[*d*]isoxazol-3-yl}butan 1-ol

Reddish gummy liquid, Yield: 28%; IR ($CHCl_3$): 3512 – 3454 (br), 2920 (s), 2854 (m), 2766 (m), 1550 (s), 1440 (m), 1256 (s), 802 (m), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26 - 7.14 (m, 5H, C_6H_5), 5.30 (d, 1H, J = 8.20 Hz, C_5H), 5.13 -5.04 (br, 1H,exchanged in D_2O), 4.36 (dd, 1H, J = 3.36, 2.23 Hz, C_3H), 4.20 (q, 1H, J = 2.54, 3.16 Hz, C_4H), 3.27 (q,1H, J = 3.26, 5.20 Hz, CHCl), 1.74 - 1.28 (m, 14H); ^{13}C NMR ($CDCl_3$): δ 132.00, 131.00, 129.50, 128.20 (aromatic carbons), 87.00 (C_5), 76.00 (C_3), 63.60 (CH_2OH), 55.40 (C_4), 51.20 (CHCl), 30.00, 29.15, 28.00, 25.40, 24.00, 21.30 (6 CH_2 carbons); MS (*m/z*): 309 (M^+), 278, 250, 211, 227, 202, 148, 124, 107, 82, 77, 59, 31; HRMS-EI: Calcd. for $C_{17}H_{24}O_2NCl$ (M) 309.6330, Found M^+ 309.6314.

6. Synthesis of *N*-methyl maleimide cycloadducts



Scheme 8

To a stirred solution of nitrone **1** (1 mmol) in 15 mL water was added *N*-methyl maleimide (1 mmol) at RT under nitrogen atmosphere and the reaction mixture was stirred for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.38, 0.40). The products were extracted with ether (2 x 25 mL), the organic layers were washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as white solids.

6a. Spectral data of (3*S*)-3-(1-chloro-4 hydroxy butyl)-5 methyl-2-phenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione:

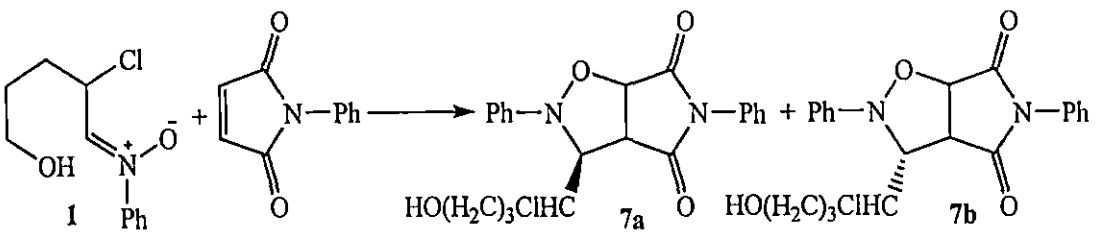
White solid, 75.6%; IR ($CHCl_3$): 3590 - 3460 (br), 2924 (m), 2840 (m), 1755 (s), 1660 (s), 1485 (m), 1340 (m), 803 (s), 774 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.15 – 6.98 (m, 5H, C_6H_5), 5.22 (d, 1H, J = 6.8 Hz, C_5H), 5.08 – 5.00 (br, 1H, OH, exchanged in D_2O), 4.55 (dd, 1H, J = 6.84, 9.2 Hz, C_3H), 3.76 (dd, 1H, J = 8.06, 9.20 Hz, C_4H),

3.40 (s, 3H, CH_3), 3.14 – 2.96 (dt~m, 1H, CHCl), 1.95 - 1.52 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 174.60, 173.40 (carbonyl carbons), 134.50, 133.20, 132.00, 130.60 (aromatic carbons), 88.00 (C_5), 73.00 (C_3), 62.20 (CH_2OH), 58.00 (C_4), 52.40 (CHCl), 39.42 (CH_3), 26.00, 23.00 (2 CH_2 carbons); MS (*m/z*): 340 (M^+ +2), 338 (M^+), 323, 307, 261, 247, 231, 107, 77, 59; HRMS – EI: Calcd. for $C_{16}H_{19}O_4N_2Cl$ (M) 338.1338, Found M^+, 338.1324; Found: C, 56.57, H, 5.49, N, 8.19 %; $C_{16}H_{19}O_4N_2Cl$ requires C, 56.63, H, 5.60, N, 8.25 %

6b. Spectral data of (3*R*)-3-(1-chloro-4 hydroxy butyl)- 5 methyl-2-phenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione:

White solid, 20.4%; IR ($CHCl_3$): 3580 – 3465 (br), 2895 (m), 1764 (s), 1660 (s), 1482 (m), 1355 (m), 805 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.20 – 7.08 (m, 5H, C_6H_5), 5.26 (d, 1H, J = 6.0 Hz, C_5H), 5.10 – 4.94 (br, 1H, OH, exchanged in D_2O), 4.10 (dd, 1H, J = 2.50, 4.06 Hz, C_3H), 3.60 (dd, 1H, J = 2.52, 4.26 Hz, C_4H), 3.44 (s, 3H, CH_3), 3.22 – 3.05 (dt~m, 1H, CHCl), 1.88 - 1.44 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.5, 171 (carbonyl carbons), 133, 132, 130.3, 128.6 (aromatic carbons), 88.6 (C_5), 74 (C_3), 61.4 (CH_2OH), 58.2 (C_4), 54 (CHCl), 37 (CH_3), 24, 21 (2 CH_2 carbons); MS (*m/z*): 338 (M^+), 307, 261, 246, 231, 139, 111, 107, 77, 31; HRMS – EI: Calcd. for $C_{16}H_{19}O_4N_2Cl$ (M) 338.1338, Found M^+, 338.1320; Found: C, 56.50; H, 5.52; N, 8.16 % ; $C_{16}H_{19}O_4N_2Cl$ requires C, 56.63; H, 5.60; N, 8.25 %.

7. Synthesis of *N*-phenyl maleimide cycloadducts



Scheme 9

To a stirred solution of nitrone **1** (1 mmol) in 15 mL water was added *N*-phenyl maleimide (1 mmol) at RT under nitrogen atmosphere and the reaction mixture was stirred for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.34, 0.42).The products were extracted with ether (2 x 25 mL), the organic layers were washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The mixture of diastereomers were purified and separated by

column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as yellow and yellowish white solids.

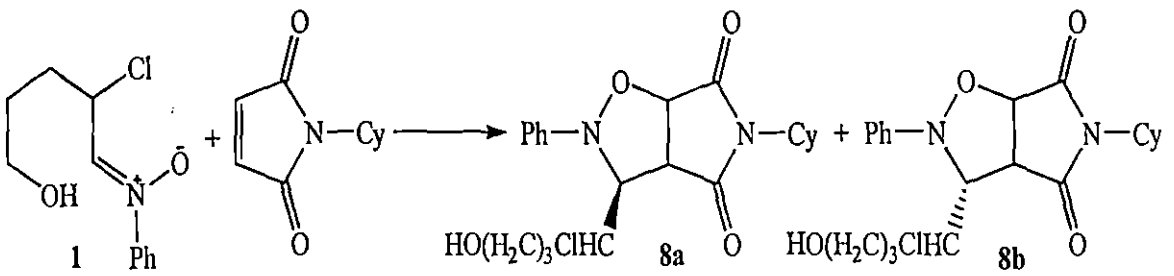
7a. Spectral data of (3*S*)-3-(1-chloro-4 hydroxy butyl)-2,5-diphenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione:

White solid, 70.8%; IR ($CHCl_3$): 3660 – 3408 (br), 3016 (s), 2937 (s), 2362 (m), 1720 (s), 1482 (s), 1217 (s), 1078 (s), 758 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55 - 7.40 (m, 2 x5H, C_6H_5 protons), 5.42 (d, 1H, J = 8.24 Hz, C_5H), 5.05 - 4.95 (br, 1H, OH, exchanged in D_2O), 4.46 (dd, 1H, J = 9.25, 7.28 Hz, C_3H), 3.76 (dd, 1H, J = 9.22, 6.08 Hz, C_4H), 3.22 – 3.07 (dt~m, 1H, CHCl), 1.82 - 1.35 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 175.50, 173.60 (carbonyl carbons), 138.00, 137.00, 135.60, 134.35, 133.70, 132.00, 131.40, 130.00 (aromatic carbons), 87.50 (C_5), 76.00 (C_3), 64.00 (CH_2OH), 59.40 (C_4), 52.00 (CHCl), 28.00, 26.00 (2 CH_2 carbons); MS (*m/z*): 400 (M^+), 341, 323, 287, 246, 216, 173, 107, 77, 59, 31; HRMS – EI: Calcd. for $C_{21}H_{21}O_4N_2Cl$, (M) 400.1494, Found M^+, 400.1478, Found C, 66.70; H, 5.20; N, 6.82 %; $C_{21}H_{21}O_4N_2Cl$, requires C, 66.84; H, 5.23; N, 6.98%.

7b. Spectral data of (3*R*)-3- (1-chloro-4 hydroxy butyl)- 2,5 diphenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5H,6a*H*)-dione:

Yellowish white solid, 23.2%; IR ($CHCl_3$): 3560 – 3470 (br), 2865 (m), 1760 (s), 1684 (s), 1465 (m), 1370 (m), 810 (m), 772 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35 - 7.14 (m, 2 x 5H, C_6H_5 protons), 5.24 (d, 1H, J = 7.20 Hz, C_5H), 5.00 - 4.92 (br, 1H, OH, exchanged in D_2O), 4.38 (dd, 1H, J = 3.25, 2.24 Hz, C_3H), 3.52 (dd, 1H, J = 4.42, 2.08 Hz, C_4H) , 3.37 – 3.20 (m, 1H, CHCl), 1.74 - 1.46 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 174.40, 171.80 (carbonyl carbons), 137.20, 136.40, 135.00, 134.50, 133.00, 132.80, 130.60, 129.00 (aromatic carbons), 85.00 (C_5), 72.60 (C_3), 64.50 (CH_2OH), 57.40 (C_4), 53.60 (CHCl), 28.00, 27.00 (2 CH_2 carbons); MS (*m/z*): 402 (M^+ +2), 400 (M^+), 295, 246, 216, 211, 189, 154, 107, 77, 31; HRMS – EI: Calcd. for $C_{21}H_{21}O_4N_2Cl$, (M), 400.1494, Found M^+ 400.1483, Found C, 66.54; H, 5.14; N, 6.75 %; $C_{21}H_{21}O_4N_2Cl$, requires C, 66.84; H, 5.23; N, 6.98%.

8. Synthesis of *N*-cyclohexyl maleimide cycloadducts



Scheme 10

To a stirred solution of nitrone 1 (1 mmol) in 15 mL water was added *N*-cyclohexyl maleimide (1 mmol) at RT under nitrogen atmosphere and the reaction mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.39, 0.44). The products were extracted with ether (2 x 25 mL), the organic layers were washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as dark yellow and yellow crystals.

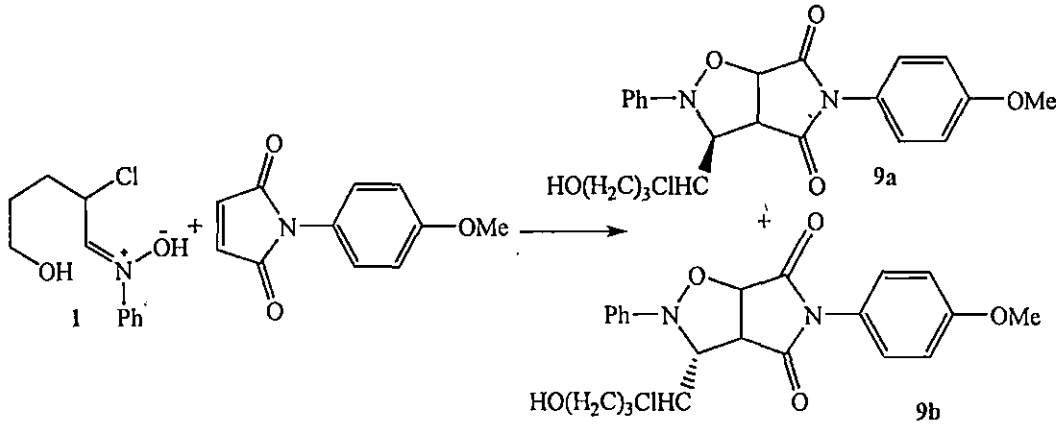
8a. Spectral data of (3*S*)-3- (1-chloro-4 hydroxy butyl)-5-cyclohexyl – 2- phenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*, 6a*H*)-dione:

Dark yellow crystals, 68%; IR ($CHCl_3$): 3510 – 3370 (br), 2930 (s), 2350 (s), 1710 (s), 1598 (m), 1502 (s), 1457 (m), 1394 (s), 1145 (s), 1073 (s), 1029 (s), 831 (s), 756 (s), 696 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.02 – 6.92 (m, 5H, C_6H_5), 5.32 (d, 1H, J = 6.12 Hz, C_5H), 5.10 - 5.02 (br, 1H, OH, exchanged in D_2O), 4.52 (dd, 1H, J = 9.26, 6.08 Hz, C_3H), 4.26 (dd, 1H, J = 9.24, 7.06 Hz, C_4H), 3.20 – 2.94 (dt~m, 1H, CHCl), 1.64 – 1.24 (m, 17H, cyclohexyl and CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.30, 170.20 (carbonyl carbons), 131.30, 130.50 128.60, 127.40 (aromatic carbons), 86.00 (C_5), 78.00 (C_3), 62.50 (CH_2OH), 55.52 (C_4), 50.66 (CHCl), 30.00, 28.40, 26.70, 25.40, 24.35, 23.50, 22.20, 19.00 (cyclohexyl and CH_2 carbons); MS (*m/z*): 406 (M^+), 375, 347, 329, 324, 222,107,77,59,31; HRMS – EI: Calcd. for $C_{21}H_{27}O_4N_2Cl$ (M) 406.1962, Found M^+ 406.1949.

8b. Spectral data of (3*R*)-3- (1-chloro-4 hydroxy butyl)-5-cyclohexyl – 2- phenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*, 6 a*H*)-dione:

Yellow crystals, 27%; IR ($CHCl_3$): 3630 – 3535 (br), 2865 (s), 1760 (s), 1680 (s), 1440 (m), 1375 (m), 1265 (m), 810 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.22 – 7.04 (m, 5H, C_6H_5), 5.26 (d, 1H, J = 7.22 Hz, C_5H), 5.18 - 5.06 (br, 1H, OH, exchanged in D_2O), 4.43 (dd, 1H, J = 4.32, 3.26 Hz, C_3H), 4.14 (dd, 1H, J = 3.22, 2.08 Hz, C_4H), 3.38 – 3.20 (m, 1H, CHCl), 1.72 – 1.38 (m, 17H, cyclohexyl and CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 170.70, 169.80 (carbonyl carbons), 135.30, 134.50, 133.80, 132.50 (aromatic carbons), 84.30 (C_5), 75.00 (C_3), 61.60 (CH_2OH), 53.50 (C_4), 53.00 (CHCl), 27.00, 26.50, 25.40, 24.00, 23.00, 21.50, 20.00, 19.00 (cyclohexyl and CH_2 carbons); MS (*m/z*): 408 (M^+ +2), 406 (M^+), 323, 216, 179, 139, 107, 83, 77, 59; HRMS – EI: Calcd. for $C_{21}H_{27}O_4N_2Cl$ (M) 406.1962, Found M^+, 406.1943..

9. Synthesis of *p*-OMe-*N*-phenyl maleimide cycloadducts



Scheme 11

To a well stirred solution of nitrone 1(1 mmol) in 15 mL water, *p*-OMe-*N*-phenyl maleimide (1 mmol) was added at RT under N_2 atmosphere and the reaction mixture was stirred further for 5 hour. The progress of the reaction was monitored by TLC (R_f = 0.38, 0.40). After completion of the reaction the products were extracted with a ether (2 x 25 mL). The organic layer was washed with brine water (2 x 15 mL), dried over sodium sulphate and concentrated. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as white solids.

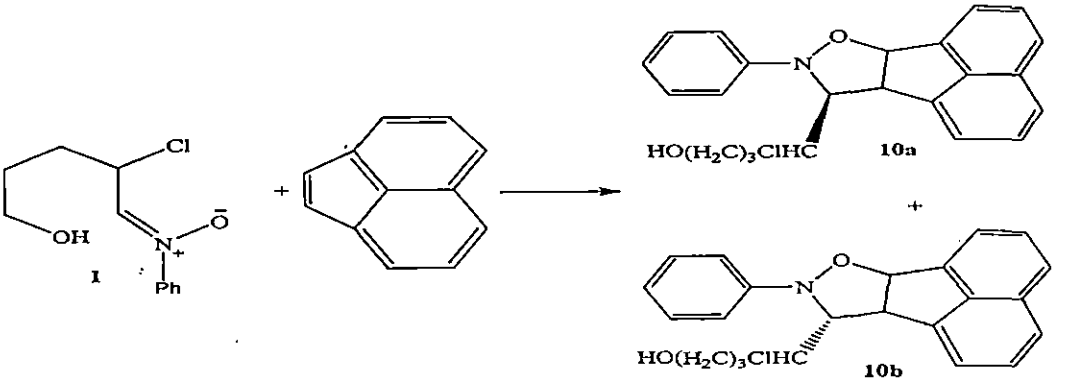
9a. Spectral data of (3*S*)-3-(1-chloro-4-hydroxybutyl)-5-(4-methoxyphenyl)-2-phenyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione:

White solid, 70.8%; IR ($CHCl_3$): 3520 – 3465 (br), 2874 (m), 1765 (s), 1670 (s), 1445 (m), 1370 (m), 1175 (m), 805 (m), 772 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50-7.34 (m, 9H, C_6H_5 protons), 5.28 (d, 1H, J = 6.88 Hz, C_5H), 5.08 - 4.93 (br, 1H, OH, exchanged in D_2O), 4.84 (dd, 1H, J = 9.20, 8.02 Hz, C_3H), 3.86 (dd, 1H, J = 9.24, 7.08 Hz, C_4H), 3.34 (s, 3H, OCH_3), 3.26 - 3.14 (dt~m, 1H, CHCl), 1.85-1.42 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 175.20, 174.00 (carbonyl carbons), 159.80, 135.00, 134.60, 133.20, 131.40, 130.60, 129.50, 128.00 (aromatic carbons), 86.00 (C_5), 72.00 (C_3), 62.00 (CH_2OH), 56.00 (C_4), 54.00 (OMe), 50.00 (CHCl), 18.00, 17.00 (2 CH_2 carbons); MS (*m/z*): 432 (M^+ +2), 430 (M^+), 399, 371, 353, 323, 322, 219, 211, 108, 107, 59, 31; HRMS – EI: Calcd. for $C_{22}H_{23}O_5N_2Cl$, (M) 430.1599, Found M^+, 430.1586.

9b. Spectral data of (3*S*)-3-(1-chloro-4-hydroxybutyl)-5-(4-methoxyphenyl)-2-phenyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione:

White solid, 21.2%; IR ($CHCl_3$): 3510 – 3420 (br), 2880 (m), 1760 (s), 1680 (s), 1455 (m), 1360 (m), 1160 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45 - 7.30 (m, 9H, C_6H_5 protons), 5.23 (d, 1H, J = 7.40 Hz, C_5H), 5.14 - 4.90 (br, 1H, OH, exchanged in D_2O), 4.72 (dd, 1H, J = 4.20, 2.32 Hz, C_3H), 3.54 (q, 1H, J = 2.84, 3.25 Hz, C_4H), 3.30 (s, 3H, OCH_3), 3.38 – 3.22 (dt~m, 1H, CHCl), 1.68 - 1.32 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 174.40, 172.50 (carbonyl carbons), 158.40, 135.60, 134.30, 133.00, 132.00, 130.50, 129.30, 128.80 (aromatic carbons), 82.50 (C_5), 74.00 (C_3), 63.00 (CH_2OH), 55.50 (C_4), 53.80 (-OMe), 51.40 (-CHCl), 16.00, 15.00 (2 CH_2 carbons); MS (*m/z*): 430 (M^+), 399, 270, 246, 155, 139, 108, 107, 77, 59; HRMS – EI: Calcd. for $C_{22}H_{23}O_5N_2Cl$, (M) 430.1599, Found, M^+, 430.1566.

10. Synthesis of Acenaphthylene cycloadducts



Scheme 12

To a stirred solution of nitrone **1** (1 mmol) in 15 mL water was added acenapthylene (1equivalent) *in-situ* at the time of formation of nitrone (monitored by TLC) at RT under nitrogen atmosphere and the reaction mixture was stirred for further 7 hr. The progress of the reaction was monitored by TLC (R_f = 0.40, 0.38). The products were extracted with ether (2 x 25 mL), the organic layers were washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and were concentrated under a rotary evaporator and finally the cycloadducts were purified and separated by silica gel column chromatography using ethyl acetate-hexane and were obtained as bright yellow crystals.

10a. Spectral data of 4-chloro-4-((9*S*) 8-phenyl-6b,8,9,9a-tetrahydroacenaphtho[1,2-*d*]isoxazol-9-yl)butan-1-ol:

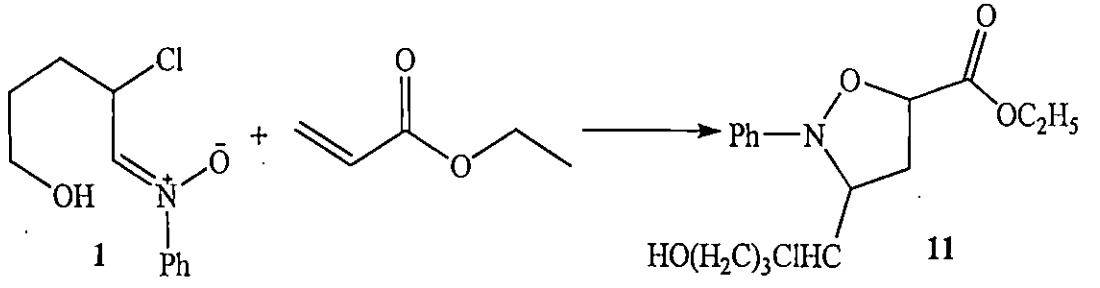
Bright yellow crystals, 73 %; IR ($CHCl_3$): 3455 - 3370 (br), 2960 (m), 2720 (m), 1710 (s), 1480 (m), 1280 (s), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.28 – 7.20 (m, 5H, C_6H_5), 6.96 – 6.93 (m, 6H, napthylene ring protons), 5.26 (d, 1H, J = 6.50 Hz, C_5H), 4.88 (br, 1H exchanged in D_2O), 4.79 (dd, 1H, J = 9.2, 7.34 Hz, C_3H), 4.12 (dd, 1H, J = 9.40, 7.10 Hz, C_4H), 3.51 (dt~m, 1H, J = 4.26, 6.20 Hz, CHCl), 1.64 – 1.21 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 138.00, 137.70, 136.96, 135.40, 134.30, 133.00, 132.45, 131.76, 130.68, 128.64, 127.40, 126.30 (aromatic carbons), 86.90 (C_5), 78.10 (C_3), 66.20 (CH_2OH), 54.35 (C_4), 52.60 (CHCl), 31.00, 29.70, 27.65 (3 CH_2 carbons); MS (*m/z*): 379 (M^+), 320, 302, 272, 227, 152, 107, 77, 59; HRMS – EI: Calcd. for $C_{23}H_{22}O_2NCl$ (M) 379.8980, Found M^+ 379.8963.

10b. Spectral data of 4-chloro-4-((9*R*)8-phenyl-6b,8,9,9a-tetrahydroacenaphtho[1,2-*d*]isoxazol-9-yl)butan-1-ol:

Bright yellow crystals, 23 %; IR ($CHCl_3$): 3456 - 3375 (br), 2967 (m), 2726 (m), 1720 (s), 1474 (m), 1280 (s), 786 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36 – 7.27 (m, 5H, C_6H_5), 7.05 – 6.90 (m, 6H, napthylene ring protons), 5.30 (d, 1H, J = 7.16 Hz, C_5H), 4.82 – 4.73 (br, 1H exchanged in D_2O), 4.60 (dd, 1H, J = 2.34, 2.53 Hz, C_3H), 4.28 (dd, 1H, J = 4.12, 3.10 Hz, C_4H), 3.46 (q, 1H, J = 6.08, 7.42 Hz, CHCl), 1.76 – 1.60 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 137.34, 136.10, 135.00, 134.63, 133.24, 132.00, 131.00, 130.16, 128.60, 127.45, 126.00, 124.70 (aromatic carbons), 87.00 (C_5), 76.30 (C_3), 68.50 (CH_2OH), 53.30 (C_4), 50.74 (CHCl), 30.00, 29.00, 28.35 (3 CH_2 carbons); MS (*m/z*):

381 (M^++2), 379 (M^+), 320, 302, 272, 227, 152, 107, 77, 59; HRMS – EI: Calcd. for $C_{23}H_{22}O_2NCl$ (M) 379.8980, Found M^+, 379.8967.

11. Synthesis of ethyl-3-(1-chloro-4 hydroxy butyl)-2-phenyl isoxazolidine-5-carboxylate (Ethyl acrylate cycloadduct)



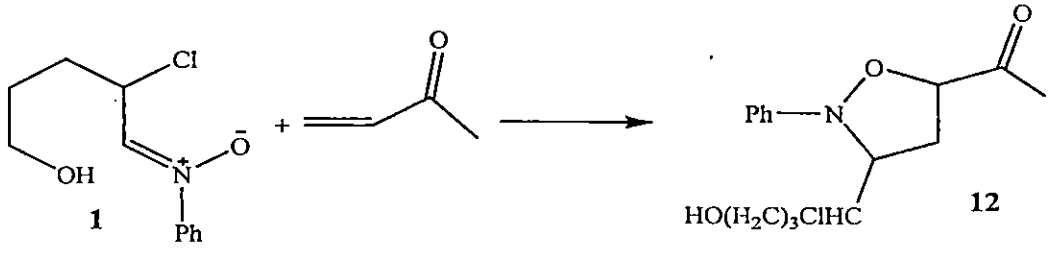
Scheme 13

To a stirred solution of nitrone **1** (1 mmol) in 15 mL water was added ethyl acrylate (1 mmol) at RT under nitrogen atmosphere and the reaction mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.48).The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified and separated by column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as white gummy liquid.

Spectral data:

White gummy liquid, 93%; IR ($CHCl_3$): 3580 – 3480 (br), 3095 (m), 2250 (m), 1898 (m), 1711 (s), 1636 (s), 1503 (m), 1392 (s), 1144 (s), 1029 (s), 908 (m), 831 (s), 756 (s) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.28 (m, 5H, C_6H_5), 4.88 (br, 1H, -OH, exchanged in D_2O), 4.11 (t, 1H, J = 8.2 Hz, C_5H), 3.86 (q, 1H, J = 7.22 Hz, C_3H), 3.51 (dd, 2H, J = 9.24, 8.18 Hz, C_4 2H), 2.29 (dt~m, 1H, CHCl), 1.64 (t, 3H, J = 7.22 Hz, CH_3CH_2CO), 1.23 (q, 2H, J = 7.52 Hz, -OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 167.40 (carbonyl carbon), 136.40, 134.50, 133.20, 132.60 (aromatic carbons), 88.00 (C_5), 76.00 (C_3), 63.00 (CH_2OH), 60.00 (CH_2 carbon of -OCH_2CH_3), 58.00 (C_4), 55.00 (CHCl), 32.00, 24.50 (2 CH_2 carbons), 16.00 (CH_3 carbon of -OCH_2CH_3); MS (*m/z*): 329 (M^+ +2), 327 (M^+), 296, 282, 254, 221, 219, 207, 177, 147, 142, 108, 107, 77, 73, 31; HRMS - EI: Calcd. for $C_{16}H_{22}O_4NCl$ (M) 327.8190, Found M^+, 327.8179.

12. Synthesis of 1-(3-(1-chloro-4-hydroxy butyl)-2-phenyl isoxazolidin-5yl) ethanone (Methyl vinyl ketone cycloadduct)



Scheme 14

To a stirred solution of nitrone **1** (1 mmol) in 15 mL water was added methyl vinyl ketone (1 mmol) at RT under nitrogen atmosphere and the reaction mixture was stirred for 8 hr. The progress of the reaction was monitored by TLC (R_f = 0.44).The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified and separated by column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as pale yellow oil.

Spectral data:

Pale yellow oil, 91%; IR ($CHCl_3$): 3570 - 3440 (br), 3042 (s), 2924 (m), 2166 (m), 1930 (s), 1628 (s), 1422 (s), 1199 (m), 1147 (s), 1080 (s), 826 (s), 773 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.16 - 7.04 (m, 5H, C_6H_5), 5.32 (t, 1H, J = 7.82 Hz, C_5H), 5.10 – 5.00 (br, 1H, exchanged in D_2O), 4.54 – 4.43 (dt, 1H, J = 8.30 Hz, C_3H), 4.28 (dd, 2H, J = 9.48, 7.10 Hz, C_4 2H), 3.78 – 3.62 (m, 1H, CHCl), 2.12 (s, 3H, $COCH_3$), 1.86 - 1.54 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 195.22 (carbonyl carbon), 132.00, 131.55, 130.00, 128.40 (aromatic carbons), 88.00 (C_5), 78.00 (C_3), 66.00 (CH_2OH), 58.00 (C_4), 53.50 (CHCl), 24.60 ($COCH_3$), 19.00, 17.00 (2 CH_2 carbons); MS (*m/z*): 297 (M^+), 282, 267, 265, 254, 221, 211, 191, 177, 147, 107, 86, 77, 43, 31; HRMS-EI: Calcd. for $C_{15}H_{20}O_3NCl$ (M) 297.1437, Found M^+, 297.1426.

Synthesis of α-amino nitrones[7,8]

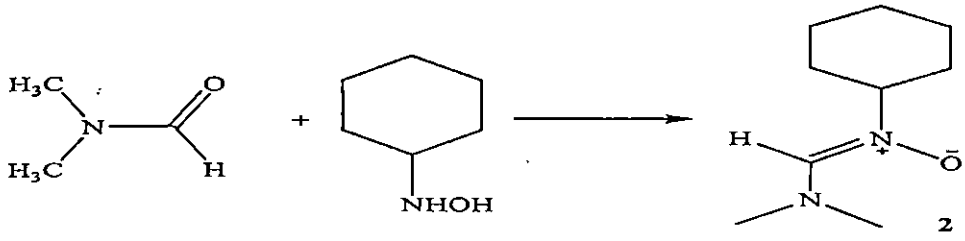
Reaction type II

General procedure for the preparation of nitrone 2 at elevated temperature

Initially, the preparation of *N*-cyclohexyl-α-amino nitrone was carried out at elevated temperature following the general methodology of synthesis of α-amino nitrones as

suggested by Eschenmoser et al[9]. To a well stirred solution of *N*-cyclohexyl hydroxylamine[10] (8.7 mmol) and *N,N*-dimethyl formamide (9 mL, 1 equivalent) was added about 2 gms of anhydrous $MgSO_4$ and the reaction mixture was refluxed for 8-10 hour but no definite conclusion for the formation of nitrone **2** was observed. The isolated product under constant observation did not show specific bands for α-amino nitrone in the ^1H NMR, ^{13}C NMR and IR spectrum. Therefore it was concluded that the gummy liquid obtained was a decomposed product. And hence this methodology was not followed.

General procedure for the preparation of *N*-cyclohexyl-α-aminonitrone (2) at room temperature



Scheme 15

N-cyclohexyl hydroxylamine (8.7 mmol) was added to dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent) in presence of anhydrous $MgSO_4$. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 hour. The formation of nitrone **2** was monitored by TLC (R_f = 0.34, silica gel; ethyl acetate : benzene = 1: 10). The nitrone **2** was isolated by extraction with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over sodium sulphate and concentrated on a rotary evaporator and finally obtained as white crystalline solid (m.p 48^0c, uncorrected). The nitrone decomposes when kept at room temperature for a longer period and hence it was either used right after its synthesis (for aqueous phase cycloaddition reactions) or as *in-situ* for general cycloaddition reactions.

Spectral data of (*Z*)-*N*-((dimethylamino)methylene)cyclohexanamine oxide

White crystalline solid, 88%; IR ($CHCl_3$): 3440 (m), 1600 (s), 1360 (m), 1310 (m), 1120 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.81 (br, 6H, NMe_2), 3.30 (s,1H,$HC=N^+-O^-$), 2.50 - 2.16 (m, 1H, N-CH proton), 1.66 – 1.59 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 144.62 ($CH=N^+$), 43.00, 40.72 (*N* - methyl carbons), 32.00, 30.64, 27.32, 26.08, 25.15, 24.74

(cyclohexyl carbons); HRMS – EI: Calcd. for $C_9H_{18}N_2O$, (M) 170.2560, Found, M^+, 170.2555.

General Procedure for 1,3-dipolar cycloaddition reaction at elevated temperature

Initially, the freshly prepared nitrone **2** (prepared at RT) was used for cycloaddition reactions with dipolarophiles at elevated temperature following the conventional general methodology of cycloaddition reactions. Nitrone **2** (2.20 mmol) and *N*-phenyl maleimide (1 equivalent) was added in THF (20 mL) under N_2 atmosphere and the reaction mixture was refluxed for 12 hour. The progress of the reaction was monitored by TLC. The solvent was concentrated on a rotary evaporator and the products were purified by silica gel column chromatography using ethyl acetate – hexane combinations. But this methodology was not followed due to poor yield (nearly 40%) of cycloadducts.

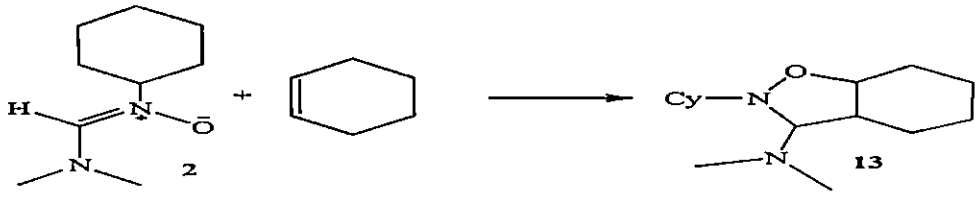
General Procedure for 1,3-dipolar cycloaddition reaction with nitrone 2 (*in-situ* synthesis)

As nitrone **2** decomposes slowly at room temperature, therefore in majority of the reactions *in-situ* reactions were performed for the synthesis of isoxazolidines directly. Dipolarophiles (1 equivalent) were added at the time of formation of nitrone **2** and the reaction mixture was stirred at RT with a magnetic stirrer under N_2 atmosphere for further 8 - 10 hour. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated on a rotary evaporator and the crude cycloadducts were purified and separated by silica gel column chromatography using ethyl acetate – hexane combinations. This procedure was followed for all the substrates (alkenes and alkynes) listed in **Table 5**.

Table 5.

Alkenes	*Alkynes*
➢ Cyclohexene	➢ Phenyl methyl propiolate
➢ *N*-Phenyl maleimide	➢ Dimethyl acetylene dicarboxylate
➢ *N*-Methyl maleimide	➢ Ethyl propiolate
➢ *N*-Cyclohexyl maleimide	➢ Propiolic acid
➢ *P*-OMe-*N*-phenyl maleimide	
➢ Ethyl acrylate	
➢ Methyl vinyl ketone	
➢ Styrene	
➢ Acenaphthylene	
➢ *p*-benzoquinone	

13. Synthesis of 2-cyclohexyl-*N,N*-dimethyloctahydrobenzo[*d*]isoxazol-3-amine (cyclohexene cycloadduct)



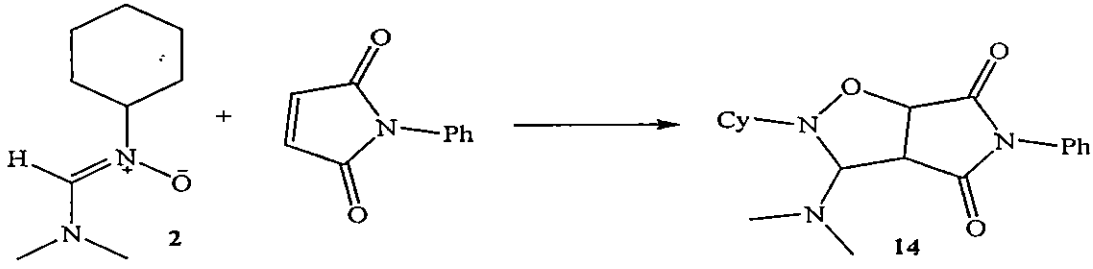
Scheme 16

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), cyclohexene (1 equivalent) was added at the time of formation of nitrone **2** (monitored by TLC) at RT under nitrogen atmosphere and the reaction mixture was stirred for further 10 hr. The progress of the reaction was monitored by TLC (R_f = 0.54). The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as reddish gummy liquid.

Spectral Data:

Reddish gummy liquid, 76 %; IR ($CHCl_3$): 3190 - 3065 (br), 2924 (s), 2850 (m), 1555 (s), 1443 (m), 1250 (s), 970 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.37 (d, 1H, J = 8.20 Hz, C_5H), 4.50 (d, 1H, J = 9.20 Hz, C_3H), 4.12 (dd, 1H, J = 9.40, 7.10 Hz, C_4H), 2.64 – 2.52 (br, 6H, $N - CH_3$ protons), 1.80 - 1.14 (m, 19H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 88.55 (C_5), 78.75 (C_3), 54.42 (C_4), 39.56, 38.00 ($N - CH_3$ carbons), 33.70, 31.82, 29.43, 27.00, 25.40, 24.14, 22.80, 20.60, 18.90, 17.42 (cyclohexyl carbons); MS (*m/z*): 252 (M^+), 208, 170, 169, 154, 153, 141, 125, 113, 111, 98, 84, 83, 82; HRMS-EI: Calcd. for $C_{15}H_{28}N_2O$ (M) 252.4020, Found M^+, 252.4006.

14. Synthesis of 2-cyclohexyl-3-(dimethylamino)-5-phenyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (*N*-phenyl maleimide cycloadduct):



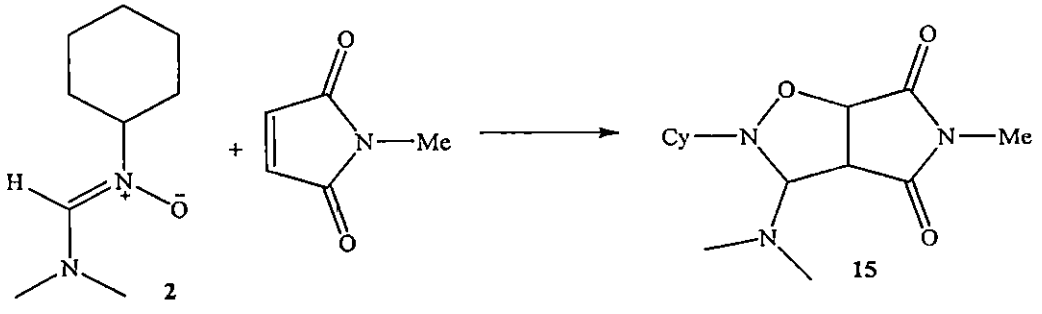
Scheme 17

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), *N*-phenyl maleimide (1 equivalent) was added *in-situ* at the time of formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 8 hour. The progress of the reaction was monitored by TLC (R_f = 0.52). The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as white solid.

Spectral data:

White solid, 93 %; IR ($CHCl_3$): 3345-3130 (br), 3013 (s), 2933 (m), 2362 (m), 1662 (s), 1508 (m), 1387 (s), 1219 (m), 1098 (s), 927 (m), 829 (w), 759 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55 - 7.44 (m, 5H, C_6H_5), 4.82 (d, 1H, *J* = 6.06 Hz, C_5H), 4.46 (d, 1H, *J* = 9.22 Hz, C_3H), 3.90 (dd, 1H, *J* = 6.06, 9.08 Hz, C_4H), 2.68 – 2.57 (br, 6H, N – CH_3 protons), 2.20 - 1.70 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 178.90, 169.50 (carbonyl carbons), 136.00, 134.70, 132.65, 130.45 (aromatic carbons), 87.50 (C_5), 76.00 (C_3), 59.40 (C_4), 37.65, 36.80 (*N* - methyl carbons), 30.00, 27.80, 26.00, 24.80, 23.20, 21.65 (cyclohexyl carbons); MS (*m/z*): 343 (M^+), 328, 313, 299, 266, 260, 230, 189, 183, 154, 113, 83, 77, 44, 30; HRMS - EI: Calcd. for $C_{19}H_{25}O_3N_3$ (M), 343.2370, Found M^+, 343.2355; Found C, 66.40; H, 7.22; N, 12.20 %; $C_{19}H_{25}O_3N_3$ requires C, 66.47; H, 7.28; N, 12.24 %.

15. Synthesis of 2-cyclohexyl-3-(dimethylamino)-5-methyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (*N*-methyl maleimide cycloadduct):



Scheme 18

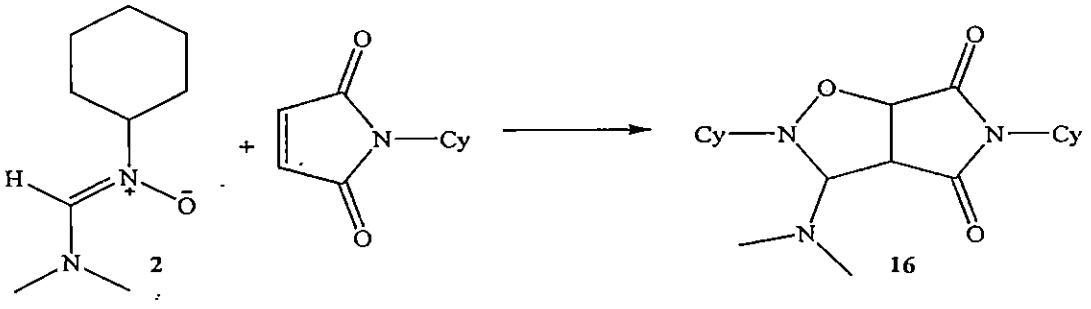
To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), *N*-methyl maleimide (1 equivalent) was

added *in-situ* at the time of formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 10 hour. The progress of the reaction was monitored by TLC (R_f = 0.48). The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as white solid.

Spectral data:

White solid, 82 %; IR ($CHCl_3$): 3445-3230 (br), 2932 (s), 2361 (s), 1660 (s), 1498 (m), 1390 (s), 1255 (s), 1102 (m), 663 (s) (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.22 (d, 1H, J = 6.0 Hz, C_5H), 4.05 (d, 1H, J = 9.0 Hz, C_3H), 3.76 (dd, 1H, J = 6.14, 9.00 Hz, C_4H), 3.40 (s, 3H, CH_3), 2.85 - 2.76 (br, 6H, *N*-CH_3 protons), 1.95 - 1.62 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 169.64, 167.20 (carbonyl carbons), 88.00 (C_5), 73.00 (C_3), 58.00 (C_4), 39.00, 38.00 (*N*-CH_3 carbons), 36.50 (methyl carbon), 28.80, 26.95, 25.00, 24.30, 22.84, 20.55 (cyclohexyl carbons); MS (*m/z*): 281 (M^+), 266, 251, 237, 198, 168, 142, 113, 83, 44, 30; HRMS – EI: Calcd. for $C_{14}H_{23}O_3N_3$ (M) 281.2160, Found M^+, 281.2148; Found C, 59.97; H, 7.69; N, 15.01 %; $C_{14}H_{23}O_3N_3$ requires C, 60.04; H, 7.85; N, 15.08 %.

16. Synthesis of 2,5-dicyclohexyl-3-(dimethylamino)dihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (*N*-cyclohexyl maleimide cycloadduct):



Scheme 19

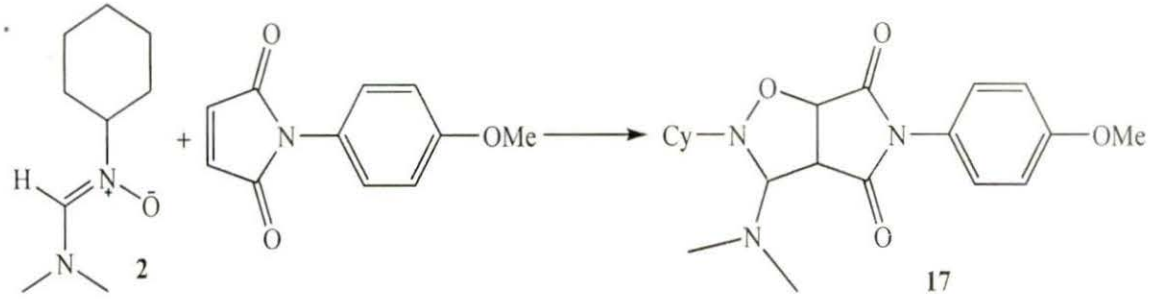
To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N*,*N*-dimethyl formamide (9 mL, 1 equivalent), *N*-cyclohexyl maleimide (1 equivalent) was added *in-situ* at the time of formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 11 hour. The progress of the reaction was monitored by TLC (R_f = 0.42). The product was

extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as pale yellow solid.

Spectral data:

Pale yellow solid, 90 %; IR ($CHCl_3$): 3150 (br), 2920 (s), 1770 (s), 1680 (s), 1440 (m), 1260 (m), 1130 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.31 (d, 1H, J = 6.10 Hz, C_5H), 2.99 (br, 6H, $N - CH_3$ protons), 2.85 (d, 1H, J = 9.30 Hz, C_3H), 2.50 – 2.46 (m, 10 H, maleimide substituted cyclohexyl protons), 2.19 (dd, 1H, J = 8.00, 9.32 Hz, C_4H), 1.66 - 1.57 (m, 10H, 2-substituted cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 173.80, 171.14 (carbonyl carbons), 86.80 (C_5), 78.65 (C_3), 55.30 (C_4), 39.00, 38.00 (2 methyl carbons), 33.00, 31.00, 28.90, 27.00, 25.86, 24.30, 23.00, 22.75, 21.00, 20.20, 18.70, 16.30 (12 signals, cyclohexyl carbons); MS (*m/z*): 349 (M^+), 319, 305, 266, 251, 226, 195, 183, 154, 113, 83, 44, 30; HRMS – EI: Calcd. for $C_{19}H_{31}O_3N_3$ (M) 349.4750, Found M^+ 349.4745; Found C, 65.26; H, 8.74; N, 12.06 %; $C_{19}H_{31}O_3N_3$ requires C, 65.32; H, 8.88; N, 12.03 %.

17. Synthesis of 2-cyclohexyl-3-(dimethylamino)-5-(4-methoxyphenyl)dihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (*p*-OMe-*N*-phenyl maleimide cycloadduct):



Scheme 20

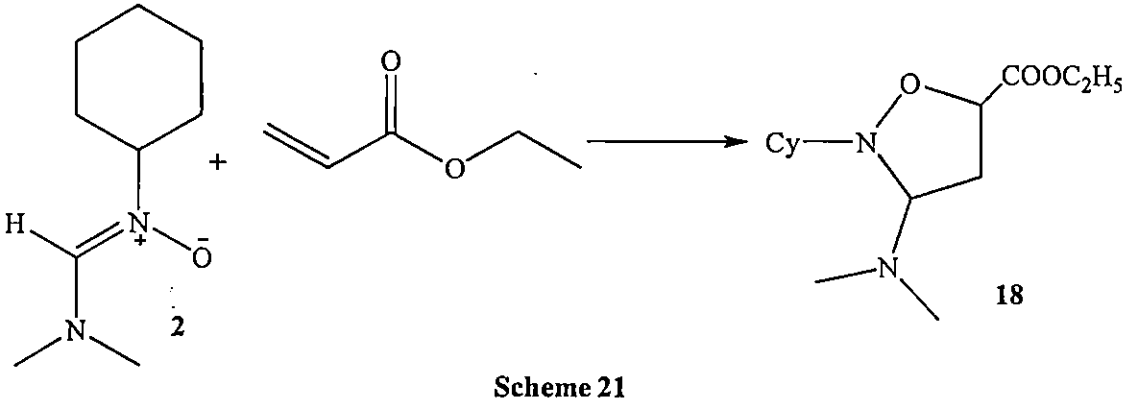
To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), *p*-methoxy-*N*-phenyl maleimide (1 equivalent) was added *in-situ* at the time of formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 9 hour. The progress of the reaction was monitored by TLC (R_f = 0.46). The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water

(2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as white crystalline solid.

Spectral data:

White crystalline solid; 89 %; IR ($CHCl_3$): 3223 (br), 2932 (s), 2361 (s), 1660 (s), 1498 (m), 1390 (m), 1255 (m), 1102 (m), 773 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.83 - 7.77 (m, 4H, C_6H_5 proton), 5.10 (d, 1H, J = 6.24 Hz, C_5H), 4.43 (d, 1H, J = 8.40 Hz, C_3H), 3.72 (dd, 1H, J = 9.23, 7.10 Hz, C_4H), 3.40 (s, 3H, -OCH_3 protons), 2.58 - 2.50 (br, NMe_2), 1.94 – 1.62 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 174.54, 172.90 (carbonyl carbons), 88.60 (C_5), 75.74 (C_3), 52.30 (C_4), 41.50, 40.00 (*N*-Me carbons), 33.80 (methoxy carbon), 33.44, 30.76, 28.55, 26.80, 24,32, 22.40 (cyclohexyl carbons); MS (*m/z*): 373(M^+), 342, 290, 260, 246, 203, 170, 166, 113, 107, 83; HRMS – EI: Calcd. for $C_{20}H_{27}O_4N_3$ (M) 373.2530, Found M^+, 373.2514; Found C, 65.26; H, 8.74; N, 12.06 %; $C_{19}H_{31}O_3N_3$ requires C, 65.32; H, 8.88; N, 12.03 %.

18. Synthesis of ethyl 2-cyclohexyl-3-(dimethylamino)isoxazolidine-5-carboxylate (Ethyl acrylate cycloadduct)



Scheme 21

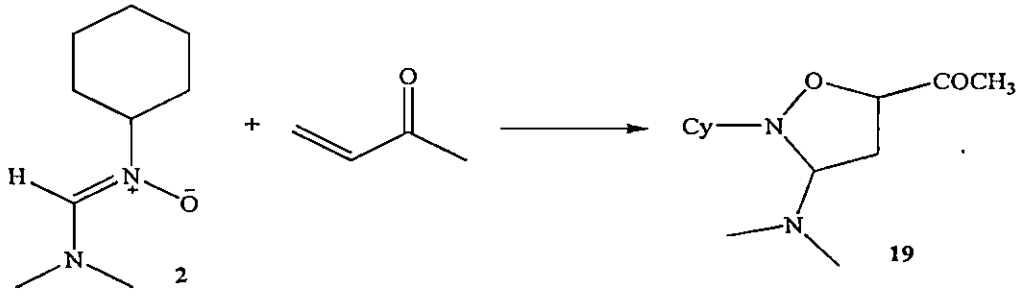
To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), ethyl acrylate (1 equivalent) was added *in-situ* at the time of formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 12 hour. The progress of the reaction was monitored by TLC (R_f = 0.60). The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was

purified by silica gel column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as white gummy liquid.

Spectral data:

White gummy liquid, 87 %; IR ($CHCl_3$): 3340-3230 (br), 2936 (s), 2121 (m), 1661 (s), 1495 (s), 1440 (s), 1390 (m), 1254 (m), 1105 (s), 1063 (m), 665 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.24 (t, 1H, J = 6.80 Hz, C_5H), 4.82 (t, 1H, J = 9.25 Hz, C_3H), 4.54 (q, 2H, J = 4.50, 6.60 Hz, -O$\underline{CH_2}CH_3$), 3.80 (dd, 2H, J = 9.24, 8.60 Hz, C_4 2H), 2.54 – 2.46 (br, 6H, N – CH_3 proton), 1.46 (t, 3H, J = 6.00 Hz, $OCH_2\underline{CH_3}$), 1.30 – 0.94 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 204.30 (ester carbonyl carbon), 88.70 (C_5), 76.43 (C_3), 58.22 (C_4), 42.56 ($COO\underline{CH_2}CH_3$), 38.60, 36.86 (NMe_2), 33.60, 32.00, 30.20, 28.40, 25.32, 23.00 (cyclohexyl carbons),18 ($COOCH_2\underline{CH_3}$); MS (*m/z*): 270 (M^+), 226, 225, 197, 157, 154, 116, 113, 83, 73, 44; HRMS-EI: Calcd. for $C_{14}H_{26}O_3N_2$ (M) 270.1935, Found M^+, 270.1926.

19. Synthesis of 1-(2-cyclohexyl-3-(dimethylamino)isoxazolidin-5-yl)ethanone (Methyl vinyl ketone cycloadduct):



Scheme 22

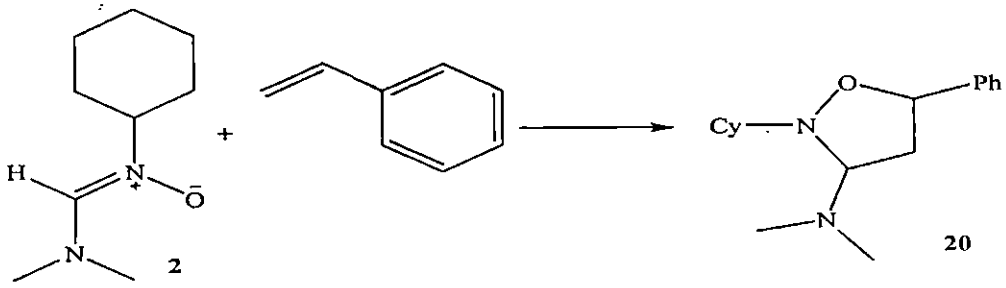
To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1equivalent), methyl vinyl ketone (1 equivalent) was added *in-situ* at the time formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 14 hour. The progress of the reaction was monitored by TLC (R_f = 0.52). The crude product was concentrated under a rotary evaporator and finally the cycloadduct was purified by silica gel column chromatography using ethyl acetate-hexane and was obtained as yellow oil.

Spectral data:

Yellow oil, 90 %; IR ($CHCl_3$): 3205 (br), 2925 (s), 2780 (m), 1740(s), 1660 (s), 1480 (m), 1280 (s), 970 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.90 (t, 1H, J = 7.82 Hz, C_5H), 4.54 (t,

1H, J = 9.24 Hz, C_3H), 4.14 (dd, 2H, J = 9.48, 7.10 Hz, C_4 2H), 3.64 (s, 3H, $COCH_3$), 2.64 - 1.92 (br, 6H, NMe_2), 1.36 - 0.94 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 190.50 (carbonyl carbon), 86.00 (C_5), 76.00 (C_3), 55.80 (C_4), 43.00, 40.20 (NMe_2), 30.52 ($CO\underline{CH_3}$), 28.40, 27.00, 25.70, 23.65, 22.00, 20.40 (6 CH_2carbons); MS (*m/z*): 240 (M^+), 197, 196, 186, 154, 127, 113, 83, 44, 43; HRMS-EI: Calcd. for $C_{13}H_{24}O_2N_2$ (M) 240.1830, Found M^+, 240.1814.

20. Synthesis of 2-cyclohexyl-*N*,*N*-dimethyl-5-phenylisoxazolidin-3-amine (styrene cycloadduct):



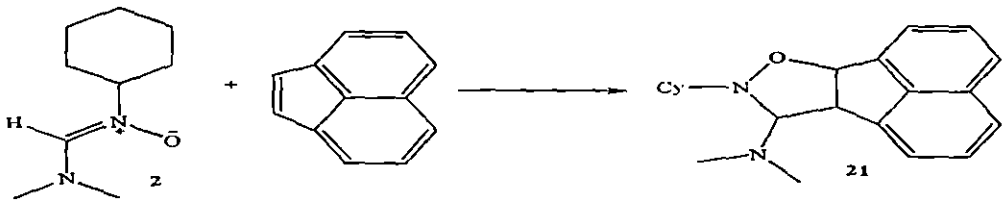
Scheme 23

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N*,*N*-dimethyl formamide (9 mL, 1 equivalent), styrene (1 equivalent) was added *in-situ* at the time formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 14 hour. The progress of the reaction was monitored by TLC (R_f = 0.52). The crude product was concentrated under a rotary evaporator and finally the cycloadduct was purified by silica gel column chromatography ethyl acetate - hexane and was obtained as colourless liquid.

Spectral data:

Colourless liquid, 88%; IR ($CHCl_3$): 3210 (m), 1735 (s), 1660 (s), 1420 (m), 1300 (m), 1225 (s), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60 - 7.44 (m, 5H, C_6H_5 protons), 5.10 (t, 1H, J = 6.16 Hz, C_5H), 4.35 (t, 1H, J = 6.24 Hz, C_3H), 3.55 (dd, 2H, J = 7.12, 8.10 Hz, C_4 2H), 2.45 - 2.30 (br, 6 *N*-methyl protons), 1.76 – 1.24 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 134.00, 133.00, 131.50, 130.40 (aromatic carbons), 85.00 (C_5), 74.00 (C_3), 56.00 (C_4), 36.00, 35.00 (2 x CH_3 carbons), 26.00, 24.70, 23.00, 22.00, 20.60, 18.00 (cyclohexyl carbons); MS (*m/z*): 274 (M^+), 230, 197, 191, 153,111, 83, 77, 51,44; HRMS – EI: Calcd. for $C_{17}H_{26}N_2O$ (M) 274.4054, Found M^+, 274.4039.

21. Synthesis of 8-cyclohexyl-*N*,*N*-dimethyl-6b,8,9,9a-tetrahydroacenaphtho[1,2-*d*]isoxazol-9-amine (acenaphthylene cycloadduct):



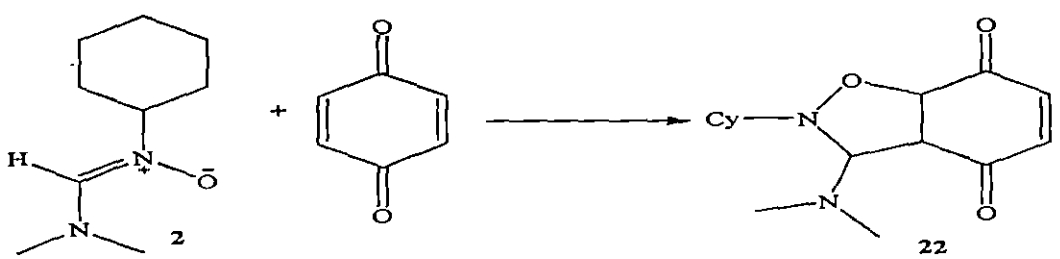
Scheme 24

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), acenaphthylene (1 equivalent each) was added *in-situ* at the time formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 48 hour. The progress of the reaction was monitored by TLC (R_f = 0.52). The crude product was concentrated under a rotary evaporator and finally the cycloadduct was purified by silica gel column chromatography using ethyl acetate-hexane and was obtained as bright yellow crystalline solid.

Spectral data:

Bright yellow crystalline solid, 95%; IR ($CHCl_3$): 3425 (m), 1710 (s), 1680 (s), 1390 (m), 1260 (s), 760 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 - 7.26 (m, 6H, naphthalene ring protons), 4.37 (d, 1H, J = 6.08 Hz, C_5H), 3.18 (d, 1H, J = 6 Hz, C_3H), 2.89 (dd, 1H, J = 6.08, 6.28 Hz, C_4H), 2.45 (br, 6 *N*-Me protons), 1.90 – 1.11 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 138.00, 136.40, 135.00, 133.75, 132.80, 130.70, 128.55, 127.00 (aromatic carbons), 84.90 (C_5), 73.88 (C_3), 58.50 (C_4), 46.00, 44.22 (2 x CH_3 carbons), 26.32, 25.00, 24.10, 22.65, 20.43, 19.54 (cyclohexyl carbons); MS (*m/z*): 322 (M^+), 239, 209, 195, 170, 152, 113, 83, 44; HRMS – EI: Calcd. for $C_{21}H_{26}N_2O$ (M) 322.2420, Found M^+ 322.2408.

22. Synthesis of 2-cyclohexyl-3-(dimethylamino)-3,3a-dihydrobenzo[*d*]isoxazole-4,7(2*H*,7a*H*)-dione (*p*-benzoquinone cycloadduct):



Scheme 25

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), *p*-benzoquinone (1 equivalent each) was added *in-situ* at the time formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 45 hour. The progress of the reaction was monitored by TLC (R_f = 0.49). The crude product was concentrated under a rotary evaporator and finally the cycloadduct was purified by silica gel-column chromatography using ethyl acetate-hexane and was obtained as dark brown crystals.

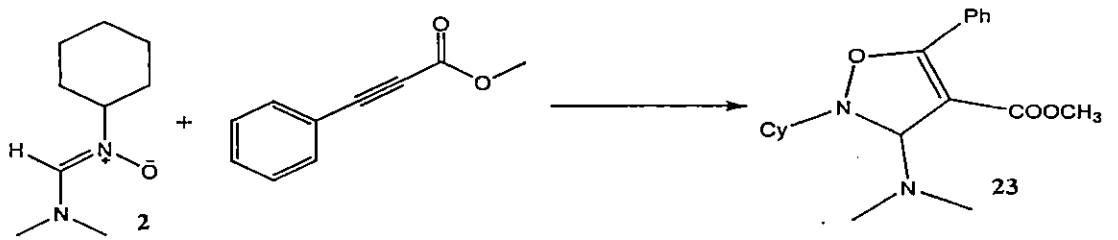
Spectral data:

Dark brown crystals, 94%; IR ($CHCl_3$): 3230 (br), 2950 (s), 2845 (m), 2766 (m), 1750 (s), 1610 (s), 1445 (m), 1230 (s), 810 (m), 790 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 – 7.26 (m, 2H, aromatic protons), 5.24 (d, 1H, J = 6.02 Hz, C_5 H), 3.68 (d, 1H, J = 7.42 Hz, C_3H), 3.34 (dd, 1H, J = 6.80, 6.88 Hzs, C_4H), 2.45 (br, 6 H, NMe_2), 1.80 – 1.25 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 192.50, 190.00 (carbonyl carbons), 87.00 (C_5), 74.00 (C_3), 57.40 (C_4), 41.00, 39.50 (NMe_2), 34.40, 32.58 ($CO\underline{CH_2CH_2}CO$), 28.40, 27.00, 25.70, 23.65, 22.00, 20.40 (6 CH_2 carbons); MS (*m/z*): 278 (M^+), 250, 222, 206, 195, 167, 139, 124, 83; HRMS – EI: Calcd. for $C_{15}H_{22}N_2O_3$ (M) 278.2020, Found M^+ 278.2008.

General Procedure for 1,3-dipolar cycloaddition reaction of nitrone 2 with alkynes[7a]

N-cyclohexyl-α-amino nitrone is highly unstable and decomposes at RT and hence the nitrone was used immediately after its isolation for the cycloaddition reaction with dipolarophiles (alkynes) in a 1:1 ratio. In a 100 mL conical flask nitrone **1** (2.20 mmol), ethyl propiolate (1 equivalent) was added to 50 mL dry ether and stirred at RT with a magnetic stirrer under N_2 atmosphere for 12 hour. The progress of the reaction was monitored by TLC (R_f = 0.72). The crude product was concentrated under a rotary evaporator and finally the product was purified by silica gel column chromatography using ethyl acetate-hexane combinations and was obtained as colourless gummy liquid. This procedure was followed for all the substrates listed in Table **5**.

23. Synthesis of methyl 3-(dimethylamino)-2,5-diphenyl-2,3-dihydroisoxazole-4-carboxylate (phenyl methyl propiolate cycloadduct):



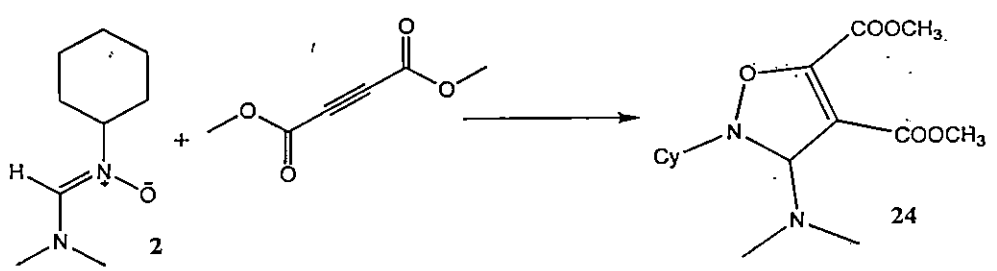
Scheme 26

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N*,*N*-dimethyl formamide (9 mL, 1 equivalent), phenyl methyl propiolate was added (1 equivalent) *in-situ* at the time formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 14 hour. The progress of the reaction was monitored by TLC (R_f = 0.62). The crude product was concentrated under a rotary evaporator and finally the cycloadduct was purified by silica gel column chromatography using ethyl acetate-hexane combinations and was obtained as colourless gummy liquid.

Spectral data:

Colourless gummy liquid, 96 %; IR ($CHCl_3$): 3379-3125 (br), 2936 (s), 1900 (m), 1780 (s), 1445 (m), 1295 (m), 1106 (s), 900 (s), 758 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.64 – 7.53 (m, 5H, C_6H_5 protons), 4.05 (s, 1H, C_3H), 3.63 (s, 3H, – $COOCH_3$), 2.76 (br, 6H, NMe_2), 1.95 - 1.66 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 172.50 (carbonyl carbon), 137.00, 135.40, 134.00, 132.60 (aromatic carbons), 88.42 (C_5), 73.76 (C_3), 57.40 (C_4), 45.00 (-$COOCH_3$), 33.13, 29.50 (*N* - CH_3 carbons), 26.00, 24.80, 23.40, 21.80, 20.00, 18.70 (CH_2 carbons); MS (*m/z*): 330 (M^+), 286, 247, 246, 225, 194, 148, 105 (B.P), 83, 77, 31; HRMS – EI: Calcd. for $C_{19}H_{26}O_3N_2$ (M) 330.1935, Found M^+, 330.1919.

24. Synthesis of dimethyl 3-(dimethylamino)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate (dimethyl acetylene dicarboxylate cycloadduct):



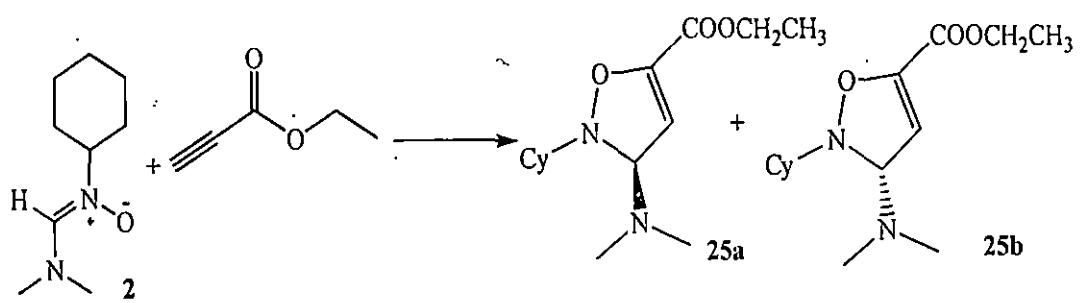
Scheme 27

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), dimethyl acetylene dicarboxylate was added (1 equivalent) *in-situ* at the time formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 18 hour. The progress of the reaction was monitored by TLC (R_f = 0.58). The crude product was concentrated under a rotary evaporator and finally the cycloadduct was purified by silica gel column chromatography using ethyl acetate-hexane combinations and was obtained as red liquid.

Spectral data:

Red liquid, 92 %; IR ($CHCl_3$): 3145 (m), 2820 (m), 1745 (s),1700 (m), 1670 (m), 1420 (s), 1260 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.75 (s, 1H, C_3H), 3.66 (s, 3H,-$COOCH_3$), 3.60 (s, 3H, -$COOCH_3$), 2.68 (br, 6H, NMe_2), 2.05 - 1.64 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 186.70, 184.67 (carbonyl carbons), 87.50 (C_5), 76.42 (C_3), 59.48 (C_4), 44.42, 43.54 ($COO\underline{C}H_3$), 31.65, 29.48 (N - CH_3 carbons), 25.80, 24.30, 23.90, 22.70, 20.60, 18.50 (CH_2 carbons); MS (*m/z*): 312 (M^+), 281, 268, 229, 228, 225 (B.P), 194, 185, 87, 83, 59, 44, 31; HRMS – EI: Calcd. for $C_{15}H_{24}O_5N_2$ (M) 312.1677, Found M^+, 312.1668.

25. Synthesis of ethyl propiolate cycloadducts (diastereomers)



Scheme 28

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), ethyl propiolate was added (1 equivalent) *in-situ* at the time formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 6 hour. The progress of the reaction was monitored by TLC (R_f = 0.44, 0.50). The crude products were concentrated under a rotary evaporator and finally the cycloadducts were purified and

separated by silica gel column chromatography using ethyl acetate-hexane and were obtained as white viscous liquids.

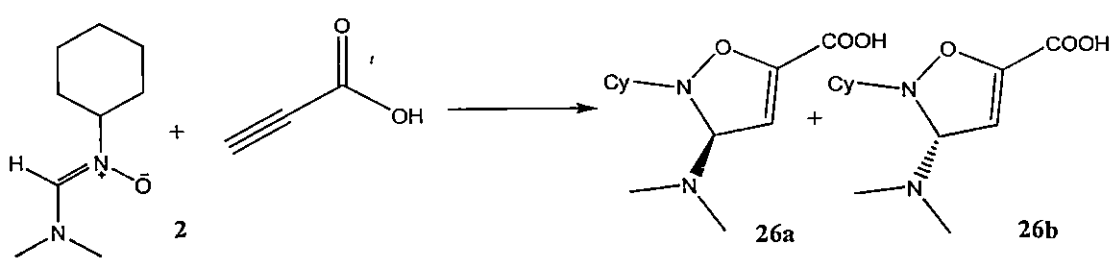
25a. Spectral data of (*S*)-methyl 3-(dimethylamino)-2-phenyl-2,3-dihydroisoxazole-5-carboxylate:

Red gummy liquids, 70 %; IR ($CHCl_3$): 3165 (m), 2945 (s), 1770 (m), 1680 (s), 1656 (s), 1430 (m), 1260 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.64 (d, 1H, J = 9.30 Hz, C_3H), 4.26 (dd, 2H, J = 6.24, 6.36 Hz, $COOCH_2CH_3$), 3.35 (d, 1H, J = 9.20 Hz, C_4H), 2.76 (br, 6H, NMe_2), 2.04 – 1.67 (m, 11H), 1.40 (t, 3H, J = 4.36 Hz, $-COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 173.40 (carbonyl carbon), 86.00 (C_5), 78.00 (C_3), 55.00 (C_4), 32.00 ($COOCH_2CH_3$), 30.00 ($COOCH_2CH_3$), 28.80, 27.30 (*N* - CH_3 carbons), 25.00, 23.70, 22.20, 20.80, 19.00, 18.40 (CH_2 carbons); MS (*m/z*): 268 (M^+), 224, 195 (B.P), 185, 184, 141, 83, 73; HRMS – EI: Calcd. for $C_{14}H_{24}O_3N_2$ (M) 268.1779, Found M^+, 268.1763.

25b. Spectral data of (*R*)-methyl 3-(dimethylamino)-2-phenyl-2,3-dihydroisoxazole-5-carboxylate:

Red gummy liquids, 22%; IR ($CHCl_3$): 3160 (m), 2955 (s), 1770 (m), 1684 (s), 1658 (s), 1435 (m), 1255 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.58 (d, 1H, J = 2.53 Hz, C_3H), 4.32 (dd, 2H, J = 7.14, 6.16 Hz, $COOCH_2CH_3$), 3.26 (d, 1H, J = 2. 58 Hz, C_4H), 2.66 (br, 6H, NMe_2), 2.24 – 2.12 (m, 1H, *N*-CH proton), 1.94 – 1.53 (m, 10H), 1.24 (t, 3H, J = 4.08 Hz, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.70 (carbonyl carbon), 88.10 (C_5), 76.60 (C_3), 57.20 (C_4), 33.40 ($COOCH_2CH_3$), 31.70 ($COOCH_2CH_3$), 29.00, 27.80 (*N* - CH_3 carbons), 26.10, 24.00, 23.00, 21.40, 20.20, 18.30 (6 CH_2 carbons); MS (*m/z*): 268 (M^+), 224, 223, 195 (B.P), 185, 184, 141, 83, 73, 45; HRMS-EI: Calcd. for $C_{14}H_{24}O_3N_2$ (M) 268.1779, Found; M^+, 268.1756.

26. Synthesis of Propiolic acid cycloadducts (diastereomers):



Scheme 29

To a stirred solution of *N*-cyclohexylhydroxylamine (8.7 mmol) and dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent), propiolic acid was added (1 equivalent) *in-situ* at the time formation of nitrone **2** (monitored by TLC) at RT under N_2 atmosphere and the reaction mixture was stirred for further 11 hour. The progress of the reaction was monitored by TLC (R_f = 0.38, 0.54). The crude products were concentrated under a rotary evaporator and finally the cycloadducts were purified and separated by silica gel column chromatography using ethyl acetate-hexane and were obtained as colourless liquids.

26a. Spectral data of (*S*)-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylic acid

Colourless liquids, 68%; IR ($CHCl_3$): 3144 (m), 2942 (s), 1765 (m), 1684 (s), 1660 (s), 1440 (m), 1310 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.8 (s, 1H, - COOH), 4.52 (d, 1H, *J* = 9.46 Hz, C_3H), 3.82 (d, 1H, *J* = 9.44 Hz, C_4H), 2.58 (br, 6H, NMe_2), 2.12 – 1.70 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 181.30 (carbonyl carbon), 87.00 (C_5), 78.50 (C_3), 56.50 (C_4), 32.20, 30.70 (N - CH_3 carbons), 27.00, 25.30, 24.20, 23.00, 21.00, 18.00 (CH_2 carbons); MS (*m/z*): 240 (M^+), 196, 195 (B.P), 167, 157, 83, 73, 45; HRMS – EI: Calcd. for $C_{12}H_{20}O_3N_2$ (M) 240.1467, Found; M^+, 240.1452.

26b. Spectral data (*R*)-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylic acid

Colourless liquids, 21%; IR ($CHCl_3$): 3155 (m), 2950 (s), 1770 (m), 1680 (s), 1655 (s), 1444 (m), 1250 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.4 (s, 1H, - COOH), 4.63 (d, 1H, *J* = 2.56 Hz, C_3H), 3.75 (d, 1H, *J* = 2. 64 Hz, C_4H), 2.53 (br, 6H, NMe_2), 2.40 – 2.28 (m, 1H, N-CH proton), 1.90 – 1.53 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 180.00 (carbonyl carbon), 88.40 (C_5), 76.70 (C_3), 57.50 (C_4), 34.00, 32.80 (*N* - CH_3 carbons), 28.00, 27.40, 25.10, 23.14, 22.20, 19.00 (6 CH_2 carbons); MS (*m/z*): 240 (M^+), 196, 195(B.P), 167, 157, 156, 83, 73, 45, 44; HRMS – EI: Calcd. for $C_{12}H_{20}O_3N_2$ (M) 240.1467, Found M^+ 240.1449.

General Procedure for 1,3-dipolar cycloaddition reaction of nitrone 2 in aqueous media

Since *N*-cyclohexyl-α-amino nitrone[7] (**2**) decomposes at room temperature therefore all the cycloaddition reactions were performed with freshly prepared nitrone **2** in

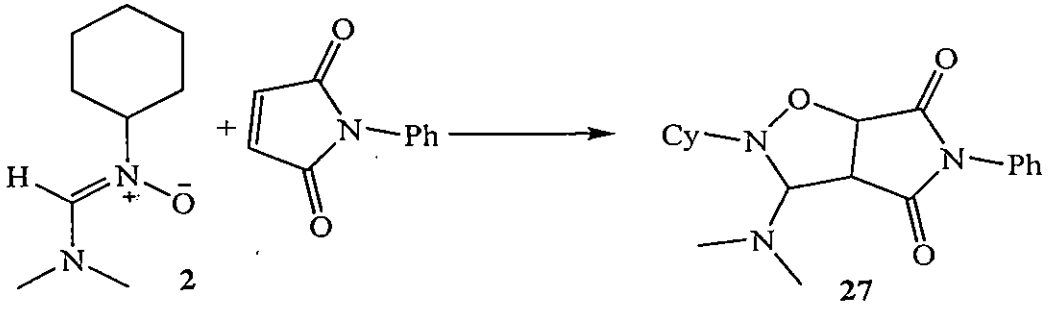
aqueous media. In a 50 mL conical flask nitrone **2** (1 mmol), dipolarophile (alkene / alkynes, 1 equivalent) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5-10 hour. The progress of the reaction was monitored by TLC. After completion of the reaction the products were extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The products were purified by column chromatography using ethyl acetate-hexane to afford pure cycloadducts. This procedure was followed for all the substrates listed in **Table 6.**

Table 6.

Alkenes

- *N*-Phenyl maleimide
- *N*-Methyl maleimide
- *N*-Cyclohexyl maleimide
- Styrene
- Ethyl acrylate
- Acenaphthylene
- Tetrachloro ethylene

27. Synthesis of 2-cyclohexyl-3-(dimethylamino)-5-phenyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (*N*-phenyl maleimide cycloadduct)



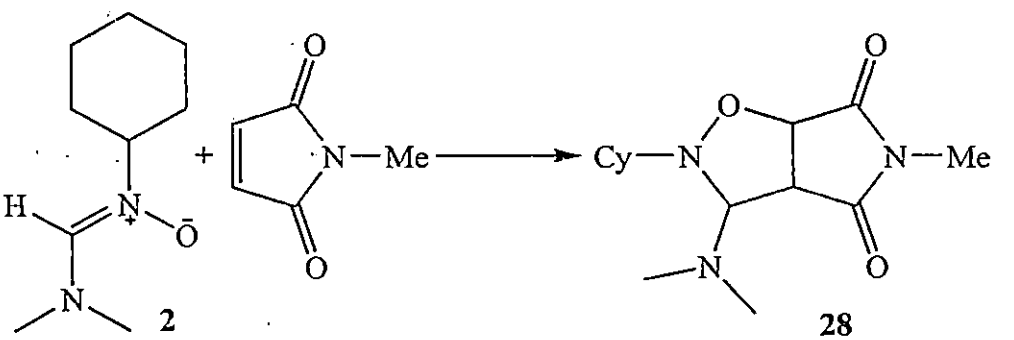
Scheme 30

In a 50 mL conical flask, nitrone **2** (1 mmol), *N*-phenyl maleimide (1 mmol) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.48). After completion of the reaction, the product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The product was purified by column chromatography using ethyl acetate-hexane and was obtained as white crystals.

Spectral data:

White crystals, 95%; IR ($CHCl_3$): 3350 (br), 3040 (s), 2900 (m), 2800 (m), 2375 (s), 1660 (s), 1470 (m), 1320 (m), 1090 (s), 938 (m), 815 (w), 775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55 - 7.44 (m, 5H, C_6H_5), 4.90 (d, 1H, J = 6.06 Hz, C_5H), 4.46 (d, 1H, J = 6.08 Hz, C_3H), 3.90 (dd, 1H, J = 6.06, 6.08 Hz, C_4H), 3.22-3.10 (m,1H,N-CH), 2.90 – 2.78 (br, 6H, *N*-Me protons), 2.20 - 1.82 (m, 10H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 168.00, 166.00 (carbonyl carbons), 136-126.5 (6 signals, 6 aromatic carbons), 87.50 (C_5), 76.00 (C_3), 59.40 (C_4), 37.00, 36.00 (2 methyl carbons), 30.00, 28.54, 27.00, 25.20, 24.00, 22.00 (6 cyclohexyl carbons); MS (*m/z*): 343 (M^+), 328, 313, 299, 266, 260, 230, 189, 183, 154, 113, 83, 77; HRMS - EI: Calcd. for $C_{19}H_{25}O_3N_3$ (M) 343.4270, Found M^+ 343.4261; Found: C, 66.40; H, 7.22; N, 12.20 %; $C_{19}H_{25}O_3N_3$ requires C, 66.47; H, 7.28; N, 12.24 %.

28. Synthesis of 2-cyclohexyl-3-(dimethylamino)-5-methyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (*N*-methyl maleimide cycloadduct):



Scheme 31

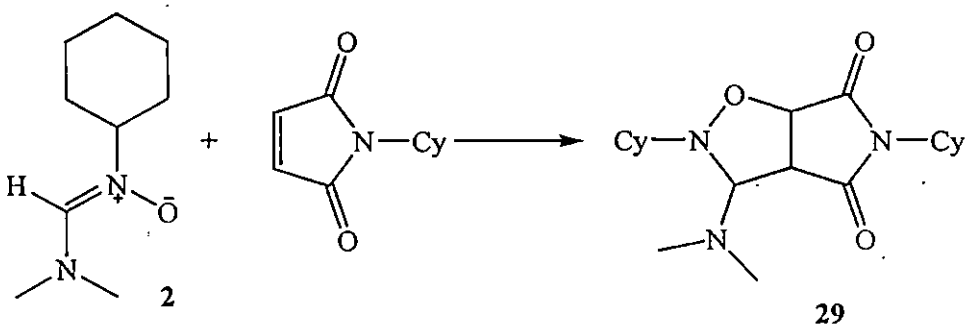
In a 50 mL conical flask, nitrone **2** (1 mmol), *N*-methyl maleimide (1 mmol) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.54). After completion of the reaction, the product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The product was purified by column chromatography using ethyl acetate- hexane and was obtained as white crystals.

Spectral data:

White crystals, 94%; IR ($CHCl_3$): 3370 (br), 2860 (s), 2310 (s), 1680 (s), 1465 (m), 1325 (m), 1280 (s), 1100 (m), 702 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.34 (d, 1H, J = 6.02

Hz, C_5H), 4.15 (d, 1H, J = 6.0 Hz, C_3H), 3.60 (dd, 1H, J = 6.14, 6.26 Hz, C_4H), 3.40 (s, 3H, CH_3), 2.85 – 2.71 (br, 6H, N-CH_3 protons); 1.95 - 1.42 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 170.00, 168.50 (carbonyl carbons), 88.00 (C_5), 73.00 (C_3), 54.42 (C_4), 39.02, 37.00, 36.34 (3 methyl carbons), 28.00, 26.80, 25.00, 23.75, 22.80, 21.00 (cyclohexyl carbons); MS (*m/z*): 281 (M^+), 266, 251, 237, 198, 153, 128, 111, 83; HRMS – EI: Calcd. for $C_{14}H_{23}O_3N_3$ (M) 281.2160, Found; M^+, 281.2143; Found: C, 59.97; H, 7.69; N, 15.01 %; $C_{14}H_{23}O_3N_3$ requires C, 60.04; H, 7.85; N, 15.08 %.

29. Synthesis of 2,5-dicyclohexyl-3-(dimethylamino)dihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (*N*-cyclohexyl maleimide cycloadduct):



Scheme 32

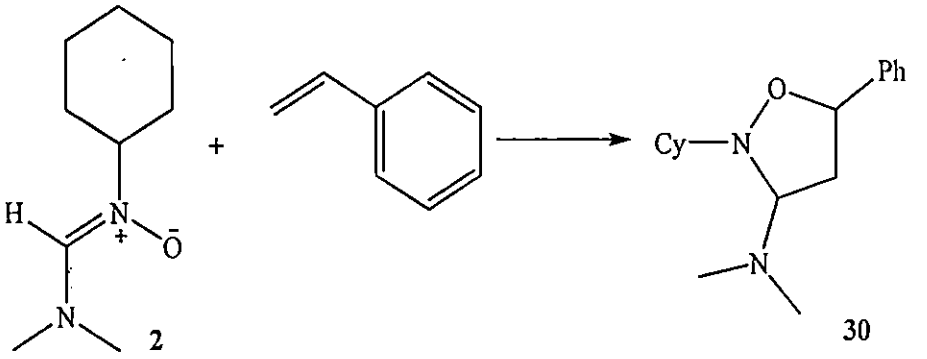
In a 50 mL conical flask, nitrone **1** (1 mmol), *N*-cyclohexyl maleimide (1 mmol) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.58). After completion of the reaction, the product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The product was purified and crystallized from ethyl acetate- hexane and was obtained as white crystals.

Spectral data:

White crystals, 95%; IR ($CHCl_3$): 3150 (br), 2920 (s), 1770 (s), 1680 (s), 1440 (m), 1260 (m), 1130 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.10 (d, 1H, J = 6.10 Hz, C_5H), 4.80 (d, 1H, J = 6.08 Hz, C_3H), 4.26 (dd, 1H, J = 6.00, 6.06 Hz, C_4 2H), 3.82-3.20 (m, 2x1H, N-CH), 2.84 – 2.73 (br, 6H, N – CH_3), 2.20 – 1.05 (m, 20H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 168.40, 166.30 (carbonyl carbons), 86.00 (C_5), 78.00 (C_3), 55.00 (C_4), 39.40, 38.00 (2 methyl carbons), 33.00, 31.86, 30.12, 28.65, 27.00,

25.86, 24.80, 23.60, 22.75, 21.00, 20.10, 18.00 (cyclohexyl carbons); MS (*m/z*): 349 (M^+), 319, 305, 266, 251, 196, 183; 153, 111, 83; HRMS – EI: Calcd. for $C_{19}H_{31}O_3N_3$ (M) 349.4750, Found; M^+, 349.4745; Found: C, 65.26; H, 8.74; N, 12.06 %; $C_{19}H_{31}O_3N_3$ requires C, 65.32; H, 8.88; N, 12.03 %.

30. Synthesis of 2-cyclohexyl-*N*,*N*-dimethyl-5-phenylisoxazolidin-3-amine (Styrene cycloadduct):



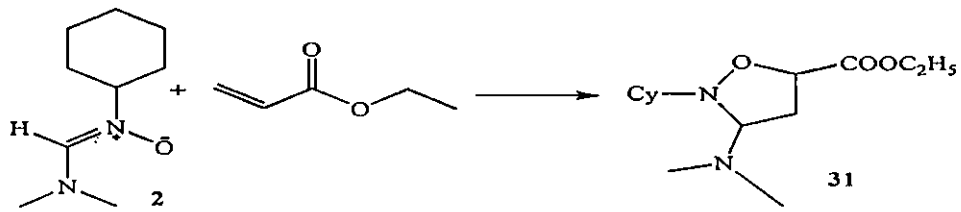
Scheme 33

In a 50 mL conical flask, nitrone **2** (1 mmol), styrene (1 mmol) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.50). After completion of the reaction, the product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The product was purified by column chromatography using ethyl acetate- hexane and was obtained as colourless liquid.

Spectral data:

Colourless liquid, 94%; IR ($CHCl_3$): 3210 (m), 1735 (s), 1660 (s), 1420 (m), 1300 (m), 1225(s), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60 - 7.44 (m, 5H, C_6H_5 protons), 5.10 (t, 1H, *J* = 6.08 Hz, C_5H), 4.35 (t, 1H, *J* = 6.16 C_3H), 3.70 (dd, 2H, *J* = 6.12, 6.10 Hz, $C_4$2H), 2.45 - 2.30 (br, m, 6 *N*-methyl protons), 1.76 - 1.24 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 134.30, 132.80, 130.64, 128.70 (aromatic carbons), 85.80 (C_5), 74.50 (C_3), 56.40 (C_4), 36.70, 35.00 (2 CH_3 carbons), 26.00, 24.20, 23.00, 22.42, 20.00, 18.90 (6 cyclohexyl carbons); MS (*m/z*): 274 (M^+), 230, 197, 191, 153,111, 83, 77; HRMS – EI: Calcd. for $C_{17}H_{26}N_2O$ (M) 274.4054, Found M^+, 274.4038.

31. Synthesis of ethyl 2-cyclohexyl-3-(dimethylamino)isoxazolidine-5-carboxylate (ethyl acrylate cycloadduct):



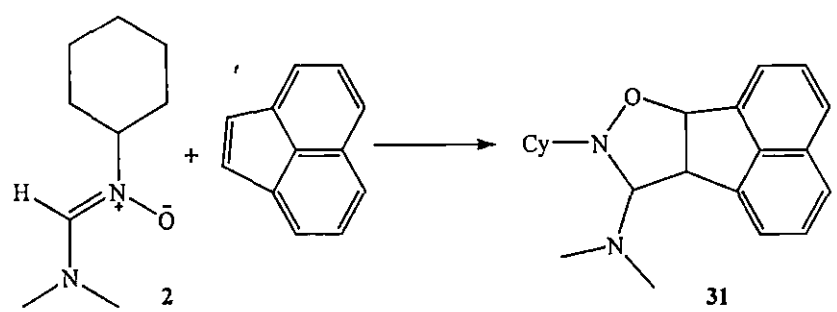
Scheme 34

In a 50 mL conical flask, nitrone **2** (1 mmol), ethyl acrylate (1 mmol) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.62). After completion of the reaction, the product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The product was purified by column chromatography using ethyl acetate-hexane and was obtained as colourless liquid.

Spectral data:

Colourless liquid, 92%; IR ($CHCl_3$): 3330 (br), 2930 (s), 2150 (m), 1781 (s), 1675 (s), 1450 (s), 1365 (m), 1254 (m), 1110 (s), 1250 (m), 670 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.20 (t, 1H, *J* = 6.76 Hz, C_5H), 4.86 (t, 1H, *J* = 9.40 Hz, C_3H), 4.56 (q, 2H, -$O\underline{CH_2}CH_3$), 3.84 (dd, 2H, *J* = 7.65, 6.62 Hz, C_4 2H), 3.44 (t, 3H, $OCH_2\underline{CH_3}$), 2.42 - 1.84 (br, m, 6H, NMe_2), 1.56 - 1.24 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 202.80 (ester carbonyl carbon); 87.80 (C_5), 76.40 (C_3), 58.85 (C_4), 44.00, 43.00 ($COOCH_2CH_3$), 37.20, 35.42 (NMe_2), 31.00, 30.00, 28.00, 27.20, 26.10, 25.00 (6 CH_2 carbons); MS (*m/z*): 270 (M^+), 226, 197, 157, 154, 116, 113, 83, 73, 44; HRMS-EI: Calcd. for $C_{14}H_{26}O_3N_2$ (M) 270.1935, Found M^+, 270.1922.

32. Synthesis of 8-cyclohexyl-*N*,*N*-dimethyl-6b,8,9,9a-tetrahydroacenaphtho[1,2-*d*]isoxazol-9-amine (acenaphthylene cycloadduct):



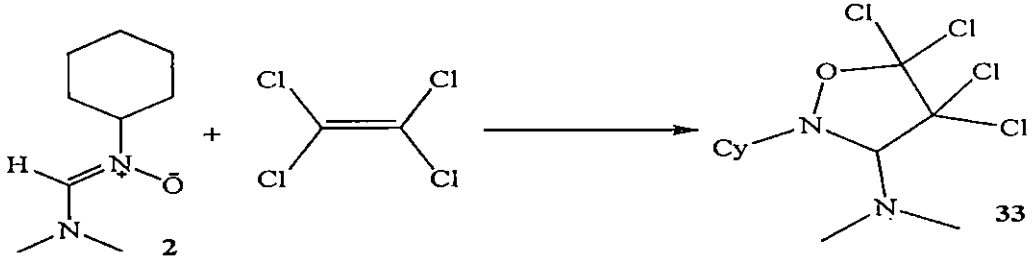
Scheme 35

In a 50 mL conical flask, nitrone **2** (1 mmol), acenaphthylene (1 mmol) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.54). After completion of the reaction, the product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The product was purified by column chromatography using ethyl acetate-hexane and was obtained as bright yellow crystalline solid.

Spectral data:

Bright yellow crystalline solid, 94%; IR ($CHCl_3$): 3425 (m), 1710 (s), 1680 (s), 1390 (m), 1260 (s), 760 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 - 7.30 (m, 6H, naphthalene ring protons); 5.00 (d, 1H, J = 6.08 Hz, C_5H), 4.50 (d, 1H, J = 6 Hz, C_3H), 3.56 (dd, 1H, J = 6.08, 6.28 Hz, C_4H), 2.40 - 2.30 (br, m, 6 *N*-Me protons), 1.66 – 1.28 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 138.00, 136.50, 134.20, 133.70, 132.24, 131.60, 130.00, 128.50, 127.00 (aromatic carbons), 83.00 (C_5), 73.20 (C_3), 58.00 (C_4), 46.00, 44.00 (2 CH_3 carbons), 32.00, 30.50, 28.50, 27.00, 25.00, 24.10 (6 cyclohexyl carbons); MS (*m/z*): 322 (M^+), 239, 209, 195, 170, 152, 113, 113, 83, 44. HRMS – EI: Calcd. for $C_{21}H_{26}N_2O$ (M) 322.2420, Found; M^+, 322.2432.

33. Synthesis 4,4,5,5-tetrachloro-2-cyclohexyl-*N*,*N*-dimethylisoxazolidin-3-amine (tetrachloro ethelene cycloadduct):



Scheme 36

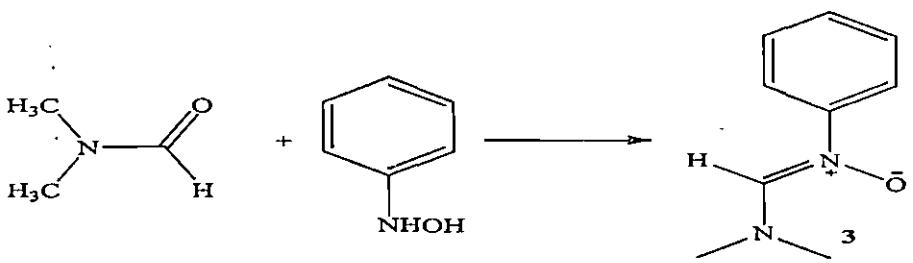
In a 50 mL conical flask, nitrone **2** (1 mmol), acenaphthylene (1 mmol) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.34). After completion of the reaction, the product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The product was purified by column chromatography using ethyl acetate-hexane and was obtained as pale yellow oily liquid.

Spectral data:

Pale yellow oily liquid, 96%; IR ($CHCl_3$): 3310 (br), 3020 (m), 2170 (s), 1860 (s), 1460 (m), 1330 (m), 1150 (s), 875 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.24 - 4.16 (br, s, 1H, C_3H), 2.33 - 2.24 (br, m, *N* - CH_3 protons), 2.05 – 1.93 (m, 1H, *N*-CH proton), 1.74 – 1.32 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 87 (C_5), 73 (C_3), 58 (C_4), 56, 55 (2 x CH_3 carbons), 39 – 28 (6 cyclohexyl carbons); MS *(m/z)*: 334 (M^+), 292, 252, 222, 153, 152, 139, 113, 111, 83, 82, 44; HRMS – EI: Calcd. for $C_{11}H_{18}N_2OCl_4$, (M) 336.0240, Found; M^+, 336.0231.

Reaction type III

General procedure for the preparation of *N*-phenyl-α-aminonitrone[8a] (nitrone 3):



Scheme 37

N-phenyl hydroxylamine (0.5161 gm, 4.7 mmol) was added to dry distilled *N,N*-dimethyl formamide (9 mL, 1 equivalent) in presence of anhydrous $MgSO_4$. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 24 hour. The formation of nitrone **3** was monitored by TLC (R_f = 0.32, silica gel; ethyl acetate : benzene = 1 : 10). The nitrone **3** was isolated by extraction with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over sodium sulphate and concentrated on a rotary evaporator and finally obtained as faint yellow crystals (m.p 52^0C,uncorrected). The nitrone decomposes when kept at room temperature for a longer period and hence it was either used right after its synthesis (for aqueous phase synthesis) or as *in-situ* for other cycloaddition reactions.

Spectral data of (*Z*)-*N*-((dimethylamino)methylene)aniline oxide:

Pale yellow crystals, 94%; IR ($CHCl_3$): 3410 (m), 1660 (s), 1610 (s), 1440 (m), 1300 (m), 1180 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.73 - 7.26 (m, 5H, C_6H_5 protons), 1.90 (br, 6H, *N*-methyl protons), 1.42 (s, 1H, $CH{=}N^+$); ^{13}C NMR ($CDCl_3$): δ 142.00

(CH=N+), 132.90, 131.00, 129.65, 127.40 (aromatic carbons), 47.42, 44.84 (methyl carbons); HRMS – EI: Calcd. for $C_9H_{12}N_2O$, (M) 164.2066, Found; M^+, 164.2052.

General Procedure for 1,3-dipolar cycloaddition reaction in aqueous phase

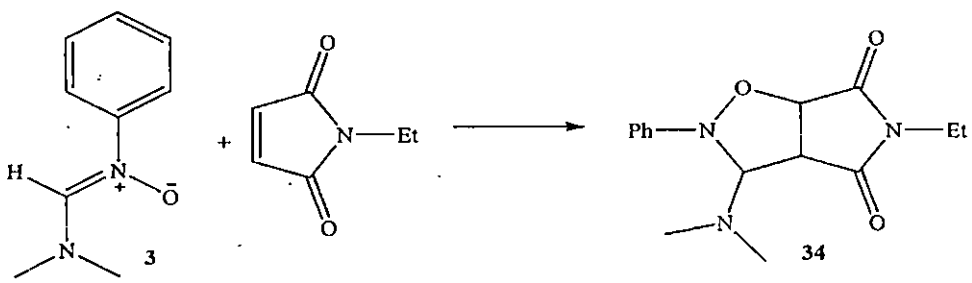
Since nitrone (**3**) decomposes when kept for longer period therefore all the cycloaddition reactions are performed with freshly prepared nitrone **3**. In a 50 mL conical flask, nitrone **3** (1 mmol), dipolarophile (1 equivalent) and water (10 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 - 6 hour. The progress of the reaction was monitored by TLC. After completion of the reaction the product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The product was purified by column chromatography using ethyl acetate – hexane. This procedure was followed for all the substrates listed in **Table 4**

Table 4: List of dipolarophiles used for cycloaddition reaction

Alkenes

- *N*-ethyl maleimide
- *p*-OMe-*N*-phenyl maleimide
- Acenaphthylene
- Ethyl acrylate
- Methyl vinyl ketone

34. Synthesis of 3-(dimethylamino)-5-ethyl-2-phenyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (Ethyl maleimide cycloadduct):



Scheme 38

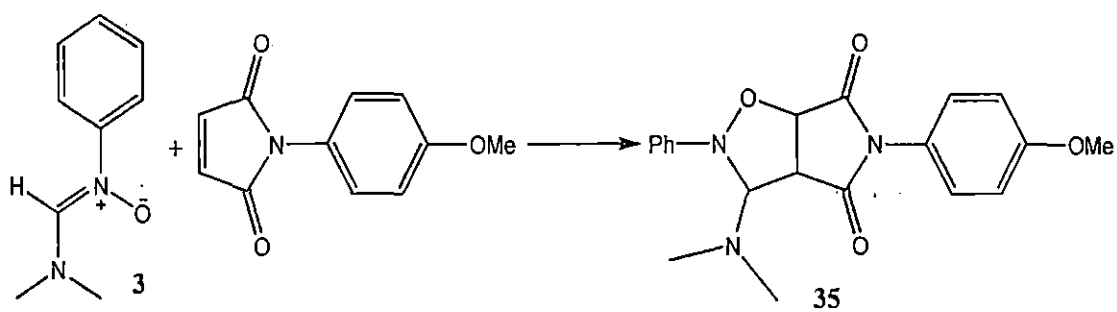
To a stirred solution of nitrone **3** (1 mmol) in 15 mL water was added *N*-ethyl maleimide (1 equivalent) at RT under nitrogen atmosphere and the reaction mixture was stirred for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.44). The product was extracted with ether (2 x 25 mL), the organic layer was washed with

brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as yellow solid.

Spectral data:

Yellow solid, 94%; IR ($CHCl_3$): 3165 - 3082 (br), 3013 (m), 2865 (m), 1760 (s), 1660 (m), 1445 (s), 1280 (m), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45 – 7.31 (m, 5H, C_6H_5), 5.26 (d, 1H, J = 8.20 Hz, C_5H), 3.62 (d, 1H, J = 7.20 Hz, C_3H), 3.38 (dd, 1H, J = 6.16, 6.32 Hz, C_4H), 2.90 – 2.78 (br, 6H, NMe_2), 2.66 (q, 2H, J = 6.12, 6.80 Hz, $\underline{CH_2}CH_3$), 1.34 (t, 3H, J = 7.10 Hz, $CH_2\underline{CH_3}$); ^{13}C NMR ($CDCl_3$): δ 200.40, 197.80 (carbonyl carbons), 136.50, 135.00, 133.20, 131.80 (phenyl carbons), 86.20 (C_5), 78.40 (C_3), 55.00 (C_4), 41.70, 39.64 (NMe_2), 23.50 ($\underline{CH_2}CH_3$), 14.00 ($CH_2\underline{CH_3}$); MS (*m/z*): 289 (M^+), 260, 212, 182, 168, 148, 141 (B.P), 107, 77 ; HRMS – EI: Calcd. for $C_{15}H_{19}O_3N_3$ (M) 289.3350, Found; M^+ 289.3334.

35. Synthesis of 3-(dimethylamino)-5-(4-methoxyphenyl)-2-phenyldihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (*p*-OMe-*N*-phenyl maleimide cycloadduct):



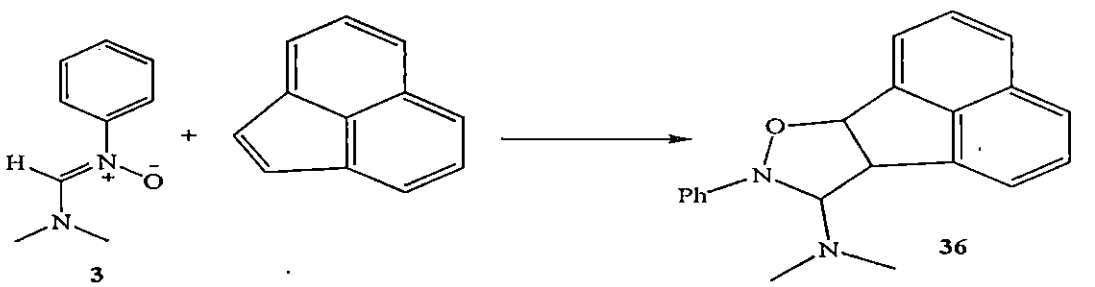
Scheme 39

To a stirred solution of nitrone **3** (1 mmol) in 15 mL water was added 4-methoxy-*N*-phenyl maleimide (1 equivalent) at RT under nitrogen atmosphere and the reaction mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.39). The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as dark yellow crystals.

Spectral data:

Dark yellow crystals, 94 %; IR ($CHCl_3$): 3084 – 3022 (br), 2880 (m), 1765 (s), 1650 (s), 1472 (m), 1365 (m), 795 (s), 775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55 - 7.40 (m, 5H, C_6H_5 protons), 6.90 – 6.78 (m, 4H, phenyl protons), 5.40 (d, 1H, J = 8.24 Hz, C_5H), 3.82 (d, 1H, J = 7.28 Hz, C_3H), 3.54 (dd, 1H, J = 9.24, 6.08 Hz, C_4H), 3.30 (s, 3H, OCH_3), 2.70 – 2.56 (br, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 204.50, 198.65 (carbonyl carbons), 138.00, 137.00, 135.64, 134.32, 133.70, 132.00, 131.46, 130.00 (aromatic carbons), 85.50 (C_5), 76.00 (C_3), 59.42 (C_4), 54.60 (OCH_3), 40.75, 38.20 (NMe_2); MS (*m/z*): 351(M^+), 320, 274, 244, 230, 167, 148, 107, 77; HRMS – EI: Calcd. for $C_{20}H_{21}O_4N_3$ (M), 351.4060, Found; M^+, 351.4044.

36. Synthesis of *N,N*-dimethyl-8-phenyl-6b,8,9,9a-tetrahydroacenaphtho[1,2-*d*]isoxazol-9-amine (acenaphthylene cycloadduct)



Scheme 40

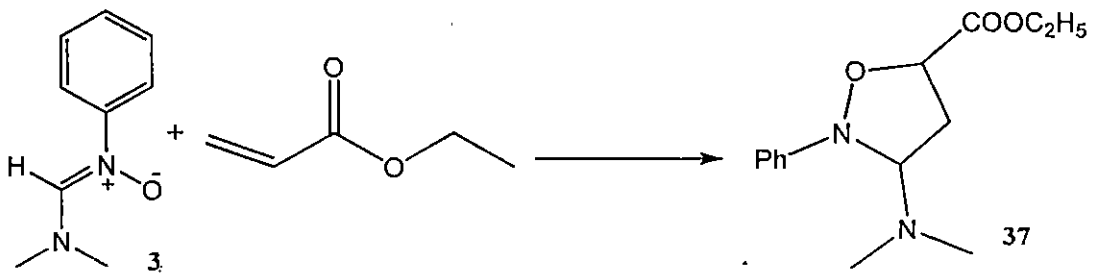
To a stirred solution of nitrone **3** (1 mmol) in 15 mL water was added 4-methoxy-*N*-phenyl maleimide (1 equivalent) at RT under nitrogen atmosphere and the reaction mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.54). The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate-hexane and finally obtained under reduced pressure as bright yellow crystals.

Spectral data:

Yellow crystals, 89%; IR ($CHCl_3$): 3084 - 3022 (br), 2848 (m), 2472 (m), 1710 (s), 1523 (m), 1523 (m), 1394 (s), 1145 (m), 1022 (m), 831 (m), 776 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 – 7.35 (m, 5H, phenyl protons), 7.12 – 6.96 (m, 6H, napthylene protons), 4.88 (d, 1H, J = 6.76 Hz, C_5H), 3.76 (d, 1H, J = 7 Hz, C_3H), 3.52 (dd, 1H, J

= 8.30, 8.0 Hz, C_4H), 2.58 – 2.43 (br, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 137.00, 135.08, 134.60, 133.00, 132.80, 131.25, 130.10, 129.45, 128.00, 126.90 (aromatic carbons), 88.70 (C_5), 76.46 (C_3), 58.00 (C_4), 36.00, 35.00 (NMe_2); MS (*m/z*): 316 (M^+), 239, 209, 195, 168, 162, 154 (B. P), 148, 107, 73; HRMS-EI: Calcd. for $C_{14}H_{26}O_3N_2$ (M) 316.1814, Found M^+, 316.1811.

37. Synthesis of ethyl 3-(dimethylamino)-2-phenylisoxazolidine-5-carboxylate (Ethyl acrylate cycloadduct):



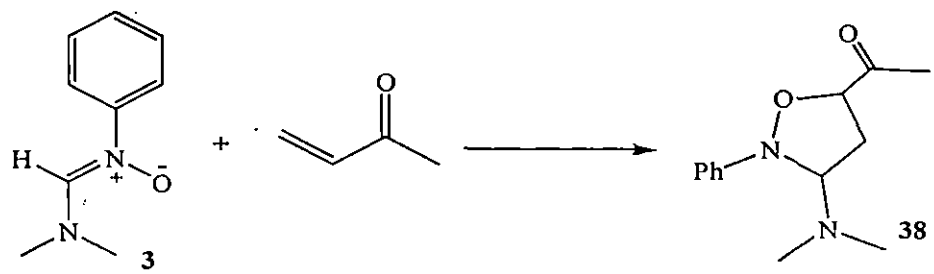
Scheme 41

To a stirred solution of nitrone **3** (1 mmol) in 15 mL water was added ethyl acrylate (1 equivalent) at RT under nitrogen atmosphere and the reaction mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.48).The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as white gummy liquid.

Spectral data:

White gummy liquid, 93%; IR ($CHCl_3$): 3155 – 3060 (br), 2930 (s), 2856 (m), 1750 (s), 1445 (s), 1340 (m), 770 (s) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.20 - 7.12 (m, 5H, C_6H_5), 4.80 (t, 1H, *J* = 8.2 Hz, C_5H), 4.26 (q, 2H, *J* = 6, 6.02 Hz, $-OCH_2CH_3$), 3.58 (t, 1H, *J* = 7.22 Hz, C_3H), 3.24 (dd, 2H, *J* = 8.40, 7.08 Hz, C_4 2H), 2.76 – 2.65 (br, 6H, NMe_2), 1.24 (t, 3H, *J* = 7.50 Hz, $-OCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 170.40 (carbonyl carbon), 135.00, 134.00, 132.25, 130.60 (aromatic carbons), 87.50 (C_5), 76.30 (C_3), 70.40 (CH_2 carbon of $-OCH_2CH_3$), 57.00 (C_4), 44.50, 42.80 (NMe_2), 20.00 (CH_3 carbon of OCH_2CH_3); MS (*m/z*): 264 (M^+), 190, 187, 157, 148, 143, 116, 107, 77; HRMS - EI: Calcd. for $C_{14}H_{20}O_3N_2$ (M) 264.3250, Found M^+, 264.3239.

38. Synthesis of methyl 3-(dimethylamino)-2,5-diphenylisoxazolidine-4-carboxylate (Methyl vinyl ketone cycloadduct):



Scheme 42

To a stirred solution of nitrone **3** (1 mmol) in 15 mL water was added methyl vinyl ketone (1 equivalent) at RT under nitrogen atmosphere and the reaction mixture was stirred for 8 hr. The progress of the reaction was monitored by TLC (R_f = 0.44).The product was extracted with ether (2 x 25 mL), the organic layer was washed with brine water (2 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as pale yellow oil.

Spectral data:

Pale yellow oil, 91%; IR ($CHCl_3$): 3172 – 3033 (br), 2936 (s), 1720 (s), 1442 (m), 1235 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.80 – 6.58 (m, 5H, C_6H_5), 4.86 (t, 1H, *J* = 7.14 Hz, C_5H), 3.74 (t, 1H, *J* = 6.80 Hz, C_3H), 3.38 (dd, 2H, *J* = 8.80, 7.40 Hz, C_4H), 2.82 – 2.70 (br, 6H, NMe_2), 2.16 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 202.50 (carbonyl carbon), 133.55, 132.00, 130.86, 129.20 (aromatic carbons), 88.70 (C_5), 76.00 (C_3), 58.45 (C_4), 42.40, 40.00 (NMe_2), 31.20 (methyl carbon of $COCH_3$); FAB - MS (*m/z*): 234 (M^+), 233, 219, 191, 157, 148 (B.P), 113, 107, 86, 77; HRMS-EI: Calcd for $C_{13}H_{18}O_2N_2$ (M) 234.2990, Found M^+, 234.2978.

General Procedure for 1,3-dipolar cycloaddition reaction with alkynes at RT:

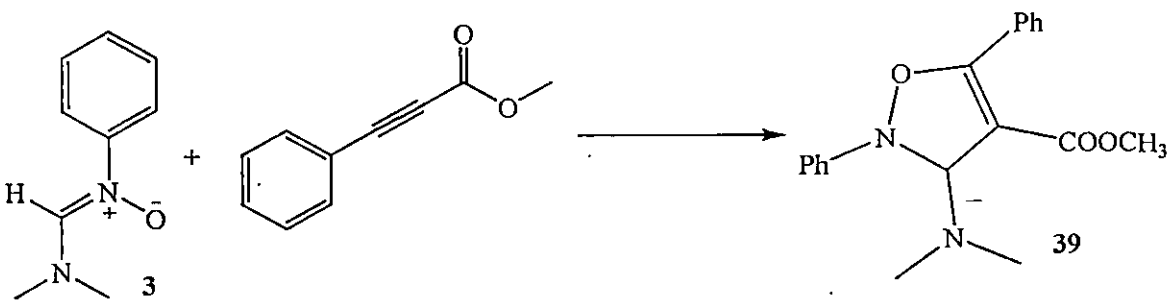
N-phenyl-α-amino nitrone (**3**) decomposes slowly at RT and hence after isolation of nitrone immediately cycloaddition reaction with alkynes were performed with 1:1 ratio. In a 100 mL conical flask, nitrone **3** (2.20 mmol), alkyne (1 equivalent) was added to 50 mL dry ether and stirred at RT with a magnetic stirrer under N_2 atmosphere for 12 hour. The progress of the reaction was monitored by TLC. After completion of the reaction the solvent was concentrated on a rotary evaporator and

the products were purified and separated by silica gel column chromatography using ethyl acetate - hexane to furnish pure cycloadducts. This procedure was followed for the substrates mentioned below.

Alkynes

- Phenyl methyl propiolate
- Dimethyl acetylene dicarboxylate

39. Synthesis of methyl 3-(dimethylamino)-2,5-diphenyl-2,3-dihydroisoxazole-4-carboxylate (phenyl methyl propiolate cycloadduct):



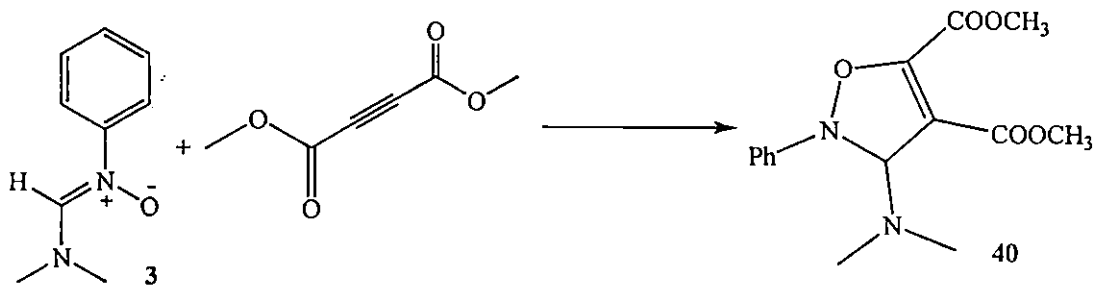
Scheme 43

In a 100 mL conical flask, nitrone **3** (2.20 mmol), phenyl methyl propiolate (1 equivalent) was added to 50 mL dry ether and stirred at RT with a magnetic stirrer under N_2 atmosphere for 10 hour. The progress of the reaction was monitored by TLC (R_f = 0.73). After completion of the reaction the solvent was concentrated on a rotary evaporator and the crude product was purified by silica gel column chromatography using ethyl acetate-hexane combinations to furnish white viscous liquid (73 mg, 70%).

Spectral data:

White viscous liquid, 70%; IR ($CHCl_3$): 3155 (m), 1750 (s), 1665 (m), 1430 (m), 1360 (m), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70 – 7.04 (m, 10H, C_6H_5 protons), 4.06 (s, 1H, C_3H), 3.32 (s, 3H, - $COOCH_3$), 2.40 (br, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 172.50 (carbonyl carbon), 137.00, 135.40, 134.00, 132.60, 131.43, 129.65, 128.00, 127.28 (aromatic carbons), 88.00 (C_5), 73.40 (C_3), 57.40 (C_4), 45.20 (-$COOCH_3$), 33.42, 29.50 (*N* - CH_3 carbons); MS (*m/z*): 324 (M^+), 296, 266, 219, 189, 188, 111. 105, 83, 77; HRMS – EI: Calcd. for $C_{19}H_{20}O_3N_2$ (M) 324.1910, Found M^+, 324.1891.

40. Synthesis of dimethyl 3-(dimethylamino)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate (dimethyl acetylene dicarboxylate):



Scheme 44

In a 100 mL conical flask nitrone **3** (2.20 mmol), dimethyl acetylene dicarboxylate (1 equivalent) was added to 50 mL dry ether and stirred at RT with a magnetic stirrer under N_2 atmosphere for 13 hour. The progress of the reaction was monitored by TLC (R_f = 0.64). After completion of the reaction the solvent was concentrated on a rotary evaporator and the crude product was purified by silica gel column chromatography using ethyl acetate-hexane combinations to furnish red liquid (64 mg, 68%).

Spectral data:

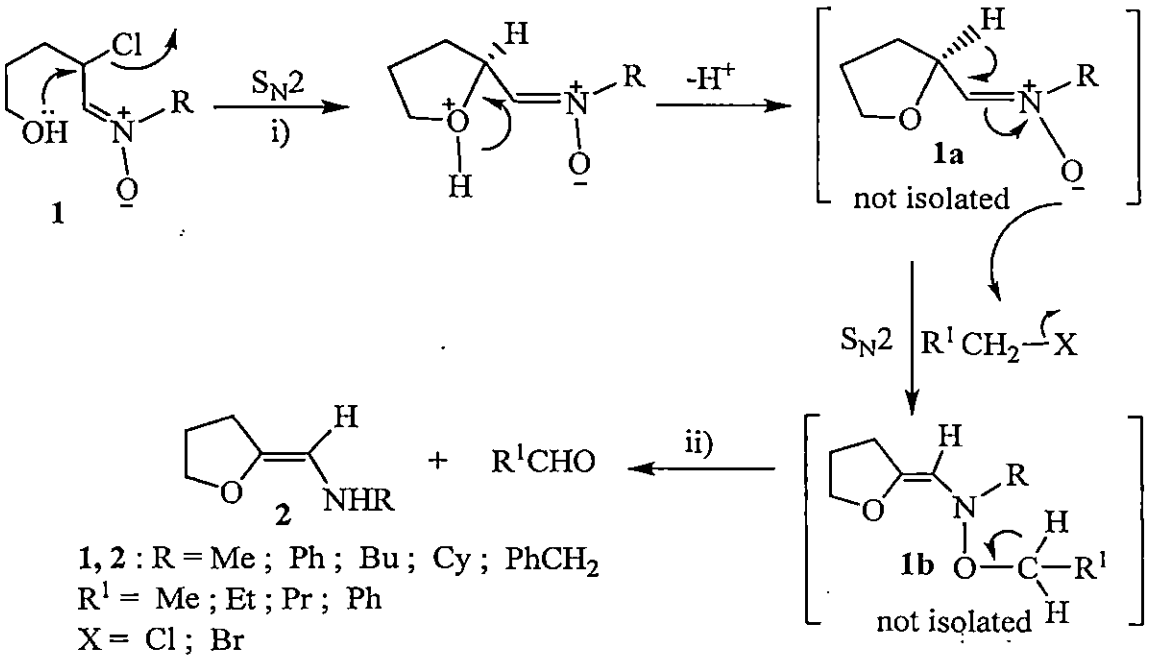
Red liquid, 68%; IR ($CHCl_3$): 3145 (m), 2820 (m), 1745 (s), 1700 (m), 1670 (m), 1420 (s), 1260 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.86 - 6.77 (m, 5H, C_6H_5 protons), 4.75 (s, 1H, C_3H), 3.66 (s, 3H, -$COOCH_3$), 3.60 (s, 3H, -$COOCH_3$), 2.68 (br, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 169.00, 167.48 (carbonyl carbons), 87.50 (C_5), 76.64 (C_3), 59.47 (C_4), 44.65, 43.72 ($COO\underline{C}H_3$), 31.00, 29.43 (*N* - CH_3 carbons); MS (*m/z*): 306 (M^+), 275, 262, 229, 219, 203, 188, 111, 87, 59; HRMS – EI: Calcd. for $C_{15}H_{24}O_5N_2$ (M) 306.1670, Found M^+, 312.1652.

Reaction type IV

Special type aldehyde synthesis using α-chloro and α-amino nitrones as oxidizing agents

Using the tremendous synthetic potentiality of α-chloro and α-amino nitrones we have synthesized a variety of aldehydes[11] with a very good yield and the most important fact during the aldehyde synthesis is the use of side product as efficient dipolarophile making the reaction atom efficient[12]. Similarly in case of amino nitrones, the side

product can be hydrolyzed under acidic medium to furnish the starting material along with imines[13].



1, 2 : R = Me ; Ph ; Bu ; Cy ; $PhCH_2$
R^1 = Me ; Et ; Pr ; Ph
X = Cl ; Br

Reagents and conditions : i) Dry ether, pyridine, r.t , N_2 atmosphere
ii) Dry ether, Na_2CO_3, r.t , N_2 atmosphere

Scheme 1

In a 100 ml conical flask *N*-phenyl-α-chloro nitrone (500mg, 2.3086 mmol), pyridine (1 equivalent) and diethyl ether (25 ml) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 1 hour and the formation of transient nitrone (not isolated) was monitored by TLC (R_f = 0.34). Benzyl chloride (292.1002mg, 1 equivalent) was added at this stage and the reaction mixture was stirred for another 2 hours till the intermediate compound (not isolated) was developed (monitored by TLC; R_f = 0.37). 2 gms of solid Na_2CO_3 was added at this stage and the reaction mixture was stirred for further 1 hr while the progress of the reaction was again monitored by TLC (R_f = 0.40, 0.46). The reaction was typically completed when the N–O bond was cleaved[14]. Basic workup, removal of pyridine hydrochloride and silica gel column chromatographic purification provided desired benzaldehyde as colourless liquid (712mg, 90%; R_f = 0.40) and furan derivative as pale yellow gummy liquid (Scheme **1**; 78 mg, 10%; R_f = 0.46).

Spectral data for benzaldehyde

Colourless liquid, 90%, IR ($CHCl_3$): 1695 (s), 1320 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.80 (s, 1H, CHO), 7.30 – 7.16 (m, 5H, C_6H_5); ^{13}CNMR ($CDCl_3$): δ 198

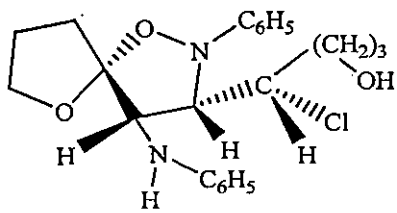
(CHO), 136, 134, 132, 131 (aromatic carbons); FAB - MS (*m/z*): 106 (M^+), 105 (B.P), 77, 51, 28; HRMS-EI: Calcd. for C_6H_5CHO (M), 106.0417, Found M^+ 106.0408.

Spectroscopic data for 2 (R = Ph) [(*E*)-1-(dihydrofuran-2-(3H)-ylidene)-*N*-phenyl methanamine (α-*N*-phenyl furan derivative)]

Pale yellow gummy liquid, 10%, IR ($CHCl_3$): 3150-3060 (br), 2860 (m), 1640 (s), 1430 (m), 1140 (m), 776 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43 – 7.28 (m, 5H, C_6H_5), 5.16 (br, 1H, N-H), 4.72 (s, 1H, C=CH), 2.95-2.34 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 137.20, 135.65, 134.00, 132.15 (aromatic carbons), 106.24, 104.18 (double bonded carbons), 28.46, 27.10, 24.84 (3 CH_2 carbons); FAB - MS (*m/z*): 175 (M^+), 98, 97, 77. HRMS-EI: Calcd. for $C_{11}H_{13}ON$ (M), 175.0993, Found M^+ 175.0981.

Cycloaddition reaction of side product (2) with *N*-phenyl-α-chloro nitrone

To a stirred solution of *N*–phenyl-α-chloro nitrone **1** (R = Ph, 61.8375 mg, 0.2855 mmol) in 25 mL dry ether was added **2** (R = Ph, 50 mg, 0.2855 mmol, 1 equivalent) and stirred at RT with a magnetic stirrer under N_2 atmosphere for 6 hr. The progress of the reaction was monitored by TLC (R_f = 0.52). After completion of the reaction, the solvent was evaporated under a rotary evaporator to afford crude cycloadduct (**3**: R=Ph) which was purified by column chromatography using ethyl acetate-hexane and was obtained as pale yellow viscous liquid (R=Ph, 95 mg, 85%).



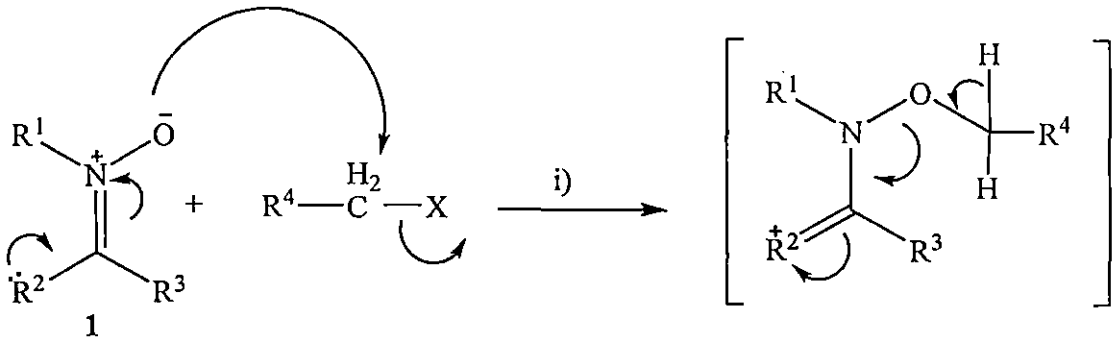
3

Spectral data:

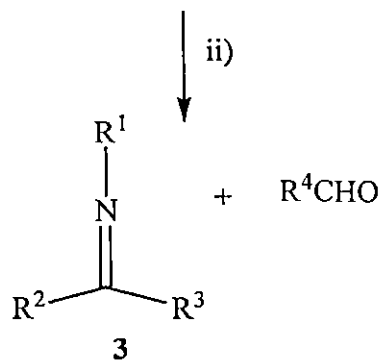
IR (KBr): 3485 – 3290 (br), 2962 (m), 2425 (m), 1620 (s), 1490 (s), 1260 (m), 1040 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.98 - 6.92 (m, 10H, 2 x C_6H_5), 5.84 (dd, 1H, *J* = 8.55, 8.20 Hz, C_3H), 5.00 (br, 1H, CH_2OH, exchanged in D_2O), 3.60 (dt, 1H, *J* = 9.34, 7.88 Hz, C_4H), 3.40 (s, 1H, N – H proton of NHPh), 2.68 (dt~m, 1H, CHCl), 1.90 (dt, 1H, *J* = 6.82, 6.64 Hz, C_3·H), 1.50 – 1.12 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 138.00, 136.50, 134.30, 133.80, 131.75, 130.42, 129.46, 128.64 (aromatic carbons), 95.10 (CHCl), 86.40 (C_5), 73.75 (C_3), 53.30 (C_4), 30.20, 28.55, 27.34, 26.22, 25.73,

24.37 (6 CH_2 carbons); MS (*m/z*): 404 (M^++2), 402 (M^+), 325, 310, 309, 218 (B.P), 107, 91, 77. HRMS-EI: Calcd. for $C_{22}H_{27}O_3N_2Cl$ (M), 402.7130, Found M^+, 402.7122.

Scheme for aldehyde synthesis from α-amino nitrone



1 : R^1 = Ph, Cy
R^2 = NH_2, NMe_2
R^3 = H, CH_2, CH_3CH_2, $CH_3CH_2CH_2$, $CH_3CH_2CH_2CH_2$, Ph
X = Cl / Br / I



Scheme 2

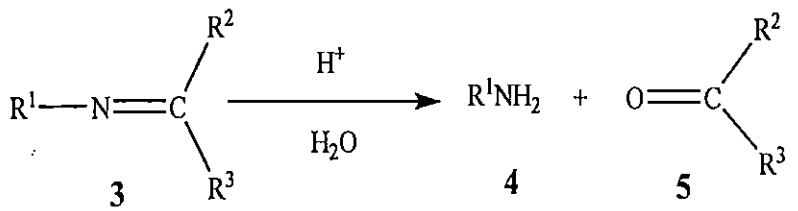
In a 100 ml conical flask, *N*-phenyl-α-amino nitrone (500 mg, 2.3570 mmol), benzyl chloride (295.8670 mg, 1 equivalent) and diethyl ether (25 ml) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 1 hour. During this process nitrone underwent S_N2 reaction very quickly with benzyl chloride and developed an intermediate compound which was not isolated. The progress of the reaction was monitored by TLC (R_f = 0.38). 2 gms of solid Na_2CO_3 was added at this stage and the reaction mixture was stirred for further 3 hour and monitored by TLC. The N-O bond was easily cleaved under basic medium in a Kornblum type mechanism and developed benzaldehyde (R_f = 0.43) and imine derivative (R_f = 0.54) respectively (**Scheme 2**). The reaction mixture was filtered and concentrated on a rotary evaporator. Basic work-up followed by silica gel column chromatography using ethyl acetate – hexane results benzaldehyde as colourless liquid (706 mg, 88 %) and imine derivative (**3**) as pale yellow gummy liquid (**Scheme 2**; 84 mg, 11 %).

Spectral data:

Colourless liquid, 88%, IR ($CHCl_3$): 2824 (s), 1695 (s), 1320 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.80 (s, 1H, CHO), 7.30 – 7.16 (m, 5H, C_6H_5); $^{13}CNMR$ ($CDCl_3$): δ 198 (CHO), 136.00, 134.00, 132.50, 131.00 (aromatic carbons). MS-FAB (m/z): 106 (M^+), 105 (B.P), 77, 51; HRMS-EI: Calcd. for C_6H_5CHO (M) 106.1240, Found M^+ 106.1228.

Pale yellow gummy liquid, 11 %, IR ($CHCl_3$): 3450 (m), 1680 (s), 785 (s); ^1H NMR ($CDCl_3$): δ 7.32 – 7.25 (m, 5H, C_6H_5), 6.76 – 6.68 (m, 5H, C_6H_5), 3.75 – 3.62 (br, 2H, NH_2); $^{13}CNMR$ ($CDCl_3$): δ 136.84, 135.24, 134.25, 132.80, 131.25, 130.00, 128.50, 127.45 (phenyl carbons), 86.86 (C=N); FAB – MS (*m/z*): 196 (M^+), 119, 103 (B.P), 77. HRMS-EI: Calcd. for $C_{13}H_{12}N_2$ (M) 196.2530, Found M^+ 196.2519.

General procedure of acid hydrolysis of imine 3



a: R^1 = Ph; Cy
b: R^2 = NH_2; NMe_2
c: R^3 = H; CH_3; Ph

Scheme 3

In a 100 mL R.B flux, imine derivative 3 (70 mg), 20 mL 10% HCl was taken and refluxed in water bath for 30 minutes. The formation of the desired hydrolysed products were monitored by TLC. During the hydrolysis process, the double bond between carbon and nitrogen of the imine derivative was cleaved and benzamide (R^2 = NH_2; R^3 = Ph; R_f = 0.42) and aniline (R^1 = Ph; R_f = 0.64) was developed[15]. The products were extracted with ether (2 x 25 mL) when aniline passes into organic layer while benzamide remains in aqueous phase. The ether extract containing aniline was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator and finally purified by silica gel column chromatography using ethyl acetate – hexane as pale yellow liquid (24 mg, 34%). Benzamide was obtained as white crystalline solid when aqueous part of the solution was evaporated in a temperature controlled water bath

and was crystallized from ethanol (**Scheme 3**; 42 mg, 60%; m.p. 126^{0}C). This general hydrolysis procedure was followed for all the imine derivatives.

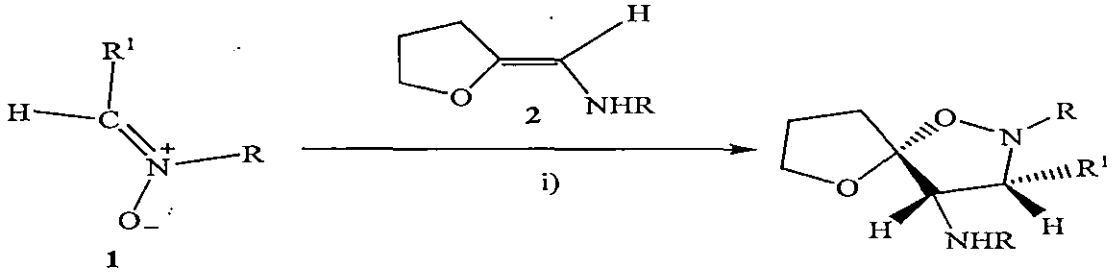
Spectroscopic data for product 4

IR ($CHCl_3$): 3440 (m), 3205 (s), 1635 (s), 1280 (m), 778 (s); ^{1}H NMR ($CDCl_3$): δ 6.88 – 6.76 (m, 5H, C_6H_5), 3.82 – 3.66 (br, 2H, NH_2); ^{13}CNMR ($CDCl_3$): δ 135.50, 134.00, 132.00, 129.20 (phenyl carbons); FAB – MS (*m/z*): 93 (M^+). HRMS-EI: Calcd. for C_6H_7N (M) 93.0690, Found; M^+ 93.0683.

Spectral data for product 5

White crystalline solid, 60%, m.p.126^{0}C, IR ($CHCl_3$): 3455 (s), 1675 (s), 1630 (m), 780 (s); ^{1}H NMR ($CDCl_3$): δ 7.14 – 7.08 (m, 5H, C_6H_5), 6.94 – 6.76 (br, $CONH_2$); ^{13}CNMR ($CDCl_3$): δ 177.50 (C=O), 130.50, 129.00, 128.00, 127.20 (phenyl carbons); FAB – MS (*m/z*): 121 (M^+), 77; HRMS-EI: Calcd. for C_7H_7NO (M) 121.0690, Found; M^+ 121.0681.

General procedure for cycloaddition (for regioselective *spiro* cycloadducts)



R = C_6H_5
R^1 = C_6H_5 ; $CHCl(CH_2)_3OH$; NH_2
Reagents and conditions: i) Dry ether, RT, N_2 atmosphere, 4 - 6 hr

Scheme 4

To a well stirred solution of nitrone **1** (**R = Ph**; 1 mmole) in diethyl ether (20 mL) taken in a 50 mL conical flask, was added α-*N*-methyl furan derivative [(*E*)-1-(dihydrofuran-2-(3*H*)-ylidene)-*N*-methyl methanamine)] (1 equivalent) and was stirred at RT with a magnetic stirrer under N_2 atmosphere for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.53). After completion of the reaction and work-up, the crude spiro cycloadduct was concentrated in a rotary evaporator and finally purified by column chromatography using ethyl acetate - hexane to afford pure spiro cycloadduct **3**[16] (**Scheme 4**). This procedure was followed for the reaction of nitrone **1** (**R = Ph**) with α-*N*-methyl/phenyl furan derivatives **2** [(*E*)-1-(dihydrofuran-

2-(3*H*)-ylidene)-*N*-methyl methanamine) / (*E*)-1-(dihydrofuran-2-(3*H*)-ylidene)-*N*-phenyl methanamine)].

Spectroscopic data for 2 (R=Ph; α-*N*-phenyl furan derivative) [(*E*)-1-(dihydrofuran-2-(3*H*)-ylidene)-*N*-phenyl methanamine)]

IR (KBr): 3150-3060 (br), 2860 (m), 1640 (s), 1430 (m), 1140 (m), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.83 (m, 5*H*, C_6H_5), 6.29 (br, 1H, *N-H*), 2.17 (s, 1H, C=CH), 1.79 - 1.18 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 137.20, 135.65, 134.00, 132.15 (aromatic carbons), 106.24, 104.18 (double bonded carbons), 28.46, 27.10, 24.84 (3 CH_2 carbons); FAB - MS (*m/z*): 175 (M^+), 98, 97, 77. HRMS-EI: Calcd. for $C_{11}H_{13}ON$ (M) 175.0993, Found M^+, 175.0981.

3: Spectral data of (*S*)-4-chloro-4-((3*S*,4*S*,5*R*)-2methyl-4-(methylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol

Pale yellow gummy liquid. Yield 88%, R_f = 0.53; IR (KBr): 3460 – 3326 (br), 2948 (m), 2420 (m), 1485 (s), 1325 (m), 810 (m), 774 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.83 (br, 1H, CH_2OH, exchanged in D_2O), 4.60 (s, 1H, $NHCH_3$), 3.37 (s, 6H, 2 x *N*-CH_3), 3.12 (dd, 1H, *J* = 9.20, 8.32 Hz, C_3H), 2.70 (dt, 1H, *J* = 8.10, 7.88 Hz, C_4H), 2.35 (dt~m, 1H, CHCl), 1.88 – 1.42 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 93.00 (CHCl), 87.55 (C_5), 76.20 (C_3), 55.20 (C_4), 41.97 (N-CH_3), 40.24 (NH-CH_3), 33.37, 31.50, 28.68, 26.00, 25.12, 23.40 (6 CH_2 carbons); MS (*m/z*): 280 (M^++2), 278 (M^+), 263, 248, 156 (B.P), 141, 107; HRMS-EI: Calcd. for $C_{12}H_{23}O_3N_2Cl$ (M) 278.6710, Found M^+, 278.6698.

4: Spectral data of (*S*)-4-chloro-4-((3*S*,4*S*,5*R*)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol

Dark red viscous liquid. Yield 86%, R_f = 0.48; IR (KBr): 3485 – 3290 (br), 2962 (m), 2425 (m), 1620 (s), 1490 (s), 1260 (m), 1040 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.98 - 6.92 (m, 10H, 2 x C_6H_5), 5.84 (dd, 1H, *J* = 8.55, 8.20 Hz, C_3H), 5.00 (br, 1H, CH_2OH, exchanged in D_2O), 3.60 (dt, 1H, *J* = 9.34, 7.88 Hz, C_4H), 3.40 (s, 1H, N – H proton of NHPh), 2.68 (dt~m, 1H, CHCl), 1.90 (dt, 1H, *J* = 6.82, 6.64 Hz, C_3-H), 1.50 – 1.12 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 138.00, 136.50, 134.30, 133.80, 131.75, 130.42, 129.46, 128.64 (aromatic carbons), 95.10 (CHCl), 86.40 (C_5), 73.75 (C_3), 53.30 (C_4), 30.20, 28.55, 27.34, 26.22, 25.73, 24.37 (6 CH_2 carbons); MS (*m/z*): 404 (M^++2), 402

(M^+), 325, 310, 309, 218 (B.P), 107, 91, 77; HRMS-EI: Calcd. for $C_{22}H_{27}O_3N_2Cl$ (M), 402.7130, Found M^+, 402.7122.

5. Spectral data of *(S)*-3-amino-(3*S*,4*S*,5*S*)-2-methyl-4-(methylamino)-1,6-dioxa-2-azaspiroisoxazole

Gray viscous liquid. Yield 84%, R_f = 0.52; IR (KBr): 3430 - 3380 (br), 3033 (m), 2955 (m), 1773 (s), 1662 (s), 1480 (s), 1282 (m), 1178 (s), 806 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.90 (br, s, 2H, NH_2, exchanged in D_2O), 4.60 (br, 1H, $NHCH_3$), 3.36 (s, 6H, 2 x *N*-CH_3), 3.00 (d, 1H, *J* = 7.54 Hz, C_3H), 2.70 (dt, 2H, *J* = 6.24, 6.28 Hz, $C_3'2H$), 2.38 (dt, 1H, *J* = 7.12, 6.70 Hz, C_4H), 1.70 – 1.48 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 88.50 (C_5/C_2'), 77.12 (C_3), 56.26 (C_4), 40.94 (N-CH_3), 38.13 (NH-CH_3), 32.07, 31.22, 29.34 (3',4',5' CH_2 carbons); MS (*m/z*): 187 (M^+), 172, 157, 156 (B.P), 141. HRMS-EI: Calcd. for $C_8H_{17}O_2N_3$ (M) 187.1633, Found M^+, 187.1613.

6: Spectral data of (*S*)-3-amino-(3*S*,4*S*,5*S*)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiroisoxazole

Dark gray viscous liquid, Yield 81%, R_f= 0.48; IR (KBr): 3436 - 3390 (br), 3030 (m), 2952 (m), 1780 (s), 1674 (s), 1480 (m), 1276 (m), 815 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.02 - 6.90 (m, 10H, 2 x C_6H_5), 5.86 (d, 1H, *J* = 6.30 Hz, C_3H), 5.00 (br, s, 2H, NH_2, exchanged in D_2O), 3.50 (dt, 2H, *J*= 6.74, 6.06 Hz, $C_3'2H$), 3.38 (br,s,1H, NHC_6H_5), 2.70 (dt, 1H, *J* = 7.20, 6.18 Hz,C_4H), 1.52 – 1.28 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 137.21, 135.44, 134.00, 133.10, 130.66, 129.40, 128.32, 127.84 (aromatic carbons), 86.94 (C_5/C_2'), 74.24 (C_3), 55.70 (C_4), 27.87, 25.63, 24.00 (3',4',5' CH_2 carbons); MS (*m/z*): 311 (M^+), 295, 218, 203 (B.P), 202, 92, 77; HRMS-EI: Calcd. for $C_{18}H_{21}O_2N_3$ (M), 311.2054, Found; M^+, 311.2037.

7: Spectral data of (*S*)-3-phenyl-(3*S*,4*S*,5*S*)-2-methyl-4-(methylamino)-1,6-dioxa-2-azaspiroisoxazole

Colourless gummy liquid, Yield 78%, R_f= 0.52; IR (KBr): 3040 (m), 2965 (m), 1760 (s), 1685 (m), 1464 (s), 1290 (m), 1084 (s), 808 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.81 (s, 5H, C_6H_5), 4.67 (s, 1H, $NHCH_3$), 3.36 (s, 6H, 2 x N-CH_3), 3.00 (d, 1H, *J* = 5.74 Hz, C_3H), 2.74 (dt, 1H, *J* = 6.64, 6.30 Hz, C_4H), 2.30 (dt, 2H, *J* = 5.10, 4.92 Hz, $C_3'2H$), 1.80 – 1.55 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 129.05, 128.53, 128.27, 127.22 (aromatic carbons), 80.28 (C_5/C_2'), 70.36 (C_3), 59.70 (C_4), 45.17 (N-CH_3), 41.64 (NH-CH_3), 32.07, 31.22, 29.34 (3',4',5' CH_2 carbons); MS (*m/z*): 248 (M^+), 218, 171, 156

(B.P), 141, 77. HRMS-EI: Calcd. for $C_{14}H_{20}O_2N_2$ (M) 248.1862, Found M^+, 248.1853.

8: Spectral data of (*S*)-3-phenyl-(3*S*,4*S*,5*S*)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiroisoxazole

Colourless gummy liquid. Yield 78%, R_f= 0.48; IR (KBr): 3024 (m), 2950 (m), 1772 (s), 1670 (s), 1468 (m), 1382 (m), 805 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50 - 6.62 (m, 15H, 3 x C_6H_5), 5.84 (s, 1H, NHC_6H_5), 4.63 (d, 1H, *J* = 6.06 Hz, C_3H), 4.02 (dt, 1H, *J* = 6.18, 6.20 Hz, C_4H), 2.64 (dt, 2H, *J* = 5.28, 4.10 Hz,C_3'2H), 2.00 – 1.26 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 136.76, 136.53, 136.24, 135.15, 134.90, 134.62, 134.30, 133.78, 132.44, 132.18, 130.92, 130.37 (aromatic carbons), 83.22 ($C_5/C_{2'}$), 71.52 (C_3), 52.89 (C_4), 23.61, 22.57, 21.14 (3',4',5' CH_2 carbons); MS (*m/z*): 372 (M^+), 295, 280, 218, 203 (B.P), 92, 77; HRMS-EI: Calcd. for $C_{24}H_{24}O_2N_2$ (M) 372.2286, Found M^+, 372.2270.

REFERENCES

1. Sarkar R, "*Text book of Inorganic Chemistry*", Vol I, New Central Book Agency, **2007**.

2. Dey A K, "*Text book of Inorganic Chemistry*", Books and Allied, **1998**.

3. Fieser L M & Fieser M, "*Reagents for Organic Synthesis*", John Wiley & sons, (Inc, NY), **1967**, 487.

4. Heaney F., Rooney O, Cunningham D, Mcarde P, *J Chem Soc, Perkin Trans II*, **2001**, 373.

5. Chakraborty B, Kafley S & Chhetri M S, *Indian J Chem, Sec B*, (in press: paper no SCCB 1225).

6. Chakraborty B, Kafley S & Chhetri M S, *Indian J Heterocyclic Chem*, 18, **2008**, 204.

7. a) Chakraborty B & Chhetri M S, *Indian J Chem,* 49B, **2010**, 102; b) Chakraborty B & Chhetri M S, *Indian J Heterocyclic Chem*, 18, **2008**, 201.

8. a) Chakraborty B & Chhetri M S, *Indian J Heterocyclic Chem*, 17, **2008**, 213; b) Chakraborty B & Chhetri M S, *Indian J Heterocyclic Chem*, 19, **2009**, 63.

9. a) Heinzer F, Saukup M, Eschenmoser A, *Helv Chim Acta*, 61, **1978**, 2851 – 28; b) Nanda A, *PhD dissertation*, University of North Bengal, Darjeeling, **1982**.

10. Ghosh A R, *Indian J Chem,* 23B, **1984**, 449.

11. Chakraborty B, Chhetri M S, *Indian J Chem, 47B*, **2008**, 485.

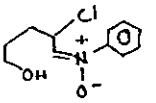
12. a) Chakraborty B, Chhetri M S, Kafley S, Sharma P K, *Journal of Chemical Research* (in press), **2010**; b) Chakraborty B, Sharma P K, Chhetri M S, Kafley S & Ghosh A R, *Rasayan J Chem*, 2 (4), **2010**, 946.

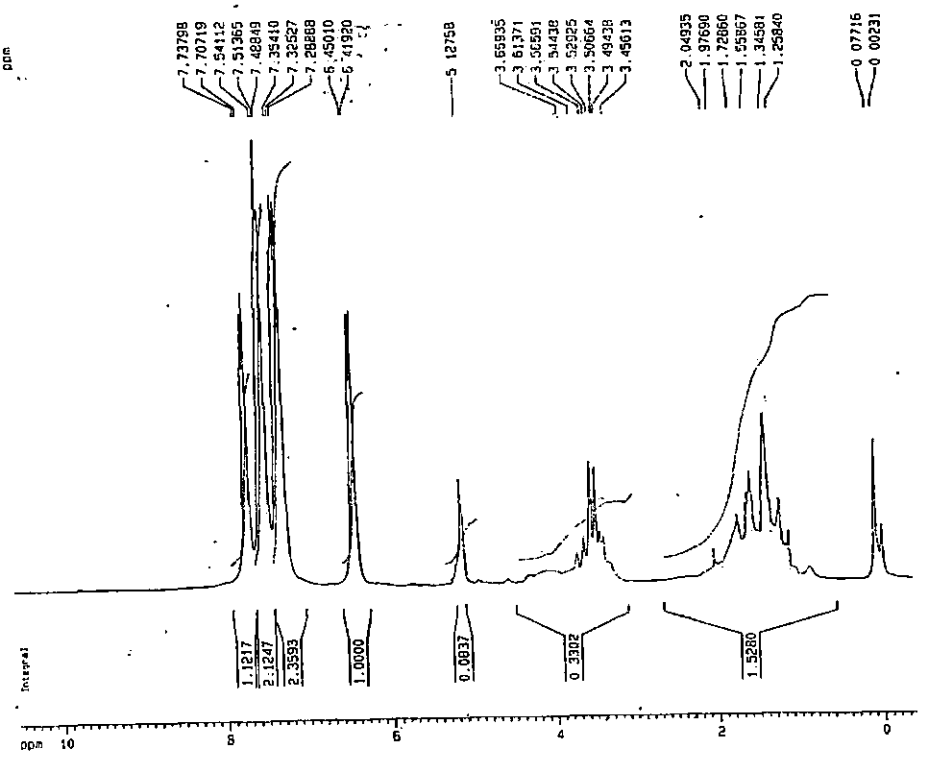
13. Chakraborty B, Chhetri M S, Kafley S, Sharma P K, *Indian J Heterocyclic Chem* (in press), **2010.**

14. Hoffmann W R, Eichler G, Endesfelder A, *Leibigs Ann Chem*, **1983**, 2000.

15. Vogel A I, Tatchell A R, Hannaford A G, Smith P N G, "*Vogel's text book of practical organic chemistry*" 5th Ed, (Printace Hall), **1996.**

16. a) Houk K N, Sims J & Luskus C R, *J Am Chem Soc,* 95, **1973**, 7302; b) Newton R, Savage P G, *Australian J Chem*, 61, **2008**, 432 and references cited therein; c) Aouadik K, Vidal S, Praly P J, *Synlett*, 19, **2006**, 3299 and references cited therein.





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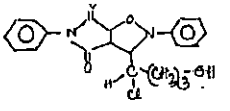

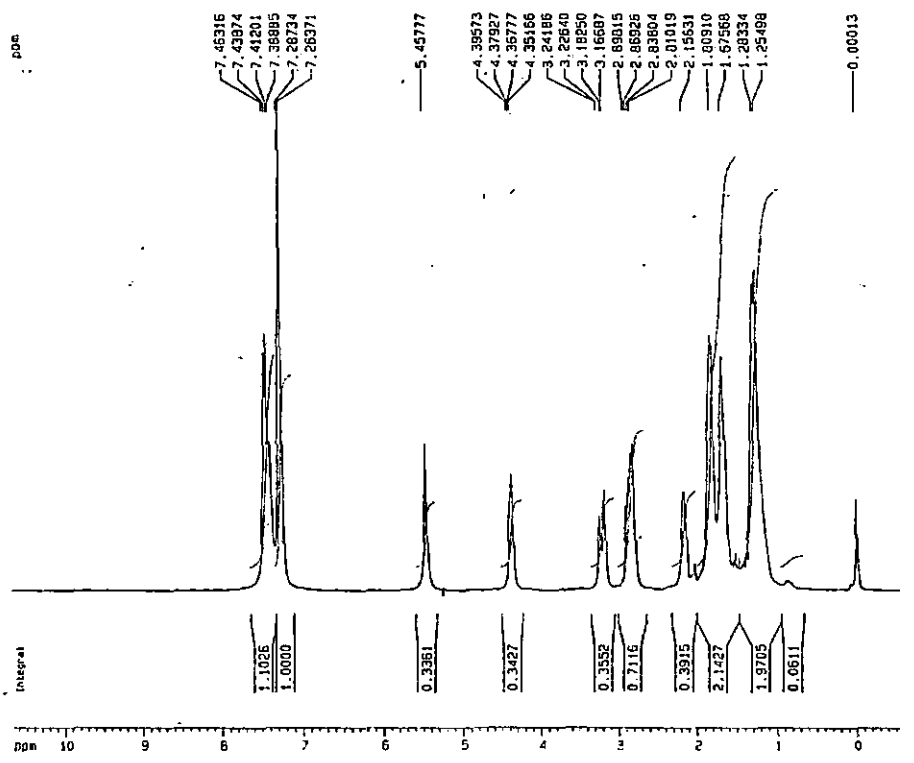

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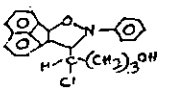
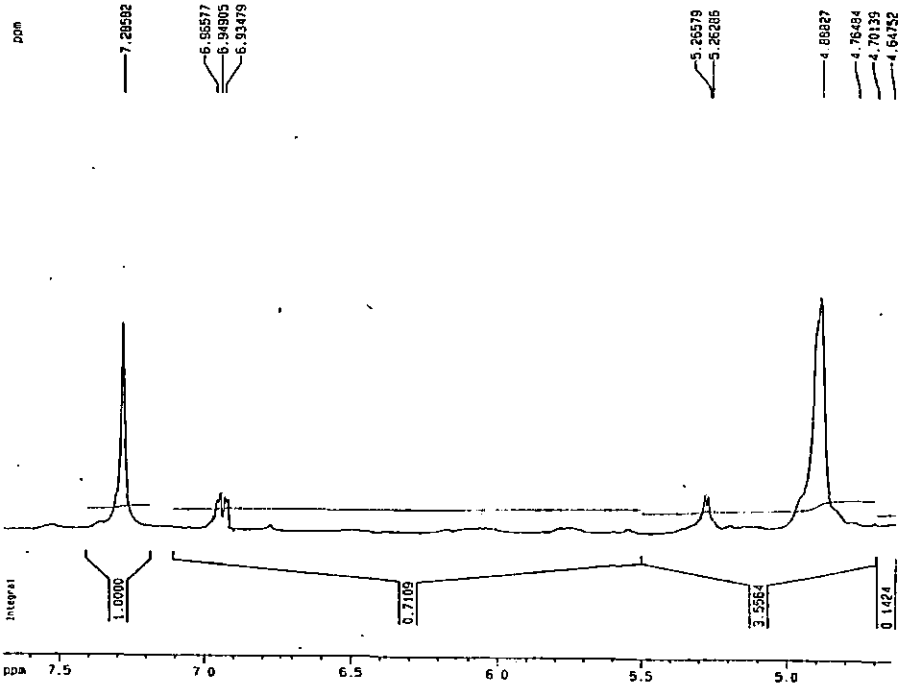
S-22



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Current Data Parameters
NAME                  2719 s22
EXPNO                        1
PROCNO                       1

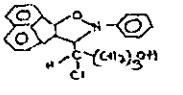
F2 - Acquisition Parameters
Date_              20080430
Time                    12 16
INSTRUM                 spect
PROBHD     5 mm Multinucl
PULPROG                 zg30
TD                     65536
SOLVENT                 CDCl3
NS                         32
DS                          2
SWH                 7183.908 Hz
FIDRES              0.109618 Hz
AQ                  4.5613556 sec
RG                        128
DW                   69.600 usec
DE                    6.00 usec
TE                    310.3 K
D1                  1.00000000 sec
MCREST              0.00000000 sec
MCWRK               0.01500000 sec

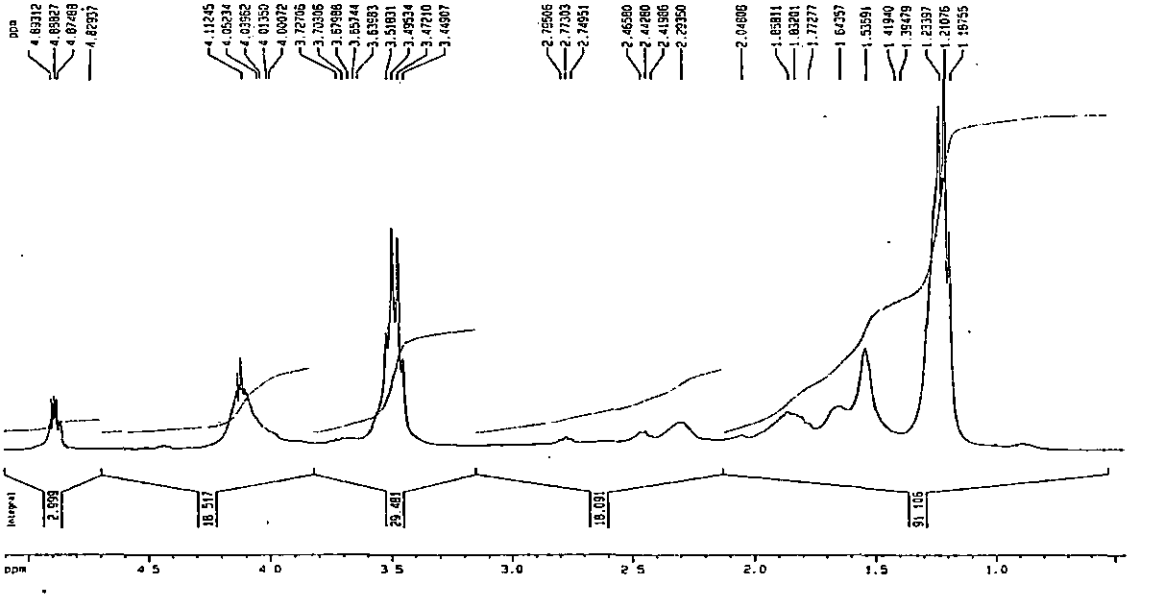
-------- CHANNEL f1 --------
NUC1                       1H
P1                    6.68 usec
PL1                  -3.00 dB
SFO1             300.1315782 MHz

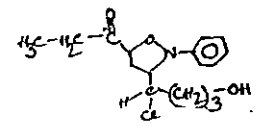
F2 - Processing parameters
SI                       32768
SF           300.1299979 MHz
WDW                        EM
SSB                         0
LB                   0.30 Hz
GB                          0
PC                       1.00

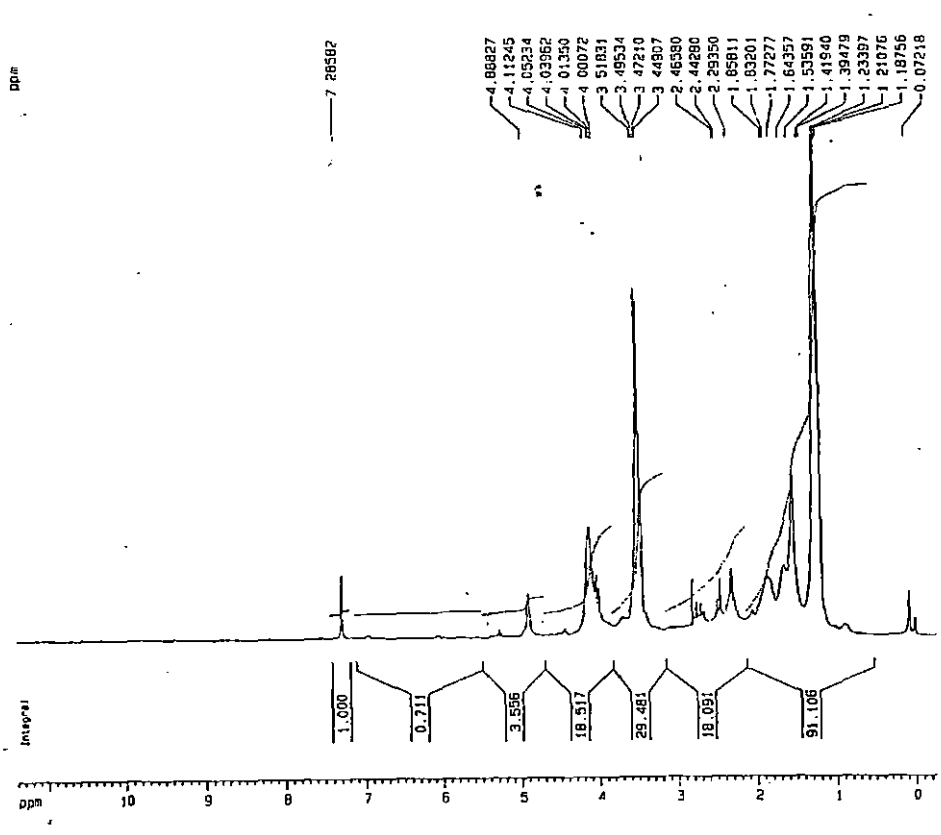
1D NMR plot parameters
CX                   20.00 cm
CY                   88.00 cm
F1P                  7.695 ppm
F1                 2309.52 Hz
F2P                  4.629 ppm
F2                 1389.22 Hz
PPMCM              0.15332 ppm/cm
HZCM              46.01505 Hz/cm
```

S-22







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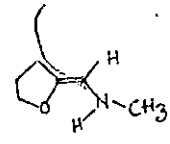
Current Data Parameters
NAME                  2719 s22
EXPNO                        7
PROCNO                       1

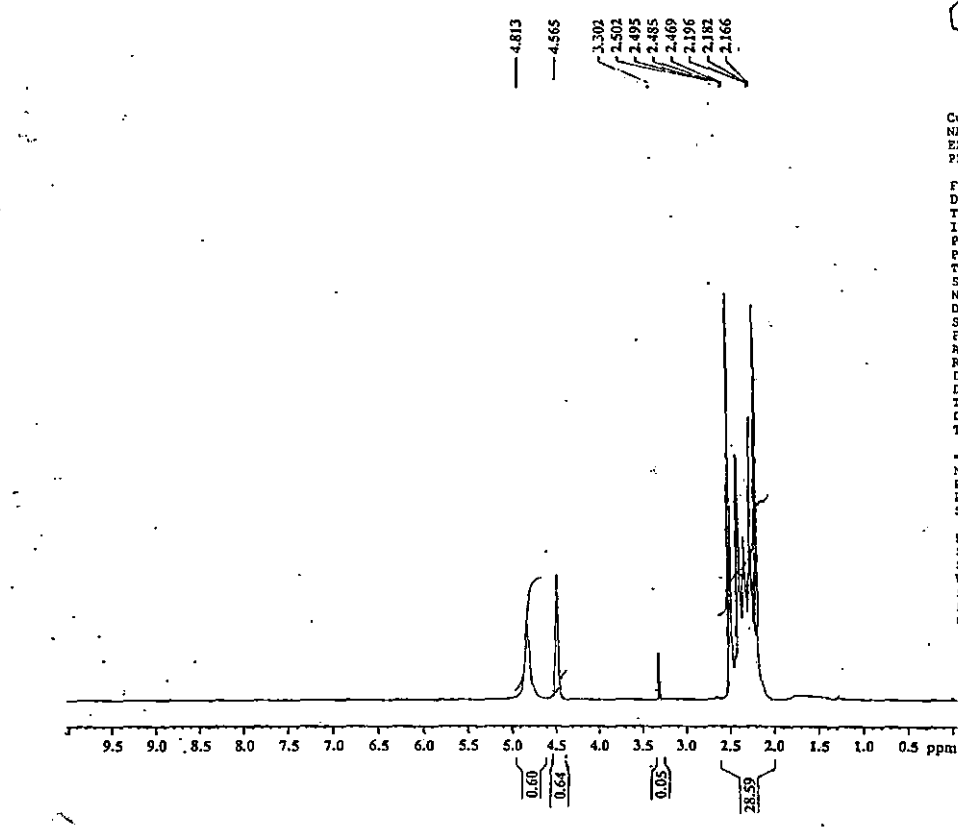
F2 - Acquisition Parameters
Date_               20060420
Time                    12 16
INSTRUM                 spect
PROBHD     5 mm Multinucl
PULPROG                 zg30
TD                     65536
SOLVENT                 CDCl3
NS                         32
DS                          2
SWH                7183.908 Hz
FIDRES             0.109616 Hz
AQ                 4.5613556 sec
RG                        128
DW                     69.600 usec
DE                      6.00 usec
TE                     310.3 K
D1                 1.00000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      6.86 usec
PL1                    -3.00 dB
SFO1          300.1315782 MHz

F2 - Processing parameters
SI                        32768
SF          300.1299979 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.00

1D NMR plot parameters
CX                      20.00 cm
CY                      14.00 cm
F1P                    11.405 ppm
F1                   3423.02 Hz
F2P                   -0.275 ppm
F2                    -82.56 Hz
PPMCM                 0.56401 ppm/cm
HZCM                175.27670 Hz/cm
```





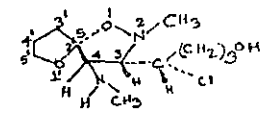

```
Current Data Parameters
NAME              SAIF_1946_17
EXPNO                        1
PROCNO                       1

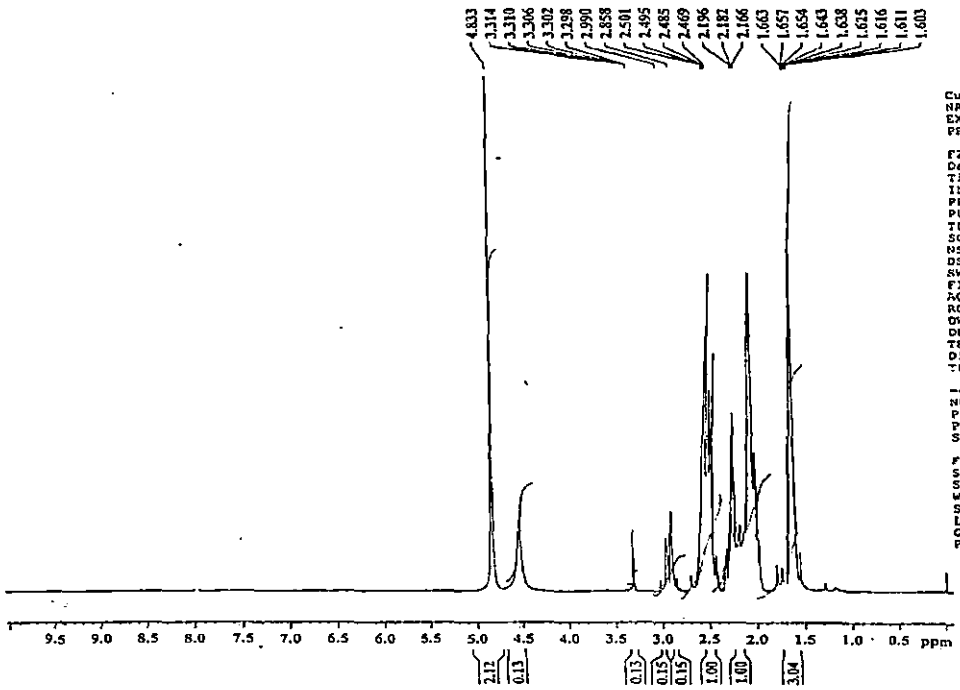
F2 - Acquisition Parameters
Date_               20070829
Time                    10.43
INSTRUM                 spect
PROBHD     5 mm BBI 1H/D-
PULPROG                 zg30
TD                     65536
SOLVENT                 MeOD
NS                         16
DS                          0
SWH                6393.862 Hz
FIDRES             0.097563 Hz
AQ                 5.1249652 sec
RG                         16
DW                    78.200 usec
DE                     6.00 usec
TE                     300.0 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      7.00 usec
PL1                     2.50 dB
SFO1          400.1324008 MHz

F2 - Processing parameters
SI                        32768
SF          400.1300091 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.00
```

25





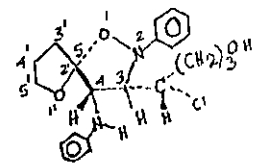
Current Data Parameters
NAME SAIF_1946_25
EXPNO 1
PROCNO 1

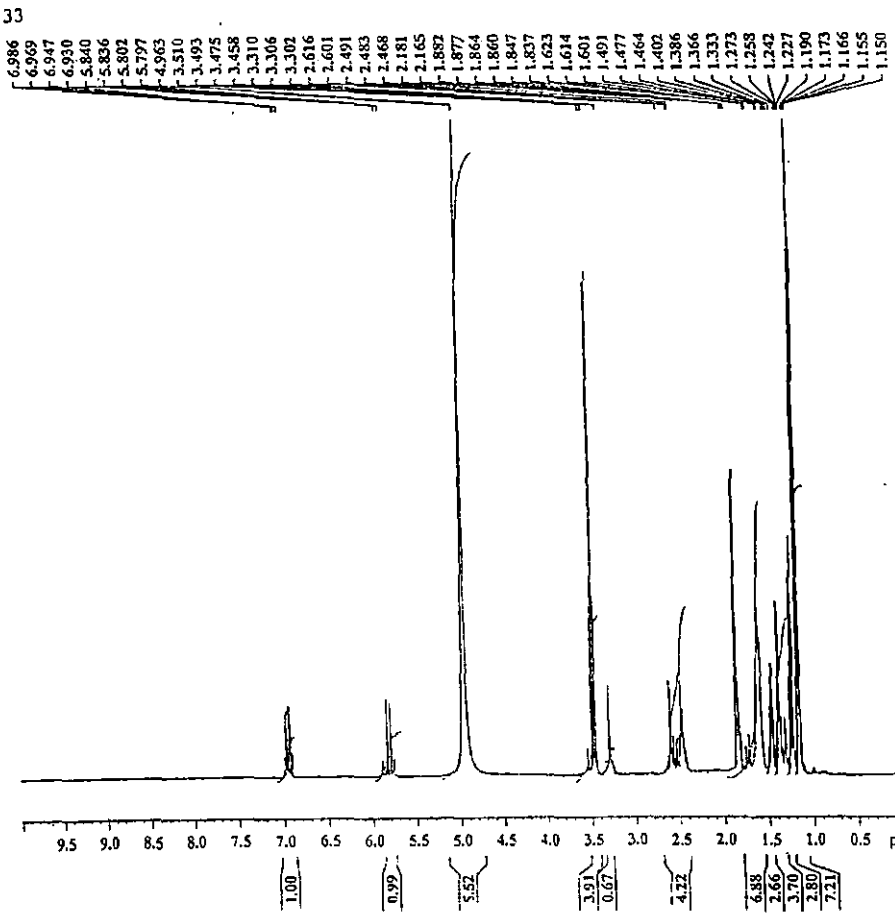
F2 - Acquisition Parameters
Date_ 20070829
Time 11 11
INSTRUM spect
PROBHD 5 mm BBI 1H/D-
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 0
SWH 6393.862 Hz
FIDRES 0.097563 Hz
AQ 5.1249652 sec
RG 45.2
DW 78.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

---------- CHANNEL f1 ----------
NUC1 1H
P1 7.00 usec
PL1 2.50 dB
SFO1 400.1324008 MHz

F2 - Processing parameters
SI 32768
SF 400.1300091 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

33





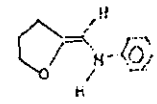
Current Data Parameters
NAME SAIF_1946_33
EXPNO 1
PROCNO 1

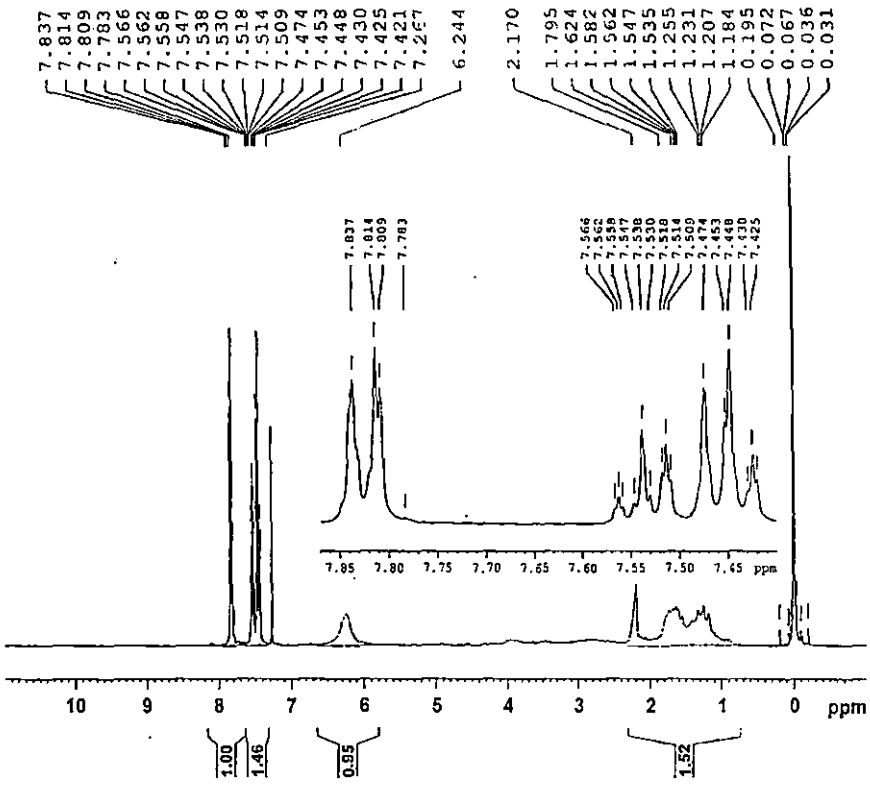
F2 - Acquisition Parameters
Date_ 20070829
Time 11 20
INSTRUM spect
PROBHD 5 mm BBI 1H/D-
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 0
SWH 6393.862 Hz
FIDRES 0.097563 Hz
AQ 5.1249652 sec
RG 20.2
DW 78.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

---------- CHANNEL f1 ----------
NUC1 1H
P1 7.00 usec
PL1 2.50 dB
SFO1 400.1324009 MHz

F2 - Processing parameters
SI 32768
SF 400.1300091 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Bhskar-4





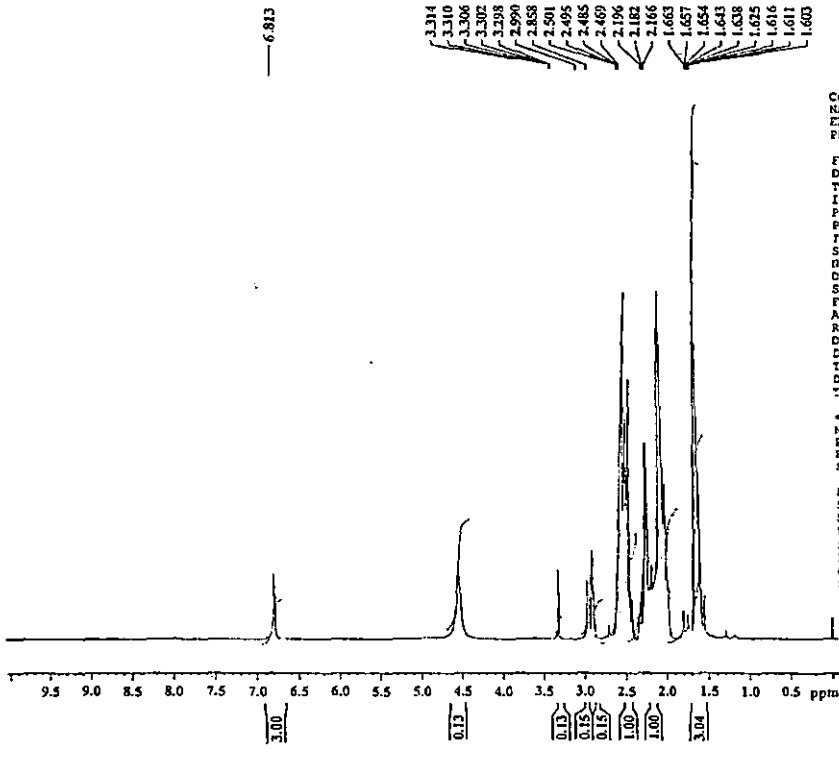
Current Data Parameters
NAME 1Hbhaskar4
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20081005
Time 11.42
INSTRUM av300
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 64
DS 0
SWH 6172.839 Hz
FIDRES 0.094198 Hz
AQ 5.3084660 sec
RG 181
DW 81.000 usec
DE 6.00 usec
TE 0.0 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 13.10 usec
PL1 0.00 dB
SFO1 300.1321909 MHz

F2 - Processing parameters
SI 32768
SF 300.1300043 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

Bha-1

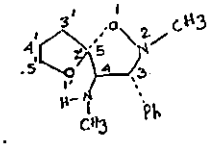


Current Data Parameters
NAME SAIF_ 3-1
EXPNO 1
PROCNO 1

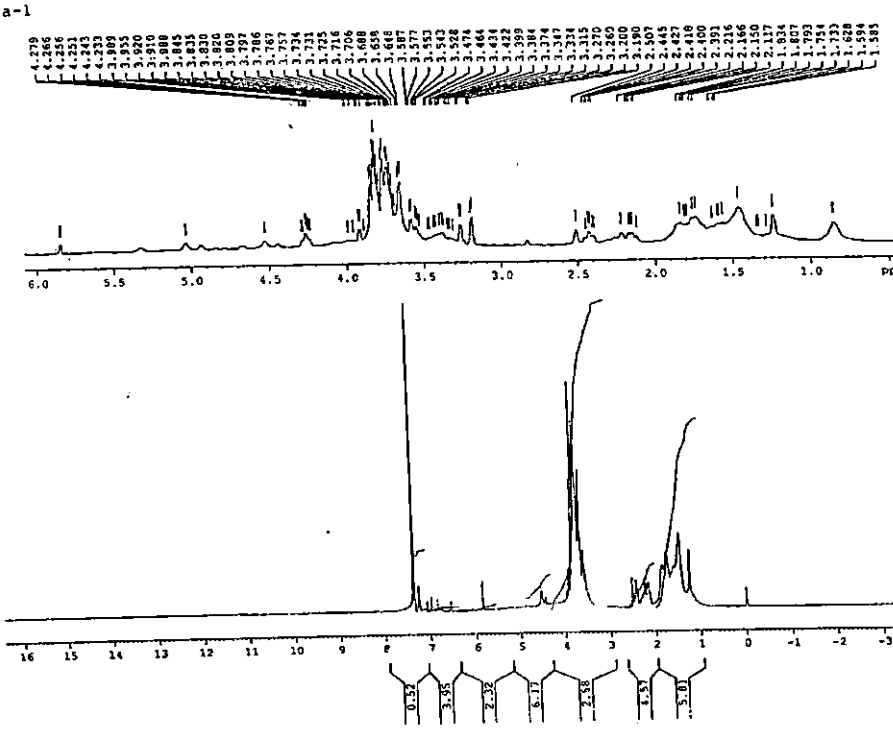
F2 - Acquisition Parameters
Date_ 20091016
Time 11.11
INSTRUM spect
PROBHD 5 mm BBI 1H/D-
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 0
SWH 6393.862 Hz
FIDRES 0.097563 Hz
AQ 5.1249652 sec
RG 45.2
DW 78.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 7.00 usec
PL1 2.50 dB
SFO1 400.1324008 MHz

F2 - Processing parameters
SI 32768
SF 400.1300091 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Bha-1



```
Current Data Parameters
NAME                  1H-2-1
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20091016
Time                   17.17
INSTRUM                av300
PROBHD   5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               DMSO
NS                        16
DS                         0
SWH                6172.839 Hz
FIDRES             0.094150 Hz
AQ                 5.3084650 sec
RG                      45.3
DW                 81.000 usec
DE                      6.00 usec
TE                    0.0 K
D1                 2.00000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                     12.25 usec
PL1                    -2.00 dB
SFO1           300.1318536 MHz

F2 - Processing parameters
SI                        32768
SF                 300.1300002 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.40
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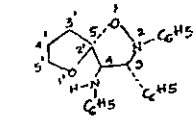
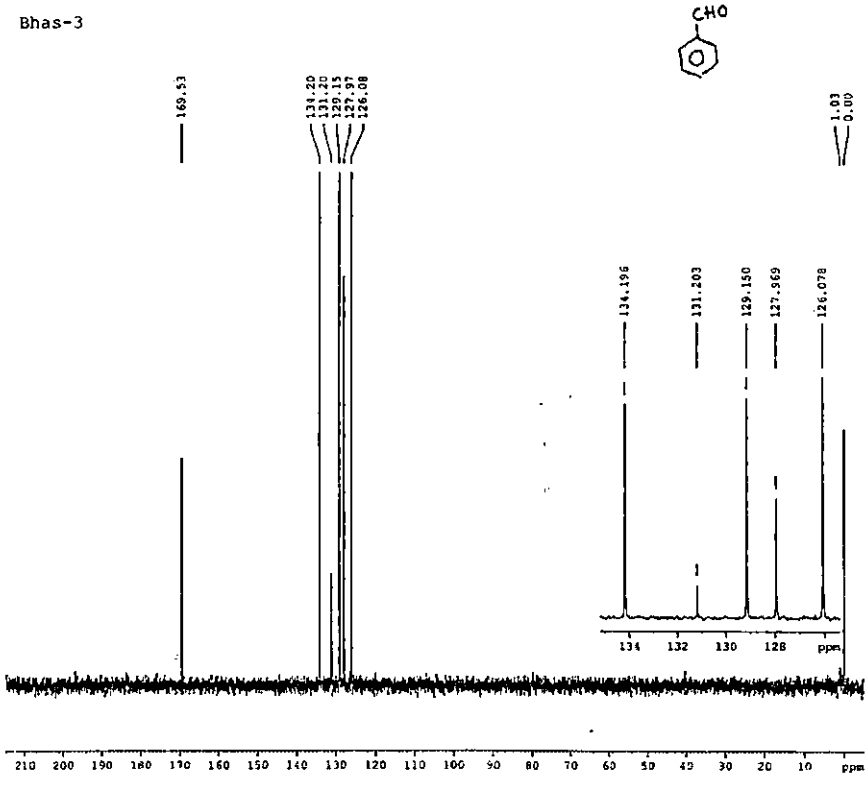


Bhas-3



```
Current Data Parameters
NAME                 13C Bhas3
EXPNO                      1
PROCNO                     2

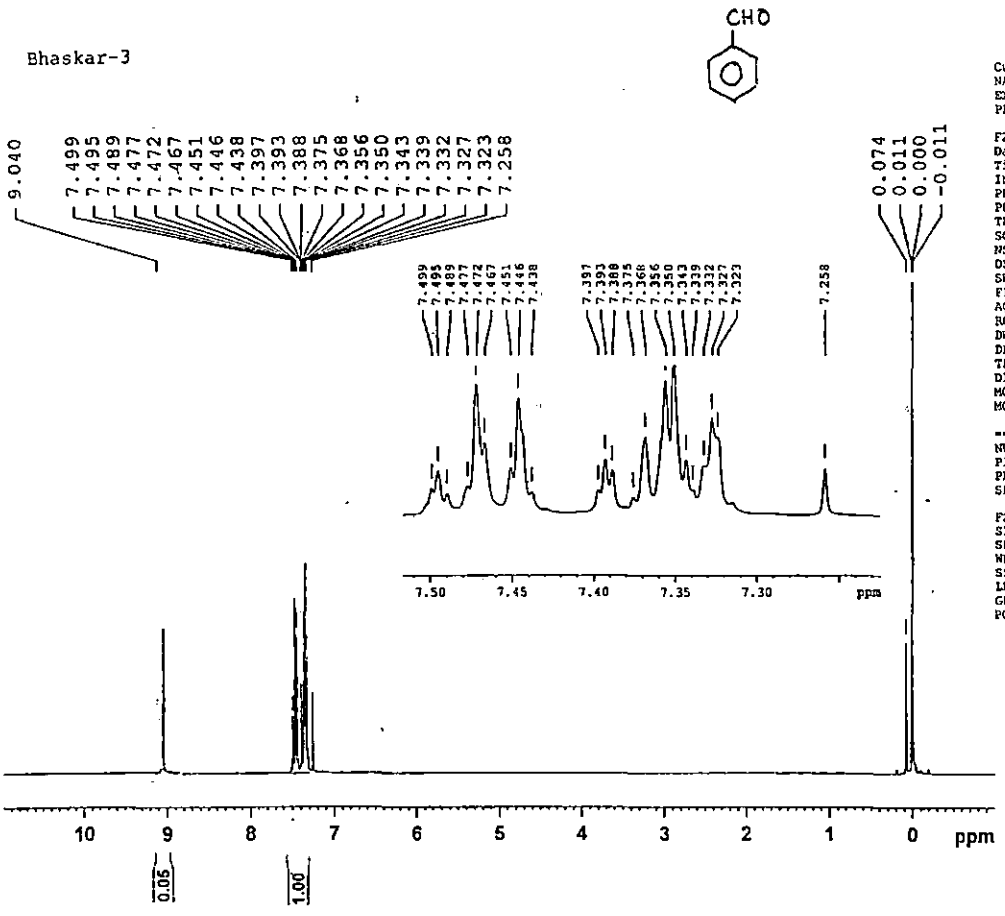
F2 - Acquisition Parameters
Date_              20081011
Time                   13.25
INSTRUM                av300
PROBHD   5 mm BBO BB-1H
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       512
DS                         4
SWH               17985.611 Hz
FIDRES             0.274439 Hz
AQ                 1.8219508 sec
RG                     32768
DW                 27.800 usec
DE                      6.00 usec
TE                    0.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                     12.25 usec
PL1                     0.00 dB
SFO1           75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2               waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                    -2.00 dB
PL12                   15.00 dB
PL13                   19.00 dB
SFO2           300.1312005 MHz

F2 - Processing parameters
SI                        32768
SF                 75.4677505 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

Bhaskar-3

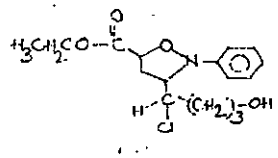


Current Data Parameters
NAME 1Hbhaskar3
EXPNO 3
PROCNO 1

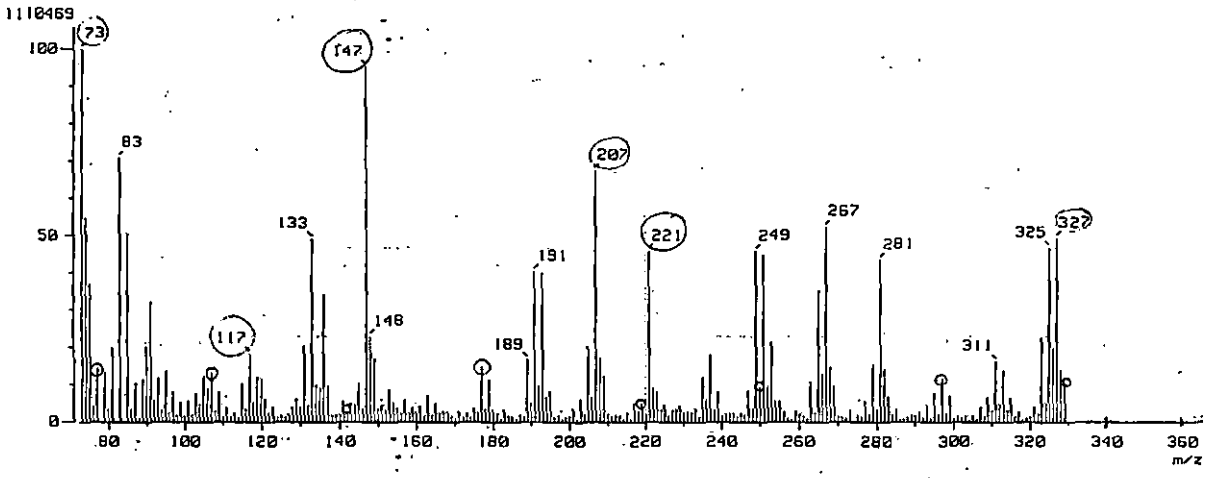
F2 - Acquisition Parameters
Date_ 20081005
Time 11.16
INSTRUM av300
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 64
DS 0
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 181
DW 81.000 usec
DE 6.00 usec
TE 0.0 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

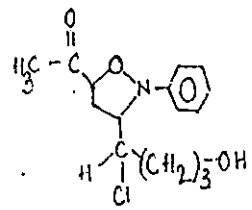
-------- CHANNEL f1 --------
NUC1 1H
P1 13.10 usec
PL1 0.00 dB
SFO1 300.1321909 MHz

F2 - Processing parameters
SI 32768
SF 300.1300068 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

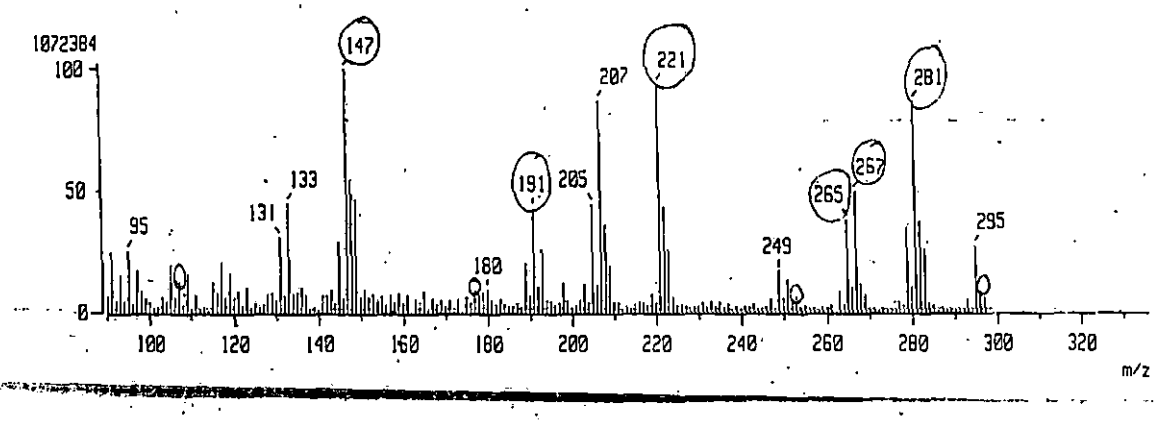


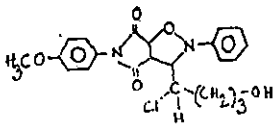
[Mass Spectrum]
Data : BE30APR196 Date : 30-Apr-2008 15:01
Sample: S-21 DR B CHAKRABORTY SIKKIM GOVT COLL. #2719
Note : -
Inlet : Direct Ion Mode : FAB+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.00 min Scan# : 1
BP : m/z 73.0000 Int. : 100.00



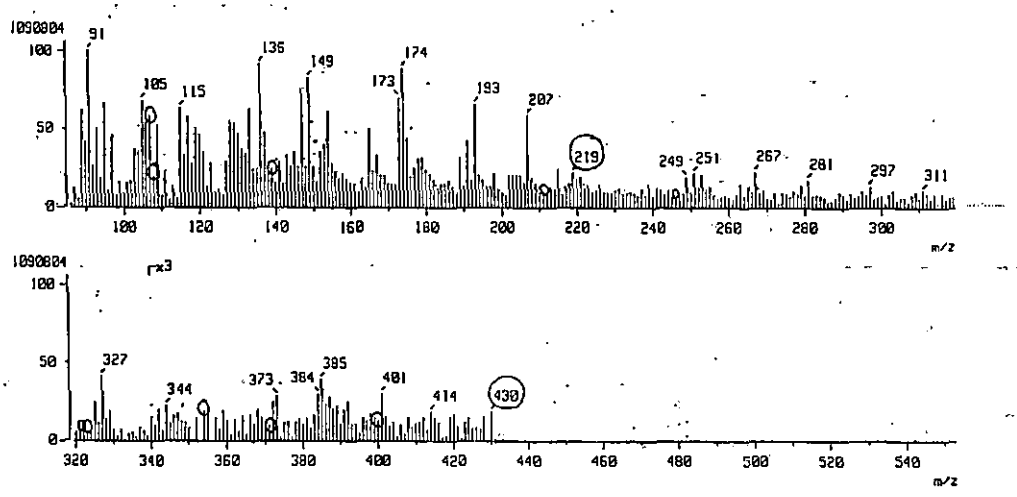


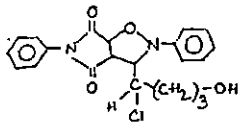
[Mass Spectrum]
Data : 7E16NOV123 Date : 16-Nov-2007 14:44
Sample: D-51 DR B CHAKRABORTY GANGATOK #2173
Note : -
Inlet : Direct Ion Mode : FAB+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.98 min Scan# : (8,10)
BP : m/z 147.0000 Int. : 100.00



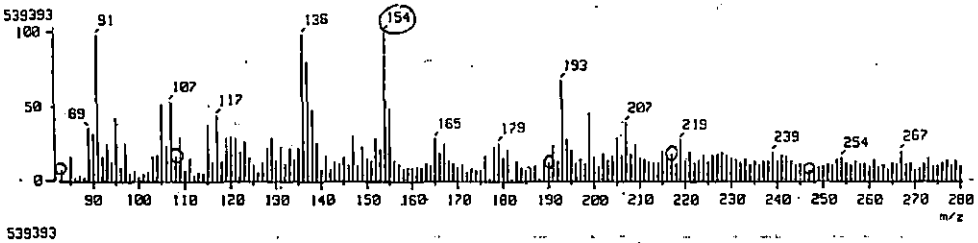


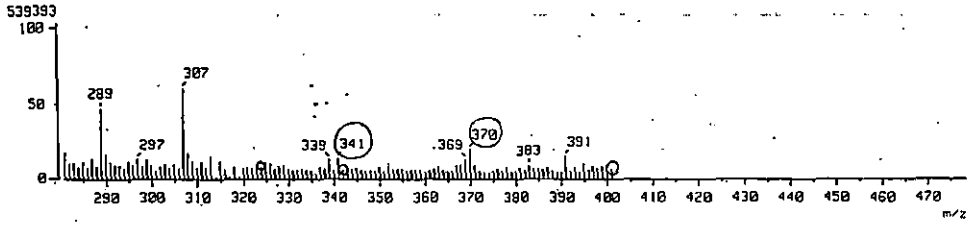
[Mass Spectrum]
Data : 7E21SEPT181 Date : 21-Sep-2007 10:56
Sample: S5 DR B CHAKRABORTY SIKKIM GOVT COLL TADONG #2081
Note : -
Inlet : Direct Ion Mode : FAB+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.00 min Scan# : (1,2)
BP : m/z 91.0000 Int. : 98.55

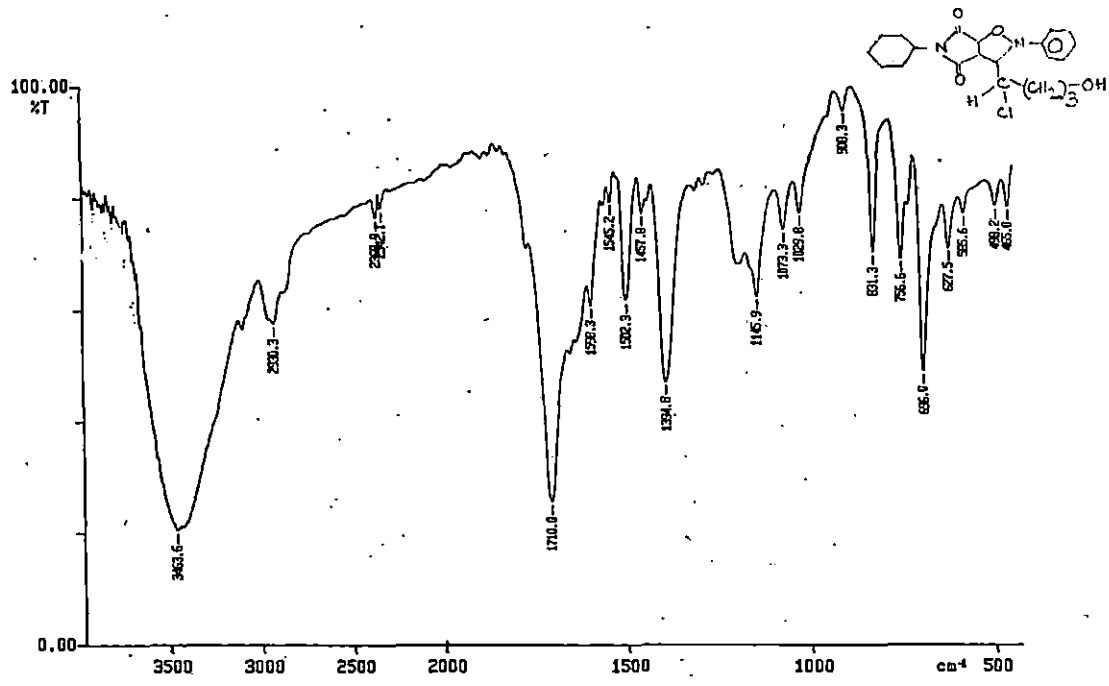




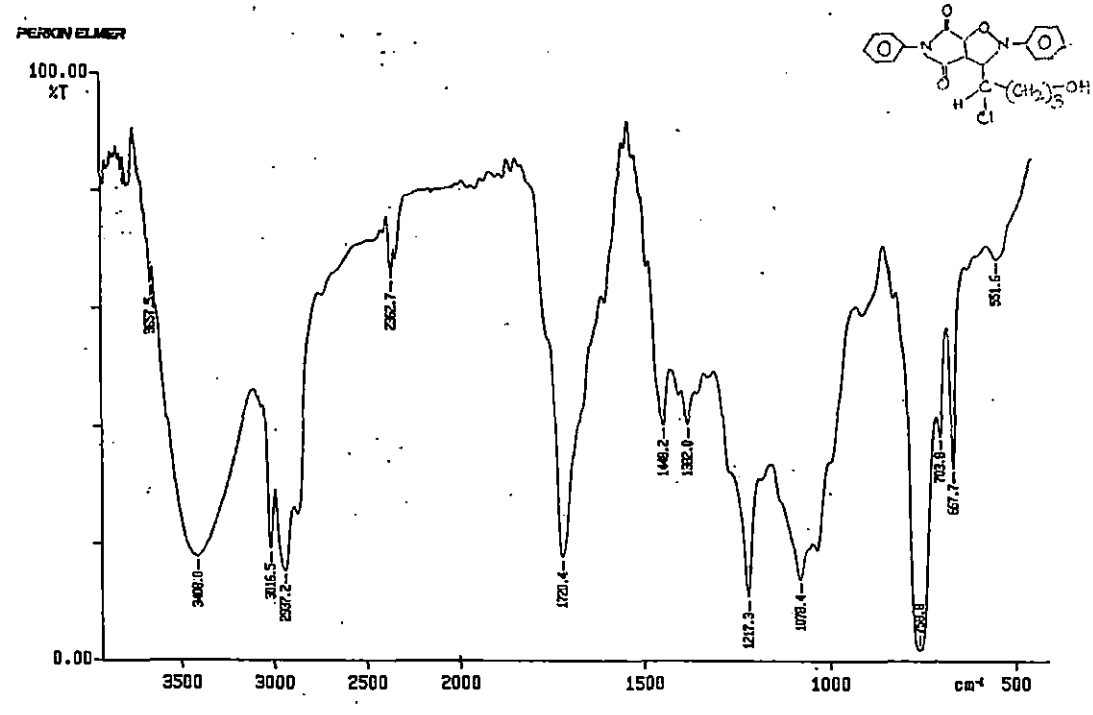
[Mass Spectrum]
Data : 7E10AUG117 Date : 13-Aug-2007 15:05
Sample: BOTTLE-37 DR B CHAKRABORTY SIKKIM GOVT COLL TADONG #1946
Note : -
Inlet : Direct Ion Mode : FAB+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.12 min Scan# : (1,3)
BP : m/z 154.0000 Int. : 49.99



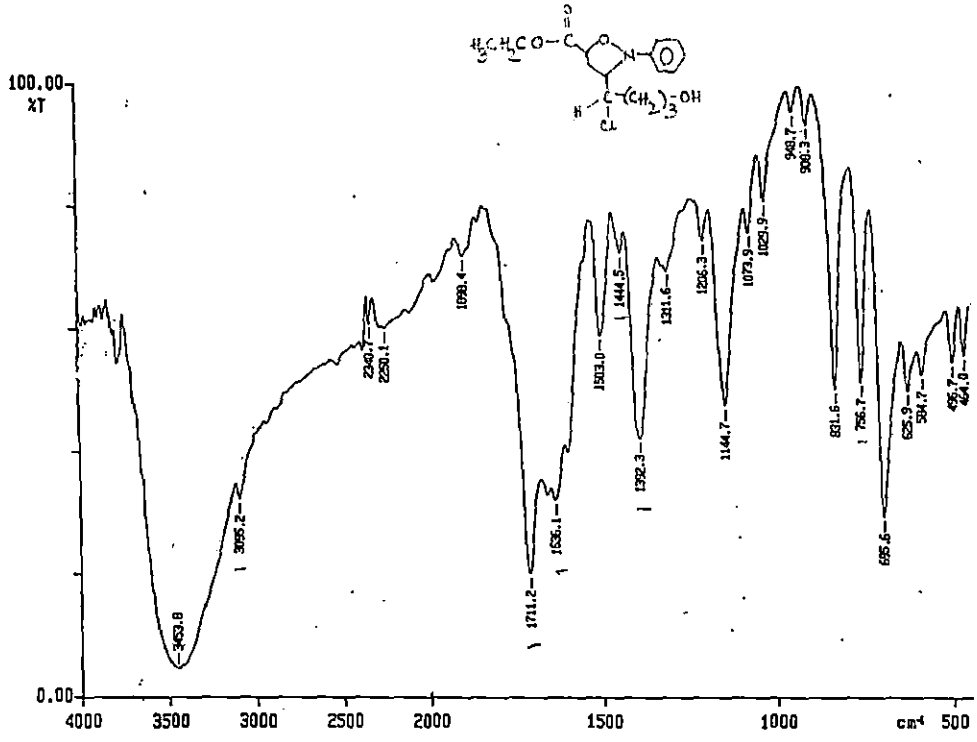




07/09/19 10:39 AH, CODE- S5
X: 4 scans, 4.0cm-1, flat, smooth, abex



07/10/24 10:44 PKA CODE- S-13
X: 4 scans, 4.0cm-1, flat, smooth, abex
SAIF No.-2173



07/08/17 16:07 AH, CODE-32
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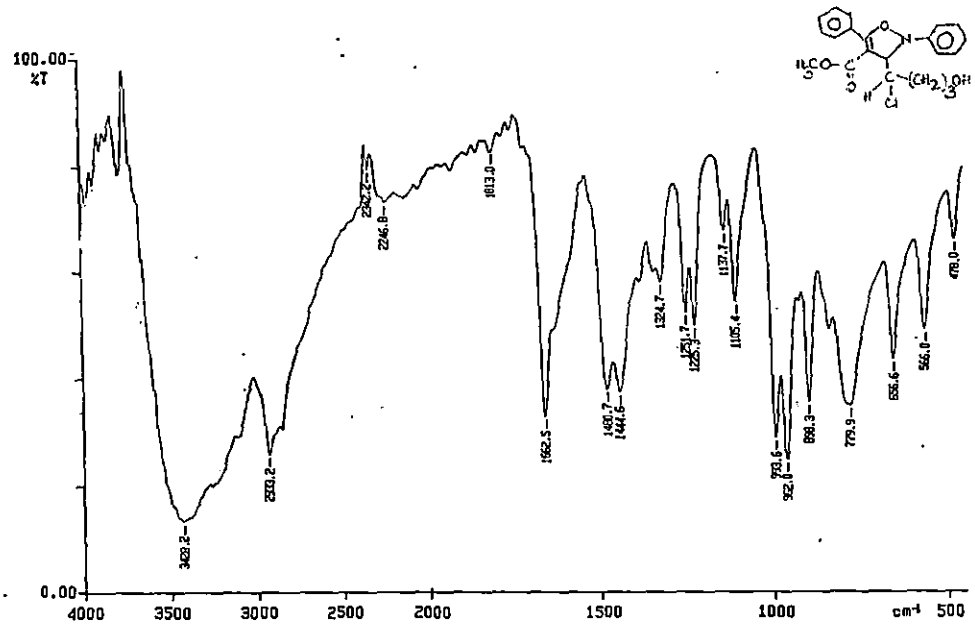

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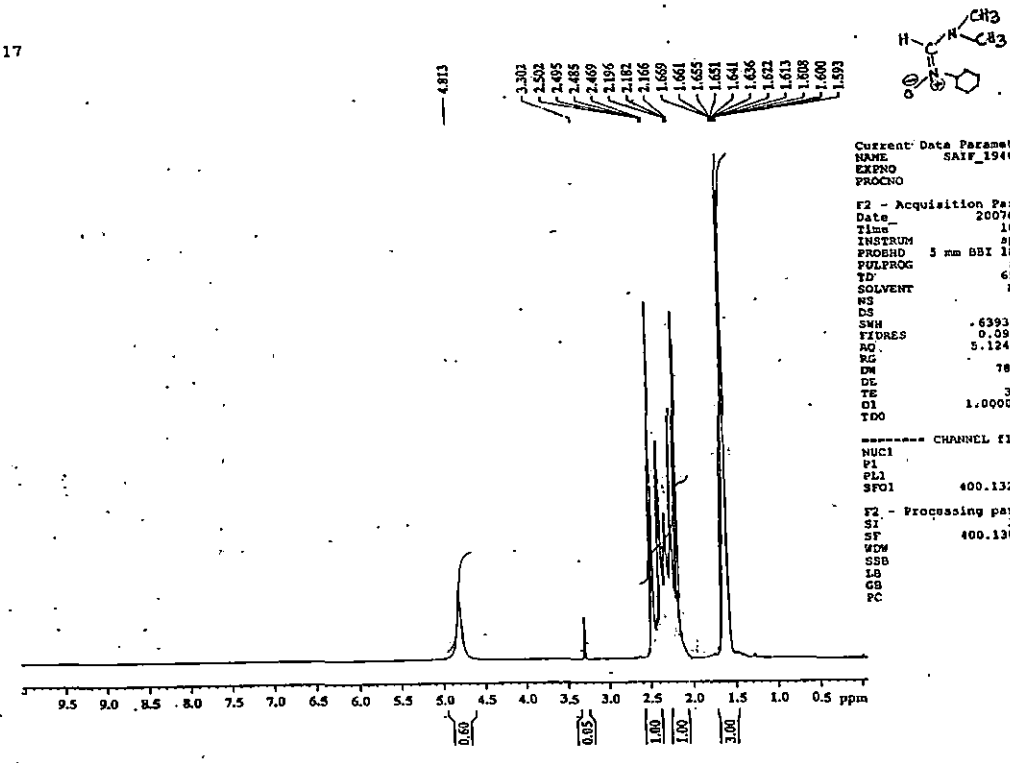
17



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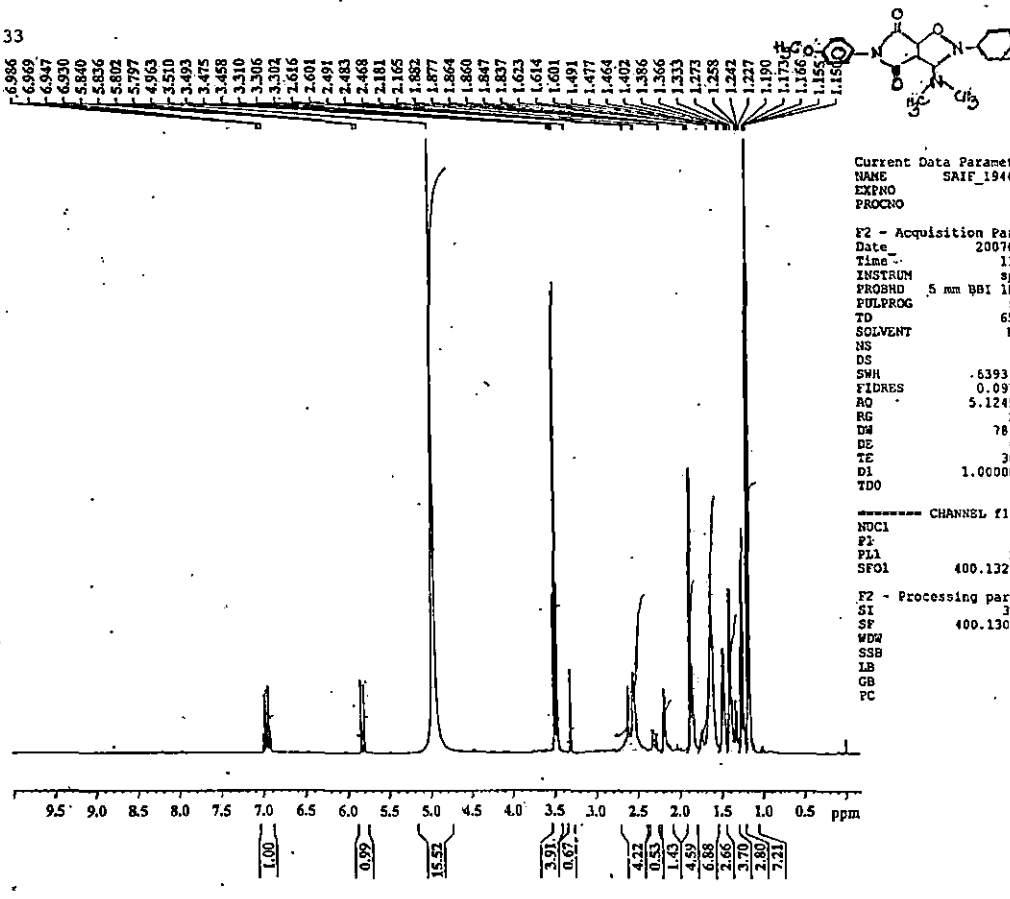

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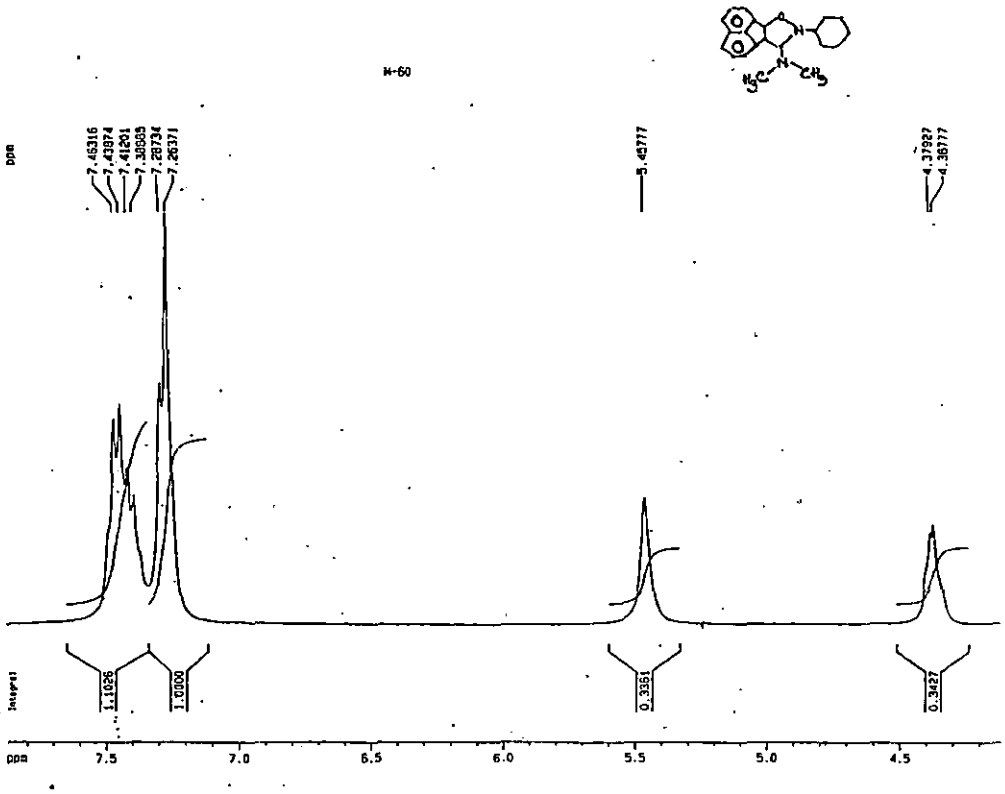
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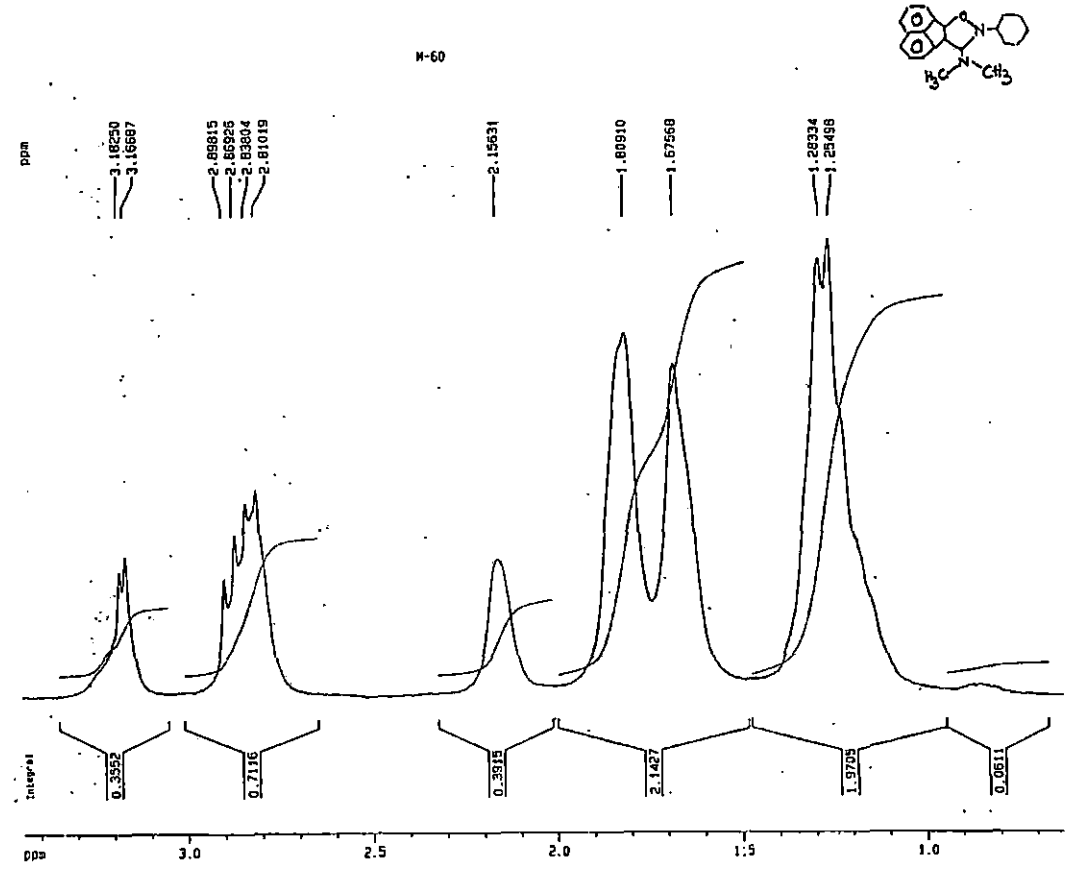
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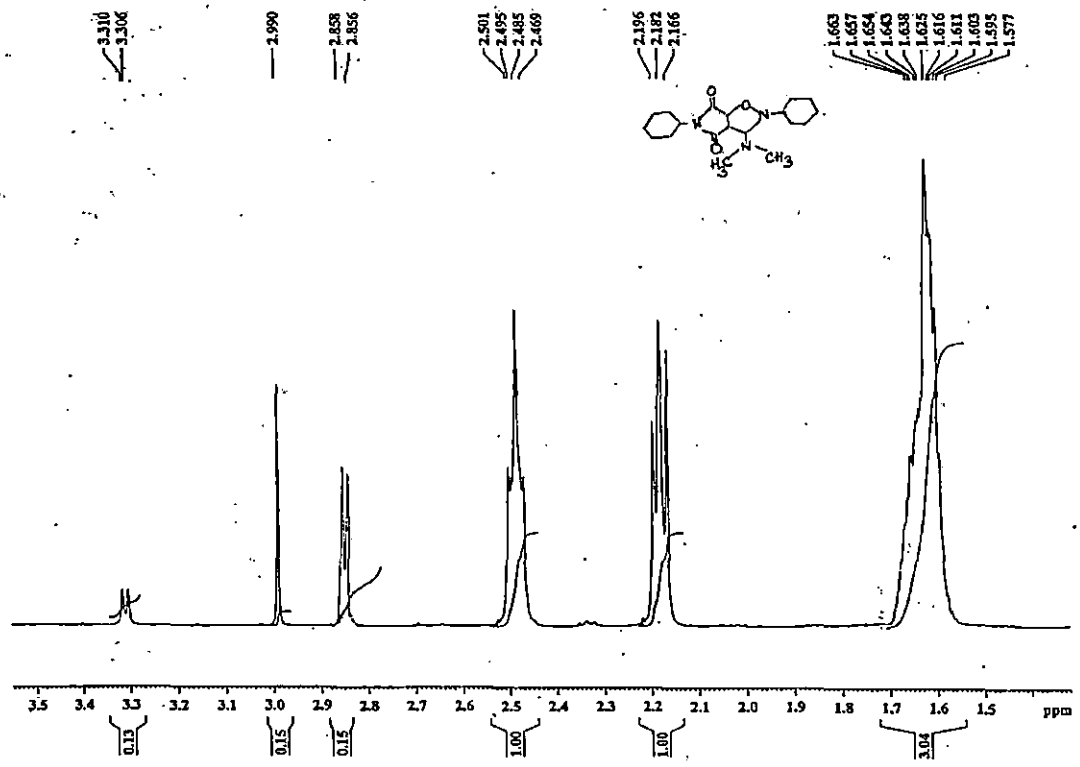

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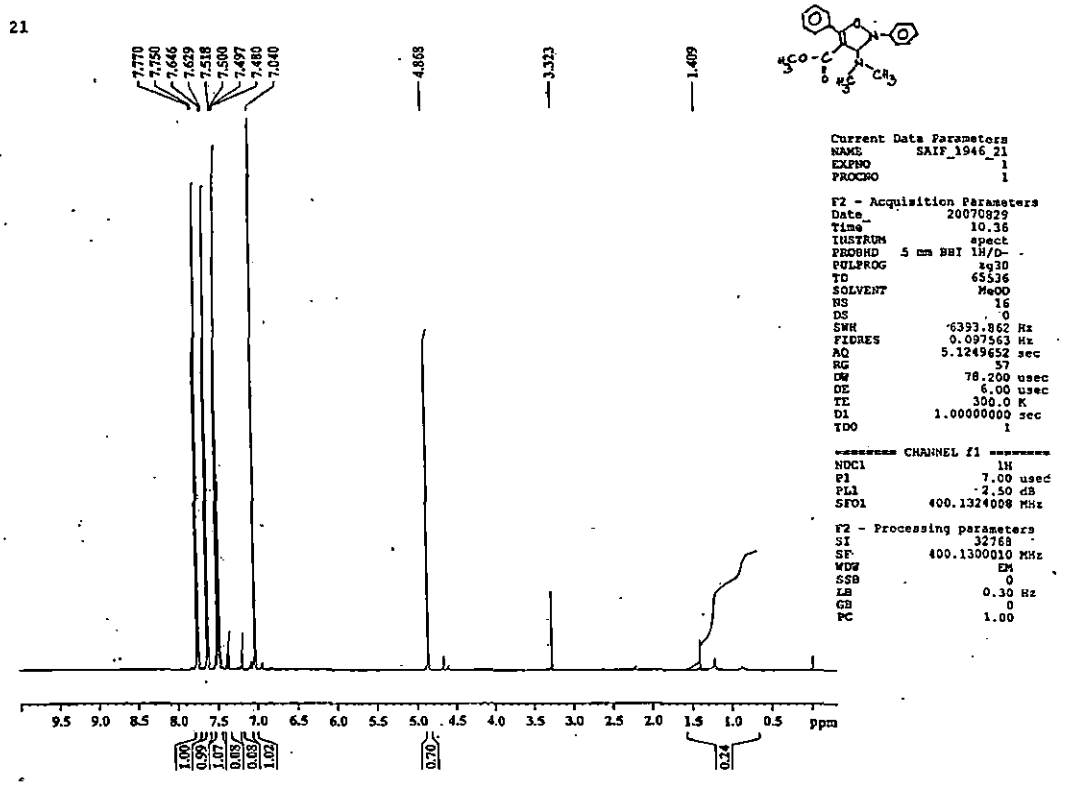


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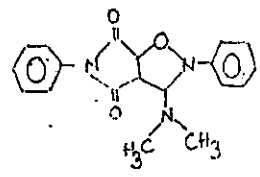

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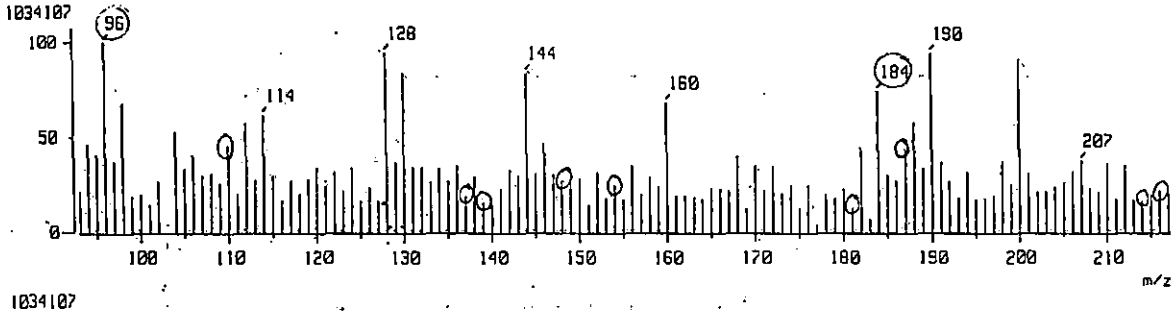

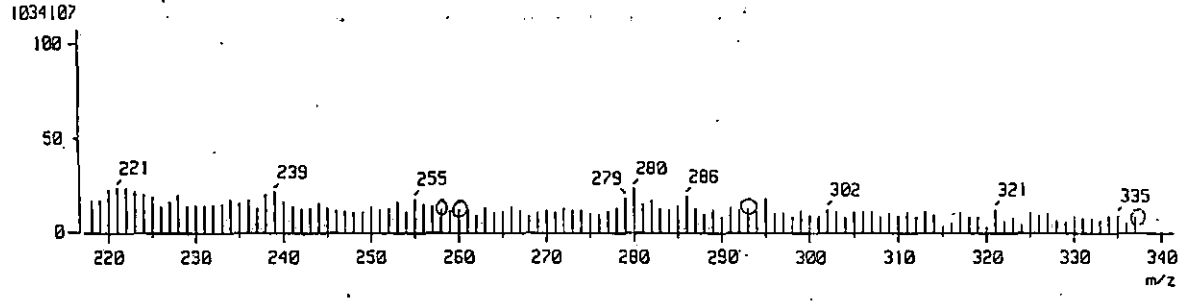

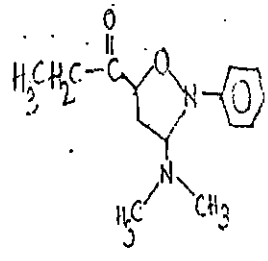

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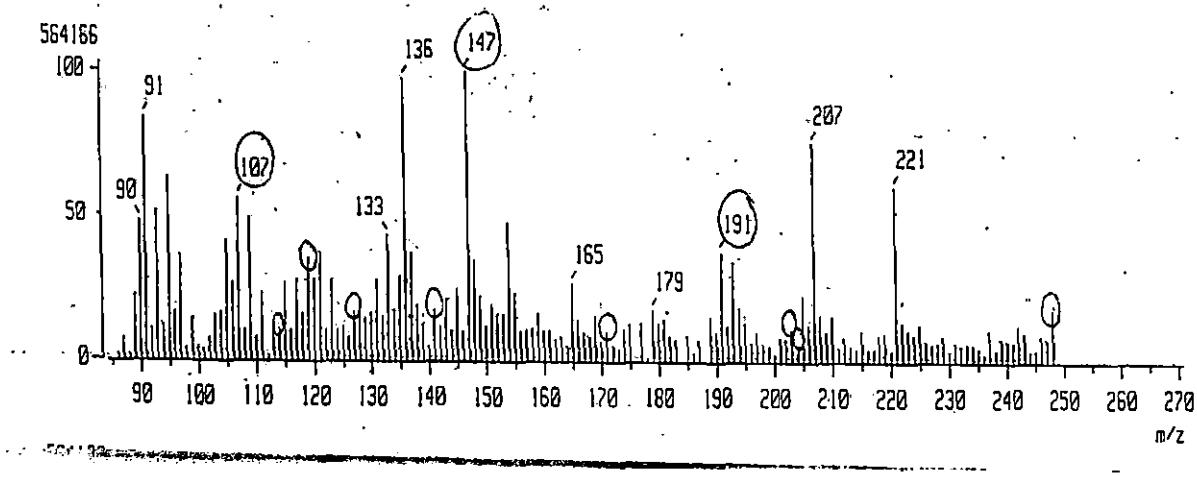

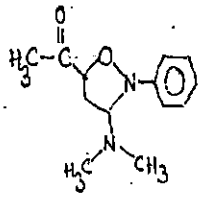

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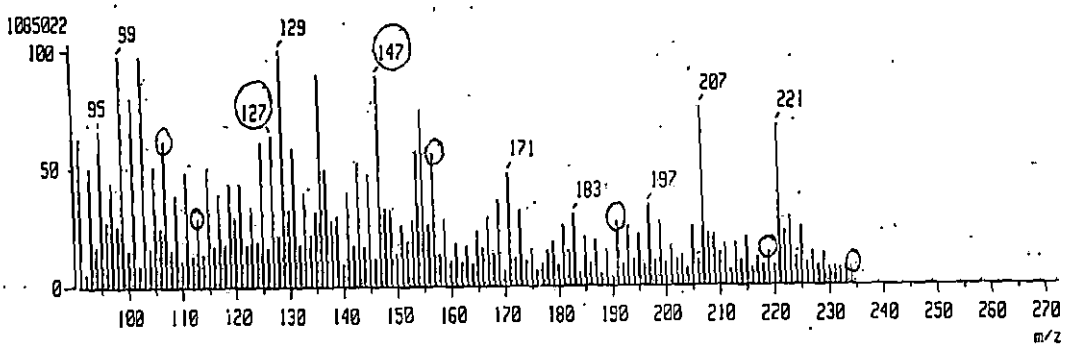
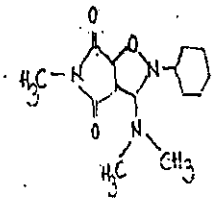
BP : m/z 129.0000 Int. : 100.00





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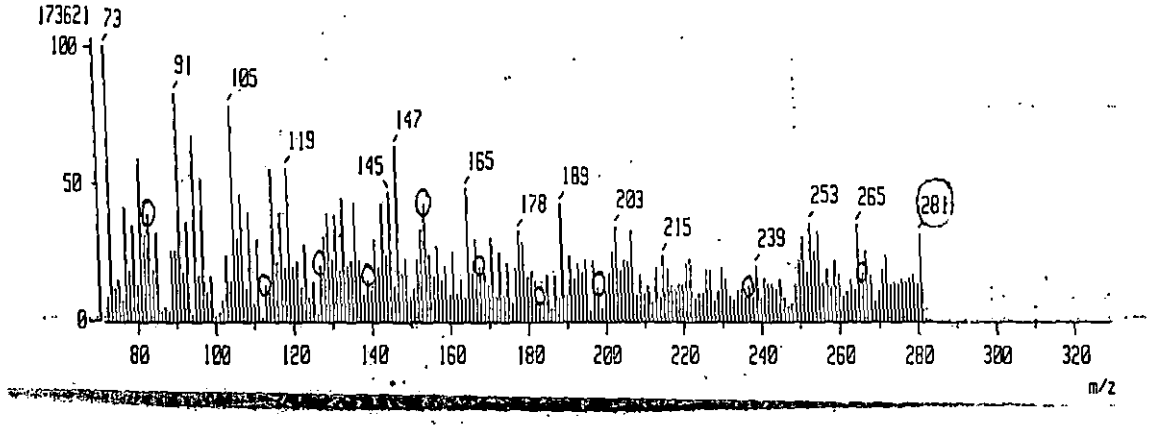

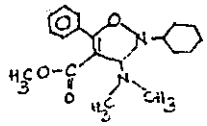

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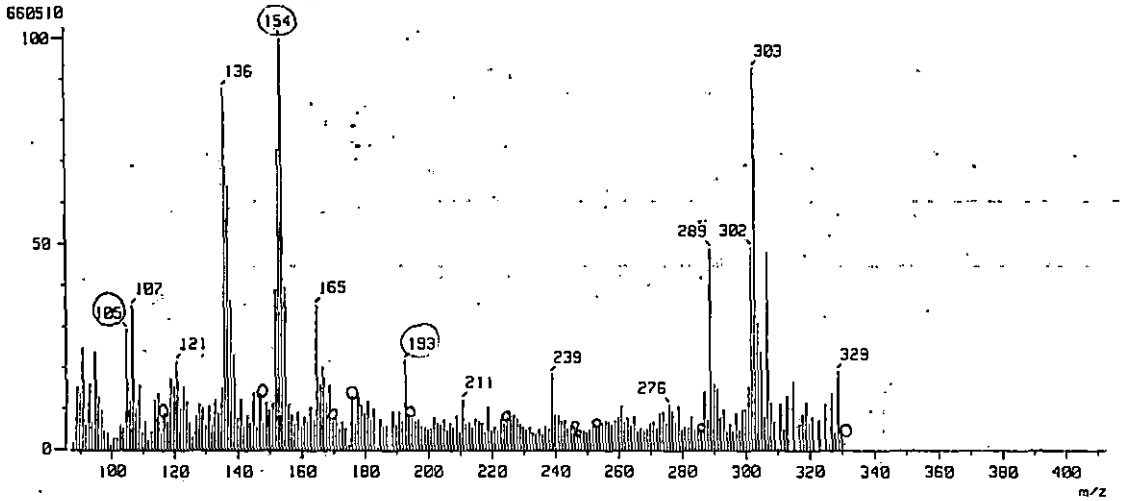

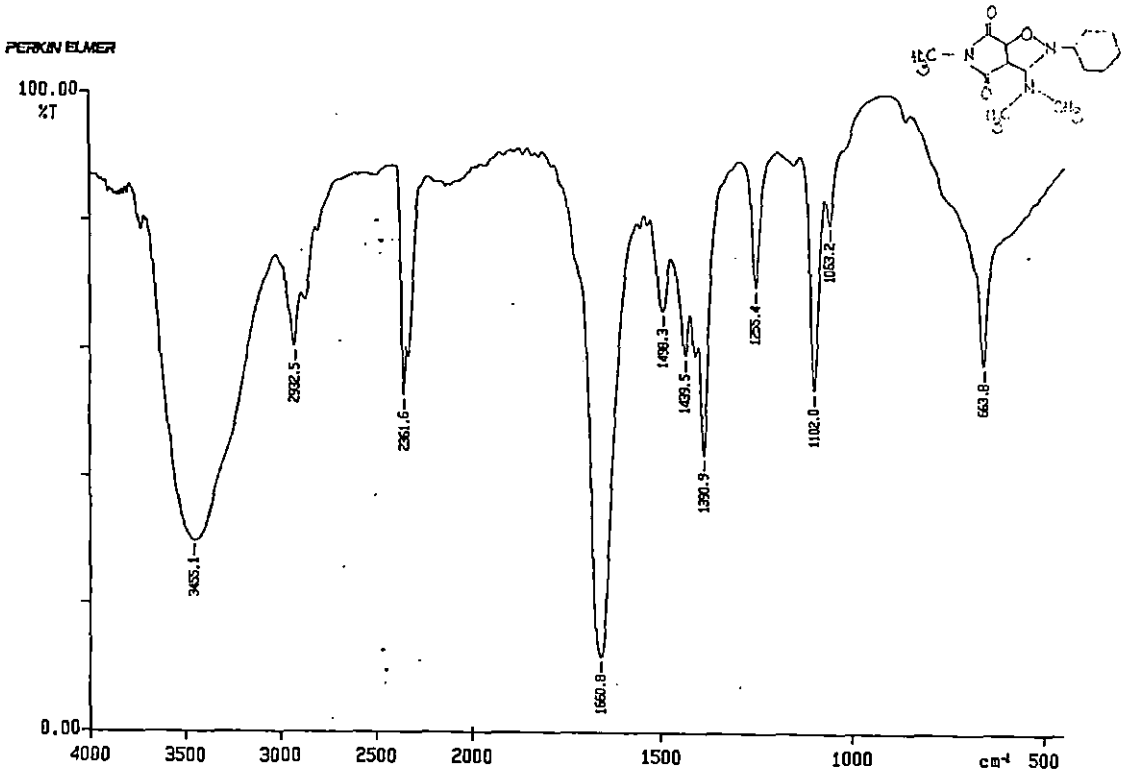

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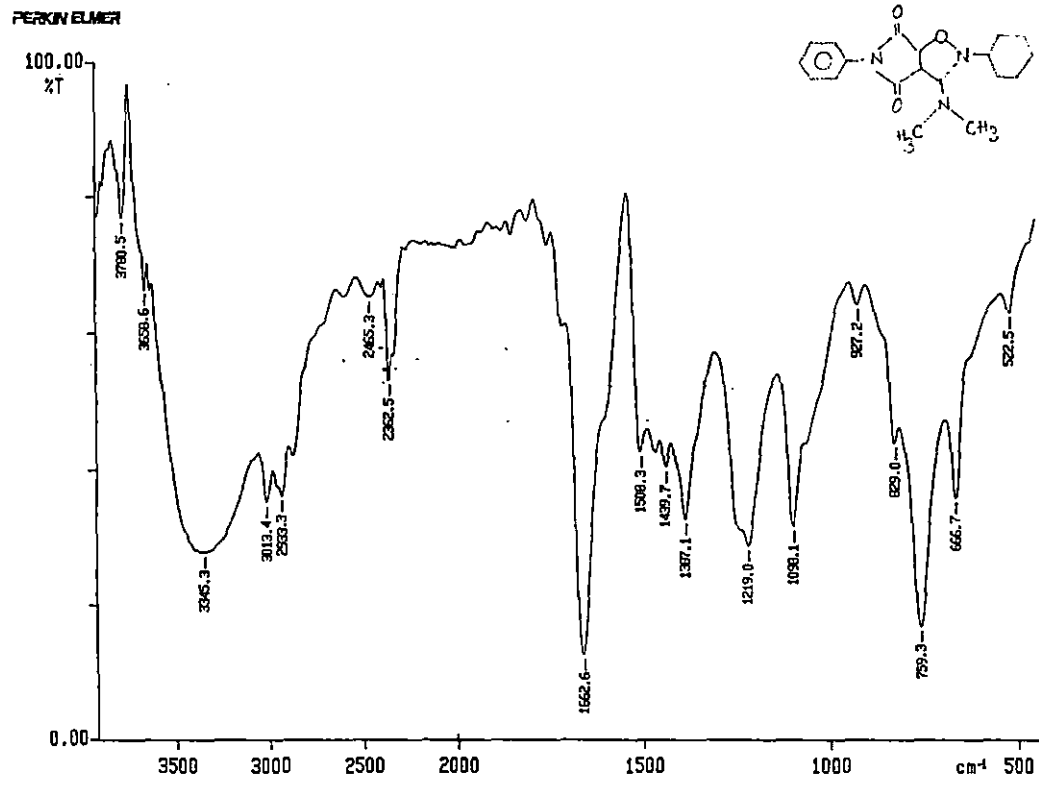

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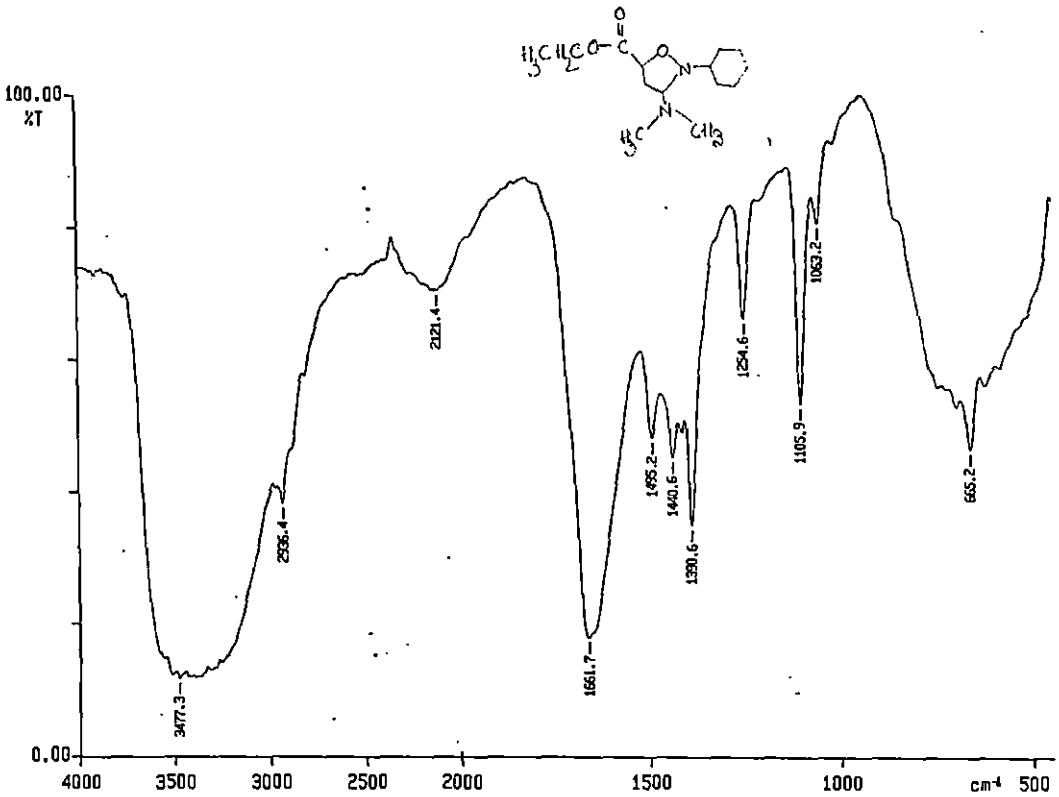
SAIF No.- 2173



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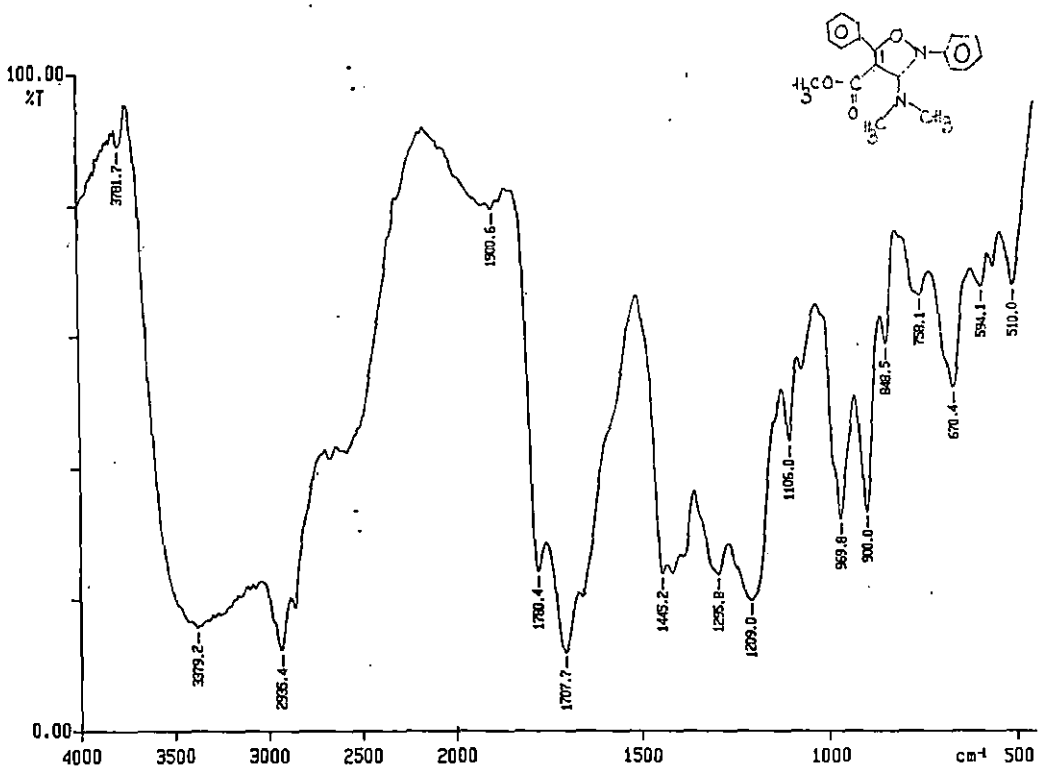
SAIF NO - 1946



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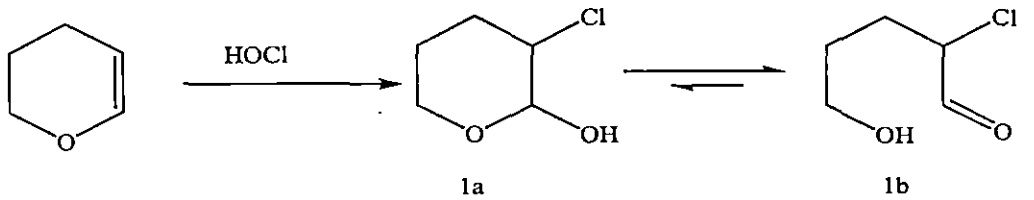
CHAPTER III

Results and Discussion

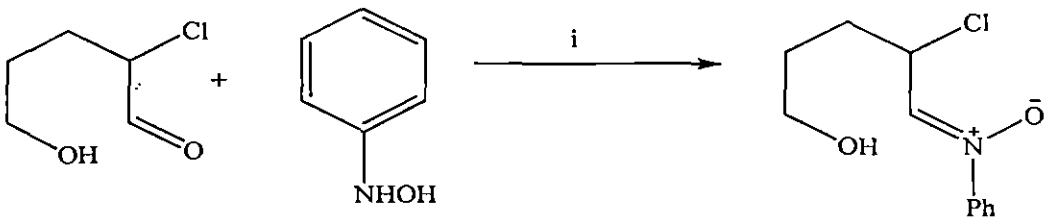
The present study reports about the synthesis, cycloaddition reaction and applications of α-chloro and α-amino nitrones[1-15]. Eschenmoser et al. have shown the synthetic potentiality of α-chloro nitrone in 1,4-dipolar cycloaddition reactions with inactivated double bonds[16]. We have reported an application of α-chloro nitrone in 1,3-dipolar cycloaddition reactions with different dipolarophiles[1]. Similarly we have reported the synthesis of α-amino nitrones[17] following the methodology of α-amino nitrone synthesis from DMF-diacetal[18]. *N*-phenyl-α-chloro nitrone was synthesized from a mixture of chlorohydrin and its tautomer with *N*-phenylhydroxylamine in dry ether and an anhydrous $MgSO_4$ with constant stirring for 8-10 hour under N_2 atmosphere at RT. The cycloaddition reactions were carried out in aqueous phase as well as in conventional solvents. The synthesis and cycloaddition reactions of *N*-cyclohexyl-α-chloro nitrone[14] using chlorohydrin and *N*-cyclohexylhydroxylamine has been already reported from this laboratory using conventional solvents. The most important application of these nitrones are as very effective oxidizing reagents for the production of aldehydes when the nitrones are treated with various alkyl halides and the side products can be used as efficient dipolarophiles for the production of *spiro* cycloadducts in case of α-chloro nitrone[3] and simple nitrones. The side products obtained during aldehyde synthesis using α-amino nitrone can be hydrolysed to recyclable products.

Chlorohydrin and its tautomer was obtained when 2,3-dihydro-4*H*-pyran was subjected to chlorohydrination with hypochlorous acid[19]. The nitrone was generated by treating chlorohydrine with *N*-phenylhydroxylamine with constant stirring at RT. The nitrone was isolated as colourless crystalline solid, m.p 58°C (uncorrected) and decomposes when kept at room temperature for a longer period. Hence the nitrone was trapped *in-situ* for the cycloaddition reactions mainly and in some cases used immediately after its formation.



1a 1b

Preparation of Chlorohydrin



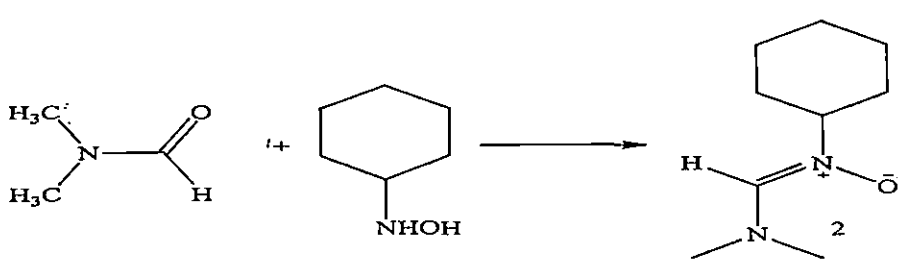
Preparation of *N*-phenyl-α-chloronitrone

Scheme 1

Spectral data:

White needle, 93 %; IR ($CHCl_3$): 3660 – 3520 (br), 1610 (s), 1440 (m), 1150 (s), 784 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.73 – 7.28 (m, 5H, C_6H_5), 6.45 (d, 1H, J = 6.06 Hz, $CH{=}N^+$), 5.12 (br, 1H, OH, exchanged in D_2O), 3.66 (dt~m, 1H, J = 6.06, 6.08 Hz, CHCl), 2.04 – 1.25 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 142.04 ($CH{=}N^+$), 134.80, 133.00, 131.60, 130.00 (aromatic carbons), 95.30 (CHCl), 31.45, 28.60, 25.40 (3 CH_2 carbons); HRMS – EI: Calcd. for $C_{11}H_{14}O_2NCl$, (M), 225.0864, found M^+, 225.0852.

Both the α-amino nitrones (*N*-phenyl, *N*-cyclohexyl-α-amino nitrones) were synthesized from DMF by direct synthetic methodology as suggested by Eschenmoser et al[18]. Details are given in experimental section. Between the nitrones, *N*-cyclohexyl-α-amino nitrone is comparatively stable (m.p: 48^{0}C,uncorrected) and can be used for cycloaddition reactions in 1:1 ratio for aqueous phase and conventional solvents while *N*-phenyl-α-amino nitrone is unstable and decomposes when kept at RT for a longer period and is used *in-situ* in the majority of cycloaddition reactions.

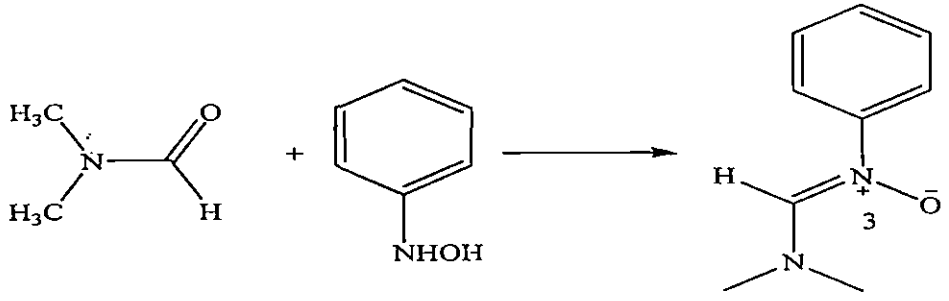


Preparation of *N*-cyclohexyl-α-aminonitrone (**2**)

Scheme 2

Spectral data:

White crystalline solid, 88%; IR ($CHCl_3$): 3440 (m), 1600 (s), 1360 (m), 1310 (m), 1120 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.81 (br, 6H, NMe_2), 3.30 (s,1H,$HC=N^+-O^-$), 2.50 - 2.16 (m, 1H, N-CH proton), 1.66 – 1.59 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 144.62 ($CH=N^+$), 43.00, 40.72 (*N* - methyl carbons), 32.00, 30.64, 27.32, 26.08, 25.15, 24.74 (cyclohexyl carbons); HRMS – EI: Calcd. for $C_9H_{18}N_2O$, (M) 170.2560, Found, M^+ 170.2555.



Preparation of *N*-phenyl-α-aminonitrone (3)

Scheme 3

Spectral data:

Pale yellow crystals, 94%; IR ($CHCl_3$): 3410 (m), 1660 (s), 1610 (s), 1440 (m), 1300 (m), 1180 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.73 - 7.26 (m, 5H, C_6H_5 protons), 1.90 (br, 6H, *N*-methyl protons), 1.42 (s, 1H, $CH=N^+$); ^{13}C NMR ($CDCl_3$): δ 142.00 (CH=N+), 132.90, 131.00, 129.65, 127.40 (aromatic carbons), 47.42, 44.84 (methyl carbons); HRMS – EI: Calcd. for $C_9H_{12}N_2O$, (M) 164.2066, Found, M^+ 164.2052.

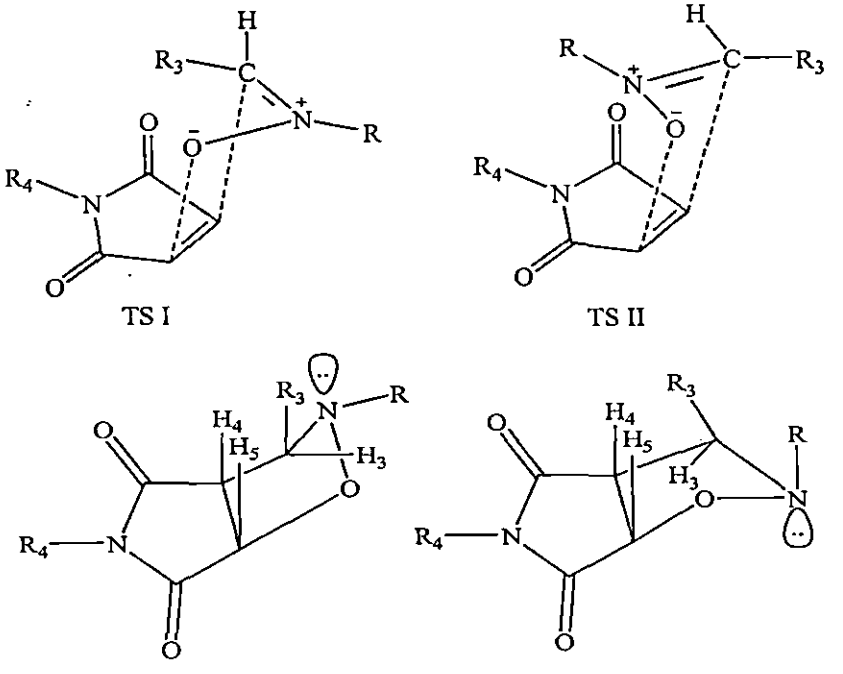
In the case of α-chloro nitrone, the reactions were found to be highly stereoselective to form diastereomeric cycloadducts with the predominance of one of the isomers in case of *N*-phenyl maleimide, *N*-methyl maleimide, *N*-cyclohexyl maleimide, acenapthylene etc. while regioselective cycloadducts are formed in case of methyl vinyl ketone, acrylonitrile, styrene etc. respectively in aqueous phase. The regioselectivity in these reactions were rationalized by the use of frontier orbital theory[20,21]. The α-chloro nitrone has considerably higher ionization potential than normal nitrones due to the electron withdrawing effect of chlorine. Therefore nitrone (LUMO)-dipolarophile (HOMO) interactions were so important that it completely dominates the reaction and leads to the formation of only five substituted adducts. One of the most important features of these cycloaddition reactions are the introduction of three to four asymmetric centers in a single step.

Almost all the reactions in water are very fast (4 - 6 hrs in case of maleimides and 8-10 hrs for other olefines) compared to the normal cycloaddition reactions in organic solvents which were reported to take longer periods (26 - 48 hrs). It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β-unsaturated carbonyl compounds and thereby increasing the eletrophilic character at the β-carbon which is attacked by nucleophilic oxygen atom of the nitrone. Thus water activates the maleimide, ethyl acrylate, methyl vinyl ketone and thereby greatly facilitates the reaction. Reactions and yields are comparatively slower in case of alkenes like cyclohexene, styrene because of very lesser possibility of the formation of hydrogen bonding between water and alkenes but still the rate of the reaction and the yield is higher than the cycloaddition reactions performed in solvents like THF, CH_2Cl_2 (**Table 1**). We suggest an explanation for these results in terms of the frontier molecular orbital (FMO) theory which has been used extensively to explain and predict the yield, rate in 1,3-dipolar cycloadditions[21]. This theory states that the Gibbs energy of activation is related to the energy gap between the interacting HOMO and LUMO. The dipolarophiles like styrene, cyclohexene etc are weak hydrogen bond acceptors, which means that their FMO's are only slightly affected by hydrogen bond interactions and lead to a reduction of the energy gap between the interacting FMO's (in this case, the HOMO of the dipolarophile and LUMO of the 1,3 dipole). Consequently, the Gibbs energy of activation of the reaction is reduced and the reaction is accelerated in water with good yield.

Excellent diastereofacial selectivity is observed in α-chloro nitrone additions described here in water. The addition of nitrone **1** to maleimides result in a mixture of diastereomers (almost 70 : 30 ratio in all cases) and as many as three to four chiral centers in a single step. Studies of organic reactions in aqueous media shows that there is a more possibility of the formation of mixture of diastereomer when water is used as solvent rather than conventional solvents[22,23]. These results can be rationalized by an *exo* approach of the nitrone **1** for the major cycloadducts which have the *Z* configuration (transition state **I**). The minor cycloadducts are formed by the *endo* approach of *Z* nitrone (transition state **II**). The mixture of diastereomers is identified by considering the multiplicity of the proton signals at 3-H and 4-H along with their coupling constant values (*J*). The most significant differences in the ^{1}H NMR data for the diastereomers are the position and multiplicity of the 3-H signal. In the minor

adducts 3-H resonates upfield around δ_H 4.10 ppm while for the same proton in major adducts around δ_H 4.85 ppm and $J_{3,4}$ ~ 9.16 Hz for major adducts whilst for minor adducts $J_{3,4}$ is ~ 2.26 Hz. These differences can be explained on consideration of the available isoxazolidine ring conformations. Due to the 4,5 fused pyrrolidinedione, the isoxazolidine ring adopts an envelope conformation and allowing for inversion, its nitrogen atom will either extend out from the envelope, i.e. minor conformation (1), or point inside the envelope, i.e. major conformation (2). The minor conformer has the *N* - lone pair antiperiplanar and therefore capable of shielding 3-H proton, so this conformation is assigned to the minor conformer (**Fig 1**). The diastereomeric isoxazolidines were separated by column chromatography and obtained in analytically pure form[24]. The *endo/exo* stereochemistry mentioned above is based on extensive NMR investigations. Most relevant are the coupling constants ($J_{H3,\ H4}$) of the diastereomers. For major adducts, this coupling constant is almost 9.2 – 9.4 Hz, implying a *cis* relationship between *H*-3 and *H*-4, whereas for minor adducts, the coupling constant is almost 2.5 – 4.2 Hz which implies a *trans* relationship between *H*-3 and *H*-4[25]. In all the diastereomers, the configurations of *H*-5 & *H*-4 are *cis* as evidenced from their coupling constant values. For ethyl acrylate and methyl vinyl ketone the regioselectivity was rationalized by using frontier orbital theory[20] and ^{1}H NMR experiments. Since α-chloro nitrone exist exclusively in *Z* configuration, the cycloadducts were formed from *Z* nitrones through an *exo* transition state geometry. Cycloadditions to α,β unsaturated carboxylic acid derivatives, e.g. ethyl acrylate are particularly useful because high regioselectivity is often observed in water[23]. The reactions were found to be highly regioselective to form solely 5-substituted isoxazolidines respectively. Nitrone **1** has considerably higher ionization potential than normal nitrones due to the electron withdrawing effect of chlorine. Therefore nitrone (LUMO) – dipolarophile (HOMO) interactions were so important that it completely dominates the reaction and leads to the formation of only 5 substituted adducts[20,21]. Considering the ^{1}H NMR spectrum of regioselective cycloadducts (5 substituted adducts: ethyl acrylate, methyl acrylate, styrene, acrylonitrile etc), it has been found that clear quartet signals for H-4 protons and multiplet signals for H-3 protons are obtained in all the cases due to further coupling from vicinal hydrogens and hence confirms in favour of 5- substituted adducts. Detail investigation on the nature of these cycloaddition reactions from TLC and ^{1}H NMR spectrum studies for these cycloadducts, it was also confirmed that no diastereomers were formed. The

relative configurations of *H*-3, *H*-4 & *H*-5 protons in these adducts are *syn* and the cycloadducts are in favour of *exo* transition state geometry as evidenced from their coupling constant values ($J_{H4,\ H5}$ = 6 – 8.4 Hz; $J_{H4,\ H3}$ = 6.2 – 7.6 Hz)[25]. Similar cycloaddition reaction of other simple nitrones with these dipolarophiles usually give both 5 and 4- substituted adducts in conventional solvents with some exceptions of either 5 or 4- substituted adducts.



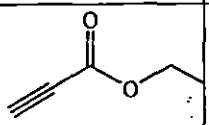
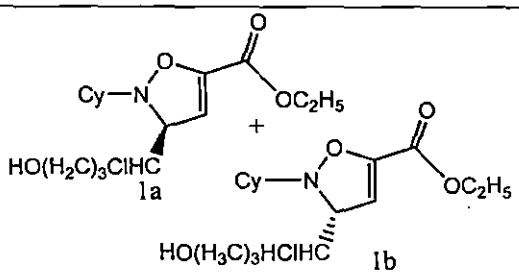
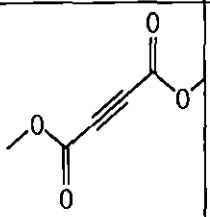
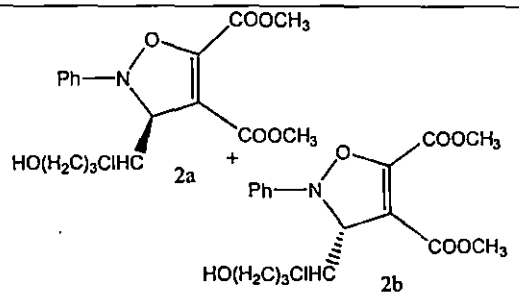
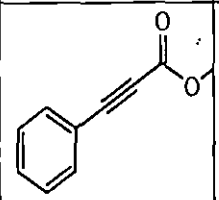
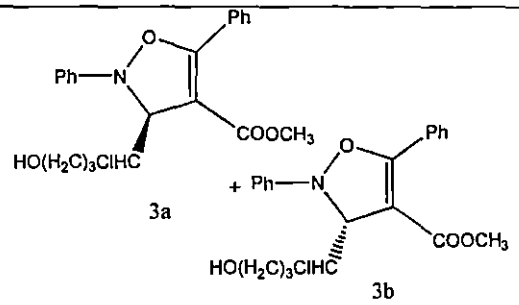
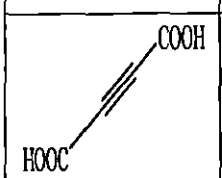
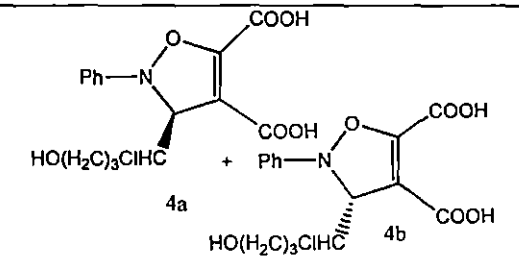
R_3 = $CHCl(CH_2)_3OH$; R_4 = Ph; Me; Cy

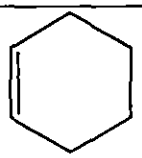
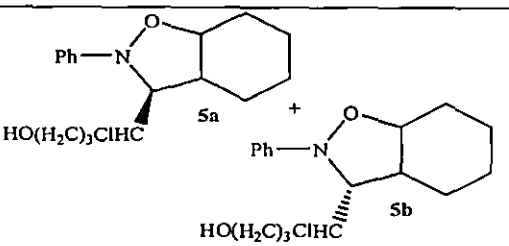
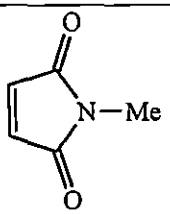
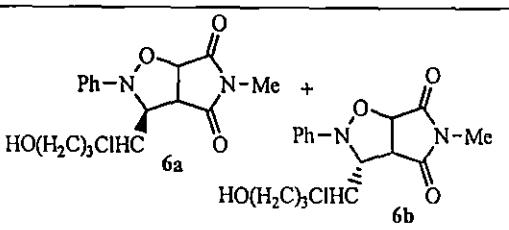
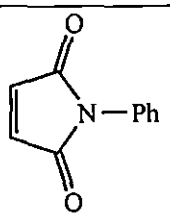
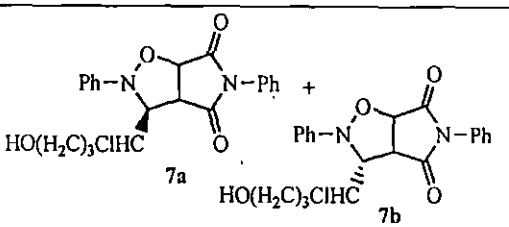
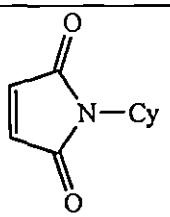
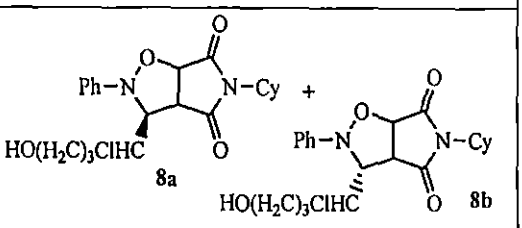
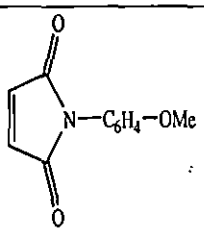
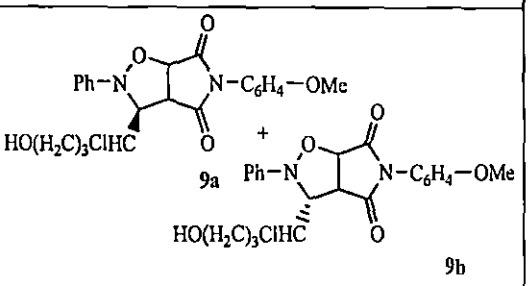
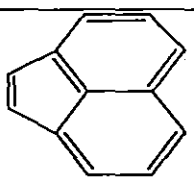
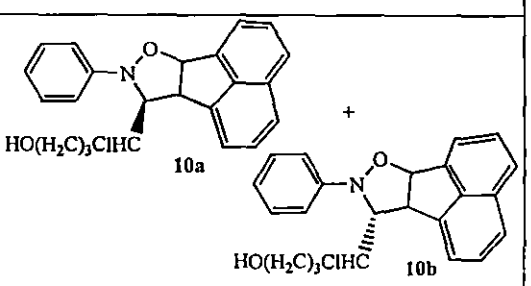
Fig. 1

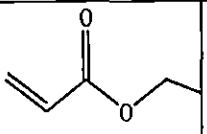
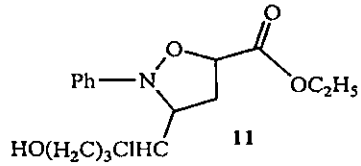
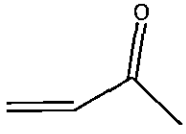
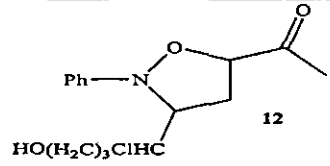
In general the reactions are very clean and high yielding compared to usual cycloaddition reactions of nitrones. The products were characterized from their spectroscopic (IR, ^{1}H NMR, HRMS, ^{13}C NMR) data. No catalyst or co-organic solvent was required. The exact stereochemistry at the asymmetric CHCl carbon atom of all the cycloadducts could not be determined due to multiplet (doublet of triplet appears almost as multiplet) signals obtained in the NMR spectrum and hence *J* value could not be calculated. In the ^{13}C NMR spectrum, four signals were obtained in case of phenyl ring carbons due to equivalent nature of C-2 & C-6 and C-3 & C-5 carbons. In the mass spectrum, significant M^++2 ion peaks obtained in most of the diastereomers and regioselective cycloadducts as the peak of highest *m/z* value. These can be explained as M^++2 isotopic peaks due to the presence of isotopic abundance of Cl^{37} atom in these compounds. In addition, mass fragmentation peaks of different

value are also obtained for diastereomers of a particular cycloadduct. Studies of HRMS spectra show almost exact masses in the majority of the compounds. The reaction conditions, major products, nature etc. are summarized in the following **Table I.**

Table 1: (Reaction of nitrone 1 with different dipolarophiles in aqueous medium)

Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Dry ether; Time = 12 hr	White viscous liquids	1a: 70%; 1b: 22 %	
	Dry ether; Time = 10 hr	White viscous liquids.	2a: 69%; 2b: 27%	
	Dry ether; Time = 13 hr	White viscous liquid	3a: 75%; 3b: 24%	
	Dry ether; Time = 14 hr	Colourles s viscous liquids	4a: 73%; 4b: 24%	

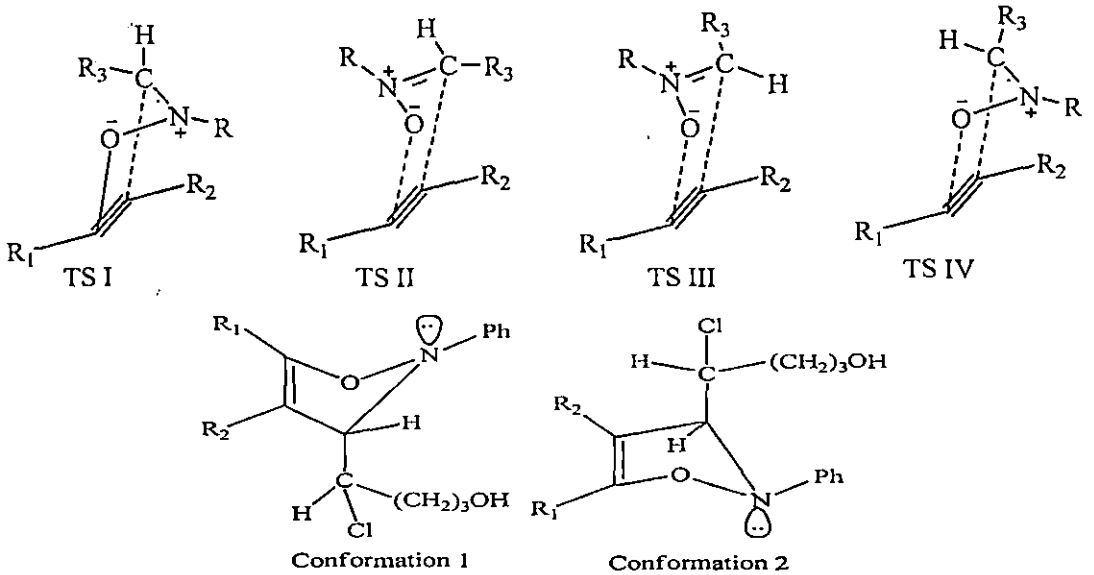
Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Water; RT; Time = 14 hr	Reddish gummy liquid	5a: 60%, 5b: 28%	
	Water; RT; Time = 4 hr	white solid	6a: 75.6%, 6b: 20.4%	
	Water; RT; Time = 4 hr	Yellowish white solids	7a: 70.8%, 7b: 23.2%	
	Water; RT; Time = 5 hr	Dark yellow crystals	8a: 68%, 8b: 27%	
	Water; RT; Time = 5 hr	White solids	9a: 70.8%, 9b: 21.2%;	
	Water; RT; Time = 7 hr	Bright yellow crystals	10a: 73%, 10b: 23%	

Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Water; RT; Time = 5 hr	White gummy liquid	11: 93%	 11
	Water; RT; Time = 8 hr	Pale yellow oil	12: 91%	 12

In case of alkynes, we examined the reactions in diethyl ether since there are less possibilities of the formation of hydrogen bonding between the nitrone and alkynes compared to alkenes. The reaction of nitrone **1** with ethyl propiolate at elevated temperatures having 34% yield of isoxazoline in 12 hr while at room temperature 92% yield of isoxazolines are reported in 12 hr which indicates the decomposition of the nitrone at elevated temperature. This could also be explained due to secondary orbital effect between the carbon of the nitrone (HOMO) and the adjacent atom of the electron withdrawing group of the dipolarophile (LUMO)[26]. The concerted nature of these cycloaddition reactions with nitrone as 1,3 dipole has been generally accepted. The regioselectivity in these reactions was rationalized by using the frontier orbital theory[20,21]. The ethyl propiolate adduct corresponds to this theory. Therefore, the 5-substituted adduct for ethyl propiolate is due to LUMO (nitrone) – HOMO (dipolarophile) interaction.

Like alkenes, excellent diastereofacial selectivity is observed in α-chloro nitrone additions described here with some alkynes. The addition of *N*-phenyl-α-chloronitrone (**1**) to alkyne results in a mixture of diastereoisomer almost in the same ratio 65 : 35 in all cases. These results can be rationalized by an *exo* approach of the nitrone for the major cycloadduct which has the *Z* configuration (transition state **I**)[27] The minor cycloadduct is formed by the *endo* approach of *Z* nitrone (transition state **II**)[28]. However these results can also be explained by an *endo* approach of the nitrone in an *E* configuration (transition state **III**) for the major adduct and the exo approach of this isomer for the minor adduct (transition state **IV**). Most relevant are the

coupling constants ($J_{H3, CHCl}$; $J_{H3, H4}$) of the diastereoisomers. For the major adducts, this coupling constant is almost 9.2 to 9.3 Hz, implying a *cis* relationship between H_3 and CHCl, whereas for minor adducts the coupling constant ($J_{H3, CHCl}$) is 2.5 to 2.58 Hz which implies a *trans* relationship between H_3 and CHCl[15,25,29]. Comparing the ^1H NMR spectrum of isoxazolines, we suggest the major and minor conformers of cycloadducts which are conformationally mobile isoxazoline ring system (Fig **2**) and it is apparent that the former is an average of the contributing forms. All the cycloadducts are stable but in the mass spectral analysis base peaks are obtained due to loss of PhCO for phenyl methyl propiolate, $COOCH_3$ for dimethyl acetylene dicarboxylate and $COOC_2H_5$ for ethyl propiolate respectively. Thus during mass fragmentation the adducts underwent rearrangement to aziridine derivatives (**Type IX** in mass spectra). Since C_4 and C_5 protons are absent in dimethyl acetylene dicarboxylate, phenyl methyl propiolate, and acetylene dicarboxylate cycloadducts therefore the coupling constant values could not be calculated.



$R_1 = Ph$; $R_2 = COOCH_3$ $R_1 = R_2 = COOCH_3$

$R_1 = COOC_2H_5$; $R_2 = H$

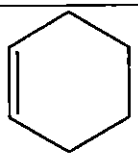
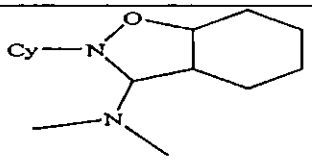
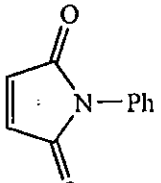
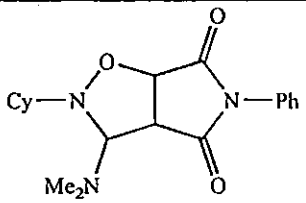
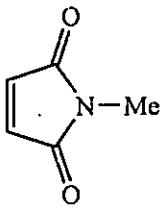
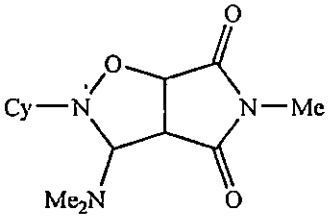
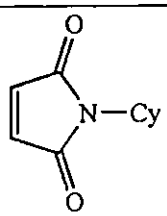
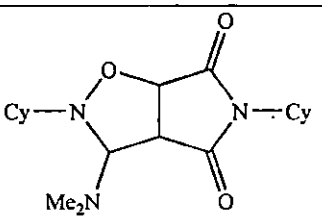
Fig. 2

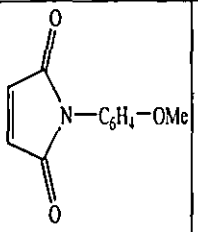
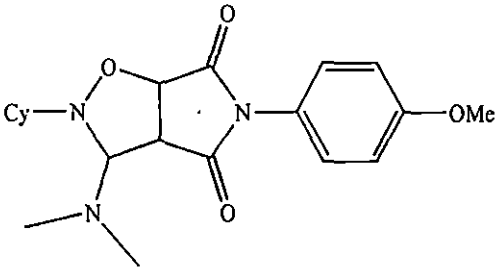
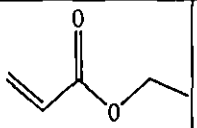
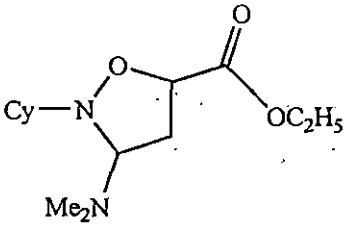
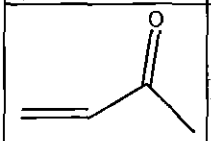
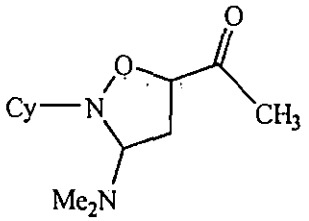
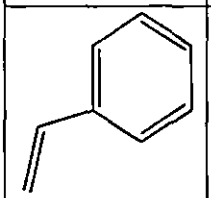
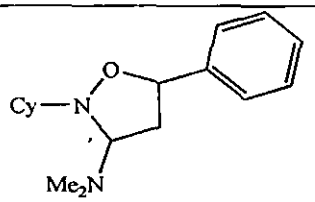
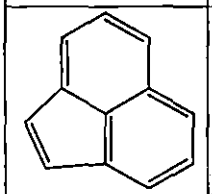
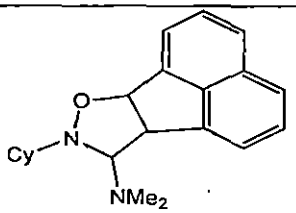
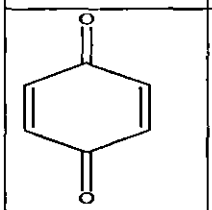
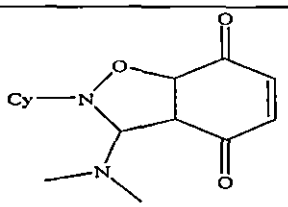
Another important aspect of the cycloaddition reactions are the *exo* addition over *endo* addition. In the majority of the cases *exo* addition were preferred since α-chloro nitrone exist exclusively in the *Z* configuration. Houk et al[21] proposed that preference for the *endo* transition state will only be large in the cycloaddition reactions when

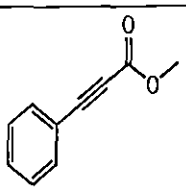
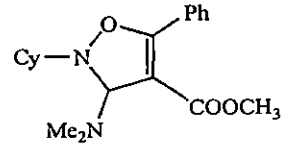
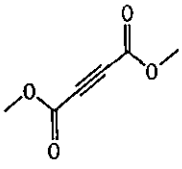
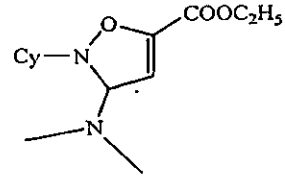
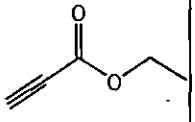
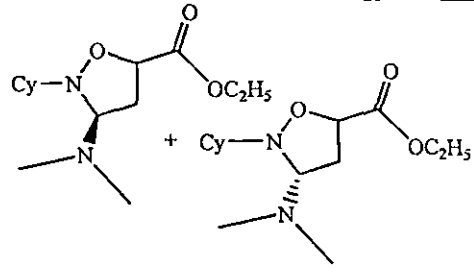
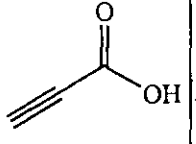
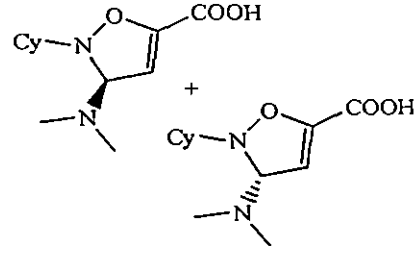
dipole (LUMO) – dipolarophile (HOMO) interactions will be important and are in accordance with P. Deshong et al[25].

Following the methodology of synthesis of α-amino nitrones from DMF-diacetal, *N*-cyclohexyl-α-amino nitrone and *N*-phenyl-α-amino nitrone was synthesized. Both the nitrones were found to be stable enough for carrying out 1:1 cycloaddition reactions with various dipolarophiles in aqueous phase and in conventional solvents (THF) with high yields but in majority of the reactions *in-situ* cycloaddition reactions were preferred to avoid decomposition of nitrones. Unlike cycloaddition reactions of α-chloro nitrone in aqueous phase, mainly single isomer was obtained in all the cycloaddition reactions of α-amino nitrone with good yields (**Table 2a, 2b, 3, 4**) with some exceptions in case of nitrone (**2**).

Table 2a: (Reaction of nitrone 2 with different dipolarophiles in solventless condition)

Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Solventless RT, Time = 10 hr	Reddish gummy liquid	76%	
	Solventless RT, Time = 8 hr	White solid	93%	
	Solventless RT, Time = 10 hr	White solid	82%	
	Solventless RT, Time = 11 hr	Pale yellow solid	90%	

Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Solventless RT, Time = 9 hr	White crystalline solid	89%	
	Solventless RT, Time = 12 hr	White gummy liquid	87%	
	Solventless RT, Time = 14 hr	Yellow oil	90%	
	Solventless RT, Time = 14 hr	Colourless liquid	88%	
	Solventless RT, Time = 48 hr	Bright yellow crystalline solid	95%	
	Solventless RT, Time = 45 hr	Dark brown crystals.	94%	

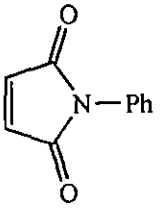
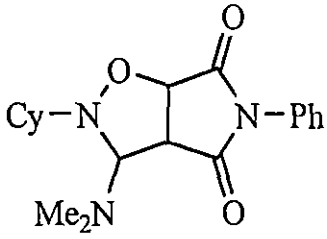
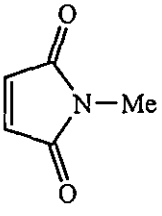
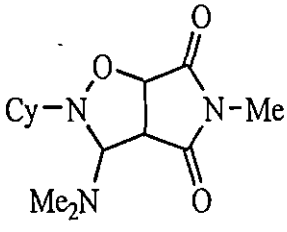
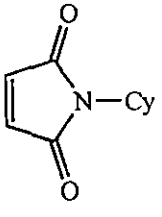
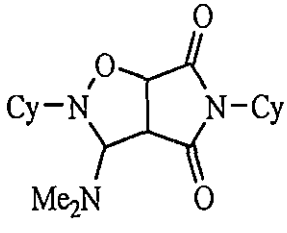
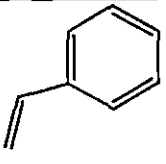
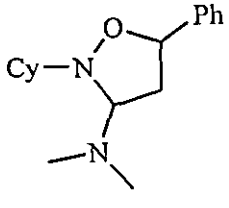
Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Solventless RT, Time = 14 hr	Colourless gummy liquid	96 %	
	Solventless RT, Time = 18 hr	Red liquid	92 %	
	Solventless RT, Time = 6 hr	Red gummy liquids	70 %, 22 %	
	Solventless RT, Time = 11 hr	colourless liquids	68 %, 21 %	

Like most of the nitrones, nitrone **2** also exist exclusively in *Z* configuration and *syn* cycloadducts are formed from *Z* nitrone through *exo* transition state geometry[25]. Another important feature of this cycloaddition reaction is the introduction of chirality by one pot synthesis. Three new chiral centers are developed in the newly formed cycloadducts (isoxazolidines) at C_3, C_4, C_5 positions. The relative configurations of C_3, C_4, C_5 protons of the cycloadducts are *syn*, as evidenced by their coupling constant (J = 6.06 - 6.18 Hz, for C_4-C_5 & J = 6.02 - 6.18 Hz, for C_3-C_4) values[25,28]. Nitrone cycloadditions are believed to be a process with similarity of LUMO and HOMO energies in dipole and dipolarophile. As such both HOMO (dipole) - LUMO (dipolarophile) and LUMO (dipole) - HOMO dipolarophile) interactions are important in determining reactivity and regiochemistry[20,21]. In these cycloaddition, the

C-C & *C-O* bond formation in the transition state may not happen in a synchronous manner. The C-C bond of isoxazolidine ring is more developed in the transition state than *C*-O bond. This process would afford products having *syn* configuration at C_3 & C_4 respectively[30,31].

α-amino nitrones are very reactive due to the presence of filled up anti bonding molecular orbital and hence can act as a powerful nucleophile[18]. Therefore nitrone **2** has a tremendous scope as far as the pericyclic reactions are concerned.

Table 2b: (Reaction of nitrone 2 with dipolarophiles in aqueous medium)

Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Water; RT, Time = 5 hr	White crystals	95 %	
	Water; RT, Time = 5 hr	White crystals	94 %	
	Water; RT, Time = 5 hr	White crystals	95 %	
	Water; RT, Time = 5 hr	Colourless liquid	94 %	

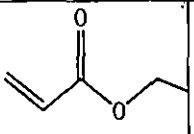
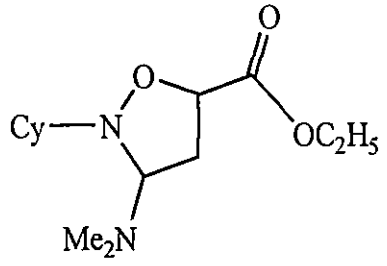
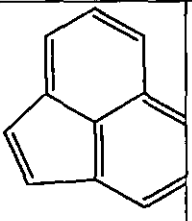
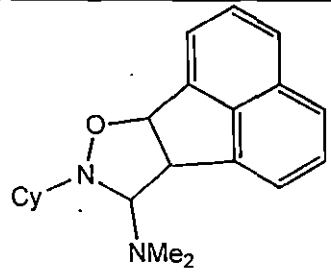
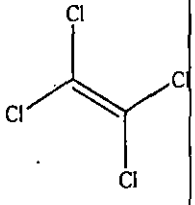
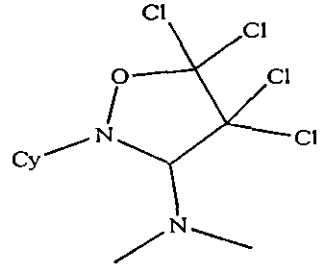
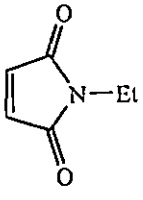
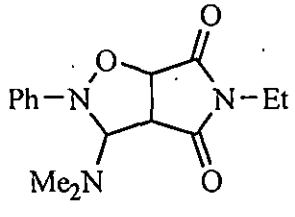
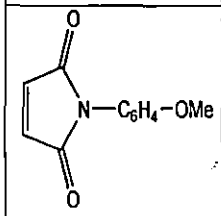
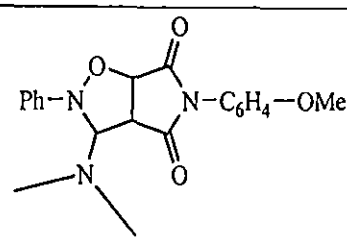
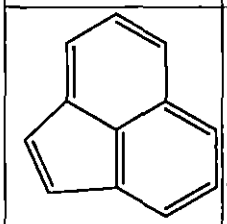
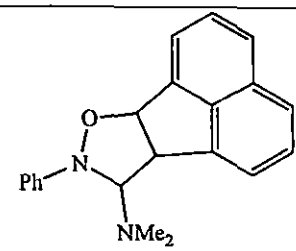
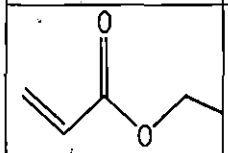
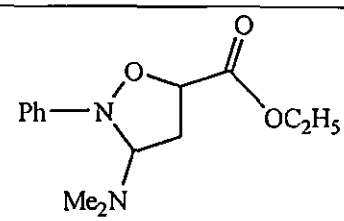
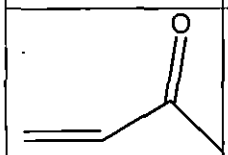
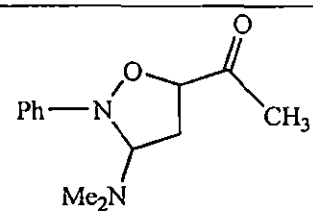
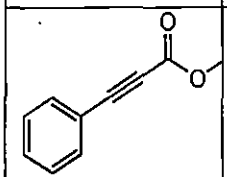
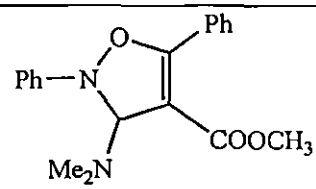
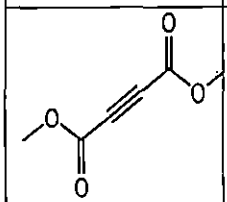
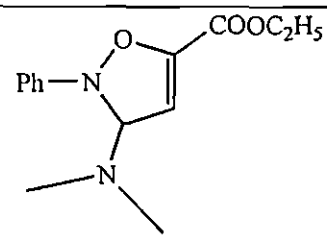
Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Water; RT, Time = 5 hr	Colourless liquid	92 %	
	Water; RT, Time = 5 hr	Bright yellow crystalline solid	94 %	
	Water; RT, Time = 5 hr	Pale yellow oily liquid	96 %	

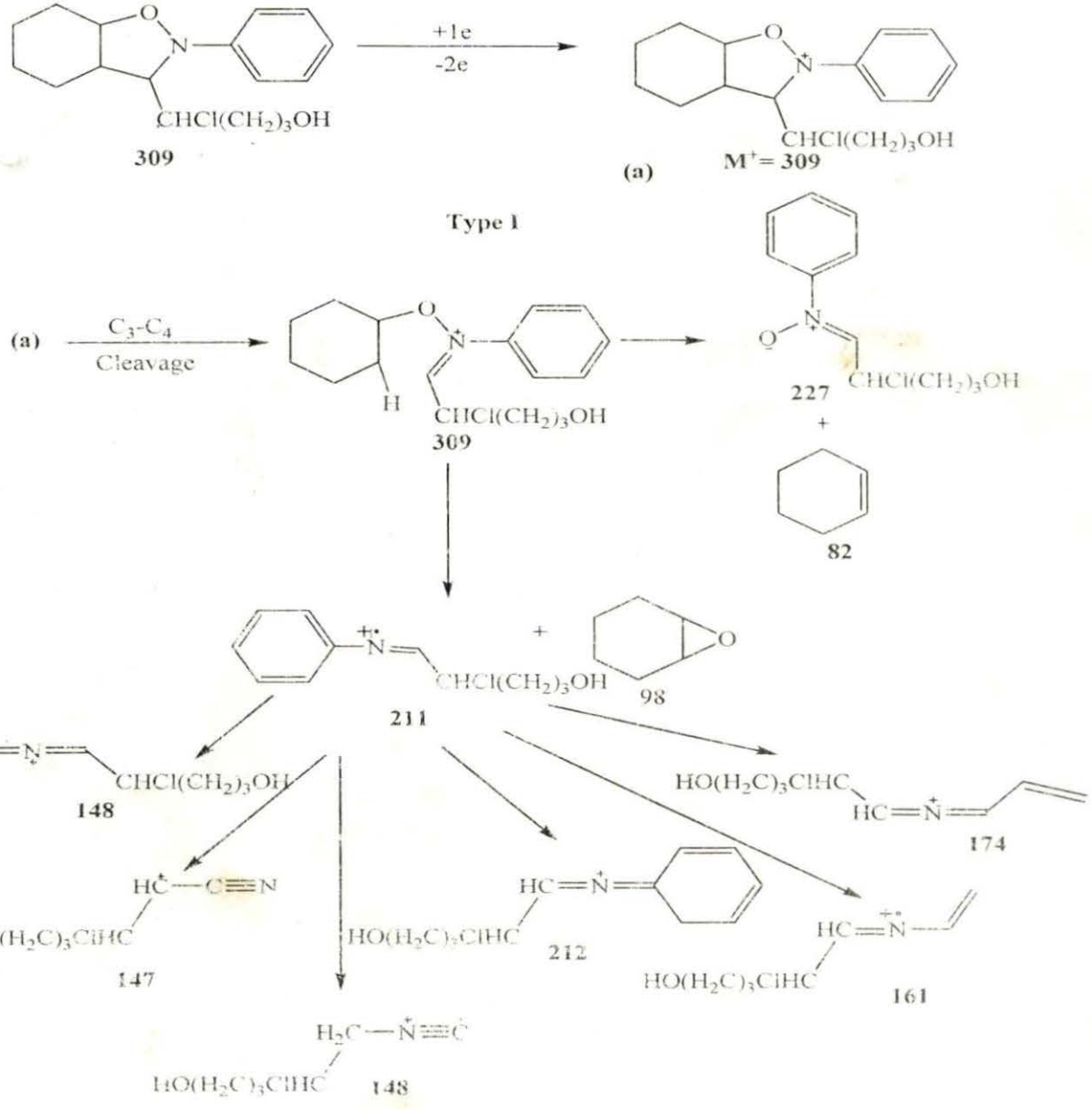
Table 3: (Reaction of nitrone 3 with different dipolarophiles in solvent less condition)

Dipolarophile	Solvent/Reaction condition	Nature of product	Yield	Structure of product/s
	Water, RT, Time = 4 hr	Yellow solid	94 %	

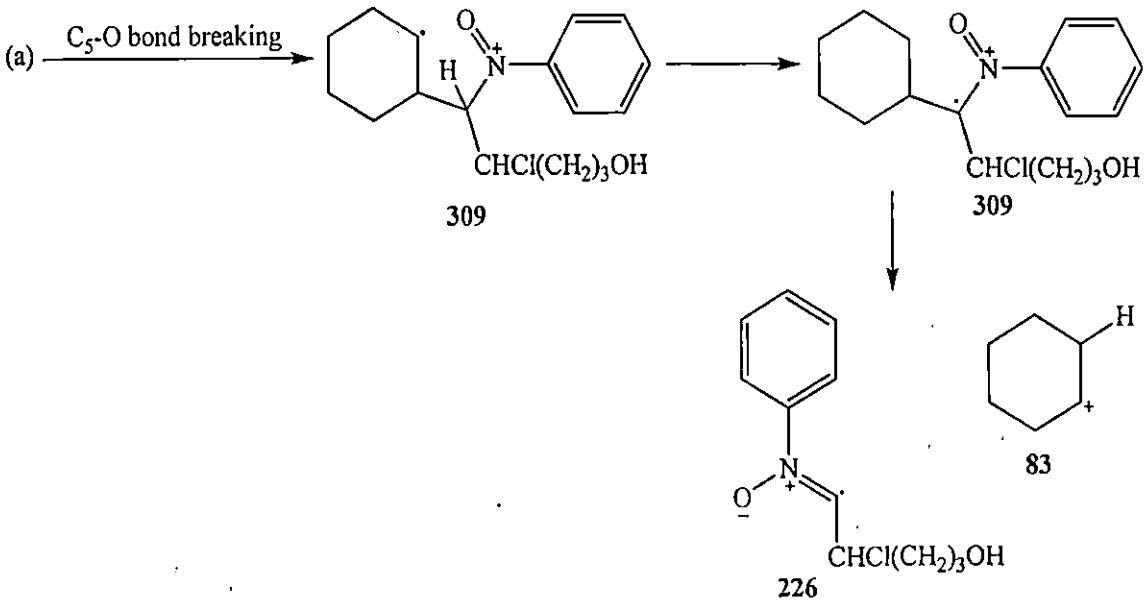
Dipolarophile	Solvent/Reaction condition	Nature of product	Yield	Structure of product/s
	Water, RT, Time = 5 hr	Dark yellow crystals	94 %	
	Water, RT, Time = 5 hr	Yellow crystals	89 %	
	Water, RT, Time = 5 hr	White gummy liquid	93 %	
	Water, RT, Time = 8 hr	Pale yellow oil	91 %	
	Dry ether, RT, Time = 10 hr	white viscous liquid	70 %	
	Dry ether, RT, Time = 13 hr	Red liquid	68 %	

Interpretation of mass spectra

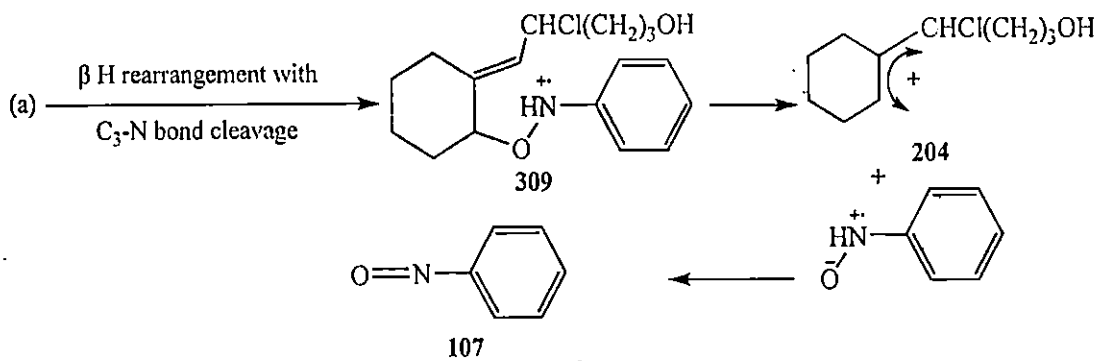
In the case of *N*-phenyl-α-chloronitrone, all the cycloadducts formed possess 2-phenyl-3-chloro butanol-1,2-isoxazolidine moiety in common. Therefore it was very usual to expect same rationalization in the mass fragmentation pattern. On electron impact mass fragmentation of a molecule would generate generally a radical ion and expectedly one of the non bonding electrons of the nitrogen atom of 1,2-isoxazolidine ring would be removed as the nitrogen atom is tertiary in nature. Taking cyclohexene as an example, a general scheme was formulated (**Type I – IX**). The fragmentation pattern of all the cycloadducts were discussed in the light of this fission pattern.



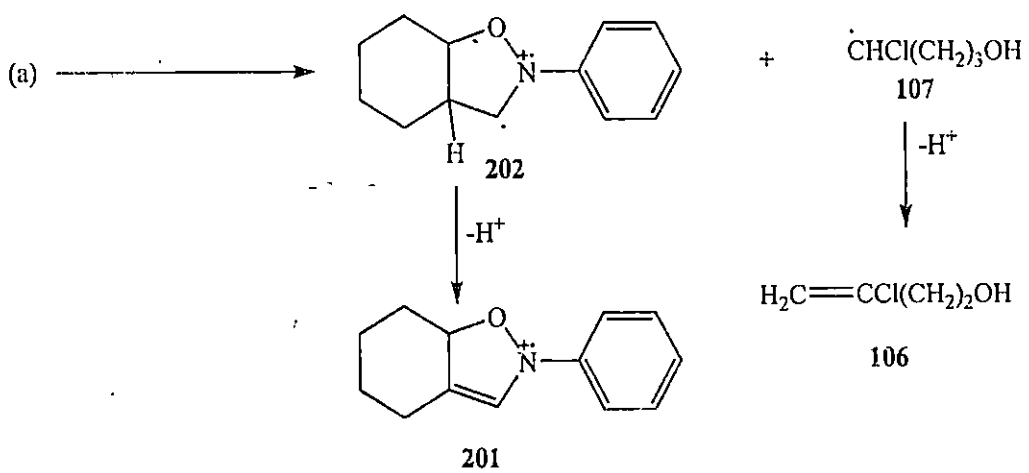
Type II



Type III



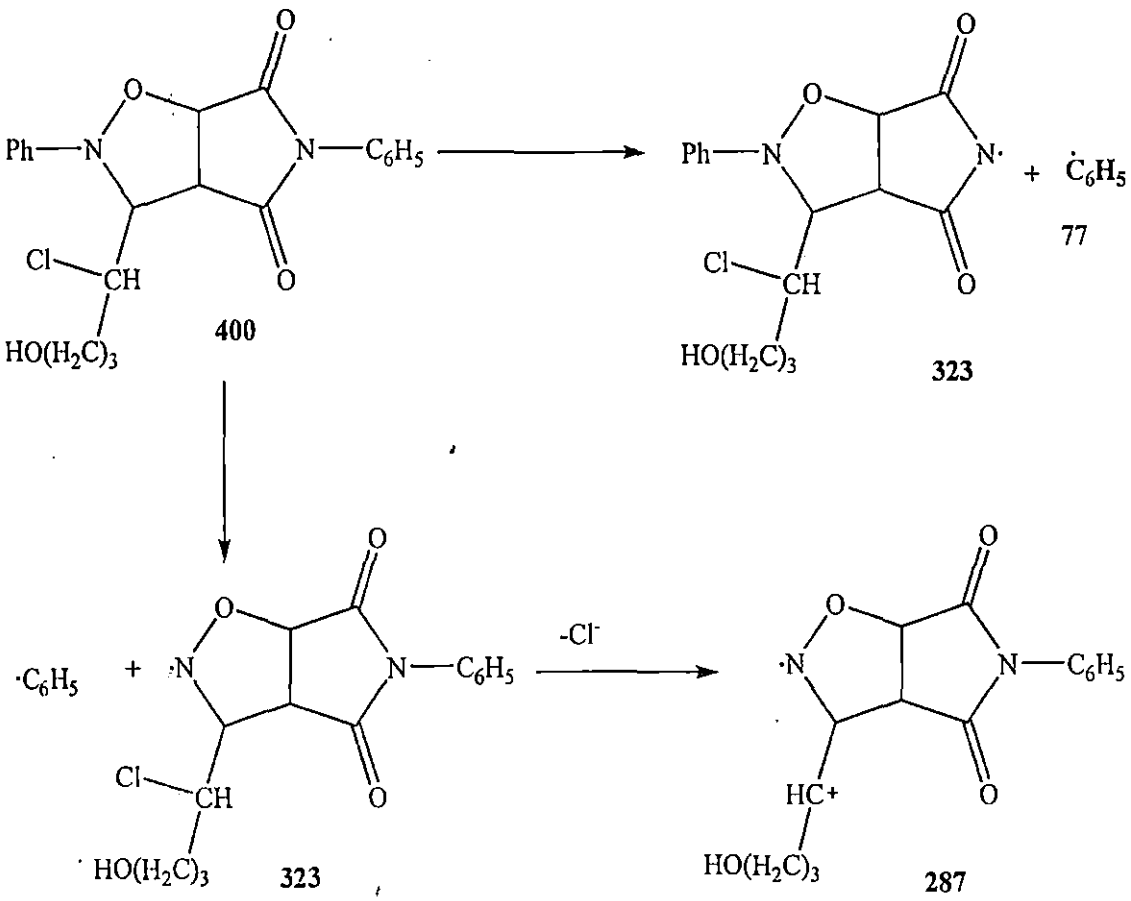
Type IV



In the case of cycloadducts formed from α-chloro nitrone the major fission pattern is molecular ion due to α-cleavage. Among the probable mode for α-cleavage i.e. C_3-C_4 and C_6-C_7, the latter cleavage was not possible because this leads to highly substituted bond cleavage. Another type of bond cleavage is C_5-O bond cleavage which leads to the formation of ion *m/e* = 309, 226. The process of β-*H* rearrangement with *C-N* bond cleavage might occur in two ways leading to *m/e* = 309, 107 and *m/e* = 202, 201. The ions produced in this process may further be fragmented.

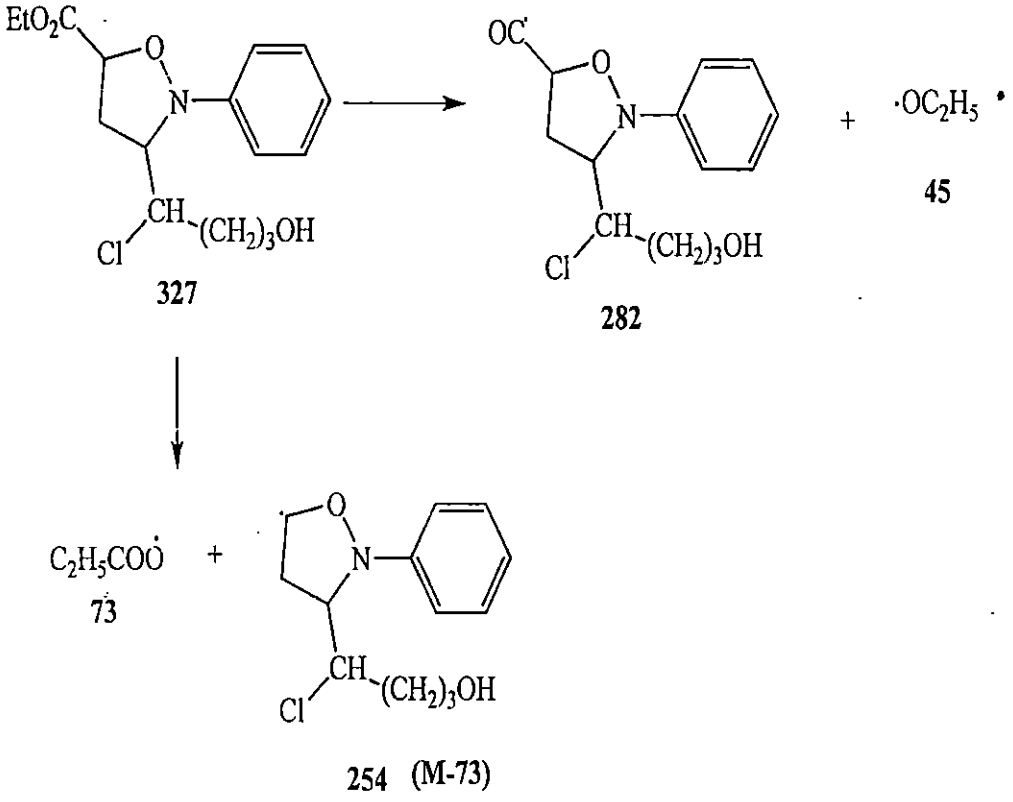
In the mass fragmentation pattern of maleimides (*N*-phenyl, *N*-cyclohexyl, *N*-methyl etc.) both the nitrones in addition to the common expected fragments, other prominent peaks at *m/e* = 77, 83, 15 for phenyl, cyclohexyl, methyl were also obtained.

Type V



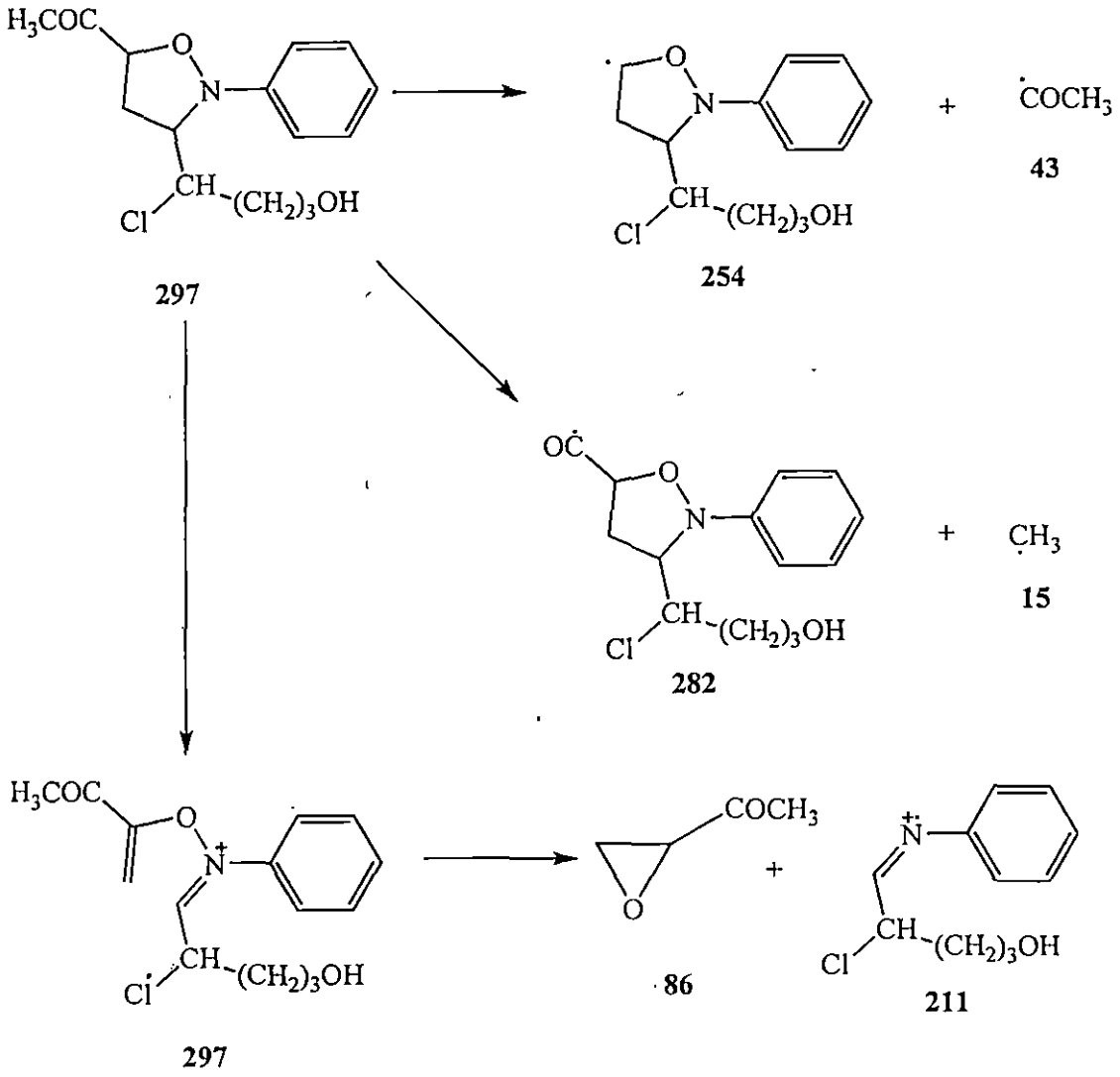
The fragmentation pattern of ethyl acrylate cycloadduct followed the general pattern with some typical peaks *i.e.* CH_3-CH_2-O (45), CH_3-CH_2-COO (73) shown in **Type VI.**

Type VI



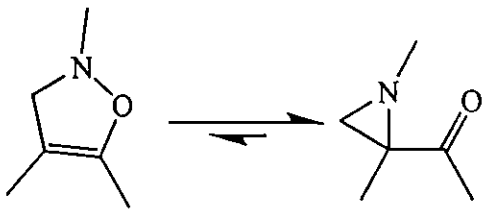
The fragmentation pattern of methyl vinyl ketone shows some special peaks in addition to the general pattern **(Type VII)**

Type VIII

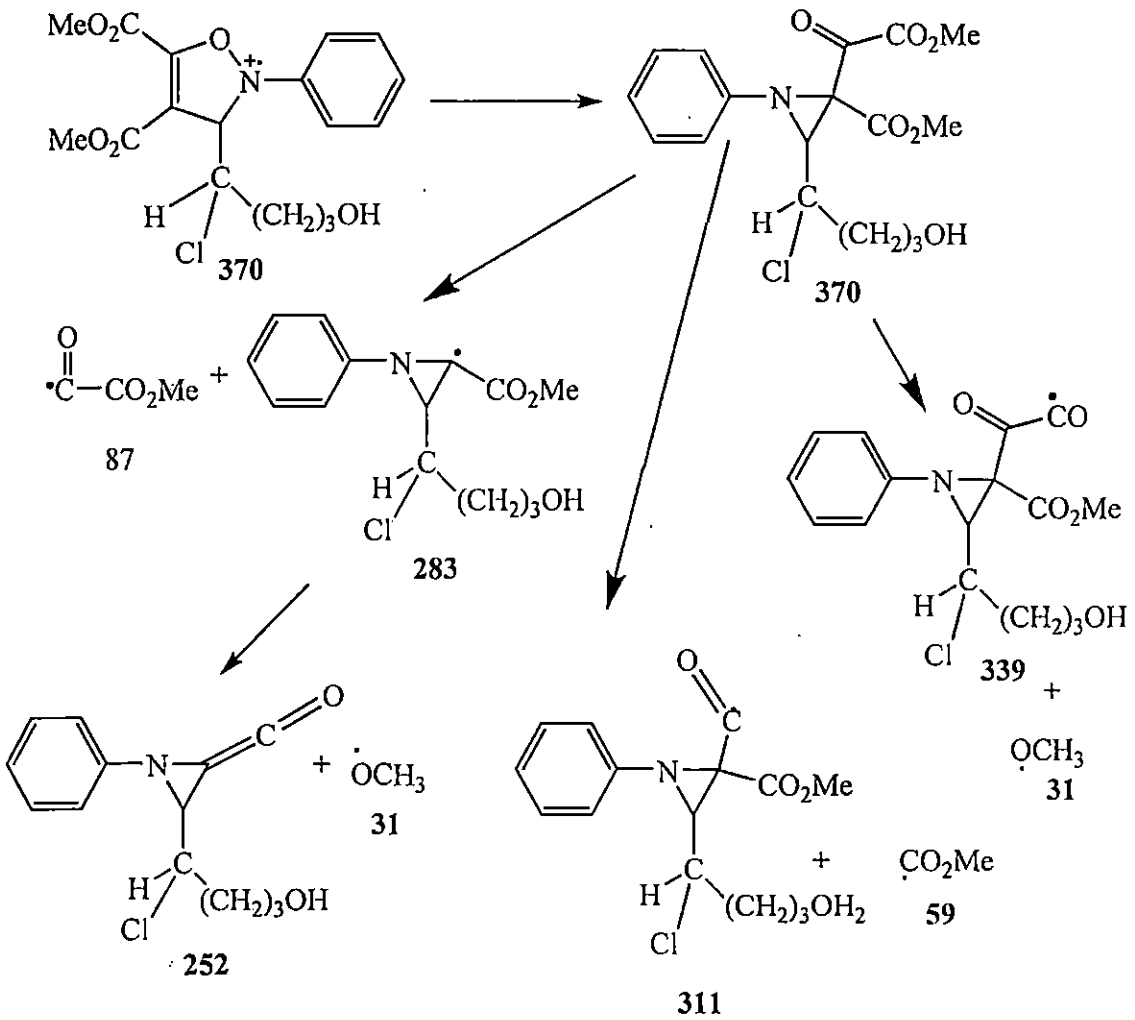


The fragmentation pattern of acetylene adducts are completely different and are explained in **Type IX**.

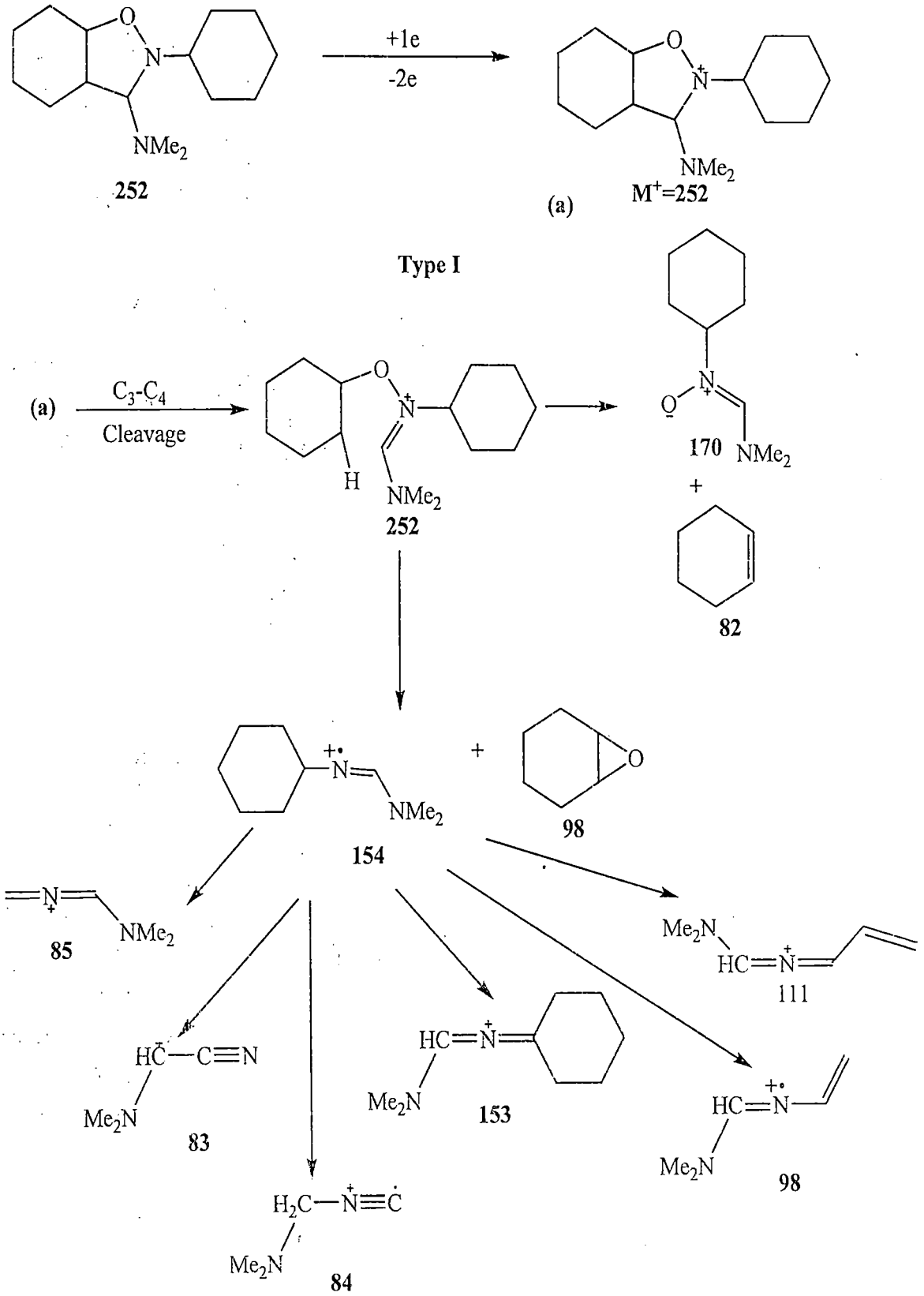
Type IX



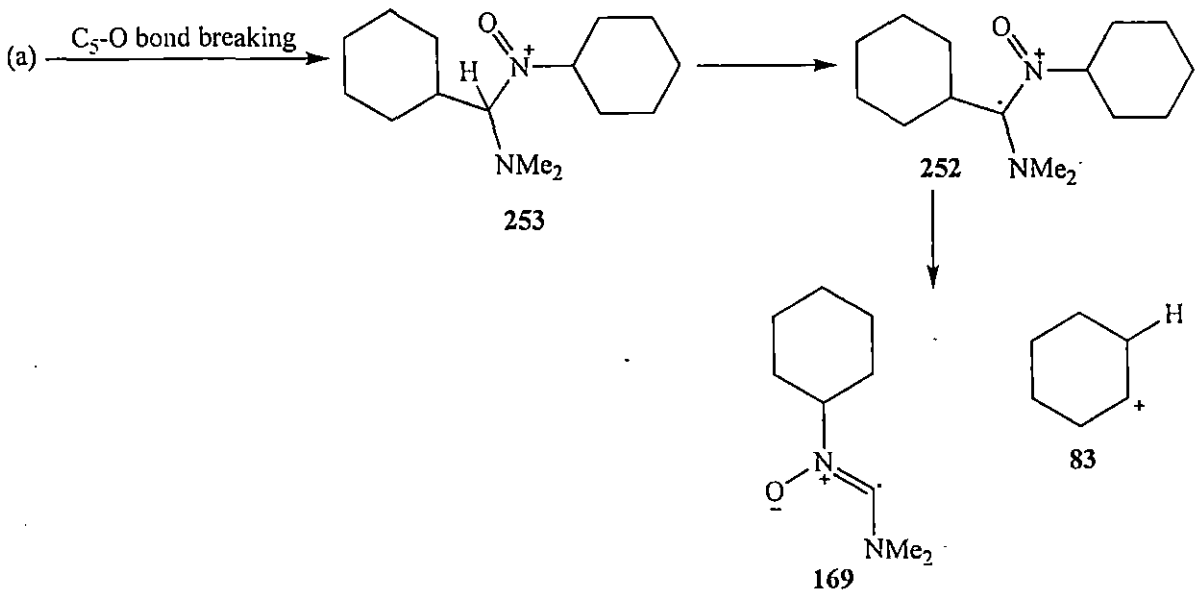
Example with $H_3COOC-C\equiv C-COOCH_3$ adduct



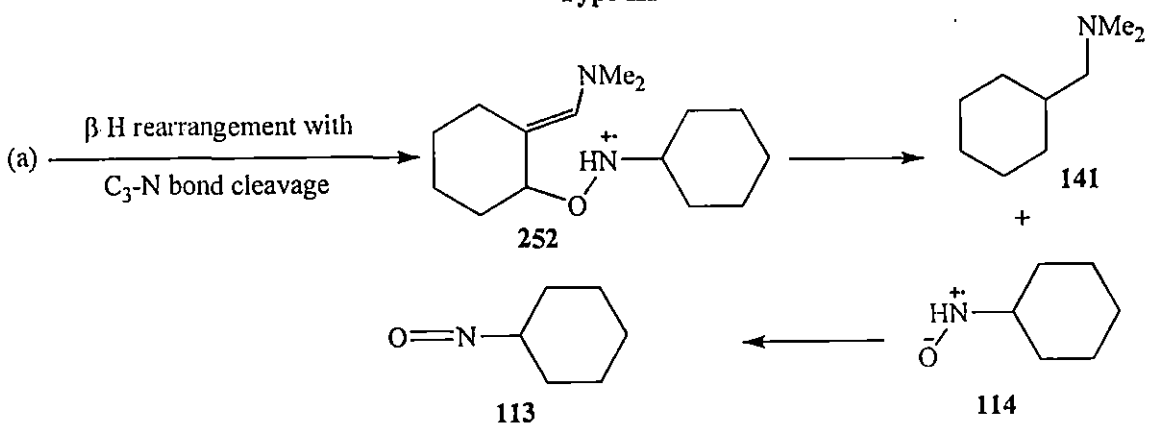
Similarly mass fragmentation pattern of the cycloadducts formed by the reaction of α-amino nitrone with different dipolarophiles can be understood. A general scheme is discussed as below (taking cycloadduct formed from the reaction of *N*-cyclohexyl-α-amino nitrone with cyclohexene as an example).


+1e
-2e
252
(a)
M+=252
Type I
(a)
C3-C4
Cleavage
170
82
98
154
85
83
153
111
84

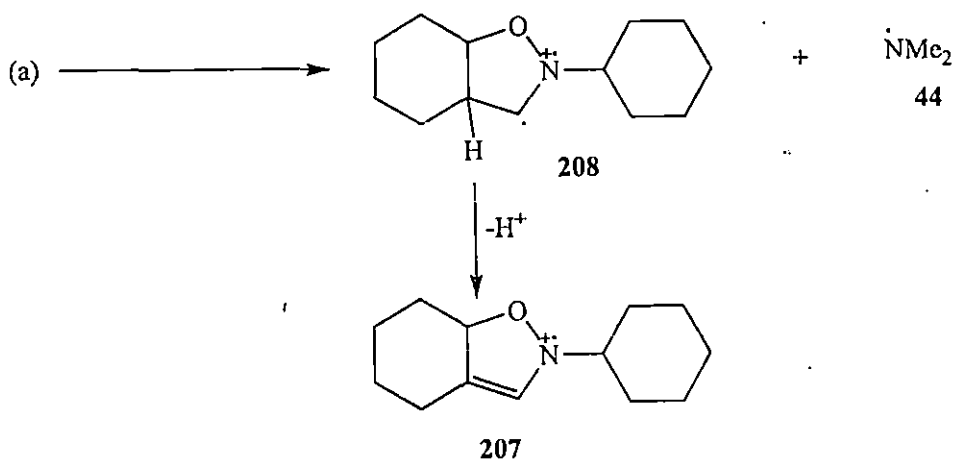
Type II



Type III



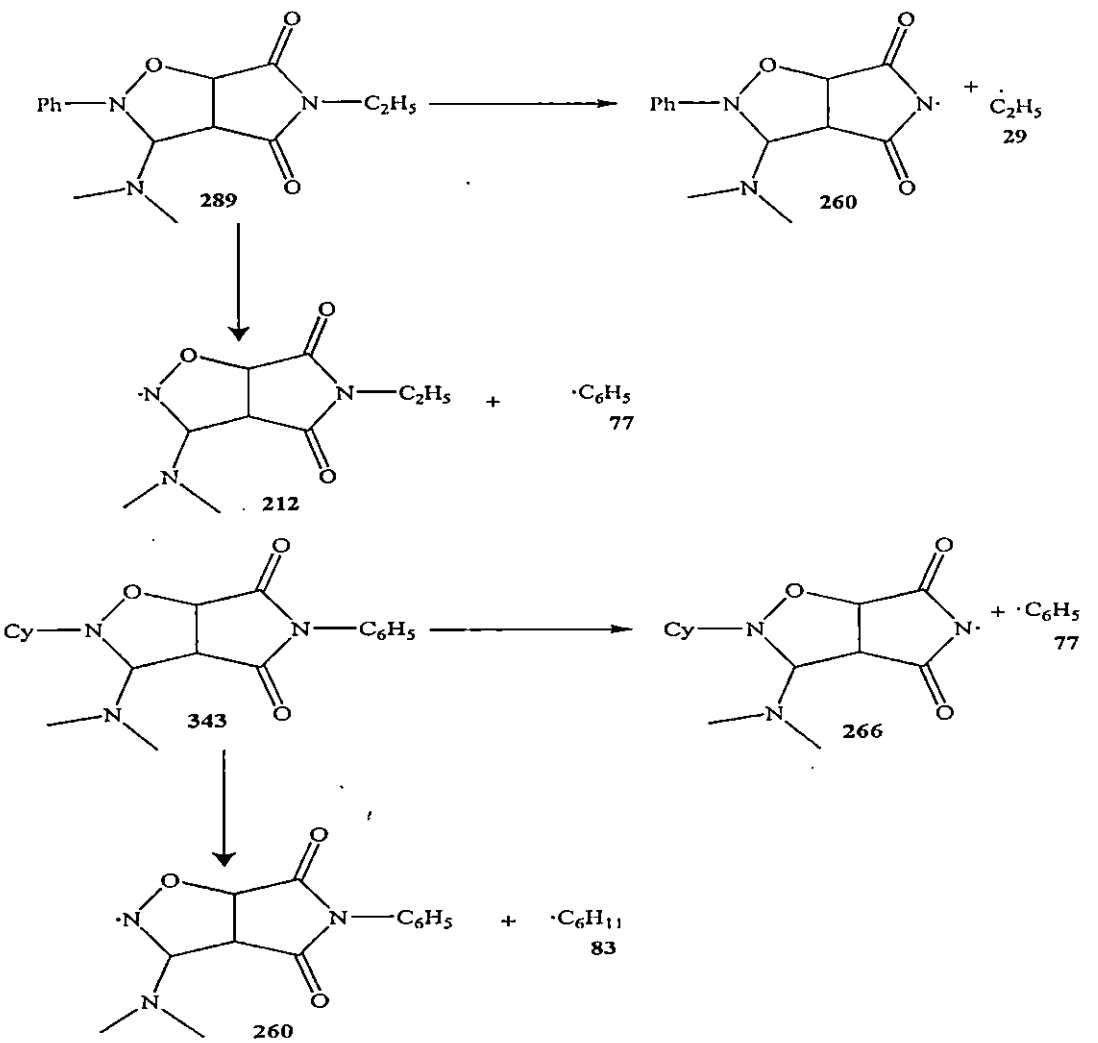
Type IV



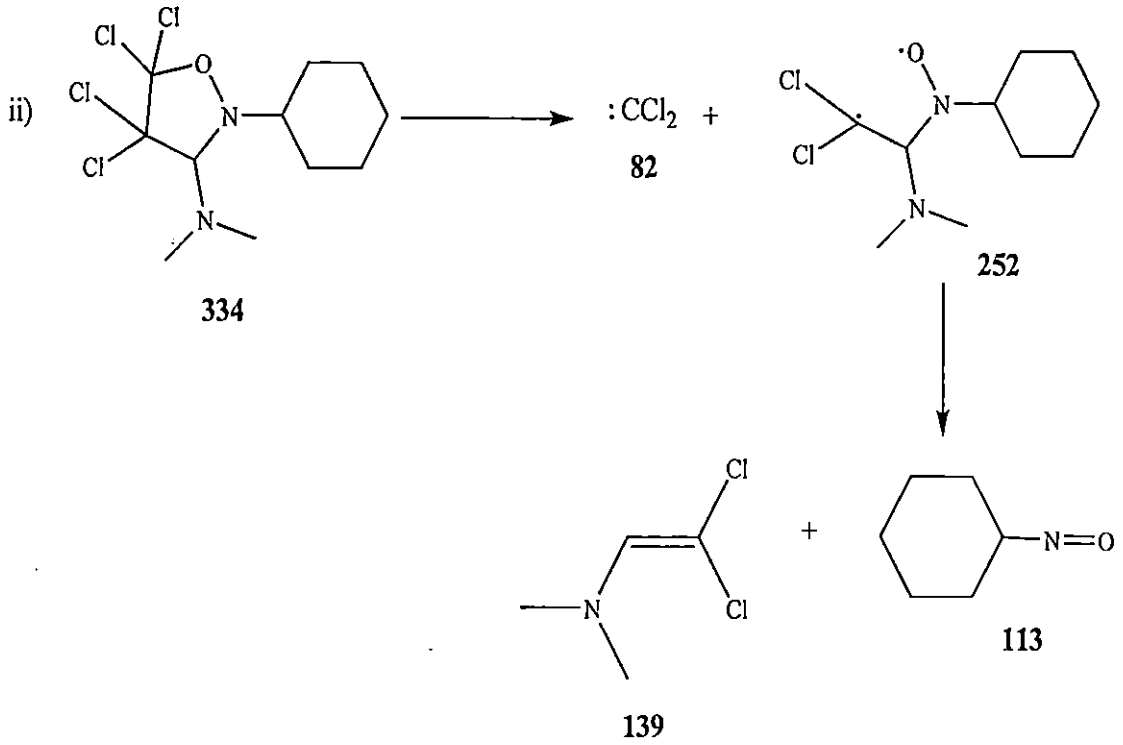
In the case of cycloadducts formed from α-amino nitrone the major fission pattern is molecular ion due to α-cleavage. Among the probable mode for α-cleavage i.e. C_3-C_4 and C_6-C_7, the latter cleavage was not possible because this leads to highly substituted bond cleavage. Another type of bond cleavage is C_5-O bond cleavage which leads to the formation of ion *m/e* = 253, 169. The process of β-*H* rearrangement with *C-N* bond cleavage might occur in two ways leading to *m/e* = 252, 208, 207. The ions produced in this process may further be fragmented.

In the mass fragmentation pattern of maleimide cycloadducts (*N*-phenyl, *N*-cyclohexyl, *N*-ethyl, *N*-methyl etc.) in addition to the common expected fragments, other prominent peaks at *m/e* 77, 83, 29, 15 for phenyl, cyclohexyl, ethyl, methyl were also obtained. For example for *N*-phenyl maleimide cycloadduct the fragmentation pattern may be shown as follows.

Type V

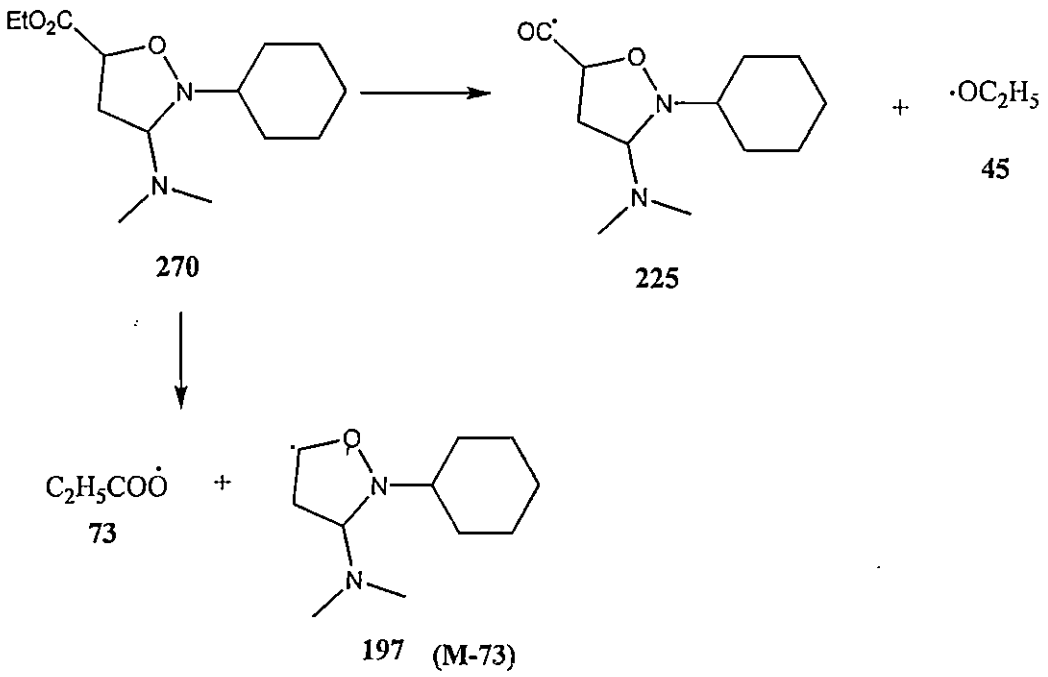


Type VI



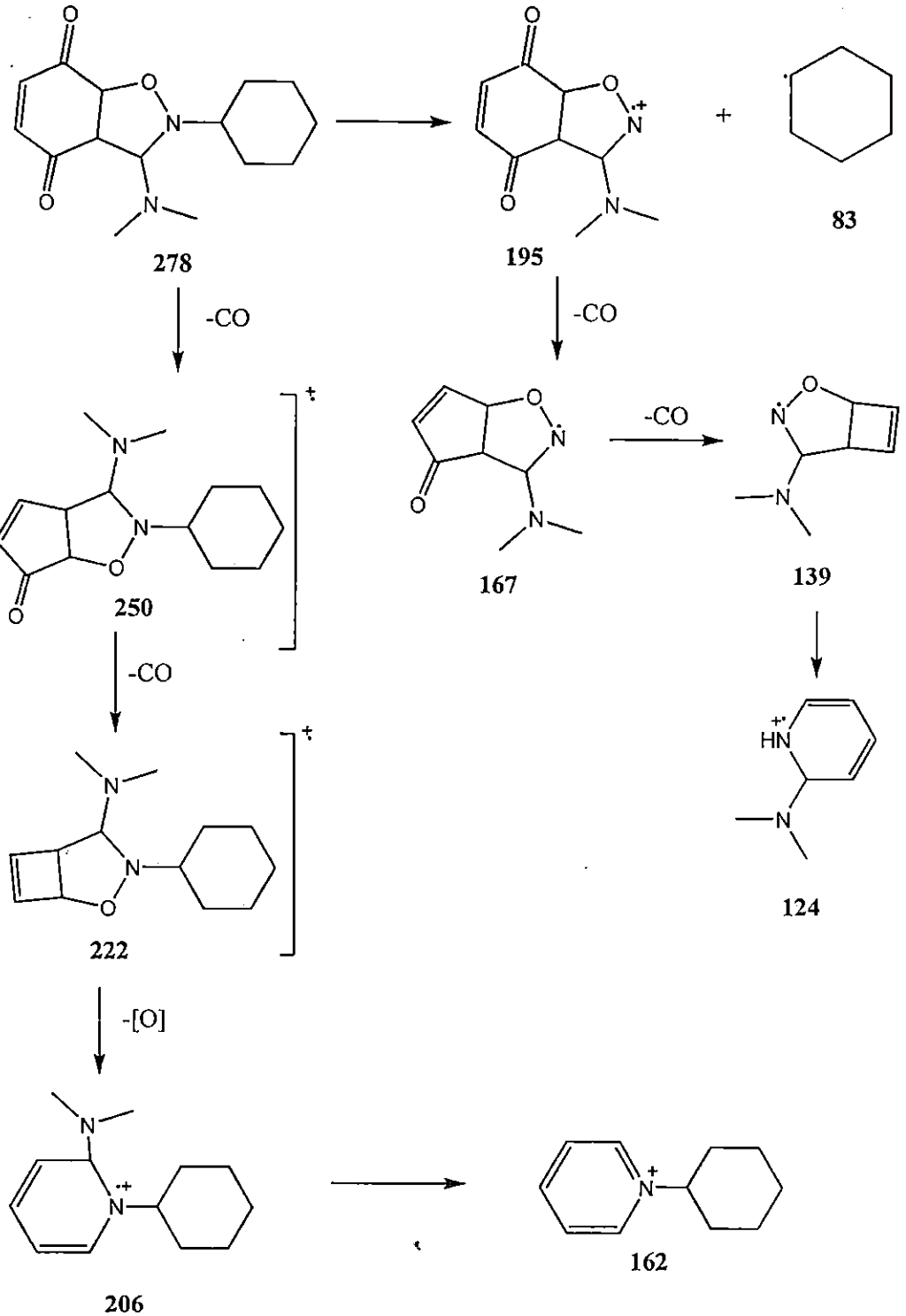
The fragmentation pattern of ethyl acrylate cycloadduct followed the general pattern with some typical peaks *i.e.* CH_3-CH_2-O (45), CH_3-CH_2-COO (73) as shown in **Type VII**.

Type VII

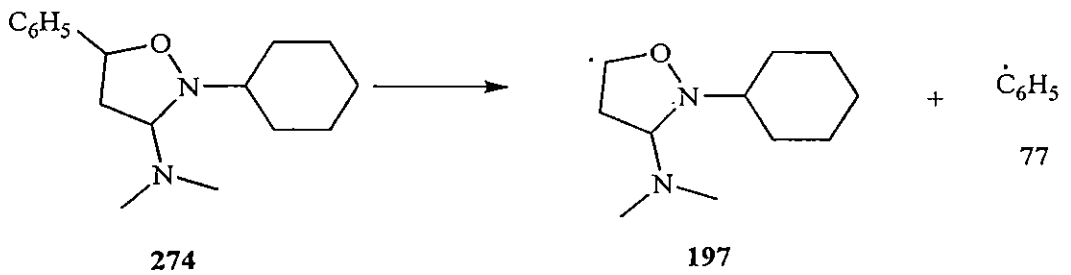


Type VIII

i)

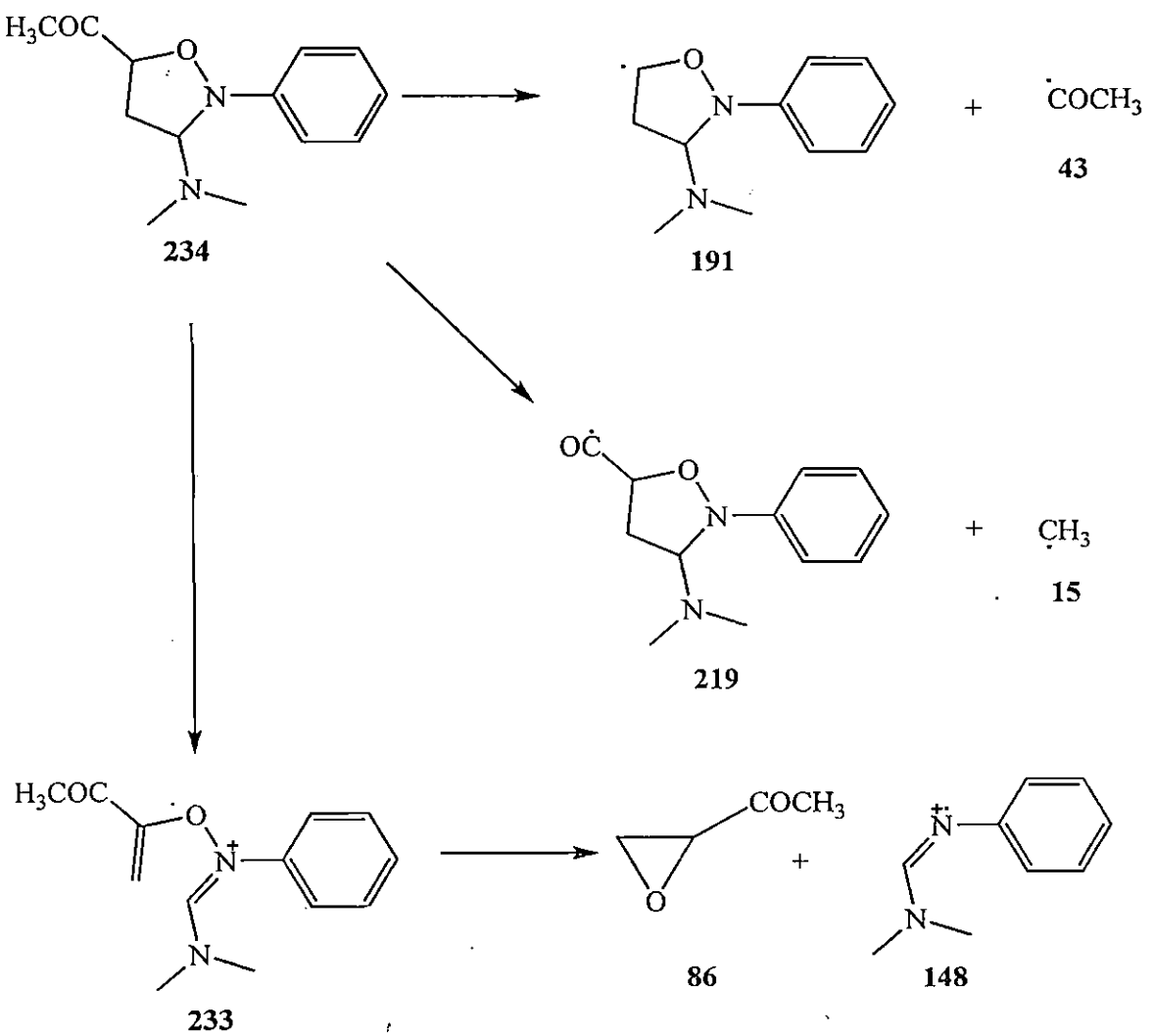


Type IX



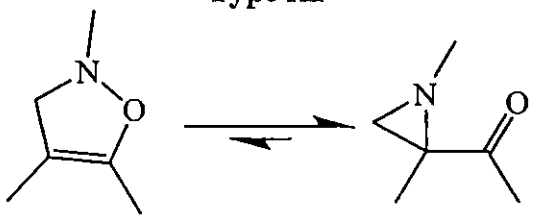
274 **197** **77**

Type X

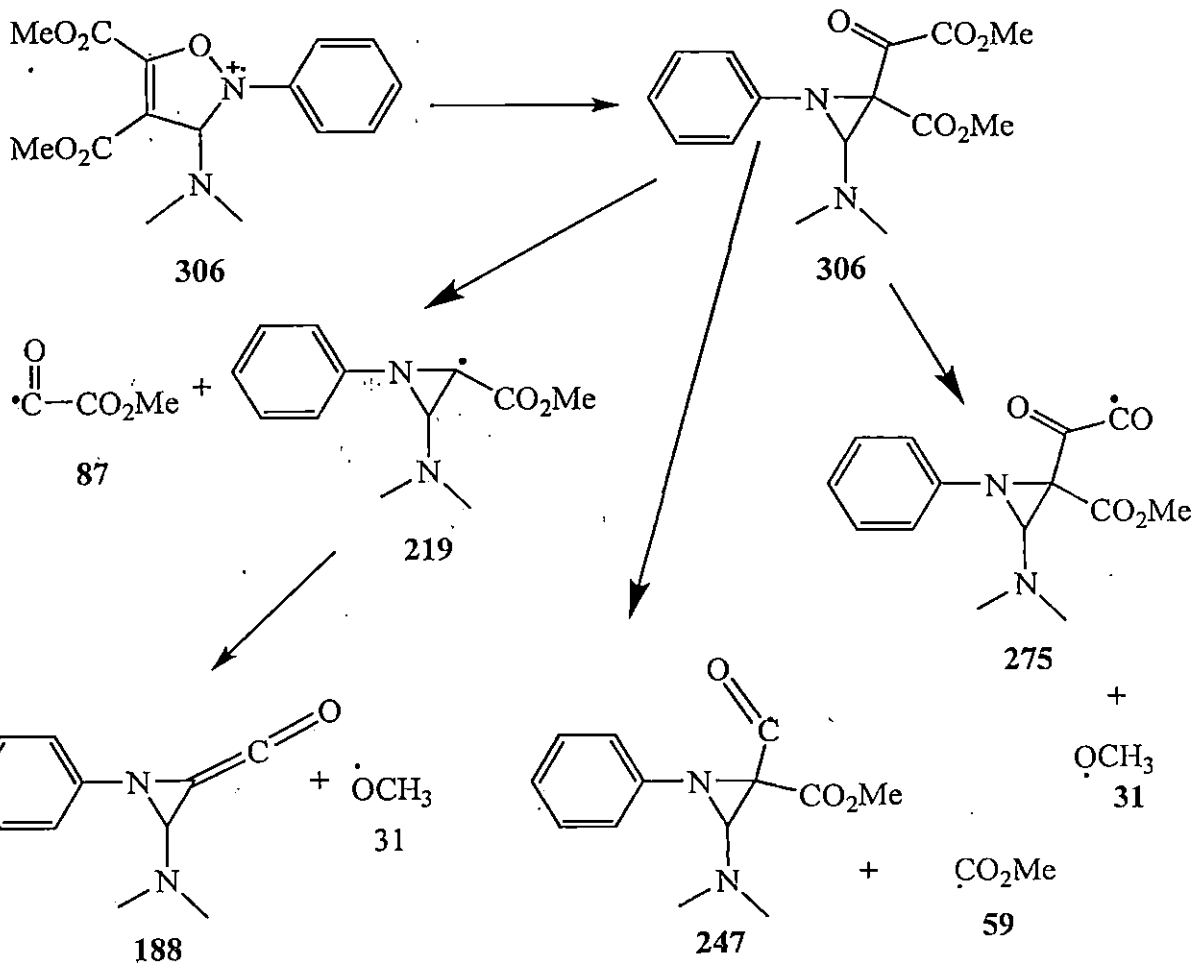


234 **191** **43** **219** **15** **233** **86** **148**

Type XI



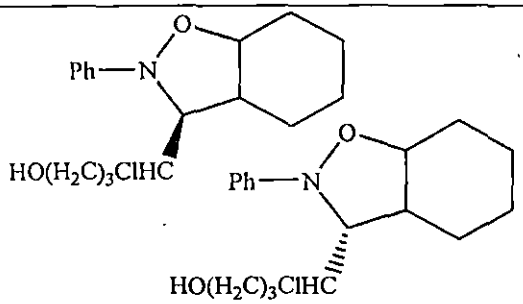
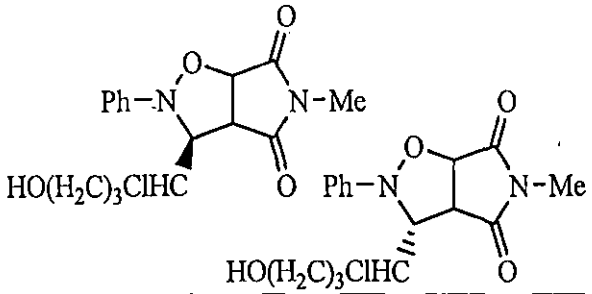
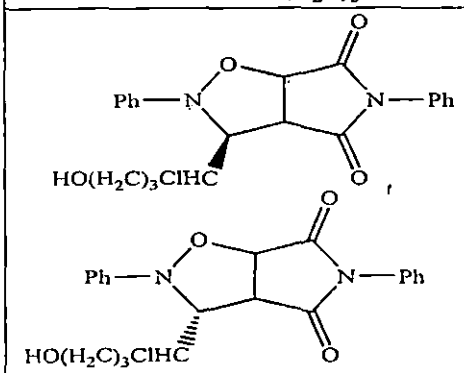
Example with $H_3COOC—C\equiv C—COOCH_3$ adduct



Interpretation of ^{1}H NMR spectra

On interpretation of ^{1}H NMR spectra of the cycloadducts, the chemical shifts and the coupling constants for C_5, C_4, C_3 were considered. The J value i.e. coupling constant determines the stereochemistry at these positions. In most often cases C_5, C_4, C_3 are asymmetric in nature. In case of diastereomers the products were identified considering the multiplicity of the proton signals at 3-*H* and 4-*H* along with coupling constant values. During the course of the study regarding the J values of the cycloadducts the following representation gives us an idea regarding the stereochemistry of the cycloadducts.

Table 4: (^{1}H NMR values in δ ppm) Cycloadducts derived from nitrone **1** in aqueous phase.

Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.37 (8.20) 5.30 (8.20)	4.12 (9.40, 7.10) 4.20 (2.54, 3.16)
	5.22 (6.8) 5.26 (6.0)	3.76 (8.06, 9.20) 3.60 (2.52, 4.26)
	5.42 (8.24) 5.24 (7.20)	3.76 (9.22, 6.08) 3.52 (4.42, 2.08)

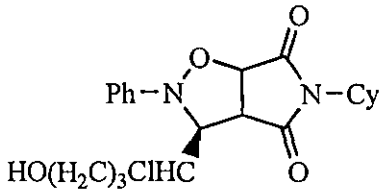
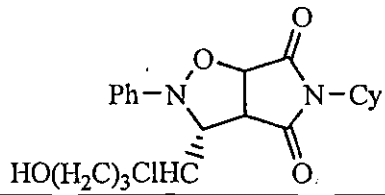
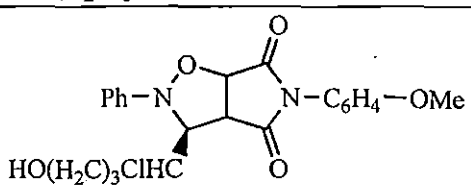
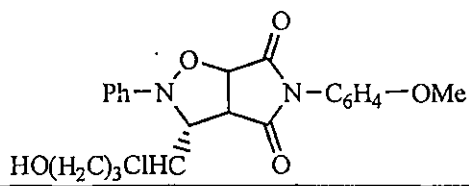
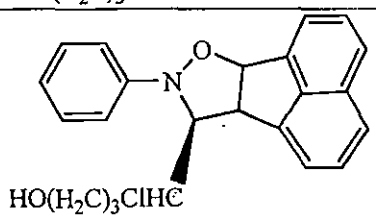
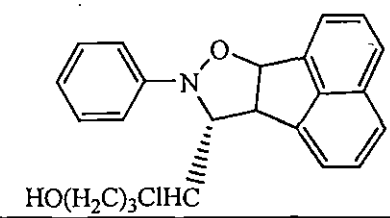
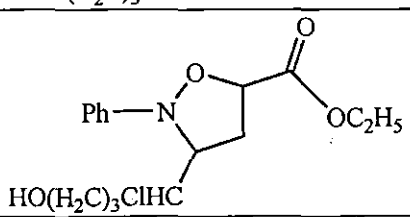
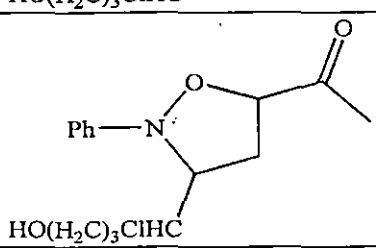
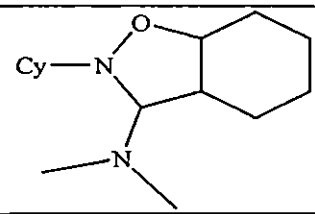
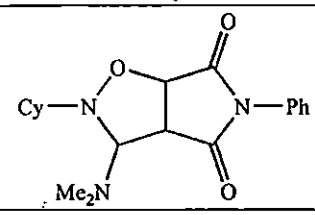
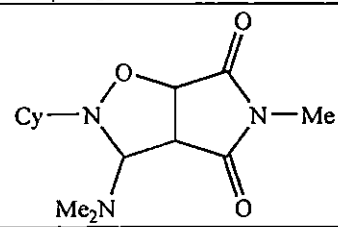
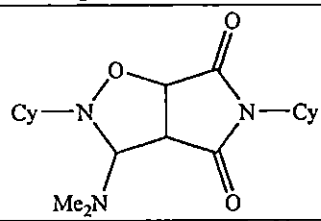
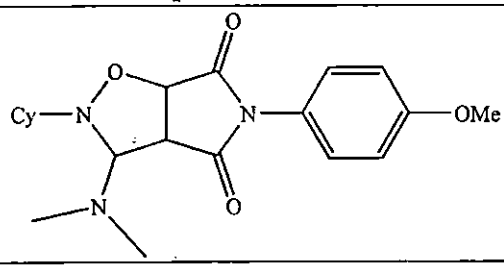
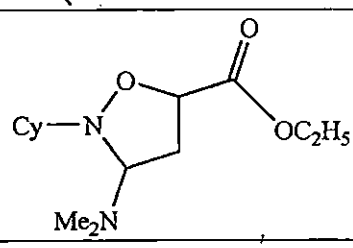
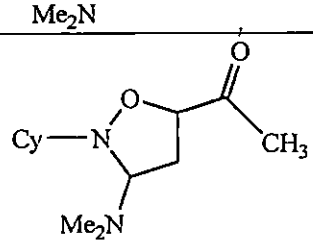
Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.32 (6.12)	4.26 (9.24, 7.06)
	5.26 (7.22)	4.14 (3.22, 2.08)
	5.28 (6.88)	3.86 (9.24, 7.08)
	5.23 (7.40)	3.54 (2.84, 3.25)
	5.26 (6.50)	4.12 (9.40, 7.10)
	5.30 (7.16)	4.28 (4.12, 3.10)
	4.11 (8.2)	3.51 (9.24, 8.18)
	5.32 (7.82)	4.28 (9.48, 7.10)

Table 5: (^{1}H NMR values in δ ppm) Cycloadducts from nitrone **2** and different dipolarophiles in solvent less condition.

Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.37 (8.20)	4.12 (9.40, 7.10)
	4.82 (6.06)	3.90 (6.06, 9.08)
	5.22 (6.0)	3.76 (6.14, 9.00)
	3.31 (6.10)	2.19 (8.00, 9.32)
	5.10 (6.24)	3.72 (9.23, 7.10)
	5.24 (6.80)	3.80 (9.24, 8.60)
	4.90 (7.82)	4.14 (9.48, 7.10)

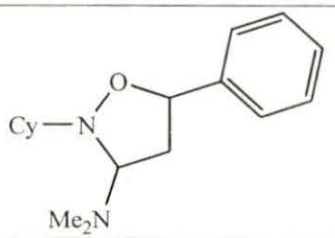
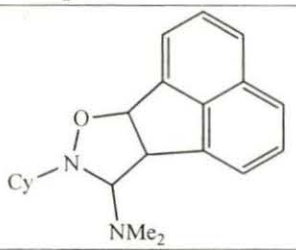
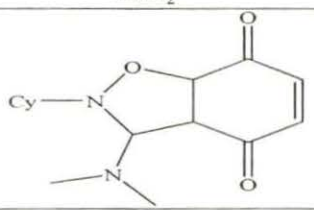
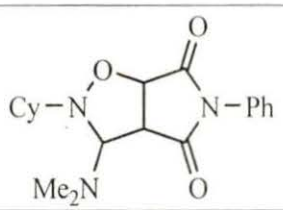
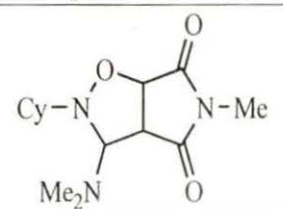
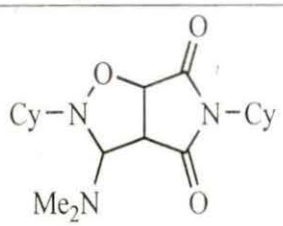
Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.10 (6.16)	3.55 (7.12, 8.10)
	4.37 (6.08)	2.89 (6.08, 6.28)
	5.24 (6.02)	3.34 (6.80, 6.88)

Table 6: (^{1}H NMR values in δ ppm) Cycloadducts from nitrone **2** and different dipolarophiles in aqueous phase

Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	4.90 (6.06)	3.90 (6.06, 6.08)
	5.34 (6.02)	3.60 (6.14, 6.26)
	5.10 (6.10)	4.26 (6.00, 6.06)

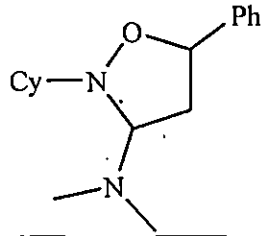
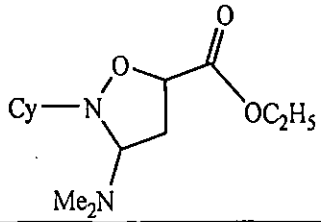
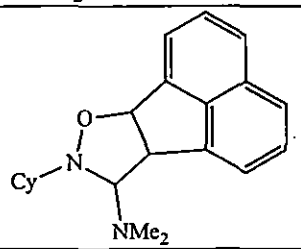
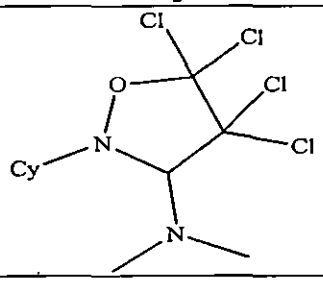
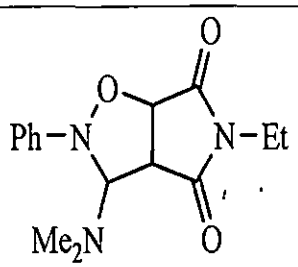
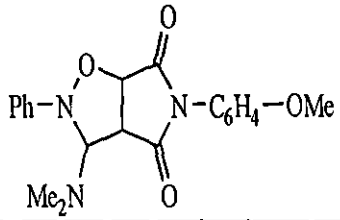
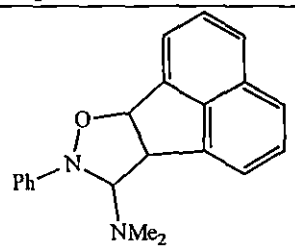
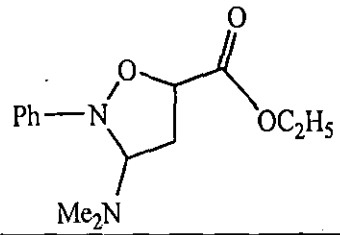
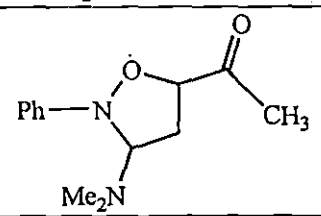
Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.10 (6.08)	3.70 (6.12, 6.10)
	5.20 (6.76)	3.84 (7.65, 6.62)
	5.00 (6.08)	3.56 (6.08, 6.28)
	—	—

Table 7: (^{1}H NMR values in δ ppm) Cycloadducts from nitrone **3** and different dipolarophiles in solvent less condition.

Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.26 (8.20)	3.38 (6.16, 6.32)

Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.40 (8.24)	3.54 (9.24, 6.08)
	4.88 (6.76)	3.52 (8.30, 8.0)
	4.80 (8.2)	3.24 (8.40, 7.08)
	4.86 (7.14)	3.38 (8.80, 7.40)

Nitrone **1, 2 & 3** exists exclusively in *Z* configuration and *syn* cycloadducts are formed from *Z* nitrone through *exo* transition state geometry. The relative configurations of C_3, C_4, C_5 protons of the cycloadducts are *syn*, as evidenced by their coupling constant (J ~ 6.06-8.18Hz, for C_4-C_5 & J ~ 6.02-7.50 Hz, for C_3-C_4) values[25]. It may be concluded from the J values that the dipolarophiles with *cis* configuration about the double bond gave rise to *cis* adducts and therefore the nitrone additions were stereospecifically *syn* in nature. From the coupling constant values for *C*-5 proton of the nitrone cycloadducts we have calculated the dihedral angles between *C*-5 and *C*-4 protons from standard graph (**Fig 4**). From these calculated values and with the assumption that 2-phenyl-1,2-isoxazolidines will prefer the envelope configuration with *N*-phenyl group at equatorial position and $CHCl(CH_2)_3OH$ and NMe_2 group will also be at equatorial position at *C*-3 (**Fig 5**).

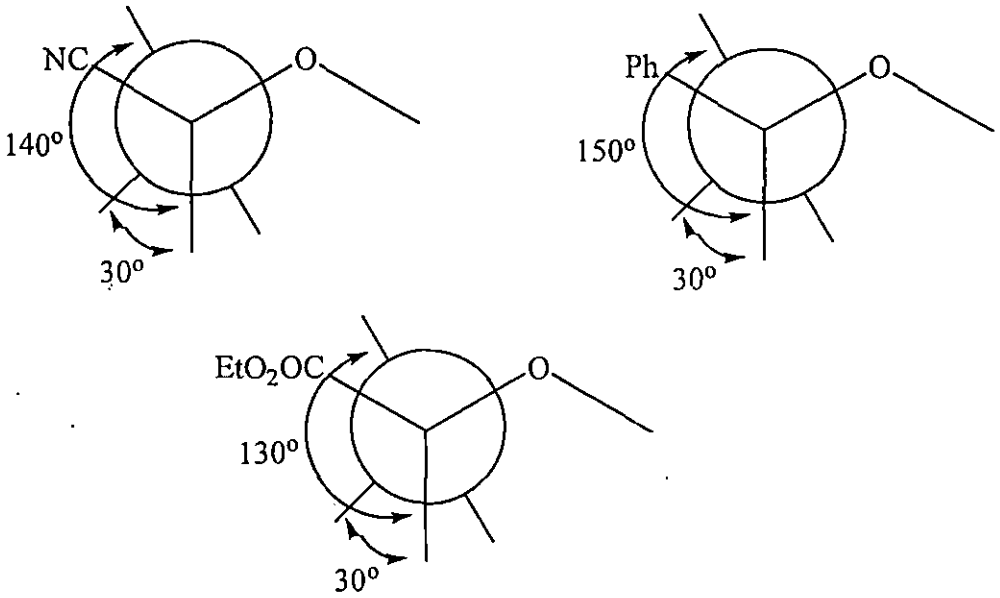
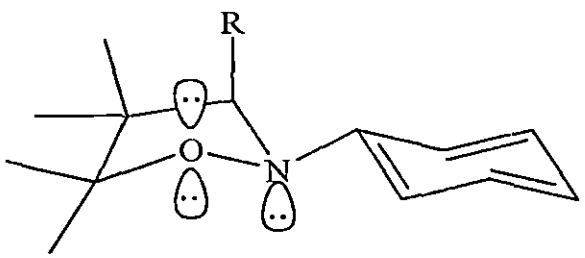


Fig. 4



R = -CHCl$(CH_2)_3$OH, NMe_2

Fig. 5

From these figures it is clear that the substituent at the *C*-3 position tries to have an equatorial position as well as the substituent at the *C*-5 position form the quasi equatorial position of the envelope form. As a result the 1,2-isoxazolidine conformation shifts from envelope to half chair form depending upon the bulkiness of the *C*-5 substituent (**Fig 5**). This indicates that in each of the cycloadducts the *C*-5 and *C*-4 protons couple in the same way and comparison with the corresponding dihedral angles suggests that the angles of the protons are nearly 50°. The normal dihedral angle has been found to be 70-60° as found from dihedral angle reported for the cycloadducts. The deviation is due to the strain of the cyclohexene ring.

In most of the cases, 5-substituted isoxazolidines were formed and has been confirmed by considering the proton NMR spectrum of the cycloadducts. It has been found that double doublet signal for *C*-4 proton and doublet of triplet signal for *C*-3 proton (in case of α-chloro nitrones only), triplet signal for C_3 (in case of α-amino

nitrones) were obtained due to further coupling from vicinal protons and hence confirms in favour of 5-substituted adducts (e,g: ethyl acrylate, methyl vinyl ketone, styrene etc). In case of the triple bonded dipolarophiles (acetylene compounds) the explanation is quite simpler since C_4 protons and C_5 protons are absent hence C_3 protons plays an important role. The stereochemistry of these cycloadducts is rationalized by considering the proton signals at C_3 and CHCl protons while it becomes irrelevant in case of α-amino nitrones.

Three new chiral centers are developed in the newly formed cycloadducts (isoxazolidines) at C_3, C_4, C_5 positions. The relative configurations of C_3, C_4, C_5 protons of the cycloadducts are *syn*, as evidenced by their coupling constant ($J \sim 6.06$ -8.18Hz, for C_4-C_5 & $J \sim 6.02$ - 7.50 Hz, for C_3-C_4) values[25,28]. Nitrone cycloadditions are believed to be a process with similarity of LUMO and HOMO energies in dipole and dipolarophile. As such both HOMO (dipole) - LUMO (dipolarophile) and LUMO (dipole) - HOMO dipolarophile) interactions are important in determining reactivity and regiochemistry[20,21]. In these cycloaddition, the *C-C* & *C-O* bond formation in the transition state may not happen in a synchronous manner. The *C-C* bond of isoxazolidine ring is more developed in the transition state than *C-O* bond. This process would afford products having *syn* configuration at C_3 & C_4 respectively[29].

In addition to the above explanations, all expected signals are obtained and the values are at par with the reported values. For example, the δ 7.60-6.80, δ 3.20-2.90, δ 1.20-1.00 are obtained for phenyl, ethyl, methyl groups respectively. The chlorobutanol group proton signals are generally merged with cyclohexyl protons. The hydroxyl and dimethylamino groups have shown broad signals around δ 5.00 – 4.00 & 2.75 – 2.20 region. All significant peaks in the case of ethyl acrylate cycloadduct was obtained.

In the present work, *cis* and *trans* conformation as well as the stereochemistry of the isolated cycloadducts are obtained based upon P. Deshong and P. Grunanger's work on the *J* value calculations. In the present text, following abbreviations are used for identifying NMR signal.

s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet. dt = doublet of triplet, q = quartet, m = multiplet, br = broad.

Interpretation of ^{13}C NMR Spectra

On exhaustive study regarding ^{13}C NMR spectra of reported cycloadducts, we have seen in almost all the cycloadducts the expected signals for *C*-5, *C*-4, *C*-3, phenyl, cyclohexyl, carbonyl carbons are obtained. Remarkably the deviated values for the carbonyl groups are obtained when the carbonyl group is methyl ester, ethyl ester. The values obtained for the phenyl carbons in most often cases are four ranging between δ 138-120 ppm. These four values are due to the fact that 2,6 and 3,5 are identical positions and give rise to only one signal. When the carbonyl carbon is methyl or ethyl ester absorptions at δ 178-180 ppm are obtained while δ 168-170 ppm are obtained for normal C=O bond absorption. *C*-5, *C*-4, *C*-3 carbons absorb in the range of δ 85-88, δ 50-60 and δ 70-75 ppm with some deviations for some certain cycloadducts. The absorption due to –CHCl carbon is usually in the range of δ 58-65 ppm while cyclohexyl and other methylene carbons absorb in the range of δ 16-28 ppm. The absorption of methyl carbons of NMe_2 group has been found to be around δ 46.00 – 37.00. Although ^{13}C NMR spectra cannot confirm the stereochemistry of the cycloadducts but plays an important role in identifying the particular functional groups of the cycloadducts.

Interpretation of other spectra

In addition to ^{1}H NMR and ^{13}C NMR, IR, MS, HRMS and elemental analysis were most important tools for the confirmation of the cycloadducts reported in this dissertation. In the IR spectrum broad absorption peak at 3600-3350 cm^{-1} represents the absorption of hydroxyl group while 3100-2950 cm^{-1} represents the NMe_2 group. Sharp singlet absorption around 750-780 cm^{-1} is due to phenyl *C-H* stretching absorption. The carbonyl absorption were obtained around 1680-1720 cm^{-1} depending upon the carbon functionality while *C-N-H* stretching was generally obtained around 1240-1320 cm^{-1}. In case of isoxazoline cycloadducts, which are comparatively stable than isoxazolidine cycloadducts, study of mass spectrum reveals that prominent molecular ion peak and the base peak are obtained as expected. The molecular ion clearly indicates the stability of isoxazoline cycloadducts. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate and $-COOCH_3$ for dimethyl acetylene dicarboxylate cycloadducts for both α-chloro & α-amino nitrones. Studies of HRMS spectra shows almost exact masses in the majority of the compounds and

also indicate the purity of the isolated compounds. In some of the cases elemental analysis was carried out and the calculated values and the analyzed values were at par and also confirms in favour of isolated cycloadducts.

One of the remarkable feature in the mass and HRMS spectrum was the presence of significant M^++2 ion peaks. This is due to the fact that isotopic abundance of Cl^{37} atoms is higher compared to Cl^{35} atoms in these cycloadducts. In addition, different mass fragmentation peaks are also obtained for distereoisomers of a particular cycloadduct which also confirms in favour of the fact that they were fragmented in a different fashion during mass fragmentation.

In the case of ethyl acrylate cycloadduct, it has been found that 5- substituted adduct was converted into 4- substituted adduct when kept at room temperature (in case of α-chloro nitrones) for a longer period (nearly one month) and this phenomenon has been confirmed on the basis of ^{1}H NMR and reminds us the brilliant work of Sk. Ali and his group[31]. It has been found from HRMS spectra that the purity of 4-substituted adduct was very low compared to that of 5-substituted adduct. This indicates the fact that prolonged keeping might lead to decomposition of the cycloadduct.

Finally, we would like to report for the first time aldehyde and ketone synthesis using the tremendous synthetic potentiality of *N*-phenyl-α-chloro nitrone as a stable, potential oxidizing reagent. The side products of the aldehyde & ketone synthesis *viz.* α-*N*-methyl/phenyl furan derivatives have been used as dipolarophile in the regioselective synthesis of 5-spiro isoxazolidines with an excellent yield[3]. It could be due to the fact that nitrone (LUMO) – dipolarophile (HOMO) interactions are strong enough to dominate the reaction and leads to the formation of solely 5-spiro isoxazolidines[21] via an *exo* approach of nitrone (in *Z* configuration) to the furan derivatives (**Fig 7 & 8**; transition state **I** & **II**). The relative configurations of H_3 & H_4 protons in the *spiro* adduct are in favour of *exo* transition state geometry. The H_3 & H_4 protons are *syn* in these cycloadducts and their coupling constants ($J_{H3,H4}$ = 6 – 8.4 Hzs) are also indicative of this stereochemical relationship[25]. In regioselective *spiro* cycloadducts, the CHCl proton resonates upfield around δ_H 3.48 ppm. The 3-*H* and CHCl protons are also *syn* as evidenced from their coupling constant values ($J_{H3,CHCl}$ ~ 9.40 Hz)[25].

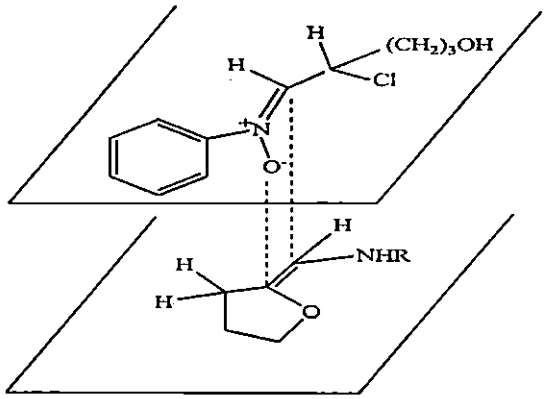


Fig. 7 (**TS I** spiro cycloadducts)

Similarly, the novel dipolarophiles (α-*N*-methyl/phenyl furan derivatives) were also employed for the synthesis of novel *spiro* cycloadducts with α-amino nitrones and the yield of the products were significantly high in a very short reaction time (accepted manuscript of *Journal of Chemical Research is enclosed in annexure).*

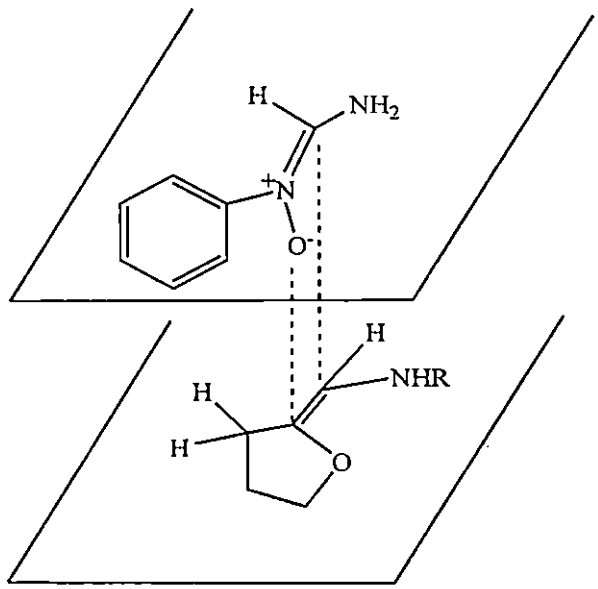


Fig. 8 (**TS - II** spiro cycloadducts)

REFERENCES

1. Chakraborty B, Kafley S & Chhetri M S, *Indian J Chem*, *48B*, **2009**, 447.
2. Chakraborty B, Chhetri M S & Kafley S, *Indian J Heterocyclic Chem*, 18, **2009**, 283.
3. a) Chakraborty B, Chhetri M S, *Indian J Chem*, *47B*, **2008**, 485; b) Chakraborty B, Chhetri M S, Kafley S, Sharma P K, *Journal of Chemical Research* (in press), **2010**; c) Chakraborty B, Sharma P K, Chhetri M S, Kafley S & Ghosh A R, *Rasayan J Chem*, 2 (4), **2009**, 946.
4. Chakraborty B, Chhetri M S, *Indian J Heterocyclic Chem*, 17, **2008**, 213.
5. Chakraborty B, *Indian J Heterocyclic Chem*, 17, **2008**, 293.
6. Chakraborty B, *Indian J Heterocyclic Chem*, 9, **1999**, 79.
7. Chakraborty B, *Indian J Heterocyclic Chem*, 9, **1999**, 77.
8. Chakraborty B, *Indian J Heterocyclic Chem*, 8, **1999**, 243.
9. Chakraborty B, *Indian J Heterocyclic Chem*, 7, **1997**, 77.
10. Chakraborty B., *Indian J Heterocyclic Chem*, 6, **1997**, 231.
11. Chakraborty B, *Indian J Heterocyclic Chem*, 6, **1997**, 233.
12. Chakraborty B, *Indian J Heterocyclic Chem*, 6, **1996**, 75.
13. Chakraborty B & Ghosh A R, *Indian J Heterocyclic Chem*, 5, **1996**, 317.
14. Chakraborty B & Ghosh A R, *Indian J Heterocyclic Chem*, 5, **1995**, 99.
15. Chakraborty B & Ghosh A R, *Indian J Chem*, 33B, **1994**, 1113.
16. Dasgupta T K, Felix D, Kempe U M, Eschenmoser A, *Helv Chim Acta*, 55, **1972**, 2198.
17. a) Chakraborty B & Chhetri M S, *Indian J Chem*, 49B, **2010**, 102; b) Chakraborty B & Chhetri M S, *Indian J Heterocyclic Chem*, 18, **2008**, 201.
18. a) Heinzer F, Saukup M, Eschenmoser A, *Helv Chim Acta*, 61, **1978**, 2851; b) Nanda A, *Ph.D dissertation*, University of North Bengal, Darjeeling, **1984**.
19. Fieser L M & Fieser M, "*Reagents for Organic Synthesis*", John Wiley & Sons, Inc, (NY), **1967**, 487.
20. Sustman R, *Pure Appl Chem*, 40, **1974**, 569.

21. a) Houk K N, Sims J & Luskus C R, *J Am Chem Soc,* 95, **1973**, 7302; b) Newton R, Savage P G, *Australian J Chem*, 61, **2008**, 432 and references cited therein; c) Aouadik K, Vidal S, Praly P J, *Synlett*, 19, **2006**, 3299 and references cited therein.

22. Li C J, Chang T H, "*Organic reactions in Organic Media*", Wiley, NY, **2007, 1997.**

23. Grieco P A, "*Organic reactions in water*", Blackie Academic & Professional, London, **1998.**

24. Najera C J M, *Angew Chem, Int Ed* (English), 34, **2005**, 6272.

25. Deshong P, Li W, Kennington J W & Ammon H L, *J Org Chem*, 56, **1991**, 1364.

26. Tufariello J J, "*1; 3 dipolar cycloaddition chemistry*", Edited Padwa A (New York), 2, **1984.**

27. Heaney F, Rooney O, Cunningham D, Mcarde P, *J Chem Soc, Perkin Trans II*, **2001**, 373.

28. Suwinska K, Solecka J & Chmielewski M, *Tetrahedron*, 58, **2002**, 999.

29. Yu Y, Ohno M & Eguchi S, *Tetrahedron*, 493, **1993**, 824.

30. Houk K N & Moses S R, *J Am Chem Soc*, 106, **1984**, 3880.

31. Ali S K & Wazeer M I M, *J Chem Soc, Perkin Trans I*, **1988**, 597.

CHAPTER V

Scope and objectives

Among the plethora of functional groups, the nitrone functionality has secured an important place in the arsenal of synthetic chemists. This was possible due to brilliant efforts of some of the eminent scientists in this field *viz* R. Huisgen[1], A. Eschenmoser[2], K.N Houk[3], W. Oppolzer[4], A. padwa[5], R. Grigg[6], P. Deshong[7], S. Ali[8], L. Fisera[9], V. Aggarwal[10] etc.

K.N Howk and his co-workers[3] are responsible for the pioneering investigations of regio and stereoselectivity associated with the 1,3-dipolar cycloaddition reactions of nitrone. The discovery of α-chloro nitrone and its reactions paved a new avenue in the nitrone chemistry. The chemistry of α-chloro nitrone and α-amino nitrone was originated and developed by Prof. A. Eschenmoser and his school[2] in the early 70's and developed further by other eminent scientists. Another new vista of the nitrone chemistry is the intramolecular cycloaddition reactions. Such types of reactions have been reviewed by A. Padwa[5] and W. Oppolzer[4]. Due to the vast synthetic potentiality of α-chloro nitrones, a large number of natural products and other biologically active products have been synthesized via nitrone routes therefore the scope of the nitrone chemistry is abundant. One of the objective of our present work is to utilize the vast potentiality of α-chloro nitrone in aldehyde synthesis[11] for the first time and ketone synthesis (accepted manuscript is enclosed in the annexure) for the first time.

In our present dissertation, we have focused mainly on the synthesis and cycloaddition reactions of *N*-phenyl-α-chloro nitrone[12], *N*-phenyl and *N*-cyclohexyl-α-amino nitrones[13] respectively. *N*-phenyl-α-chloro nitrone[12] has been synthesized from chlorohydrin and its tautomer (prepared from dihydropyran with hypochlorous acid treatment). All the nitrones are moderately stable and isolable but decomposes when kept at room temperature for a longer period and hence *in-situ* cycloaddition reactions were preferred rather than 1:1 nitrone-dipolarophile cycloaddition reactions.

The nitrones discussed in this dissertation are very interesting from synthetic point of view as

i) This is quite a new approach for the synthesis of α-chloro and α-amino nitrones from chlorohydrine and DMF-diacetal.

ii) The nitrones are having tremendous synthetic potentiality.

Cycloaddition reactions of α-chloro nitrone were performed in water and it has been found that the reaction rate as well as yield of the cycloadducts are considerably higher in case of aqueous phase cycloaddition reactions compared to conventional solvents[14]. Moreover, regioselectivity and stereoselectivity has also been observed in these reactions[15a]. All the reactions do occur at room temperature with stirring. Initially, the reactions were studied in a conventional way using THF and dichloromethane as solvent and the reaction mixture was refluxed in a water bath for 8 – 10 hour. These reaction conditions showed poor yield and the rate of the reactions were also slower and hence not followed. The cycloaddition reactions of *N*-phenyl-α-chloro nitrone with methyl vinyl ketone, ethyl acrylate results 5-substituted adducts over 4-substituted one and this has been established from ^{1}H NMR and mass spectral analysis data. An interesting observation of conversion of 5-substituted to 4-substituted cycloadduct was noticed in case of ethyl acrylate cycloadduct (in case of α-chloro nitrone only) when these cycloadduct was kept at room temperature for longer period (nearly one month) i.e. cycloreversion occurs and is identical with Ali's report[8].

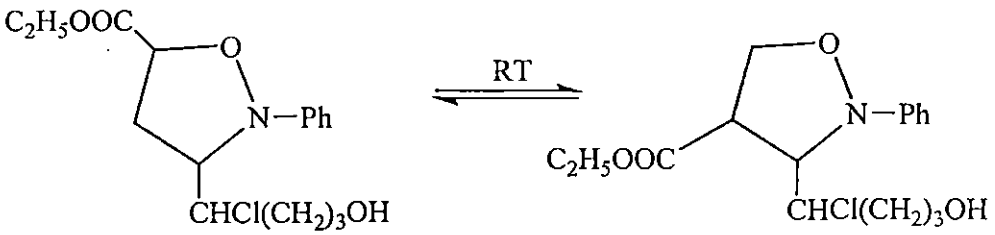
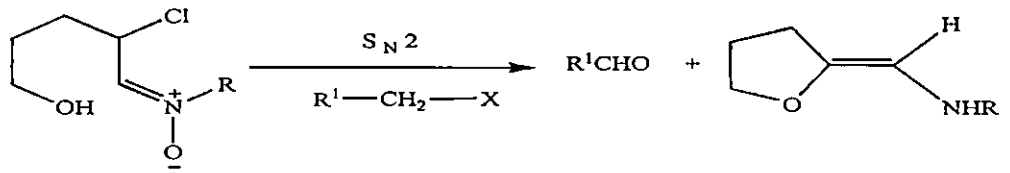


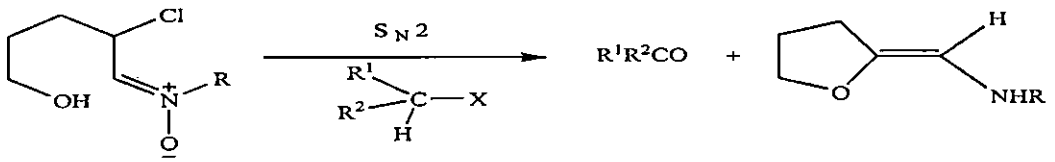
Fig. 1

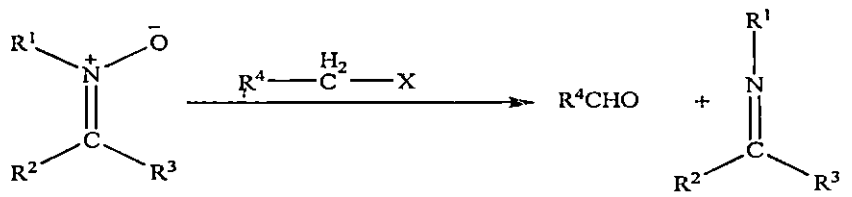
Excellent diastereofacial selectivity has been observed in nitrone additions to dipolarophiles when water, is used as a solvent. In case of maleimides and cyclohexenes mixture of diastereoisomers in the ratio of 2:1 are reported with asymmetric induction at *C*-3, *C*-4, *C*-5 position in a single step reaction. Study of organic reactions in aqueous media show that there is a more possibility of the formation of mixture of diastereoisomer when water is used on solvent rather than conventional solvents[14].

The most important application of α-chloro nitrones and α-amino nitrones are as oxidizing reagents in the aldehyde and ketone synthesis[11,16-18]. In addition to the existing methods available for the synthesis of aldehydes from alkyl halides, we would like to incorporate an efficient one pot synthesis of aldehydes from alkyl halides using for the first time α-chloro and α-amino nitrones (**Scheme 1**) as oxidizing reagent with an excellent yield. In addition, the side products *viz,* furan derivatives (obtained during aldehyde synthesis in case of α-chloro nitrones only) have been successfully used as dipolarophile in 1,3-dipolar cycloaddition reaction with a variety of nitrones for the production of *spiro* cycloadducts (**Scheme 2**) with high yields (almost 75 – 85%)[18b]. In case of simple nitrones and amino nitrones, the side product (imines) obtained during aldehyde synthesis results starting material amide and amines upon simple hydrolysis. The duly obtained amides can be successfully reused for the synthesis of amino nitrones while the amines can be used for further general reaction purposes. At the same time we have also the synthesized aldehydes from alkyl halides using some simpler nitrones as oxidizing reagent. Although the oxidizing properties of these nitrones are also same but the yield of the aldehydes are moderate while side products cannot be used as dipolarophile because of the absence of C=C bonds.



R = Cy; Ph R_1 = Me; Et; Pr; Ph X = C l ; Br ; I

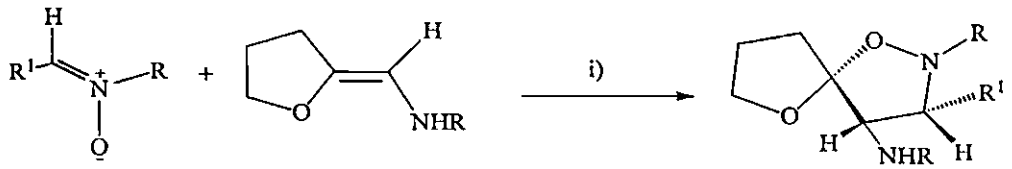




R^1 = Ph, Cy; R^2 = NMe_2; R^3 = H and R^1 = Ph,Cy; R^2 = NH_2; R^3 = H

Reagents and conditions: i) Dry ether, r.t, N_2 atmosphere, 6 - 8 hr

Scheme 1



R = Cy; Ph
R^1 = $CHCl(CH_2)_3OH$; Ph; NH_2; NMe_2

Scheme 2

Almost all the isoxazolidine and isoxazoline derivatives are having significant antibacterial activities (cycloadducts derived from α-chloro nitrone in aqueous phase & cycloadducts derived from α-amino nitrone in solvent less condition)[15]. All the synthesized cycloadducts (isoxazolidine & isoxazoline derivatives) were subjected to *in-vitro* screening against *Vibrio Parahaemolyticus*, *Klebsiella Pneumoniae*, *Bacillus Subtilis*, *Proteus Vulgaris*, *Staphylococcus Aureus*, *Shigella Flexneri*, *Eschericia Coli*, *Salmonella Typhi*, *Vibrio Cholerace*.

a) It has been observed that the derivatives of isoxazolidine have antibacterial activity against both gram positive (*S. Aureus, B. Subtilis)* and gram negative (*E. Coli, S. Flexneri)* bacteria, hence it can be concluded that the derivatives used were broad spectrum antibiotics[19]. b) The MIC value obtained for isoxazolidine derivatives ranges from 10 μg/ml - 50 μg/ml are very close to the MIC values of most commonly used antibiotics like Penicillin (10 units), Sulphonamide (300 μg/mL), Nalidixic Acid etc and hence they are equally effective and can be prescribed after testing of LD_{50}[20]. c) Moreover, these isoxazolidine derivatives may be recommended along with other antibiotics in a very low concentration to get more effective result due to the synergism and this may avoid drug resistance. d) Since all the isoxazolidine derivatives were soluble in DMSO (percentage varying from 1-4%) we can predict that the derivatives were hydrophobic in nature and it may cross the cell wall and cell membrane lipid bilayer.

The present dissertation opens up a new scope in coming days for aqueous phase synthesis of α-chloro nitrones and cycloaddition reactions leading to high regio and stereoselective products. All the α-chloro and α-amino nitrones used in this dissertation give a new dimension in the oxidizing properties and suggests that not only α-chloro and α-amino nitrones but also simpler nitrones or their derivatives can

be used as a precursor for the aldehyde synthesis. All the nitrone cycloaddition reactions reported here also indicate that the synthesis is asymmetric in nature. The dissertation may also be an example for a new route of synthesis of α-amino nitrones from benzamide following the methodology explained here.

These nitrone cycloaddition reactions are not only synthetically highly important but also opens a new path for the microbiologists as far as their potentiality is concerned to act as antifungal, antibacterial and as a whole a broad spectrum antibiotics. Works are in progress to study the gastrointestinal tract infection studies using α-chloro nitrone and simple nitrones.

Finally we would like to add two important observations in the present work we have done. Both the observations are a new approach and their synthetic potentiality is maximum. i) it has been concluded in the present study that the studied nitrones and general nitrones also can be used as potential new stable oxidizing reagent for the conversion of alkyl halides to aldehydes & ketones. ii) The side products obtained during synthesis of aldehyde and ketones using nitrones (α-chloro nitrones only) can be used as efficient dipolarophile in 1,3-dipolar cycloaddition reactions leading to regioselective *spiro* cycloadducts with high yields in a very short reaction time at RT. The regioselectivity has been studied with a variety of nitrones and has been found that the reactions are exclusively regioselective.

Therefore, we may suggest that our methodology can be incorporated for carbonyl group synthesis (aldehyde & ketones) and newly synthesized α-*N*-methyl / phenyl-furan derivatives can be employed as effective dipolarophiles in nitrone cycloaddition reactions like other available conventional dipolarophiles.

REFERENCES

1. Huisgen R, *J Org Chem*, 41, **1976**, 403.

2. a) Heinzer F, Saukup M, Eschenmoser A, *Helv Chim Acta*, 61, **1978**, 2851; b) Dasgupta T K, Felix D, Kempe U M, Eschenmoser A, *Helv Chim Acta*, 55, **1972**, 2198.

3. a) Houk K N, Sims J, Lukas C R, *J Am Chem Soc*, 95, **1973**, 7301; b) Houk K N and Moses S R, *J Am Chem Soc*, 106, **1984**, 3880.

4. a) Oppolzer W and Petrzilka M, *J Am Chem Soc*, 61, **1978**, 2755; b) Oppolzer W & Petrzilka M, *J Am Chem Soc*, 98, **1976**, 6722; c) Oppolzer W and Grayson J I, *J Am Chem Soc*, 98, **1983**, 3695.

5. Padwa A, "*Synthetic applications of 1,3–dipolar cycloaddition chemistry toward heterocycles and natural products*", Pearson W H, Ed, (John Wiley & sons, New York), **2003**.

6. a) Grigg R, Heaney F, Surendrakumar S, *Tetrahedron*, 47, **1991**, 4477; b) Grigg R, Heaney F, Surendrakumar S, Armstrong P, *Tetrahedron*, 47, **1991**, 4495; c) Grigg R, Allway P, *Tet Lett*, 47, **1991**, 4495; d) Grigg R, Allway P, *Tet Lett*, 32, **1991**, 5817.

7. Deshong P, Li W, Kennington J W & Ammon H. L, *J Org Chem*, 56, **1991**, 1364.

8. a) Ali S K, Iman M Z N, *Tetrahedron*, 63, **2007**, 9134. b) Ali S. K. and Wazeer M. I. M., *J Chem Soc, Perkin Trans I*, **1988**, 597.

9. Hyrosova E, Fisera L, Kozisek J, Fronc M, *Synthesis*, 8, **2008**, 1233.

10. Agarwal V.K, Grainger R.S, Adams H, Spargo P.L, *Journal of Organic Chem*, 63, **1998**, 3481 and references cited therein.

11. a) Chakraborty B, Chhetri M S, *Indian J Chem, 47B*, **2008**, 485; b) Chakraborty B and Ghosh A R, *Indian J Heterocyclic Chem*, 5, **1996**, 317.

12. a) Chakraborty B, Kafley S & Chhetri M S, *Indian J Chem, 48B*, **2009**, 447; b) Chakraborty B, Chhetri M S & Kafley S, *Indian J Heterocyclic Chem*, 18, **2009**, 283.

13. a) Chakraborty B & Chhetri M S, *Indian J Heterocyclic Chem*, 18, **2008**, 201; b) Chakraborty B, Chhetri M S, *Indian J Heterocyclic Chem*, 17, **2008**, 213; c) Chakraborty B & Chhetri M S, *Indian J Chem, 49B*, **2010**, 102.

14. a) Li C J, Chang T H, "*Organic reactions in Organic Media*", Wiley, NY, **2007**, 1997; b) Grieco P A, "*Organic reactions in water*", Blackie Academic & Professional, London, **1998**; c) Chakraborty B, Chhetri M S & Kafley S, *Indian J Heterocyclic Chem*, 18, **2008**, 203.

15. a) Chakraborty B, Kafley S and Chhetri M S, *Indian J Chem, Sec B*, **2010**, (paper no:SCCB-1225: in press); b) Chakraborty B & Chhetri M S, *Indian J Heterocyclic Chem*, 19, **2009**, 63.

16. Chakraborty B, Sharma P K, Chhetri M S, Kafley S & Ghosh A R, *Rasayan J Chem*, 2 (4), **2010**, 946.

17. Chakraborty B, Kafley S & Chhetri M S, *Journal of Indian Chemical Society*, **2010** (in press).

18. a) Chakraborty B, Kafley S & Chhetri M S, *Journal of Chemical Sciences*, **2010** (under revision); (b) Chakraborty B, Kafley S & Chhetri M S, *Journal of Chemical Research*, **2010** (in press).

19. Andrews J M, *J Antimicrobial Chemotherapy*, 48, **2001**, 5.

20. Chattopadhyay D, Dastidar S G & Chakrabarty A N, *Indian J Med Microbiol*, 5, **1987**, 5171.

Annexture - 1 "Corrigendum"

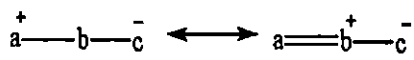
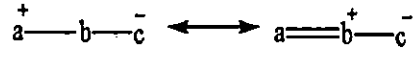
of the Ph.D thesis entitled

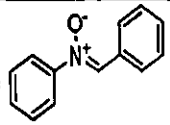
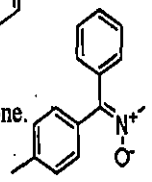
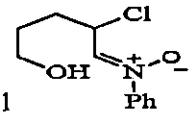
"N-cyclohexyl, N-phenyl nitrones and their potentiality in isoxazolidine and isoxazoline syntheses"

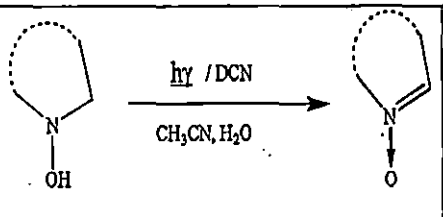
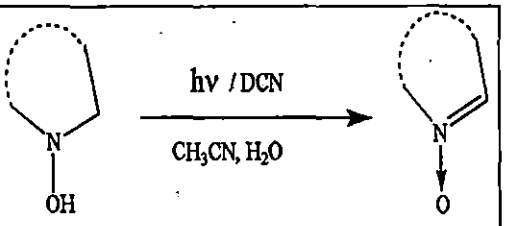
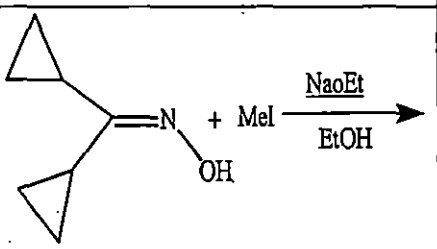
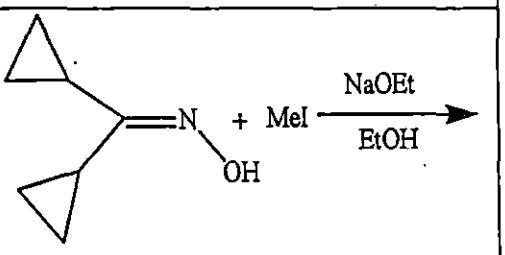
Author: Shri Manjit Singh Chhetri, Research fellow,

Sikkim Government College,

Tadong, Gangtok, Sikkim – 737102

Sl. no	Page no. and line no.	Mistakes pointed by the Referee	Corrections as desired by the Referee
1	**Page 1:**	Propagyl - Allenyl type	Propargyl - Allenyl type
2	**Page 2:** first sentence needs to be corrected	Those in which the dipolar canonical form has a single bond on the sextet atom other form a double bond	Those in which the dipolar canonical form has a single bond on the sextet atom and the other cannonical form has a double bond.
	Line 3: Fig III should be Fig 3	 **Fig III**	 **Fig 3**
	Line 4: should be is	If the central atom be a carbon function then internal octet stabilization is prevented by lack of an available free electron pair.	If the central atom is a carbon function then internal octet stabilization is prevented by lack of an available free electron pair.
	Line 8,9,14:	1,3-dipoles,	1,3-Dipoles,
	1,3 dipole should be 1,3-Dipole	1,3-dipole participates in the [3+2] cycloaddition reactions which form 5-membered ring systems, in an	1,3-Dipole participates in the [3+2] cycloaddition reactions which form 5-membered ring systems, in an analogous

		analogous way to the Diels-Alder process which forms 6 membered rings, 1,3-dipoles vary in stability greatly. Some can be isolated and stored, others are relatively stable, but are usually made the same day as their use.	way to the Diels-Alder process which forms 6 membered rings, 1,3-Dipoles vary in stability greatly. Some can be isolated and stored, others are relatively stable, but are usually made the same day as their use.
3	**Page 5:** sp-dipolarophile should be sp-dipole, propagyl should be propargyl	sp-dipolarophile (linear dipoles like the propagyl anion) sp-dipolarophile (linear dipoles like the propagyl anion)	sp-dipole (linear dipoles like the propagyl anion) sp-dipolarophile (linear dipoles like the propargyl anion)
4	**Page 8:** structure of a nitrone as an example be given	α-N-diphenyl nitrone α-phenyl-α-(p–tolyl)-N-methyl nitrone.	α-N-diphenyl nitrone  α-phenyl-α-(p -tolyl)-N-methyl nitrone. 
5	**Page 9:** Line 1: in a in should be corrected Line 5: N-phenyl-α-chloro nitrone (1) structure if any given	Similarly the nitrone can react as 1,3-dipole with alkynes in a in 1,3-dipolar cycloaddition reactions to form Isoxazolines. N-phenyl-α-chloro nitrone (1) has a chlorine group at β- position of the nitrone which has a strong electron withdrawing nature and therefore this nitrone is electrophilic in nature. In general, nitrones are HOMO-LUMO controlled 1,3-dipoles skewing towards LUMO controlled side.	Similarly the nitrone can react as 1,3-dipole with alkynes in 1,3-dipolar cycloaddition reactions to form Isoxazolines. *N*-phenyl-α-chloro nitrone (1) has a chlorine group at β- position of the nitrone which has a strong electron withdrawing nature and therefore this nitrone is electrophilic in nature. In general, nitrones are HOMO-LUMO controlled 1,3-Dipoles skewing towards LUMO controlled side.  1

6	**Page 10:** Fig 14: hγ be replaced by hυ		
7	**Page 11:** Fig 15: NaoEt------ NaoEOt		
8	**Page 12:** were-------- was	Formation of cyclic N–vinyl nitrones <u>were</u> also reported from δ-alkenyl oximes by a concerted $2n + 2\pi + 2\delta$ 1, 3 – azprotio cyclotransfer reaction[27]	Formation of cyclic N–vinyl nitrones was also reported from δ-alkenyl oximes by a concerted $2n + 2\pi + 2\delta$ 1, 3 – azprotio cyclotransfer reaction[27]
9	**Page 13:** 1,3 dipole should be 1,3-Dipole	<u>1,3-dipole</u>	1,3-Dipole
10	**Page 15:** Hauk et al------Haul etal[ref]	<u>Hauk et al</u> have treated all common 1,3-Dipoles according to this simple model and have shown that the prediction satisfactorily explains all the experimental results.	Hauk etal[38] have treated all common 1,3-Dipoles according to this simple model and have shown that the prediction satisfactorily explains all the experimental results.
11	**Page 18:** Line 3: 1,3 dipole should be 1,3-Dipole	<u>1,3-dipolar</u> cycloaddition reaction can create up to three asymmetric centers (* = stereocenter).	1,3-Dipolar cycloaddition reaction can create up to three asymmetric centers (* = stereocenter).
12	**Page 20:** Line 10 is to be corrected	<u>Another important work suggested by A. Goti and his co-workers[46] in Italy, working with C, N-diphenyl nitrone and the dipolarophiles were used are butyrolactones.</u>	Another important work was suggested by A. Goti and his co-workers[46] in Italy. They have reported cycloaddition reactions of *C*, *N*-diphenyl nitrone with butyrolactones as dipolarophiles.
13	**Page 23:** Last two lines need	<u>Some stereoselective synthesis of pyrolidinyl glycines from nitrones</u>	P. Merino and his co-workers[52] reported stereoselective synthesis of pyrolidinyl

	correction	also report moderate antifungal activities as reported by P. Merino and his co-workers[52].	glycines from nitrones and have reported moderate antifungal activity of the products.
14	**Page 28:** Lines 3,4 need correction	The work is actually diastereoselective synthesis of isoxazolidinyle nucleosides by means of 1,3-dipolar cycloaddition reaction of chiral sugar derived nitrone as the key step.	The work is actually diastereoselective synthesis of isoxazolidinyle nucleosides using 1,3-dipolar cycloaddition reaction of chiral sugar derived nitrones.
15	**Page 31:** 5^0C------5 ^{0}C	i) Methylene chloride, N_2 atmosphere, 0-5^0C, anhydrous $MgSO_4$	i) Methylene chloride, N_2 atmosphere, 0-5 °C, anhydrous $MgSO_4$
16	**Page 32-34:** Reference writing style should be same	**55.** Grigg R, J Sexton, Surendrakumar S, J Chem Soc, **1993**, 372.; **67.** Chakraborty B, Chhetri M S, Indian J Chem, *47B*, **2008**, 485.	55. Grigg R, Sexton J, Surendrakumar S, J Chem Soc, **1993**, 372; **67.** Chakraborty B, Chhetri M S, Indian J Chem, 47B, **2008**, 485.
17	**Page 36:** Number of compound pentanal be mentioned	Spectral data of 2-Chloro-5-hydroxy pentanal	Spectral data of 2-Chloro-5-hydroxy pentanal (b)
18	**Page 92:** Line 2: et al-------etal[ref]	Eschenmoser et al. have shown the synthetic potentiality of α-chloro nitrone in 1,4-dipolar cycloaddition reactions with unactivated double bonds[16]	Eschenmoser etal[16] have shown the synthetic potentiality of α-chloro nitrone in 1,4-dipolar cycloaddition reactions with unactivated double bonds.
19	**Page 101:** Fourth line from bottom: are-------is third line from bottom: addition--- additions	Another important aspect of the cycloaddition reactions are the *exo* addition over *endo* addition. In the majority of the cases *exo* addition were preferred since α-chloro nitrone exist exclusively in the *Z* configuration.	Another important aspect of the cycloaddition reactions is the *exo* addition over *endo* addition. In the majority of the cases *exo* additions were preferred since α-chloro nitrone exist exclusively in the *Z* configuration.

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ANNEXTURE-2

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Note

High yield solvent free synthesis of novel isoxazolines using novel *N*-cyclohexyl-α-amino nitrone

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Received 1 December 2008; accepted (revised) 7 September 2009

Some novel isoxazolines have been synthesized from novel *N*-cyclohexyl-α-amino nitrone using 1,3 dipolar cycloaddition reaction with alkynes in solvent free conditions at room temperature.

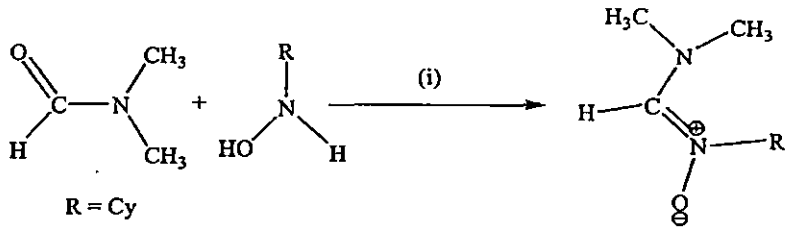
Keywords: *N*-Cyclohexyl-α-amino nitrone, 1,3 DCR, isoxazolines, stereoselectivity, solvent free conditions

In continuation of the earlier work on isoxazolidine synthesis using α-amino nitrones in solvent free conditions (synthesized from formamide and N-phenylhydroxylamine)[1,2], herein is now reported an efficient method for the stereoselective synthesis of isoxazolines from N-cyclohexyl-α-amino nitrone **1** (**Scheme I**, ref. 3) with an excellent yield under solvent free conditions[4] (**Scheme II, Table I**). The products of such cycloadditions have a variety of applications, including as potential antimicrobial agents. 1,3-Dipolar cycloadditions are powerful methods for constructing a variety of five membered heterocycles in a convergent manner from relatively simple precursors and these heterocycles have a variety of applications including as antibacterial agents[5]. Cycloadditions of alkynes even with electron deficient and unsymmetrical alkynes are often conducted at elevated temperature[6]. In this communication is reported the synthesis of isoxazolines at RT with high yield. Stereoselective synthesis of isoxazolidines at RT using nitrone **1** has been already reported[3]. This is because of the fact that N-cyclohexyl-α-amino nitrone is very reactive due to the presence of a filled up anti bonding molecular orbital which hastens cycloaddition to take place at RT (Ref. 7).

Results and Discussion

In an initial investigation, the reaction of nitrone **1** with ethyl propiolate was examined at elevated temperature having only 28% yield of isoxazoline in 14 hr while at RT 92% yield of isoxazolines are reported in 12 hr which indicates the decomposition of nitrone at elevated temperature. This could also be explained due to secondary orbital effect between the carbon of the nitrone (HOMO) and the adjacent atom of the electron withdrawing group of the dipolarophile (LUMO), (ref. 7). The concerted nature of these cycloaddition reactions with nitrone as 1,3 dipole has been generally accepted. The regioselectivity in these reactions was rationalized by using the frontier orbital theory[8]. The ethyl propiolate and propiolic acid adducts correspond to this theory. Therefore, the 5-substituted adduct for ethyl propiolate and propiolic acid is due to LUMO (nitrone)- HOMO (dipolarophile) interaction[8]. For the present study, highly electron deficient and unsymmetrical alkynes like dimethyl acetylene dicarboxylate, phenyl methyl propiolate, propiolic acid and ethyl propiolate respectively have been chosen to study the stereoselectivity in these cycloadditions.

As already reported, nitrone **1** is highly unstable and hence for 1,3-dipolar cycloaddition reaction, the nitrone was trapped *in situ* by different alkynes to afford isoxazolines with high yield. Dimerization of nitrone could also be controlled under this condition. Like most of the nitrones reported from this group[9-11], nitrone **1** also exists exclusively in the *Z* configuration and hence the cycloadducts were formed from *Z* nitrone through an *exo* transition state geometry. Excellent diastereofacial selectivity is observed in case of reaction of nitrone **1** with ethyl propiolate and propiolic acid and results in a mixture of diastereomer **4a, 4b** and **5a, 5b** (**Scheme II,** almost 70:30 ratio). These results can be rationalized by an *exo* approach of the nitrone for the major cycloadducts **4a, 5a** which have the *Z* configuration (transition state **I**)[12]. The minor cycloadducts **4b, 5b** may be formed by the *endo* approach of *Z* nitrone (transition state **II**)[12]. Most relevant are the coupling constants ($J_{H3, H4}$ for **4** and **5**) of the diastereomer. For **4a** and **5a**, the coupling constants are 9.3 and 9.4 Hz, implying a *cis* relationship between H_3 and H_4 whereas **4b** and **5b**

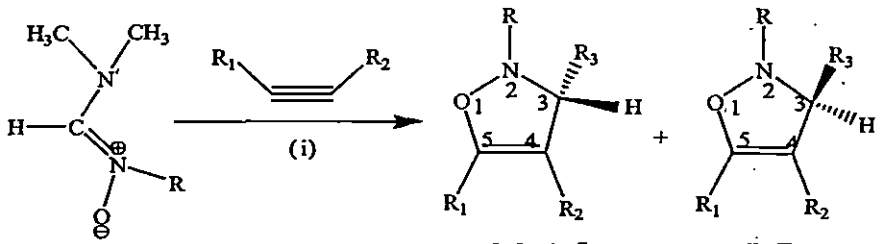


R = Cy

(i) anhydrous $MgSO_4$, RT, 8 hr, N_2 atmosphere

1

Scheme I



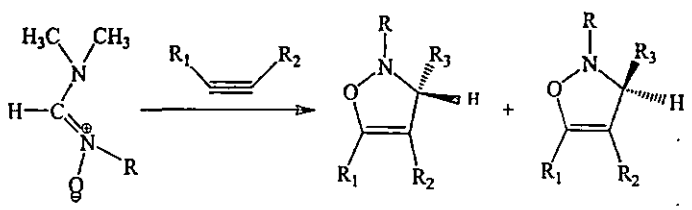
2, 3, 4a-5a 4b-5b

(i) RT, 6-8 hr, N_2 atmosphere

2 : R_1 = Ph; R_2 = $COOCH_3$
3 : $R_1 = R_2 = COOCH_3$
4 : $R_1 = COOC_2H_5$; R_2 = H
5 : R_1 = COOH ; R_2 = H
R_3 = -NMe_2
R = Cy

Scheme II

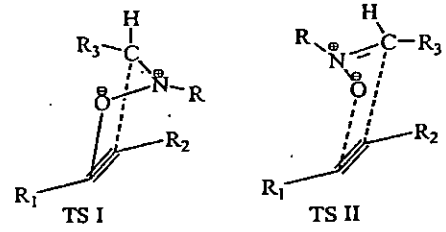
Table I — Physicochemical data of synthesized compounds



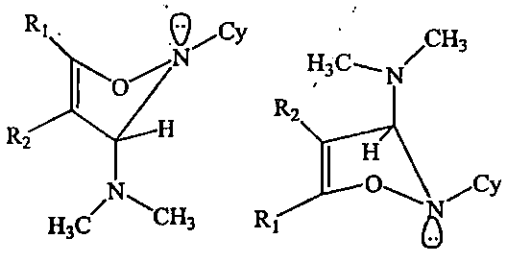
Entry	Nitrone	Dipolarophile	Time (hr)	Cycloadducts[a] (2-5)	R_f	Yield[b] (%)
1	N-cyclohexyl-α-amino nitrone	Phenyl methyl propiolate	6	Pale yellow gummy liquid	0.62	96
2	N-cyclohexyl-α-amino nitrone	Dimethyl acetylene dicarboxylate	7	Red liquid	0.58	92
3	N-cyclohexyl-α-amino nitrone	Ethyl propiolate	6	White viscous liquids	0.44, 0.50	92
4	N-cyclohexyl-α-amino nitrone	Propiolic acid	8	Yellow liquids	0.38, 0.54	89

[a]All the reactions were carried out at RT
[b]Isolated yields after purification

have coupling constants of 2.58 and 2.64 Hz respectively which implies a *trans* relationship between H_3 and H_4[13-15]. Comparing the ^{1}H NMR spectrum of **4a-5a** and **4b-5b** we suggest the major and minor conformers of isoxazoline ring systems[13] for **4a-5a** and **4b-5b** (**Figure 1**). In the cycloadducts **2** and **3**, since C-4 and C-5 protons were absent, so the coupling constant values could not be calculated.



2 R_1 = Ph; R_2 = $COOCH_3$ 3 R_1 = R_2 = $COOCH_3$
4 R_1 = $COOC_2H_5$; R_2 = H; 5 R_1 = COOH; R_2 = H
R_3 = - NMe_2



2 R_1 = Ph; R_2 = $COOCH_3$ 3 R_1 = R_2 = $COOCH_3$
4 R_1 = $COOC_2H_5$; R_2 = H 5 R_1 = COOH; R_2 = H
R_3 = - NMe_2

Figure 1

Hence, nothing could be inferred about their conformational structures. All the cycloadducts are stable and detailed study of the mass spectrum (**Scheme III**) reveals that prominent molecular ion peak and base peaks are obtained as expected. Like other isoxazoline derivatives reported in the literature[4,6], expected fragmentation peaks have also been obtained due to the development of different aziridine derivatives. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate, $COOCH_3$ for dimethyl acetylene dicarboxylate, COOH for propiolic acid and $COOC_2H_5$ for ethyl propiolate respectively. Hence, it is confirmed that during mass fragmentation, the adducts undergo rearrangement to aziridine derivatives. The detailed mass fragmentation pattern is shown in **Scheme III**.

Experimental Section

^1H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX1 881 machine as film or as KBr pellets for all the products. Mass spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q–Tof micro instrument (YA-105). Elemental analyses (CHN) were perfomed with a Perkin-Elmer 2400 series CHN analyzer. TLC were run on Fluka precoated silica gel TLC plates. N-cyclohexylhydroxylamine was prepared according to the published procedures[10]. All other reagents and solvents were used as received from commercial suppliers.

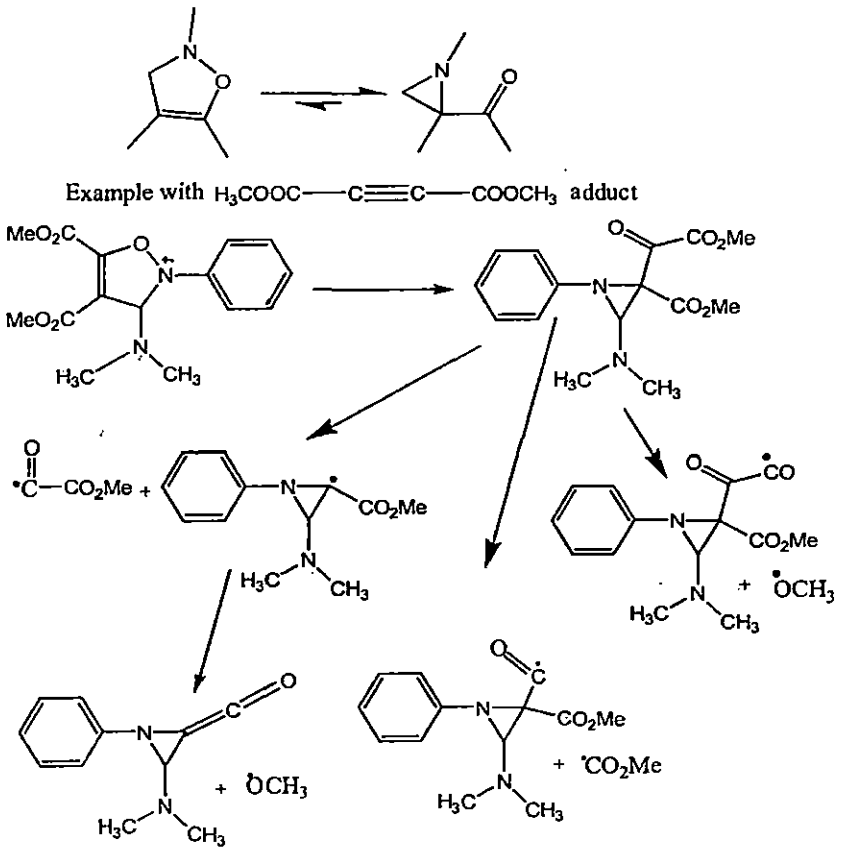
General procedure for one pot cycloaddition at elevated temperature

Initially, the cycloaddition reaction was performed at elevated temperature in case of ethyl propiolate following the methodology of cycloaddition reactions as already reported[6]. A mixture of N-cyclohexylhydroxylamine[10] (2.17 mmoles) and N,N-dimethyl formamide (9 mL) was heated in presence of anhydrous $MgSO_4$ with stirring with a magnetic stirrer for 6 hr. The formation of nitrone **1** was monitored by TLC (R_f = 0.38) and ethyl propiolate (1 equivalent) was added *in situ* at this stage and heating continued with stirring for another 6 hr (monitored by TLC). The crude products were isolated by extraction with ether and washed with saturated brine. Finally, gummy products were obtained by concentration of the organic layer under reduced pressure after column chromatography using ethyl acetate and hexane. But this methodology was abandoned because of poor yield (28%) which may be due to decomposition of nitrone at elevated temperature.

General procedure for one pot cycloaddition at room temperature

A mixture of N-cyclohexylhydroxylamine[10] (2.17 mmoles) and N,N dimethyl formamide (9 mL) was stirred in presence of anhydrous $MgSO_4$ with a magnetic stirrer at RT for 8 hr. The formation of nitrone **1** was monitored by TLC (R_f = 0.40) and ethyl propiolate (1 equivalent) was added *in situ* at this stage and stirring continued at RT for another 6 hr (monitored by TLC). The crude products were isolated by extraction with ether and washed with brine water. Finally, the cycloadducts were obtained under reduced pressure after column chromatography using ethyl acetate and hexane to furnish white viscous liquid products. **4a**:172 mg, 70%; **4b**:58 mg, 22% (**Scheme II**). This procedure was followed for other substrates listed in **Table I**.

(*S*)-methyl 2-cyclohexyl-3-(dimethylamino)-5-phenyl-2,3-dihydroisoxazole-4-carboxylate, **2**: IR ($CHCl_3$): 3155(m), 1750(s), 1665(m),1658(s),



Scheme III

1430(m), 1360(m), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.64–7.53 (m, 5H, C_6H_5 hydrogens), 4.05 (s, 1H, C_3H), 3.63 (s, 3H, - $COOCH_3$), 2.76 (br, 6H, NMe_2), 2.34–2.22 (m, 1H, N-CH proton), 1.95 - 1.66 (m, 10H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.50 (carbonyl carbon), 137.22, 135.40, 134.36, 132.64 (aromatic carbons), 88.10 (C_5), 73.42 (C_3), 57.48 (C_4), 45.00 (-$COOCH_3$), 33.25, 29.55 (N - CH_3 carbons), 26.00, 24.80, 23.44, 21.85, 20.16, 18.73 (CH_2 carbons); MS: *m/z* 330 (M^+), 286, 247, 246, 225, 194, 148, 105 (base peak), 83, 77, 31; HRMS-EI: Calcd for $C_{19}H_{26}O_3N_2$ (M) *m/z* 330.1935. Found: M^+ 330.1919.

(*S*)-dimethyl-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-4,5-dicarboxylate, 3: IR ($CHCl_3$): 3145 (m), 2820 (m),1745 (s),1700 (m), 1670 (m), 1420 (s), 1260 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.75 (s, 1H, C_3H), 3.66 (s, 3H,- $COOCH_3$), 3.60 (s, 3H,- $COOCH_3$), 2.68 (br, 6H, NMe_2), 2.40–2.28 (m, 1H, N-CH proton), 2.05 - 1.64 (m, 10H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169.00, 167.40 (carbonyl carbons), 87.54 (C_5), 76.00 (C_3), 59.40 (C_4), 44.00, 43.00 ($COOCH_3$), 31.00, 29.43 (N - CH_3 carbons), 25.80, 24.33, 23.90, 22.70, 20.64, 18.56 (CH_2 carbons); MS: *m/z* 312 (M^+), 281, 268, 229, 228, 225 (base peak), 194, 185, 87, 83, 59, 44, 31; HRMS-EI: Calcd for $C_{15}H_{24}O_5N_2$ (M) *m/z* 312.1677. Found: M^+ 312.1668.

(*S*)-ethyl 2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylate, 4a: IR ($CHCl_3$): 3165(m), 2945(s), 1770(m), 1680(s), 1656(s), 1430(m), 1260 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.64 (d, 1H, *J* = 9.3 Hz, C_3H), 4.26 (dd, 2H, *J* = 6.24, 6.36 Hz, $COOCH_2CH_3$), 3.35 (d, 1H, *J* = 9. 2 Hz, C_4H), 2.76 (br, 6H, NMe_2), 2.46–2.30 (m, 1H, N-CH proton), 2.04–1.67 (m, 10H), 1.40 (t, 3H, *J* = 4.36 Hz, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 173.44 (carbonyl carbon), 86.00 (C_5), 78.00 (C_3), 55.00 (C_4), 32.00 ($COOCH_2CH_3$), 30.00 ($COOCH_2CH_3$), 28.84, 27.35 (N-CH_3 carbons), 25.00, 23.00, 22.25, 20.83, 19.00, 18.44 (CH_2 carbons); MS: *m/z* 268 (M^+), 224, 195 (base peak), 185, 184, 141, 83, 73; HRMS-EI: Calcd for $C_{14}H_{24}O_3N_2$ (M) *m/z* 268.1779. Found: M^+ 268.1763.

(*R*)-ethyl-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylate, 4b: IR ($CHCl_3$): 3160(m), 2955(s), 1770(m), 1684(s), 1658(s), 1435(m), 1255(m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.58 (d, 1H, J = 2.53 Hz, C_3H), 4.32 (dd, 2H, J = 7.14, 6.16 Hz, $COOCH_2CH_3$), 3.26 (d, 1H, J = 2.58 Hz, C_4H), 2.66 (br, 6H, NMe_2), 2.24–2.12 (m, 1H, N-CH proton), 1.94–1.53 (m, 10H), 1.24(t, 3H, J = 4.08 Hz, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.00 (carbonyl carbon), 88.00 (C_5), 76.64 (C_3), 57.26 (C_4), 33.48 ($COOCH_2CH_3$), 31.70 ($COOCH_2CH_3$), 29.00, 27.85 (N - CH_3 carbons), 26.10, 24.00, 23.00, 21.42, 20.25, 18.36 (6 CH_2 carbons); MS: *m/z* 268 (M^+), 224, 223, 195 (base peak), 185, 184, 141, 83, 73, 45; HRMS-EI: Calcd for $C_{14}H_{24}O_3N_2$ (M) *m/z* 268.1779. Found: M^+ 268.1756.

(*S*)-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylic acid, 5a: IR ($CHCl_3$): 3144(m), 2942(s), 1765(m), 1684(s), 1660(s), 1440(m), 1310 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.8 (s, 1H, - COOH), 4.52 (d, 1H, J = 9.46 Hz, C_3H), 3.82 (d, 1H, J = 9. 44 Hz, C_4H), 2.58 (br, 6H, NMe_2), 2.33–2.24 (m, 1H, N-CH proton), 2.12–1.74 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 181.30 (carbonyl carbon), 87.00 (C_5), 78.54 (C_3), 56.52 (C_4), 32.27, 30.72 (N-CH_3 carbons), 27.00, 25.30, 24.24, 23.00, 21.00, 18.00 (CH_2 carbons); MS: *m/z* 240 (M^+), 196, 195 (base peak), 167, 157, 83, 73, 45; HRMS-EI: Calcd for $C_{12}H_{20}O_3N_2$ (M) *m/z* 240.1467. Found: M^+ 240.1452.

(*R*)-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylic acid, 5b: IR ($CHCl_3$): 3155(m), 2950(s), 1770(m), 1680(s), 1655(s), 1444(m), 1250(m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.4 (s, 1H, - COOH), 4.63 (d, 1H, J = 2.56 Hz, C_3H), 3.75 (d, 1H, J = 2. 64 Hz, C_4H), 2.53 (br, 6H, NMe_2), 2.40–2.28 (m, 1H, N-CH proton), 1.90–1.58 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 180.00 (carbonyl carbon), 88.43 (C_5), 76.00 (C_3),.57.00 (C_4), 34.00, 32.80 (N - CH_3 carbons), 28.00, 27.40, 25.00, 23.15, 22.20, 19.00 (6 CH_2 carbons); MS: *m/z* 240 (M^+), 196, 195 (base peak), 167, 157, 156, 83, 73, 45, 44; HRMS-EI: Calcd for $C_{12}H_{20}O_3N_2$ (M) *m/z* 240.1467. Found: M^+ 240.1449.

Conclusion

In conclusion, the present procedure provides an efficient solvent free methodology for the synthesis of isoxazoline and their derivatives with stereoselectivity. The notable advantages offered by this method are simple operation, mild and environment friendly reaction conditions, much faster reactions and high yield of products. Finally, a new methodology has been developed for α-amino nitrone synthesis from N,N dimethyl formamide in solvent free conditions and literature survey reveals that synthesis of isoxazoline derivatives from N,N dimethyl formamide derived α-amino nitrone is a new approach while reports of α-amino nitrone from formamide are known[1,12,14].

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References

1 Chakraborty B, Britto De J P & Ghosh A R, *Indian J Heterocycl Chem*, 6, **1996**, 77.
2 Chakraborty B & Chhetri M, *Indian J Heterocycl Chem*, 17, **2008**, 213.
3 Chakraborty B, Kafley S & Chhetri M S, *Indian J Chem, Sec B*, (in press) **2009**.
4 Nguyen B T, Martel A, Dhal R & Dujardin G, *J Org Chem*, 73, **2008**, 2621.
5 Padwa A & Pearson W H, *Synthetic application of 1,3-dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products* (Wiley, New Jersey), **2003**.
6 Shintini R & Fu G C, *J Am Chem Soc*, 125, **2003**, 10778.
7 Fisera L, Blanarikova I, Jurczak J & Hametner C, *Arkivoc*, 5, **2001**, 51 and references cited therein.
8 Houk K N, Sims J & Luskus C R, *J Am Chem Soc*, 95, **1973**, 7302.
9 Chakraborty B & Chhetri M, *Indian J Chem*, 47B, **2008**, 485.
10 Chakraborty B & Ghosh A R, *Indian J Chem*, 33B, **1994**, 1113.
11 Chakraborty B & Ghosh A R, *Indian J Heterocycl Chem*, 5, **1995**, 99.
12 Butler R N, Cunningham W J & Coyne A G, *J Am Chem Soc*, 126, **2004**, 11923 and references cited therein.
13 Heaney F, Rooney O & Cunningham D, *J Chem Soc, Perkin Trans*, 2, **2001**, 373.
14 Suwinska K, Solecka J & Chmielewski M, *Tetrahedron*, 58, **2002**, 1199 and references cited therein.
15 Deshong P, Kennington J W, Li W & Ammon H L, *J Org Chem*, 56, **1991**, 1364.

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INTRODUCING A NEW METHODOLOGY OF ALDEHYDE SYNTHESIS FROM ALKYL HALIDE USING α-CHLORO NITRONE AS A NEW, STABLE AND POTENTIAL OXIDIZING REAGENT

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ABSTRACT

Consecutive S_N2 reaction of α-chloro nitrones are studied with alkyl halides and the nitrones are found to have remarkable oxidizing properties for the conversion of alkyl halides to aldehydes with high yield. In addition, the side product obtained can serve as efficient dipolarophile in 1,3 DCR to produce spiro cycloadducts in good yields.
Keywords: α-chloro nitrone as oxidizing reagent, S_N2 reaction, aldehyde synthesis, spiro cycloadduct

INTRODUCTION

Convertion of alkyl halides to aldehydes using *N*-oxide with moderate yields have been already reported (Krohnke reaction). In addition to the existing methods available for the synthesis of aldehyde from alkyl halides,[1-6] we would like to incorporate an efficient one pot synthesis of aldehyde from alkyl halides using for the first time α-chloro nitrones (**1**) as a new, stable and potential oxidizing reagent with an excellent yield (Scheme-1, Table 1). In addition, the side product (furan derivatives, **2**) obtained during aldehyde synthesis has been successfully used as dipolarophile in 1,3-DCR with nitrone (**1**) for the production of spiro cycloadducts (**3**) with high yields (almost **75 – 85%** ; Scheme-2). α-chloro nitrones (**1**) are more reactive than other nitrones due to the electron withdrawing effect of chlorine and therefore can act as more powerful oxidizing agent than other nitrones.

Literature survey reveals that aldehyde synthesis using nitrone as active oxidizing reagent and further use of side products (obtained during aldehyde synthesis) as dipolarophile in cycloaddition reactions are not yet known and hence can be incorporated as an important application in nitrone chemistry. Synthesis and 1,3 dipolar cycloaddition reactions of *N*-phenyl-α-chloro nitrone[7,8](**1**, R=Ph) has been already reported. Following the same methodology, novel *N*-methyl-α-chloro nitrone (**1**,R=Me) has been synthesized as white crystalline solid, m.p 52^{0}C (uncorrected) and used for aldehyde synthesis as oxidizing reagent.

EXPERIMENTAL

General remarks :

^{1}H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q–Tof micro instrument (YA–105). TLC was carried out on Fluka silica gel TLC cards while column chromatography was performed with silica gel (E.Merck India) 60–200 mesh. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-methylhydroxylamine was purchased from Aldrich Chemical Company and was used as received. *N*-phenylhydroxylamine was prepared following standard methods available in literature and has been used in synthesis[9,10,11].

General procedure for the synthesis of nitrone 1 (R = Me)

N-methylhydroxylamine (250mg, 5.3127 mmole) was added to chlorohydrin (720mg,1 equivalent) in dry ether (50 mL) and anhydrous $MgSO_4$. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 10 hr. The formation of nitrone was monitored by TLC (R_f = 0.34). The nitrone was isolated under reduced pressure vaccum pump as white niddle shape crystals (920mg, 94%; m.p: 52^0C).

Spectroscopic data for nitrone 1 (R = Me)

Yield: 920mg (94%); white niddle shape crystals; R_f = 0.43, m.p: 52^0C (uncorrected); IR (KBr): 3595 – 3470 (br), 1660(s), 1610(s), 1415 (m), 1185 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.84 (d, 1H, CH=N^+), 5.79 (br,1H, -OH, exchanged in D_2O), 3.51 (dd, 1H, *J* = 6.16, 6.08 Hz, CHCl), 3.31 (s, 3H, N^+- CH_3), 1.88 - 1.15 (m, 6H, CH_2 protons); ^{13}C NMR($CDCl_3$) : δ 141.55 (CH=N^+), 55.76 (CHCl), 34.84 (N^+- CH_3), 28.50, 27.22, 26.00 (3 CH_2 carbons); HRMS – EI: Calcd. for $C_6H_{12}O_2NCl$, (M), 165.5710, Found: M^+, 165.5698.

General procedure for synthesis of aldehyde (benzaldehyde) and furan derivative 2 (entry 1;Table 1)

To a stirred solution of nitrone **1** (R=Me; 500mg, 3.0198 mmol) in dry ether (25 ml) was added pyridine (1 equivalent) and stirred at RT with a magnetic stirrer under N_2 atmosphere for 1 hr while the formation of transient nitrone **1a** (not isolated) was monitored by TLC (R_f= 0.38). Benzyl chloride (292.1002mg, 1 equivalent) was added at this stage and the reaction mixture was stirred for another 3 hr till the intermediate compound **1b** (not isolated) was developed (monitorted by TLC; R_f= 0.40). 2 gms of solid Na_2CO_3 was added at this stage and the reaction mixture was stirred for further 1 hr while the progress of the reaction was again monitored by TLC (R_f= 0.43, 0.50). The reaction was typically completed when the N-O bond was cleaved. Basic workup, removal of pyridine hydrochloride and silica gel column chromatographic purification using ethyl acetate-hexane provided desired benzaldehyde as colourless liquid (712mg, 89% ; R_f= 0.43) and furan derivative (2) as pale yellow gummy liquid (88mg, 10% ; R_f= 0.50). This procedure was followed for all the substrates listed in Table 1.

Spectroscopic data for benzaldehyde (entry 1)

Yield: 712 mg (88%); colourless liquid; R_f = 0.43; IR (KBr): 1695(s), 1320(m), 770(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.80 (s, 1H, CHO), 7.30 – 7.16 (m, 5H, C_6H_5); ^{13}CNMR ($CDCl_3$): δ 198.00 (CHO), 136.20, 134.55, 132.60, 131.00 (aromatic carbons); FAB - MS (*m/z*): 106 (M^+), 105 (B.P), 77, 51, 28; HRMS-EI: Calcd. for C_6H_5CHO (M), 106.0417, Found; M^+, 106.0408.

Spectroscopic data for 2 (R=Me; α-N-methyl furan derivative; entry 1) [(E)-1-(dihydrofuran-2-(3H)-ylidene)-N-methyl methanamine)]

Yield: 88mg (10%); pale yellow gummy liquid; R_f= 0.50; IR (KBr): 3125-3054 (br), 2838 (m), 1652 (s), 1455 (m), 1210 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.81 (br, 1H, N-H), 4.56 (s, 1H, C=CH), 3.30 (N-Me), 2.50 - 2.16 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 103.00, 101.76 (double bonded carbons), 26.22, 25.30, 23.65 (3 CH_2 carbons); FAB – MS: *m/z* 113 (M^+), 98, 97; HRMS-EI: Calcd. for $C_6H_{11}ON$ (M), 113.1000, Found: M^+, 112.9876.

Spectroscopic data for propionaldehyde (entry 2)

Yield: 592mg (87%); colourless liquid; R_f= 0.50; IR (KBr): 2920 (m), 2720 (m), 1720 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.70 (t, 1H, *J* = 6.60 Hz, -CHO), 2.30 (ddd, 2H, *J* = 6.08, 6 Hz, -CH_2), 1.00 (t, 3H, *J* = 6.30 Hz, CH_3); ^{13}CNMR ($CDCl_3$): δ 202.40 (CHO), 44.22 (CH_2 carbon), 35.55 (CH_3 carbon); FAB – MS: *m/z* 58 (M^+), 57, 29 (B.P); HRMS-EI: Calcd. for C_3H_6O (M), 58.0417, Found: M^+, 58.0403.

Spectroscopic data for 2 (R=Ph; α-N-phenyl furan derivative; entry 4) [(E)-1-(dihydrofuran-2-(3H)-ylidene)-N-phenyl methanamine)]

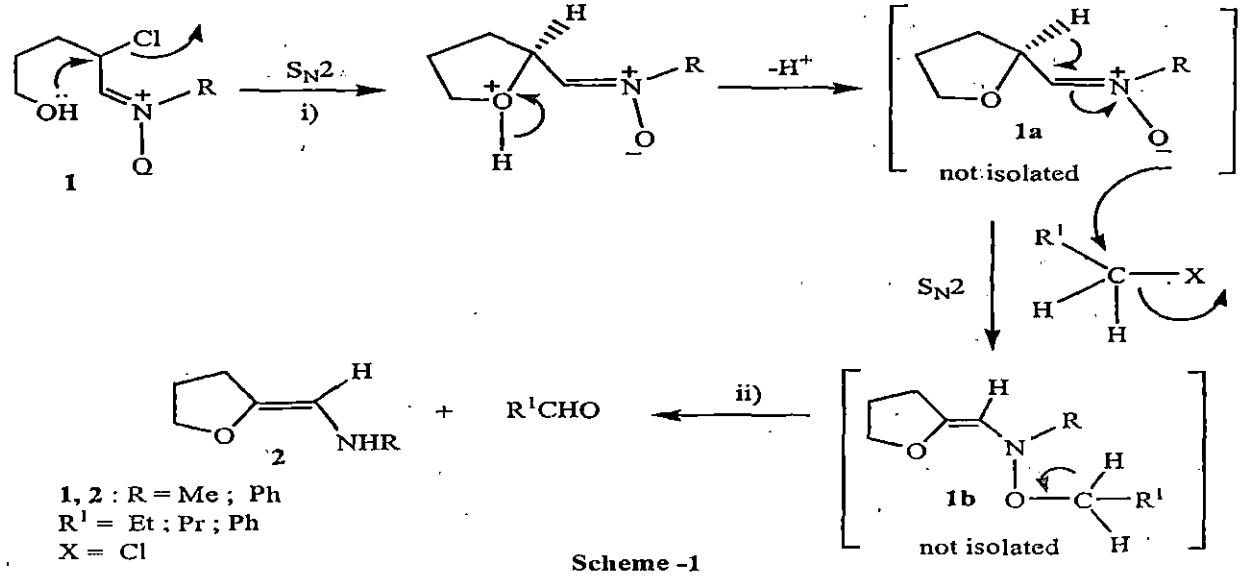
Yield: 90mg (11.5%); dark yellow viscous liquid; R_f= 0.46; IR (KBr): 3150-3060 (br), 2860 (m), 1640 (s), 1430 (m), 1140 (m), 778 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.83 (m, 5H, C_6H_5), 6.24 (br, 1H, N-H), 2.17 (s, 1H, C=CH), 1.79 - 1.18 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 137.20, 135.65, 134.00, 132.15 (aromatic carbons), 106.24, 104.18 (double bonded carbons), 28.46, 27.10, 24.84 (3 CH_2 carbons). FAB - MS (*m/z*): 175 (M^+), 98, 97, 77. HRMS-EI: Calcd. for $C_{11}H_{13}ON$ (M), 175.0993, Found; M^+, 175.0981.

Spectroscopic data for n-butyraldehyde (entry 4)

Yield: 570mg (86%); colourless liquid; R_f = 0.54; IR (KBr): 2945 (m), 2710 (m), 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.30 (t, 1H, *J* = 5.84 Hz, -CHO), 3.50 (dt, 2H, *J* = 6.50, 4.22 Hz, -C_2 2H), 1.30 (ddd, 2H, *J* = 5.50, 3.40 Hz, $C_3$2H), 0.90 (t, 3H, *J* = 4.30 Hz, CH_3); ^{13}CNMR ($CDCl_3$): δ 208.20 (CHO), 47.50 (C_2 carbon), 36.10 (C_3 carbon), 20.10 (C_4 carbon); FAB – MS: *m/z* 72 (M^+), 71, 57, 44 (B.P), 29; HRMS-EI: Calcd. for C_4H_8O (M), 72.0670, Found: M^+, 72.0523.

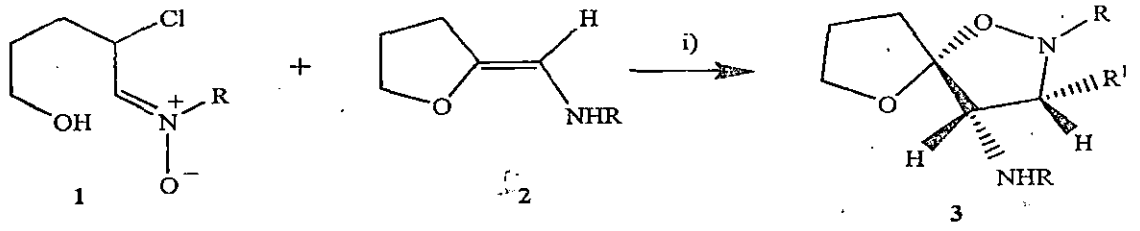
Spectroscopic data for p-hydroxy benzaldehyde (entry 5)

Yield: 776mg (89%); colourless liquid; R_f = 0.40; IR (KBr): 1690(s), 1320(m), 1210 (m), 782(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.76 (s, 1H, CHO), 7.05 – 6.93 (m, 4H, C_6H_5), 5.80 (s,1H, OH); ^{13}CNMR ($CDCl_3$): δ 201.64 (CHO), 134.10, 132.74, 130.40, 128.50 (aromatic carbons); FAB – MS: *m/z* 122 (M^+), 93, 92(B.P), 29; HRMS-EI: Calcd. for $C_7H_6O_2$ (M), 122.0530, Found: M^+, 122.0512.



Scheme -1

Reagents and conditions : i) Dry ether, pyridine, r.t , N_2 atmosphere
ii) Dry ether, Na_2CO_3, r.t , N_2 atmosphere



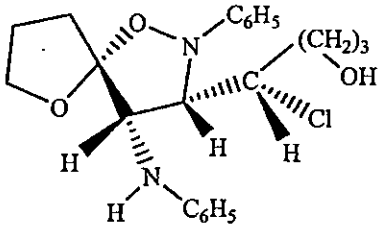
Scheme - 2

i) Reaction condition : Dry ether, RT, N_2 atmosphere, 5 - 8 hr

General procedure for cycloaddition reaction of nitrone 1 (R = Ph) with furan derivative 2 (R = Ph)

To a stirred solution of *N*–phenyl-α-chloro nitrone **1** (R = Ph; 61.8375 mg, 0.2855 mmol) in 25 mL dry ether was added **2** (R = Ph, 50 mg, 0.2855 mmol, 1 equivalent) and stirred at RT with a magnetic stirrer

under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.46). After completion of the reaction, the solvent was evaporated using a rotary evaporator to afford crude cycloadduct **3** (R=Ph) which was purified by column chromatography using ethyl acetate - hexane and was obtained as dark red viscous liquid **3** (R=Ph; 95 mg, 85% ; Scheme-2). This procedure was followed for the synthesis of other spiro cycloadducts **3** (R=Me).

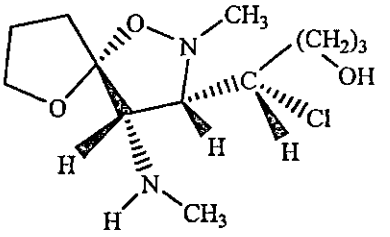


3 (R=Ph)

(S)-4-chloro-4-((3S,4S,5R)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol

Spectroscopic data for 3 (R = Ph)

Yield: 95mg (85%); dark red viscous liquid; R_f = 0.46; IR ($CHCl_3$): 3485 – 3290 (br), 2825 (m), 2425 (m), 1620 (s), 1445 (m), 1260 (m), 1040 (m), 780 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.98 - 6.93 (m, 10H, 2 x C_6H_5), 5.84 (d, 1H, J = 9.20 Hz, C_4H), 4.96 (br, 1H, CH_2OH, exchanged in D_2O), 3.51 (dd, 1H, J = 9.34, 7.88 Hz, C_3H), 3.45 (s, 1H, N – H proton), 2.61 (dt, 1H, J = 9.44, 8.72 Hz, CHCl), 1.88 – 1.15 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 138.00, 136.50, 134.30, 133.80, 131.75, 130.42, 129.46, 128.64 (aromatic carbons), 95.10 (CHCl), 86.40 (C_5), 73.75 (C_3), 53.30 (C_4), 30.20, 28.55, 27.34, 26.22, 25.73, 24.37 (6 CH_2 carbons). MS (*m/z*): 404 (M^++2), 402 (M^+), 325, 310, 309, 218 (B.P), 107, 91, 77. HRMS-EI: Calcd. for $C_{22}H_{27}O_3N_2Cl$ (M), 402.7130, Found; M^+, 402.7122.

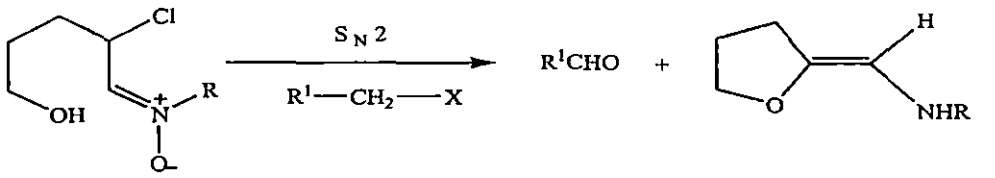


3 (R=Me)

(S)-4-chloro-4-((3S,4S,5R)-2methyl-4-(methylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol

Spectroscopic data for 3 (R = Me)

Yield: 91mg (83%); red gummy liquid; R_f = 0.40; IR ($CHCl_3$): 3460 – 3326 (br), 2835 (m), 2420 (m), 1440 (m), 1325 (m), 980 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.83 (br, 1H, CH_2OH, exchanged in D_2O), 4.50 (br, 1H, $NHCH_3$), 3.31 (s, 6H, 2 x N-CH_3), 2.99 (d, 1H, J = 9.16 Hz, C_4H), 2.50 (dd, 1H, J = 9.06, 7.60 Hz, C_3H), 2.19 (dt, 1H, J = 9.16, 8.50 Hz, CHCl), 1.66 – 1.60 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 93.00 (CHCl), 87.55 (C_5), 76.20 (C_3), 55.20 (C_4), 41.97 (N-CH_3), 40.24 (NH-CH_3), 33.37, 31.50, 28.68, 26.00, 25.12, 23.40 (6 CH_2 carbons). MS (*m/z*): 280 (M^++2), 278 (M^+), 263, 248, 156 (B.P), 141, 107. HRMS-EI: Calcd. for $C_{12}H_{23}O_3N_2Cl$ (M), 278.6710, Found; M^+, 278.6698.



R = Me ; Ph R^1 = Et; Pr; Ph X = C l

Table-1 : Aldehyde synthesis using α-chloro nitrones

Yield %	Entry	Nitrone	Alkyl halide[a]	Product[b]	Time Hrs
88	1	R = Me	Benzyl chloride	Benzaldehyde	5
87	2	R = Me	1-chloro propane	Propionaldehyde	6
88	3	R = Ph	Benzyl chloride	Benzaldehyde	5
86	4	R = Ph	n-butyl chloride	n-Butyraldehyde	6
89	5	R = Me	p-hydroxy benzyl chloride	p-hydroxy benzaldehyde	4
89	6	R = Ph	p-hydroxy benzyl chloride	p-hydroxy benzaldehyde	5

[a] Reaction condition:α-chloro nitrone (3.0198 mmol),alkyl halide (1 equivalent),dry ether,Py,Na_2CO_3,N_2 atmosphere, RT

[b] All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS spectral data.

[c] Isolated yield after purification.

RESULTS AND DISCUSSION

α-chloro nitrones (1) are moderately stable and can be isolated while transient nitrone **1a** can not be isolated because of its high unstability and undergoes decomposition at room temperature. The lone pair of electron of the OH group of α-chloro nitrone facilitates intramolecular S_N2 reaction in presence of pyridine and is actually the driving force for the development of transient nitrone **1a**. Nitrone **1a** reacts very quickly with different alkyl halides (S_N2 reaction) and develops an intermediate compound (**1b**). The labile N-O bond of **1b** undergoes cleavage[12] when the reaction mixture is stirred with solid sodium carbonate which plays an important role for the development of aldehyde and furan derivative (2) as side product in a Kornblum type process (Scheme-1;Table 1). The novelty of the study is the use of α-chloro nitrone as an oxidizing reagent in aldehyde synthesis and newly developed side product as novel dipolarophile in cycloaddition reactions. The isolated side products (2) are equally efficient like other conventional dipolarophiles used for cycloaddition reactions and leads to the formation of regioselective 5-substituted spiro cycloadduct (3)[13,14] in 1,3-dipolar cycloaddition reaction with nitrone **1** (Scheme-2) and thereby offering greater scope for its applications. The yield of the isolated aldehydes are extremely high (**85 - 89%**) in a much lesser time and are much better in case of active alkyl halides compared to inactive alkyl halides. The results are summarized in Table 1. The beauty of the reaction lies in addition of pyridine at the begining to generate transient nitrone (**1a**) which is only capable of developing furan derivative (2) as side product and can be utilized as a new efficient dipolarophile in 1,3-DCR and thereby the reaction as a whole becomes atom efficient. Simple nitrones[15](benzaldehyde derived nitrone) can also be employed as an oxidizing reagent for aldehyde synthesis (synthesized propionaldehyde:yield 67%) but the side product obtained is a waste and can not be used for further reactions. At the outset of this work it was not clear about the development of transient nitrone (**1a**) but after completion of the study and spectral analysis of side product (2) the development of transient nitrone **1a** was confirmed. The products especially aldehydes are known compounds and spectral data of the synthesized aldehydes are almost

identical to the values found in literature. For example, sharp singlet signals at δ 9.80 & 198.00 in the NMR spectrum (^1H, ^{13}C respectively) along with molecular ion peak at 106, base peak at 105 and peaks at 77, 51 in the MS spectrum give strong evidence in favour of benzaldehyde formation. The oxidation side product (**2**) was obtained as single isomer having *E* configuration in all the cases and the yield of the side product was almost **10 – 13%** when isolated in pure condition.The spectral data of the oxidation side products (**2**) also agreed well with the assigned structures. The spiro cycloadducts (**3**) were obtained as regioselective single isomer predominantly in 1,3-DCR of α-chloro nitrone (**1**) with side product (**2**) having high yields (**70 – 85%**) when isolated in pure condition. The stereochemistry of the 5-substituted regioselective spiro cycloadducts (**3**) in all the cases were rationalized by considering the multiplicity of the proton signals at 3-H, 4-H and CHCl asymmetric centres along with their coupling constant values.[16] In the spiro isoxazolidine derivatives (**3**), 3-H resonates around δ_H 3.50 to 2.50 ppm while for the 4–H around δ_H 5.80 to 3.00 ppm and the coupling constant is $J_{3,4} \sim 9.20$ Hz implying a *cis* relationship between H-3 and H-4. The CHCl proton also resonates around δ_H 2.60 to 2.20 ppm. The 3-H and CHCl protons are also *syn* as evidenced from their coupling constant values ($J_{3,CHCl} \sim 9.16$ to 9.40 Hz).[16] Cycloaddition of *Z* nitrone (both the reported α-chloro nitrones are of *Z* configuration in this communication) via *exo* transition state geometry results in the formation of *syn* isoxazolidine derivatives. Cycloaddition reaction using furan derivatives (**2**) with other simple nitrones[15,17,18] are in progress using the same methodology. A preferential conformation for the spiro regioselective isoxazolidine derivatives (**3**) may be represented in Figure 1. Reaction of nitrone **1** with methyl iodide and ethyl bromide was also studied for the synthesis of formaldehyde and acetaldehyde respectively but no significant results were obtained because of the volatility of formaldehyde and difficulculties associated with the synthesis of acetaldehyde. These are the drawbacks of this methodology.

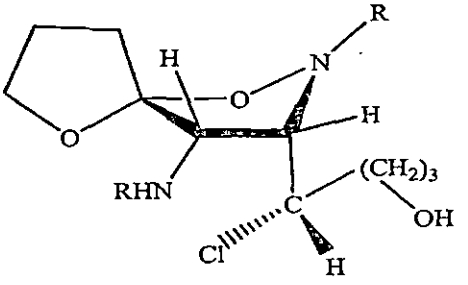


Fig 1- General conformation for the cycloadducts **3**

CONCLUSION

Finally, we developed a new atom efficient methodology for the aldehyde synthesis using α-chloro nitrone as oxidizing reagent and considered further reaction carried out on the side product with α-chloro nitrones in 1,3-dipolar cycloaddition reaction for the development of stereochemically important 5-spiro isoxazolidines. The formation of the desired cycloadducts were obtained in good yields within a short reaction time. The newly developed side products (furan derivatives, **2**) are equally effective as dipolarophile in cycloaddition reactions like other conventional dipolarophiles used for cycloaddition reactions. The notable advantages offered by this method are one pot synthesis, simple operation, easy workup, mild and faster reaction conditions with high yield of products.

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REFERENCES

1. V. Bertini, F. Lucchesini, M. Pocci, S. Alfei, *Tetrahedron.*, **61**, 9519, (2005).
2. J. Tang, J. Zhu, Z. Shen, Y. Zhang, *Tetrahedron Letters*, **48**, 1919, (2007).

3. A.R. Katritzky, M.J. Cook, S.B. Brown, R. Cruz, G.H. Millet, A. Anani, *J.Chem.Soc, Perkin I.*, 2493, (1979).
4. G. Cardillo, M. Orena, S. Sandri, *J.Chem. Soc. Chem. Commun.*, 190, (1976).
5. S.V. Lieberman, *J. Am. Chem. Soc.*, **77**, 1114, (1954).
6. W.P. Griffith, J.M. Jollife, S.V. Ley, P.D.Tiffin, K.F. Springhorn, *Syn. Commun.*, **22**, 237, (1992).
7. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem.*, **48B**, 447, (2009).
8. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem.*, 2009, (in press, MS no: SCCB-1225)
9. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Heterocycl. Chem.*, **18**, 203, (2008).
10. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem.*, 2009, (in press, MS no: SCCB-1300)
11. B. Chakraborty, M.S. Chhetri, *Indian J. Heterocycl. Chem.*, **17**, 213, (2008).
12. W.R. Hoffmann, G. Eichler, A. Endesfelder, *Liebigs Ann. Chem.*, 2000, (1983).
13. R. Newton, P.G. Savage, *Australian J. Chem.*, **61**, 432, (2008).
14. K. Aouadik, S. Vidal, P.J. Praly, *Synlett.*, **19**, 3299, (2006).
15. V.K. Aggarwal, R.S. Grainger, H.Adams, P.L. Spargo, *J.Org.Chem.*, **63**, 3481, (1998).
16. P. Deshong, W. Li, J.W. Kennington, H.L. Ammon, *J. Org. Chem.*, **56**, 1364, (1991).
17. B. Chakraborty, M.S. Chhetri, *Indian J. Heterocycl. Chem.*, **18**, 201, (2008).
18. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem.*,2009, (in press, MS no: SCCB-1206)

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STEREOSELECTIVE SYNTHESIS OF ISOXAZOLINES FROM N-CYCLOHEXYL-α-AMINO NITRONE AND THEIR ANTIBACTERIAL ACTIVITY

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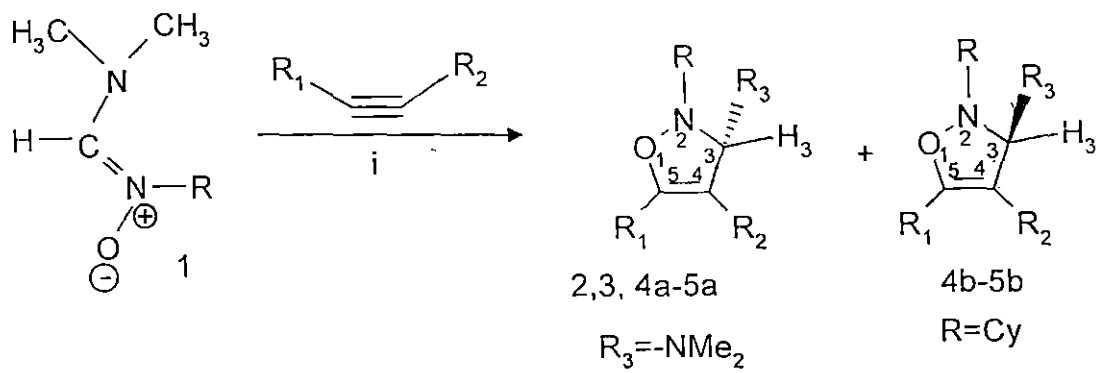
Stereoselective isoxazolines were prepared from N-cyclohexyl-α-amino nitrone using 1,3-dipolar cycloaddition reaction with alkynes at room temp. All the synthesized compounds showed significant antibacterial activity.

In continuation of our earlier work on isoxazolidine synthesis using α-amino nitrones under solvent free conditions (synthesized from formamide and N-phenylhydroxylamine)[1,2], we now wish to report one pot. stereoselective synthesis of novel isoxazolines in high yield from N-cyclohexyl-α-amino nitrone (**1**)[3] at room temp and their antibacterial activity (Scheme-1, Table-1). The products of such cycloadditions have a variety of applications[4], such as potential antibacterial agents.

Cycloadditions of alkynes even with electron deficient and unsymmetrical alkynes are often conducted at elevated temp. In this communication we have reported synthesis of isoxazolines at room temp in high yield in a very short reaction time.

Antibacterial activity

All the synthesized isoxazolines **2-5** were subjected to *in vitro* screening against *Vibrio parahaemolyticus, Klebsiella pneumoniae, Bacillus subtilis, Proteus vulgaris, Staphylococcus aureus, Shigella flexneri, Eschericia coli, Salmonella typhi, Vibrio cholerae.* The minimum inhibitory conc (MIC) was determined using cup plate assay method[4]. Nutrient agar was used as a culture medium. At first strains of desired bacteria were



i) RT, 6-8 hr, N_2 atmosphere

2: R_1=Ph; R_2=$COOCH_3$
3: R_1=R_2=$COOCH_3$
4: R_1=$COOC_2H_5$; R_2=H
5: R_1=COOH; R_2=H

SCHEME-1

Table-1
Reaction of nitrone 1 with alkynes

Cycloadducts[a] (2-5)	Time (hr)	Status	R_f	Total Yield[b] (%)
2	6	Pale yellow gummy liquid	0.62	96
3	7	Red liquid	0.58	92
4	6	White viscous liquid	4a:0.44	92 4b: 0.50
5	8	Yellow liquid	5a: 0.38	89 5b: 0.54

[a]All the reactions were carried out at RT
[b]Isolated yields after purification

isolated and were suspended in normal saline. From each bacterial suspension 0.1 ml was taken with the help of pipette and was spread on prepared nutrient agar plate, with the help of spreader. Then cups were scooped out from each plate with the help of a cork borer and then to the respective cups different derivatives of the isoxazoline (**2-5**) of conc (1000 μg/ml, 600, 400, 200, 100, 50, 25, 10 μg/ml) were added. The plates were incubated at 37° for 24 hr and results were recorded. The lowest conc, which showed no visible growth, was taken as an end point min inhibitory conc (MIC). All the compounds showed MIC 10 μg/ml except **4**a and **5**b. They showed MIC 50 μg/ml against *Bacillus subtilis* and *Proteus vulgaris*. It has been observed that the derivatives of isoxazolines **2**,**3**,**4**b, **5**a have antibacterial activity against both Gram positive (*S. aureus, B. subtilis*) and Gram negative (*E. coli, S. flexneri*) strains. The MIC value obtained for isoxazoline derivatives ranged from 10 μg/ml - 50μg/ml are very close to the MIC values of most commonly used antibiotics like Penicillin (10 units), Sulphonamide (300 μg/ml), Nalidixic Acid (512 μg/ml) etc. and hence they are equally effective[5].

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (J) are given in Hz. IR spectra were obtained on a Perkin-Elmer RX1 881 machine as film for all the products. Mass spectra were recorded on a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q-Tof micro instrument (YA-105). Elemental analyses (C,H,N) were performed on a Perkin-Elmer 2400 series CHN analyzer. TLC was carried out on Fluka silica gel TLC cards.

Cycloaddition at elevated temp.

A mixture of N-cyclohexylhydroxylamine (8.7 mmol) and N,N-dimethyl formamide (9 ml, 1 equivalent) was heated in presence of anhyd $MgSO_4$ with stirring with a magnetic stirrer for 6 hr. The formation of nitrone 1 was monitored by TLC (R_f=0.38) and ethyl propiolate (1 equivalent) was added *insitu* at this stage and heating continued with stirring for another 6 hr. (monitored by TLC, R_f=0.37, 0.42). The crude product was isolated by extraction with ether and washed with brine water. Finally gummy product purified by column chromatography using ethyl acetate and hexane. But this methodology was not followed because of poor yield (28%) which may be due to decomposition of nitrone at

elevated temp.

Cycloaddition at room temp.

A mixture of N-cyclohexylhydroxylamine (8.7 mmol), and N,N-dimethyl formamide (9 ml, 1 equivalent) was stirred in presence of anhyd $MgSO_4$ at RT for 8 hr. The formation of nitrone **1** was monitored by TLC (R_f=0.40) and ethyl propiolate (1 equivalent) was added *insitu* at this stage and stirring continued at RT for another 6 hr. The formation of isoxazoline derivatives was monitored by TLC (R_f=0.44, 0.50). The crude product was isolated by extraction with ether and washed with brine water. Finally the cycloadduct was obtained under reduced pressure after column chromatography using ethyl acetate and hexane as viscous liquids. **4a**: 172mg, 70%, **4b**: 58mg, 22%. This procedure was followed for other products listed in Table-1.

2: IR ($CHCl_3$): 3155, 1750, 1665, 1658, 1430, 1360, 770, cm^{-1} ^1H NMR ($CDCl_3$): δ 7.64-7.53 (m, 5H, C_6H_5), 4.05 (s, 1H, C_3H), 3.63 (s, 3H, $COOCH_3$), 2.76 (br, 6H, NMe_2), 2.34-2.22 (m, 1H, N-CH proton), 1.95-1.66 (m, 10H, CH_2, protons); ^{13}C NMR ($CDCl_3$): 172.5 (carbonyl carbon), 137, 135.4, 134, 132.6 (aromatic carbons), 88(C_5), 73(C_3), 57.4 (C_4), 45 (-$COOCH_3$), 33; 29.5 (N-CH_3 carbons), 26, 24.8, 23.4, 21.8, 20, 18.7 (CH_2 carbons). MS (FAB) m/z: 330 (M^+), 286, 247, 246, 225, 194, 148, 105 (B.P.), 83, 77, 31. HRMS-EI: [Found : M^+. 330.1919 $C_{19}H_{26}O_3N_2$ requires (M), 330.1935].

3 : IR ($CHCl_3$): 3145, 2820, 1745, 1700, 1670, 1420, 1260, cm^{-1}. ^1H NMR ($CDCl_3$): 4.75 (s, 1H, C_3H), 3.66 (s, 3H, $COOCH_3$), 3.60 (s, 3H, -$COOCH_3$), 2.68 (br, 6H, NMe_2), 2.40-2.28 (m, 1H, N-CH proton), 2.05-1.64 (m, 10H, CH_2 protons). ^{13}C NMR ($CDCl_3$): 169, 167.4 (carbonyl carbons), 87.5 (C_5), 76(C_3), 59.4 (C_4), 44, 43 ($COOCH_3$), 31, 29.4 (N-CH_3 carbons), 25.8, 24.3, 23.9, 22.7, 20.6, 18.5 (CH_2 carbons). MS (FAB): m/z : 312(M^+), 281, 268, 229, 228, 225 (B.P.), 194, 185, 83, 59, 44, 31. HRMS-EI: [Found : M^+, 312.1668 $C_{15}H_{24}O_5N_2$ requires (M), 312.1677].

4a: IR ($CHCl_3$): 3165, 2945, 1770, 1680, 1656, 1430, 1260, cm^{-1}. ^1H, NMR ($CDCl_3$): 4.64 (d, 1H, J=9.3 Hz, C_3H), 4.26 (dd, 2H, J=6.24, 6.36 Hz, $COOCH_2CH_3$), 3.35 (d, 1H, J=9.2 Hz, C_4H), 2.76 (br, 6H, NMe_2), 2.46-2.30 (m, 1H, N-CH proton), 2.04-1.67 (m, 10H), 1.40 (t, 3H, J=4.36 Hz, $COOCH_2CH_3$). ^{13}C NMR ($CDCl_3$): 173.4 (carbonyl carbon), 86(C_5), 78(C_3), 55(C_4), 32 ($COOCH_2CH_3$), 30 ($COOCH_2CH_3$), 28.8, 27.3 (N-CH_3 carbons), 25, 23, 22.2, 20.8, 19, 18.4 (CH_2 carbons). MS.(FAB), m/z : 268(M^+), 224, 195, (B.P.), 185, 184, 141, 83, 73. HRMS-EI [Found : M^+. 268.1763 $C_{14}H_{24}O_3N_2$ (M) 268.1779].

4b: IR ($CHCl_3$): 3160, 2955, 1770, 1684, 1658, 1435, 1255. ^1H NMR ($CDCl_3$): 4.58 (d, 1H, J=2.53 Hz, C_3H), 4.32 (dd, 2H, J=7.14, 6.16 Hz, $COOCH_2CH_3$), 3.26 (d, 1H, J=2.58 Hz, C_4H), 2.66 (br, 6H, NMe_2), 2.24-2.12 (m, 1H, N-CH proton), 1.94-1.53 (m, 10H), 1.24 (t, 3H, J=4.08 Hz, $COOCH_2CH_3$). ^{13}C NMR ($CDCl_3$): 172 (carbonyl carbon), 88 (C_5), 76.6 (C_3), 57.2 (C_4), 33.4 ($COOCH_2CH_3$), 31.7 ($COOCH_2CH_3$), 29, 27.8 (N-CH_3 carbons), 26.1, 24, 23, 21.4, 20.2, 18.3 (6 CH_2 carbons). MS (FAB) m/z : 268(M^+), 224, 223, 195 (B.P.), 185, 184, 141, 83, 73, 45. HRMS-EI : [Found : M^+, 268.1756 $C_{14}H_{24}O_3N_2$ (M) 268.1779].

5a: IR ($CHCl_3$): 3144, 2942, 1765, 1684, 1660, 1440, 1310. ^1H NMR ($CDCl_3$): 10.8 (s, 1H, COOH), 4.52 (d, 1H, J=9.46 Hz, C_3H), 3.82 (d, 1H, J=9.44 Hz, C_4H), 2.58 (br, 6H, NMe_2), 2.33-2.24 (m, 1H, N-CH proton), 2.12-1.74 (m, 10H) ^{13}C NMR ($CDCl_3$): 181.3 (carbonyl carbon), 87(C_5), 78.5(C_3), 56.5 (C_4), 32.2, 30.7 (N-CH_3 carbons), 27, 25.3, 24.2, 23, 21, 18 (CH_2 carbons). MS (FAB) m/z : 240(M^+), 196, 195, (B.P.), 167, 157, 83, 73, 45. HRMS-EI: [Found (M^+), 240.1452 $C_{12}H_{20}O_3N_2$ requires (M), 240.1467].

5b: IR ($CHCl_3$): 3155, 2950, 1770, 1680, 1655, 1444, 1250. ^1H NMR ($CDCl_3$): 11.4 (s,1H, -COOH), 4.63 (d, 1H, J=2.56 Hz, C_3H), 3.75 (d, 1H, J-2.64 Hz, C_4H), 2.53 (br, 6H, NMe_2), 2.40-2.28 (m, 1H, N-CH proton), 1.90-1.58 (m, 10H) ^{13}C NMR ($CDCl_3$): 180 (carbonyl carbon), 88.4 (C_5), 76(C_3), 57(C_4), 34, 32.8 (N-CH_3 carbons), 28, 27.4, 25, 23.1, 22.2, 19 (6 CH_2 carbons). MS (FAB) m/z : 240(M^+), 196, 195(B.P.), 167, 157, 156, 83, 73,

45, 44. HRMS-EI [Found : M^+, 240.1449 $C_{12}H_{20}O_3N_2$ requires (M), 240.1467].

Acknowledgment

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References

1. B. Chakraborty, J.P. De Britto and A.R. Ghosh, *Indian J. Heterocyclic Chem.*, **6** (1996), 77.
2. B. Chakraborty and M.S. Chhetri, *Indian J. Heterocyclic Chem.*, **17** (2008), 213.
3. B. Chakraborty, S. Kafley and M.S. Chhetri, *Indian J. Chem. Sec.B*, (2009), in press.
4. J.M. Andrews, *J. Antimicrobial Chemotherapy*, **48** (2001), 5.
5. A.N. Chakraborty, J. Molnar, S.G. Dastidar and N. Motohashi, *Non Antibiotic: A New Class of Unrecognized Antimicrobics*, (1998), NISCOM, India.

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Note

One pot stereoselective synthesis of isoxazolines from N-phenyl-α- chloro nitrone

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Isoxazolines have been synthesized from N-phenyl-α-chloro nitrone using 1,3 dipolar cycloaddition reaction with alkynes and the reactions are found to be highly stereoselective in nature. The products have been characterized by analytical and spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) data.

Keywords: N-phenyl-α-chloro nitrone, 1,3 DCR, isoxazolines, stereoselectivity

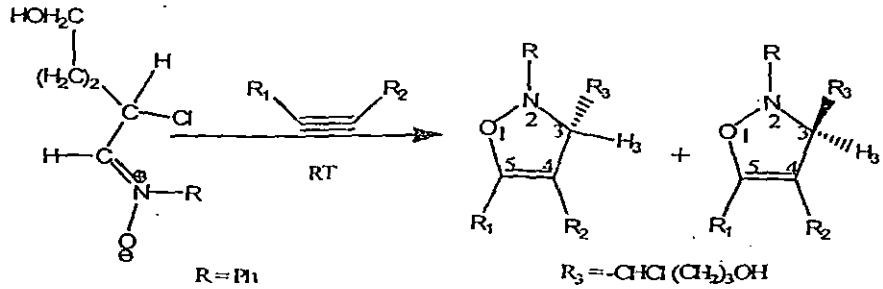
In continuation of our earlier work on isoxazolidine synthesis using α-chloro and α amino nitrones in solid phase and in hydrated media[1-3], we now wish to report an efficient method for the stereoselective synthesis of isoxazolines from N-phenyl-α-chloro nitrone with an excellent yield (**Table I**). 1,3 Dipolar cycloadditions are powerful methods for constructing a variety of five-membered heterocycles in a convergent manner from relatively simple precursors and these heterocycles have a variety of applications including as antibacterial agents[4]. Cycloadditions of alkynes even with electron deficient and unsymmetrical alkynes are often conducted at elevated temperature[5]. In this communication we have reported synthesis of isoxazolines at room temperature with high yield. This is due to the fact that N-phenyl-α-chloro nitrone has considerably higher ionization potential than normal nitrones due to the electron withdrawing effect of chlorine and therefore nitrone (LUMO) - dipolarophile (HOMO) interactions are so important that cycloadditions take place at room temperature[6].

Results and Discussion

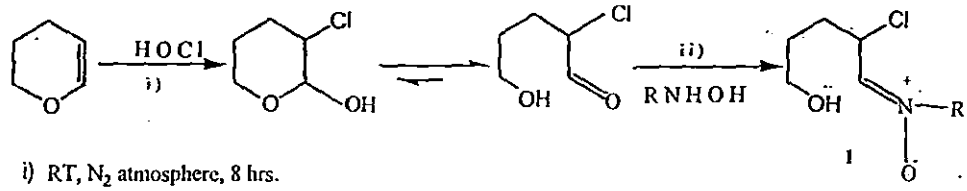
In an initial investigation, we examined the reaction of nitrone 1 with ethyl propiolate at elevated temperature having 34% yield of isoxazoline in 12 hr while at room temperature 92% yield of isoxazolines are reported in 12 hr which indicates the decomposition of the nitrone at elevated temperature. This could also be explained due to secondary orbital effect between the carbon of the nitrone (HOMO) and the adjacent atom of the electron withdrawing group of the dipolarophile (LUMO)[7]. The concerted nature of these cycloaddition reactions with nitrone as 1,3 dipole has been generally accepted. The region-selectivity in these reactions was rationalized by using the frontier orbital theory[8]. The ethyl propiolate adduct corresponds to this theory. Therefore, the 5 substituted adduct for ethyl propiolate is due to LUMO (nitrone)- HOMO (dipolarophile) interaction. For the present study, we have chosen highly electron deficient and unsymmetrical alkynes like dimethyl acetylene dicarboxylate, phenyl methyl propiolate and ethyl propiolate respectively to study the stereo-selectivity in these cycloadditions.

Excellent diastereofacial selectivity is observed in nitrone additions described here with alkynes. The addition of N-phenyl-α-chloro nitrone **1** (**Scheme I**, R = Ph) to alkyne results in a mixture of diastereoisomer **2a-4a** and **2b-4b** (**Scheme II**, almost 70 : 30 ratio in all cases). These results can be rationalized by an exo approach of the nitrone for the major cycloadducts (**2a-4a**) which have the Z configuration (transition state **I**)[9]. The minor cycloadducts (**2b-4b**) are formed by the endo approach of Z nitrone (transition state **II**)[10]. However these results can also be explained by an endo approach of the nitrone in an E configuration (transition state **III**) for the major adduct and the exo approach of this isomer for the minor adduct (transition state **IV**)[10]. Most relevant are the coupling constants ($J_{H3,CHCl}$; $J_{H3,\ H4}$ for **4**) of the diastereo-isomers. For **2a-4a** (R = Ph), this coupling constant is almost 9.2 to 9.3 Hz, implying a *cis* relationship between H_3 and CHCl and also H_3 and H_4 (for **4a** only) whereas **2b-4b** (R = Ph) has a coupling constant of 2.5 to 2.58 Hz which implies a *trans* relationship between H_3 and CHCl and also H_3 and H_4 (for **4b** only)[11-14]. Comparing the ^{1}H NMR spectrum of **2a-4a** and **2b-4b**, we suggest the major and minor conformers of isoxazoline ring systems[11] for **2a-4a** and **2b-4b** (**Figure 1**). All the cycloadducts are stable and detailed study of the mass spectrum (**Scheme III**) reveals that prominent molecular ion peak and base peaks are obtained as expected. Like other isoxazoline

Table I



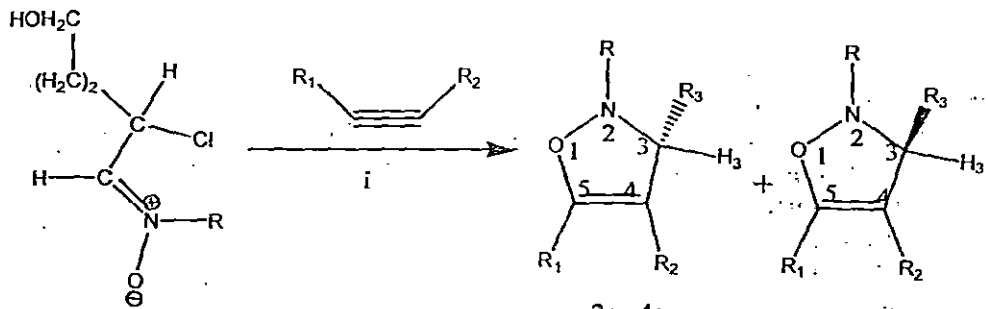
Entry	Nitrone	Dipolarophile	Time (hr)	Cycloadducts (diastereoisomers)	Total Yield (%)
1	N-phenyl-α-chloro nitrone	Phenyl methyl propiolate	10	Pale yellow gummy liquids	96
2	N-phenyl-α-chloro nitrone	Dimethyl acetylene dicarboxylate	10	Red & dark red liquids	92
3	N-phenyl-α-chloro nitrone	Ethyl propiolate	12	White viscous liquids	92



i) RT, N_2 atmosphere, 8 hrs.

ii) RT, N_2 atmosphere, dry ether, anhydrous $MgSO_4$, 8 hr.

Scheme I



i) RT, 10 - 12 hr, N_2 atmosphere

2 : R_1 = Ph; R_2 = $COOCH_3$
3 : R_1 = R_2 = $COOCH_3$
4 : R_1 = $COOC_2H_5$; R_2 = H

Scheme II

derivatives reported in the literature[5,7,10], we have also obtained expected fragmentation peaks due to the development of different aziridine derivatives. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate, $COOCH_3$ for dimethyl acetylene dicarboxylate and $COOC_2H_5$ for ethyl propiolate respectively. Hence it is confirmed that during mass fragmentation, the adducts underwent rearrangement to aziridine derivatives. The detail mass fragmentation pattern is shown in **Scheme III**. In conclusion, the present procedure provides an efficient methodology for the synthesis of isoxazoline and their derivatives with high stereoselectivity. The notable advantages offered by this method are simple operation, mild

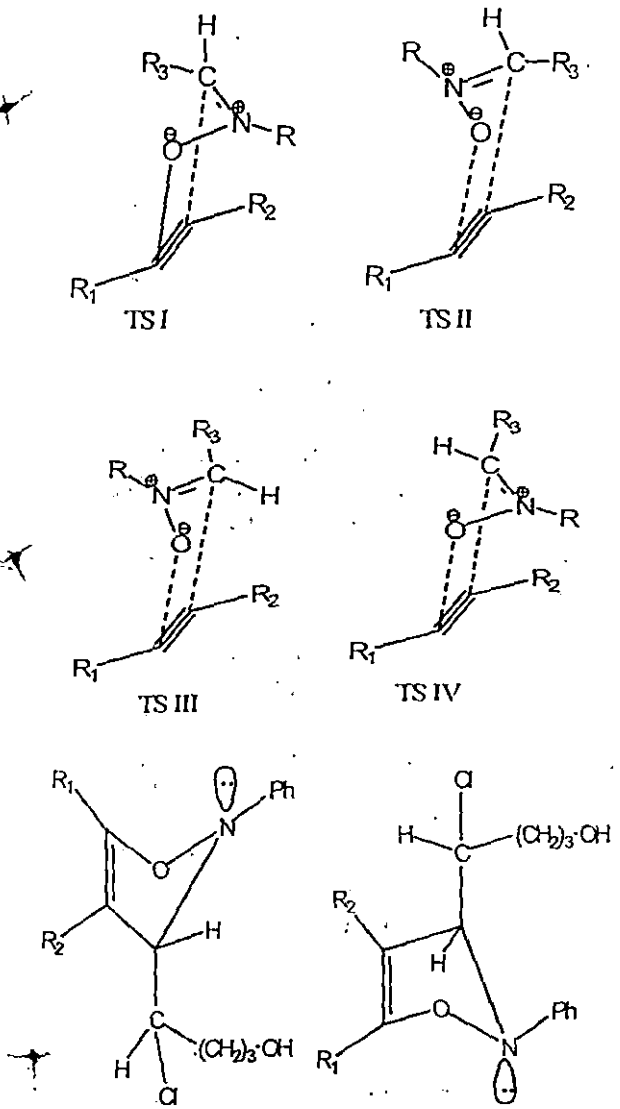


Figure 1

reaction conditions (RT), much faster reactions and high yield of products.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX1 881 machine as film for all the products. Mass spectra were recorded with a Jeol SX-102 (FAB) instrument. Elemental analyses (C,H,N) were perfomed with a Perkin-Elmer 2400 series CHN analyzer. TLC was carried out on Fluka silica gel TLC cards. N-phenylhydroxyl amine was prepared according to the published procedures[1,2]. All other reagents and solvents were used as received from commercial suppliers.

General procedure for the preparation of nitrone

N-phenyl-α-chloro nitrone was prepared following the same methodology as already reported for N-cyclohexyl-α-chloro nitrone[13,14]. N-Phenylhydroxylamine[1,2] (2.20 mmole) was added to chlorohydrin (1 equivalent) in dry ether (100 mL) and anhydrous $MgSO_4$. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 hr. The formation of nitrone was monitored by TLC having R_f = 0.36. The nitrone was isolated under reduced pressure as white neddle shape crystals (m.p: 58°C, 93%, **Scheme I**).

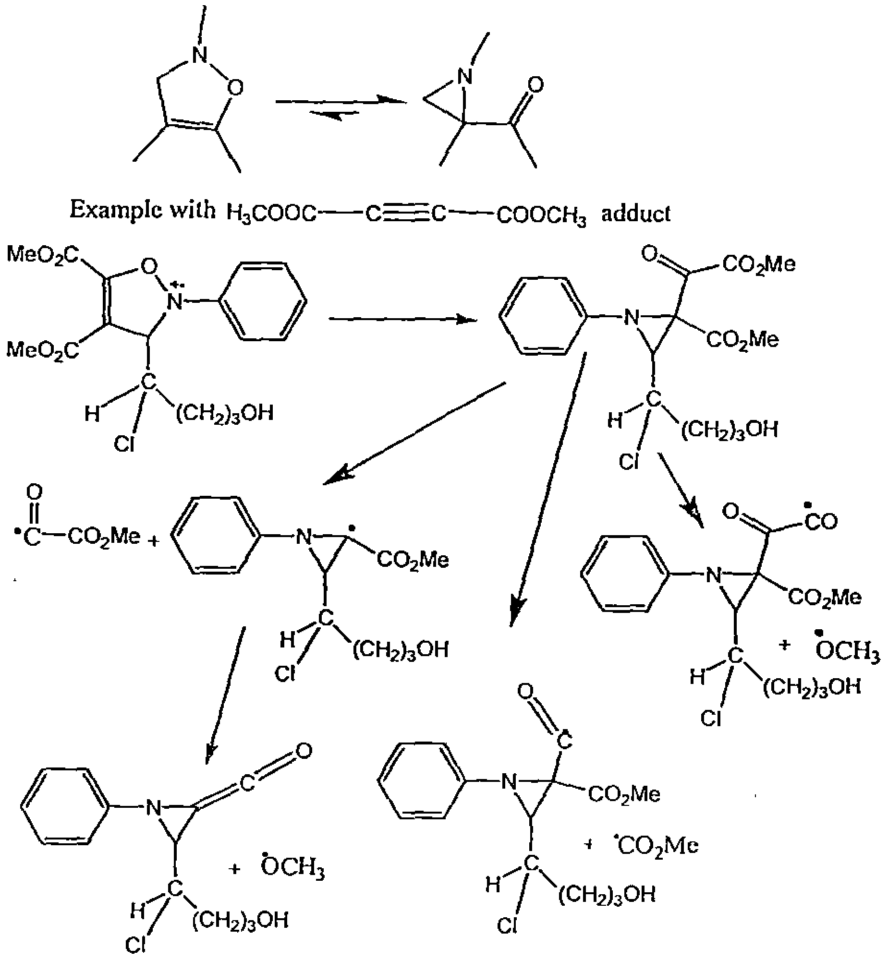
Nitrone 1. IR ($CHCl_3$): 3640-3440 (br), 1660(s), 1600(s), 1360(m), 1310(m), 770(s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.22 (d, 1H, CH=N$^+$), 7.10-6.95 (m, 5H, C_6H_5), 5.10-5.02 (br,1H, -OH, exchanged in D_2O), 4.30-4.15 (dd, 1H, *J*=6.16, 6.08 Hz, CHCl), 2.20-1.66 (m, 6H, CH_2 protons); ^{13}C NMR($CDCl_3$): δ 142.6 (CH=N$^+$), 136-126 (6 signals, 6 aromatic carbons), 54 (CHCl), 43, 40, 37 (3 CH_2 carbons); HRMS-EI: Calcd. for $C_{11}H_{14}O_2NCl$, (M), 227.8173, Found; M$^+$, 227.8158.

General procedure for cycloaddition at elevated temperature

Initially the cycloaddition reaction was performed at elevated temperature in case of ethyl propiolate following the methodology of cycloaddition reactions as already reported[13]. Nitrone **1** (2.20 mmoles) and ethyl propiolate (1 equivalent) was added in CH_2Cl_2 (20 mL) under N_2 atmosphere and the reaction mixture was refluxed for 12 hr. The reaction was monitored by TLC (R_f = 0.38, 0.33). The solvent was evaporated off and the products were isolated by column chromatography using ethyl acetate and hexane. But this methodology was not followed due to poor yield (34%) and decomposition of nitrone at elevated temperature.

General procedure for cycloaddition at room temperature

In a 100 mL conical flask, nitrone **1** (2.20 mmoles), ethyl propiolate (1 equivalent) was added to 50 mL dry ether and stirred at RT with a magnetic stirrer



Scheme III

under N_2 atmosphere for 12 hr. The progress of the reaction was monitored by TLC (R_f = 0.46, 0.40). After completion of the reaction, the solvent was evaporated under reduced pressure and the mixture of diastereoisomers were purified and separated by column chromatography using ethyl acetate-hexane to furnish white viscous liquids. **4a:** 73 mg, 70%; **4b:** 36 mg, 22 % **(Scheme II)**. This procedure was followed for other substrates listed in **Table I.**

(3S)-Methyl-3-(1-chloro-4-hydroxybutyl)-2,5-diphenyl-2,3-dihydroisoxazole-4-carboxylate, 2a

IR ($CHCl_3$): 3590-3460(br), 2920(s), 1760(s), 1665(m), 1430(m), 1360(m), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55-7.38 (m, 10H, C_6H_5 hydrogens), 5.10-4.95 (br, 1H,-OH, exchangeable in D_2O), 4.55-4.40 (dd, 1H, *J*=9.22, 6.18 Hz, CHCl), 4.05-3.90 (d, 1H, *J*=9.2 Hz, C_3H), 3.60 (s, 3H,-$COOCH_3$), 1.95-1.72 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 168 (carbonyl carbon), 137-126 (6×2 aromatic carbons), 92 (CHCl), 88 (C_5), 73(C_3), 58 (C_4), 45(-$COOCH_3$), 36, 34, 33 (3 CH_2 carbons); MS: *m/z* 388 (M^+), 357, 329, 311, 283, 280, 203, 105, 77; HRMS-EI: Calcd. for $C_{21}H_{22}O_4NCl$ (M), 387.7000, Found: M^+, 387.6990.

(3R)-Methyl-3-(1-chloro-4-hydroxybutyl)-2,5-diphenyl-2,3-dihydroisoxazole-4-carboxylate, 2b

IR ($CHCl_3$): 3520-3440 (br), 2925(s), 1755(s), 1675(m), 1440(m), 1345(m), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52-7.35 (m, 10H, C_6H_5 hydrogens), 5.15-5.05 (br, 1H,-OH, exchangeable in D_2O), 4.54-4.43 (dd, 1H, *J*=2.52, 4.18 Hz, CHCl), 4.08-3.92 (d, 1H, *J*=2.54 Hz, C_3H), 3.62 (s, 3H,-$COOCH_3$), 1.95-1.50 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 168 (carbonyl carbon), 138-126 (6x2 aromatic carbons), 90 (CHCl), 87 (C_5), 76(C_3), 54 (C_4), 45 (-$COOCH_3$), 39, 35, 33 (3 CH_2 carbons); MS: *m/z* 388 (M^+), 357, 329, 311, 283, 280, 203, 105, 77; HRMS-EI: Calcd.

for $C_{21}H_{22}O_4NCl$ (M), 387.7000, Found: M^+, 387.6982.

(3S)-Dimethyl-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate, 3a

IR ($CHCl_3$): 3545-3480 (br), 2820 (s),1745 (s),1700 (m),1670 (m),1420 (s),1260 (m),775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75-7.54 (m, 5H, C_6H_5 protons), 5.22-5.05 (br, 1H, OH, exchanged in D_2O), 4.86-4.75 (d, 1H, *J*=9.25 Hz, C_3H), 4.26-4.10 (dd, *J*=6, 9.26 Hz, CHCl), 3.68 (s,3H,- $COOCH_3$), 3.56 (s,3H,-$COOCH_3$)-phe, 2.20-2.05 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169, 168.4 (carbonyl carbons), 133-126 (6 aromatic carbons), 94 (CHCl), 87.5 (C_5), 76 (C_3), 59.4 (C_4), 44, 43 (OCH_3), 36, 34, 30 (3 CH_2 carbons); MS: *m/z* 370 (M^+), 311, 293, 262, 234, 204, 108, 77, 59, 31; HRMS-EI: Calcd. for $C_{17}H_{20}O_6NCl$, (M), 369.5840, Found; M^+, 369.5828.

(3R)-Dimethyl-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate, 3b

IR ($CHCl_3$): 3555-3485 (br), 2825 (s),1740 (s), 1710 (m), 1660 (m), 1425 (s), 1260(m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70-7.56 (m, 5H, C_6H_5 protons), 5.20-5.08 (br 1H, OH, exchanged in D_2O), 4.88-4.74 (d, 1H, *J*=2.58 Hz, C_3H), 4.36-4.26 (dd, *J*=4, 2.26 Hz, CHCl), 3.66 (s,3H,-$COOCH_3$), 3.54 (s,3H,-$COOCH_3$), 2.12-1.95 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169, 168 (carbonyl carbons), 134-126 (6 aromatic carbons), 95 (CHCl), 88.5 (C_5), 74 (C_3), 56 (C_4), 44, 42 (OCH_3), 36, 35, 30 (3 CH_2 carbons); MS: *m/z* 370 (M^+), 311, 293, 262, 234, 204, 108, 77, 59, 31; HRMS-EI: Calcd. for $C_{17}H_{20}O_6NCl$, (M), 369.5840, Found; M^+, 369.5822.

(3S)-Ethyl-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-5-carboxylate, 4a

IR($CHCl_3$): 3560-3490(br), 2945(s), 1770(m), 1680(s), 1430(m), 1260(m), 780(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.02-6.92 (m, 5H, C_6H_5), 5.10-5.02 (br, 1H, OH, exchanged in D_2O), 4.80-4.64 (t, 1H, *J*=9.26 Hz, C_3H), 4.26-4.12 (dd, 2H, *J*=6.24, 6.36 Hz, $COOCH_2CH_3$), 3.82-3.50 (dd, 1H, *J*=6, 9.28 Hz, CHCl), 3.35-3.26 (d, 1H, *J*=7.5 Hz, C_4H), 3.00-2.62 (m, 6H, CH_2 protons), 1.40-1.24 (t, 3H, *J*=4.36 Hz, $COOCH_2CH_3$); ^{13}C NMR($CDCl_3$): δ 168.4 (carbonyl carbon), 133-126 (6 aromatic carbons), 93 (CHCl), 86 (C_5), 78 (C_3), 55 (C_4), 32, 30 ($COOCH_2CH_3$), 26, 25, 23 (3 CH_2 carbons); MS: *m/z* 326 (M^+), 295, 253, 249, 219, 108, 77, 73; HRMS-EI: Calcd. for $C_{16}H_{20}O_4NCl$ (M), 325.5944, Found; M^+, 325.5932.

(3R)-Ethyl-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-5-carboxylate, 4b

IR($CHCl_3$):3550-3480(br), 2955(s), 1760(m), 1680(s), 1440(m), 1265(m), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.04-6.94 (m, 5H, C_6H_5), 5.14-5.02 (br, 1H, OH, exchanged in D_2O), 4.83-4.62 (t, 1H, *J*=2.26 Hz, C_3H), 4.22-4.10 (dd, 2H, *J*=2.24, 4.06 Hz, $COOCH_2CH_3$), 3.80-3.52 (dd, 1H, *J*=4, 2.28 Hz, CHCl), 3.38-3.22 (d, 1H, *J*=4.12 Hz, C_4H), 3.10-2.64 (m, 6H, CH_2 protons), 1.46-1.20 (t, 3H, *J*=5.24 Hz, $COOCH_2CH_3$); ^{13}C NMR($CDCl_3$): δ 168 (carbonyl carbon), 134-127(6 aromatic carbons), 95 (CHCl), 86.5 (C_5), 76 (C_3), 55.5 (C_4), 31, 30 ($COOCH_2CH_3$), 28, 26, 24 (3 CH_2 carbons); MS: *m/z* 326 (M^+), 295, 253, 249, 219, 108, 77, 73; HRMS-EI: Calcd. for $C_{16}H_{20}O_4NCl$ (M), 325.5944, Found; M^+, 325.5930.

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We are pleased to acknowledge the financial support from UGC. We are grateful to CDRI, Lucknow, for providing spectral data and also Prof. Paul Margeretha, University of Humburg, Germany, for constructive ideas related to the work.

References

1 Chakraborty B & Chhetri M, *Indian J Heterocycl Chem*, 17, 2008, 213.

2 Chakraborty B & Chhetri M, *Indian J Chem*, 47B, 2008, 485.

3 Chakraborty B & Kafley S, *Indian J Heterocycl Chem*, 17, 2008, 293.

4 Padwa A & Pearson W H, "*Synthetic application of 1,3-dipolar Cycloaddition Chemistry toward Heterocycles and Natural products*", (Wiley, New Jersy), 2003.

5 Shintini R & Fu G C, *J Am Chem Soc*, 125, 2003, 10778.

6 (a) Chakraborty B & Ghosh A R, *Indian J Heterocycl Chem*, 6, 1997, 233 and references cited therein.

(b) Chakraborty B, *Indian J Heterocycl Chem*, 6, 1997, 231 and references cited therein.

7 Manabe K, Limura S & Kobayashi S, *J Am Chem Soc*, 124, 2002, 11971.

8 Houk K N, Sims J & Luskus C R, *J Am Chem Soc*, 95, 1973, 7302.

9 Heaney F, Rooney O & Cunningham D, *J Chem Soc, Perkin Trans 2*, 2001, 373.

10 Suwinska K, Solecka J & Chmielewski M, *Tetrahedron*, 58, 2002, 1199.

11 Deshong P, Kennington J W, Li W & Ammon H L, *J Org Chem*, 56, 1991, 1364.

12 Yu Y, Ohno M & Eguchi S, *Tetrahedron*, 49, 1993, 824.

13 Chakraborty B & Ghosh A R, *Indian J Chem*, 33B, 1994, 1113.

14 Chakraborty B & Ghosh A R, *Indian J Heterocycl Chem*, 5, 1995, 99.

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STEREOSELECTIVE SYNTHESIS OF ISOXAZOLINES FROM N-PHENYL α-CHLORO NITRONE

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Isoxazolines have been synthesized from N-phenyl α-chloro nitrone **1** using 1,3 dipolar cycloaddition reaction with alkynes and the reactions are found to be highly stereoselective in nature.

In continuation[1-3] of our earlier work on isoxazolidine synthesis, we now report an efficient method for the stereoselective synthesis of isoxazolines from N-phenyl α-chloro nitrone **1** in excellent yield (Scheme-1).

Excellent diastereofacial selectivity was observed in nitrone additions described here with alkynes. The addition of N-phenyl α-chloro nitrone **1** (Scheme-1, R=Ph) to alkynes results in a mixture of diastereoisomers **1a** & **1b** (almost 70: 30 ratio in all cases).

Experimental

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 79.5 MHz. The coupling constants (J) are given in Hz. IR spectra were recorded on a Perkin-Elmer RX 1-881 machine as film for all the products. MS spectra were recorded on a Jeol SX-102 (FAB) instrument. Elemental analyses (CHN) were performed on a Perkin-Elmer 2400 series CHN analyzer. TLC was carried out on Fluka silica gel TLC cards. N-phenyl hydroxyl amine was prepared according to the published procedures[1,2].

Preparation of nitrone and cycloadducts

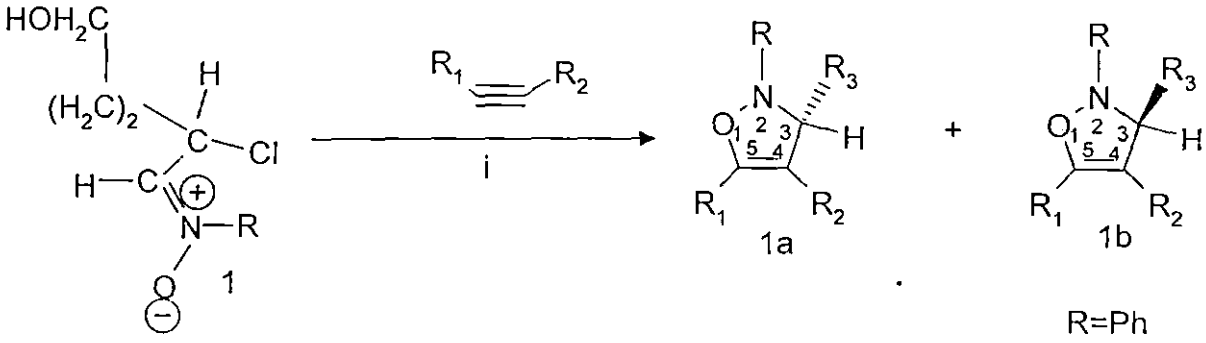
N-phenyl α-chloro nitrone **1** has been prepared following the same methodology as already reported for N-cyclohexyl α-chloro nitrone[4,5]. N-phenyl hydroxylamine[1,2] (2.20 mmol) was added to chlorohydrin (1 equivalent) in dry ether (100 ml) and anhyd $MgSO_4$. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 hr. The formation of the nitrone **1** was monitored by TLC having R_f=0.36. The nitrone was isolated under reduced pressure as white needle shaped crystals (m.p. 58°, 93%, Scheme-1).

In a 100 ml conical flask, nitrone **1** (2.20 mmol) and phenyl methyl propiolate (1 equivalent) was added to 50 ml dry ether and stirred at RT with a magnetic stirrer under N_2 atmosphere for 10 hr. The progress of the reaction was monitored by TLC (R_f = 0.42, 0.44). After completion of the reaction, the solvent was evaporated under reduced pressure and the mixture of diastereoisomers was purified and separated by column chromatography using ethyl acetate-hexane and were obtained as pale yellow, yellow gummy liquids. **1a**: 0.92mg, 75.6%, **1b**: 0.38 mg, 20.4% (Scheme-1).

Spectral data

Nitrone (1)

IR ($CHCl_3$): 3640-3440, 1660, 1360, 1310, 770. ^{1}H NMR ($CDCl_3$): 7.22 (s, 1H, CH=N$^+$), 7.10-6.95 (m, 5H, C_6H_5), 5.10-5.02 (br, 1H, OH exchanged in D_2O), 4.30-4.15 (dd, 1H, J=6.16 Hz, CHCl), 2.20-1.96 (m, 6H, CH_2 protons). ^{13}C NMR ($CDCl_3$) : 142.6 (CH=N$^+$), 136-126 (6 signals, 6 aromatic carbons), 54 (CHCl), 43, 40 37 (3 CH_2 carbons) HRMS- EI: [Found : M$^+$, 227.8158 $C_{11}H_{14}ClO_2N$ requires M, 227.8173].



SCHEME-1

i) RT, 10-12 hr, N_2 atmosphere

R_1=Ph; R_2=$COOCH_3$

R_1=R_2=$COOCH_3$

R_1=$COOC_2H_5$; R_2=H

Phenyl methyl propiolate cycloadduct

Diastereoisomer **1a**: liquid, IR ($CHCl_3$): 3590-3460, 2920, 1760, 1665, 1430, 1360, 770. ^1H NMR ($CDCl_3$): 7.55-7.38 (m, 2x5H, C_6H_5), 5.10-4.95 (br, 1H, OH-exchangeable in D_2O), 4.55-4.40 (dd, 1H, J=9.22 Hz, CHCl), 4.05-3.90 (d, 1H, J=6.08, 9.2 Hz, C_3H), 3.60 (s, 3H, $COOCH_3$), 1.95-1.72 (m, 6H, CH_2 protons). ^{13}C NMR ($CDCl_3$): 168 (carbonyl carbon), 137-126 (6x2 aromatic carbons), 92 (CHCl), 88 (C_5), 73 (C_3), 58 (C_4), 45 ($COOCH_3$), 36, 34, 33 (3 CH_2 carbons). MS: m/z: 388 (M^+), 329, 311, 283, 280, 203, 105, 77. HRMS - EI : [Found : (M^+) 387.6990 $C_{21}H_{22}ClO_4N$ requires M, 387.7000].

Diastereoisomer **1b**: liquid, IR ($CHCl_3$): 3520-3440, 2925, 1755, 1675, 1440, 1345, 770. ^1H NMR ($CDCl_3$): 7.52-7.35 (m, 2x5H, C_6H_5), 5.15-5.05 (br, 1H, OH, exchangeable in D_2O), 4.54-4.43 (dd, 1H, J=2.52, 4.18 Hz, CHCl), 4.08-3.92 (d, 1H, J=4.08-2.54 Hz, C_3H), 3.62 (s, 3H, $COOCH_3$), 1.95-1.70 (m, 6H, CH_2 protons). ^{13}C NMR ($CDCl_3$): 168 (carbonyl carbon), 138-126 (6x2 aromatic carbons), 90 (CHCl), 87 (C_5), 76 (C_3), 54 (C_4), 45 (-$COOCH_3$), 39, 35, 33 (3 CH_2 carbons). MS :m/z: 388 (M^+), 357, 329, 311, 283, 280, 203, 105, 77. HRMS -EI. [Found : (M^+), 387.6982 $C_{21}H_{22}ClO_4N$ requires M, 387.7000].

Dimethyl acetylene dicarboxylate cycloadduct

Diastereoisomer **1a**: liquid, IR ($CHCl_3$): 3545-3480, 2820, 1745, 1700, 1670, 1420, 1260, 774. ^1H NMR ($CDCl_3$) : 7.75-7.54 (m, 5H, C_6H_5 protons), 5.22-5.05 (br, 1H, OH, exchanged in D_2O), 4.86-4.75 (d, 1H, J=9.25, 6.08 Hz, C_3H), 4.26-4.10 (dd, J=6, 9.26 Hz, CHCl), 3.68 (s, 3H, $COOCH_3$), 3.56 (s, 3H, $COOCH_3$), 2.20-2.05 (m, 6H, CH_2 protons). ^{13}C NMR ($CDCl_3$): 169, 168.4 (carbonyl carbons), 133-126 (6 aromatic carbons), 94 (CHCl), 87.5 (C_5). 76(C_3), 59.4 (C_4), 44, 43 (OCH_3), 36, 34, 30 (3 CH_2 carbons). MS :m/z: 370 (M^+), 311, 293, 262, 234, 204, 108, 77, 59, 31. HRMS - EI. [Found : (M^+), 329.5828 $C_{17}H_{20}ClO_6N$ requires M, 369.5840].

Diastereoisomer **1b**: liquid: IR (CHCl): 3555-3485, 2825, 1740, 1710, 1660, 1425, 1260, 770. ^1H NMR ($CDCl_3$) :7.70-7.56 (m, 5H, C_6H_5 protons), 5.20-5.08 (br, 1H, OH, exchanged in D_2O), 4.88-4.74 (d, 1H, J=2.58, 4.08 Hz, C_3H), 4.36-4.26 (dd, J=4, 2.26 Hz, CHCl), 3.66 (s, 3H, $COOCH_3$), 3.54 (s, 3H, $COOCH_3$), 2.12-1.95 (m, 6H, CH_2 protons). ^{13}C NMR ($CDCl_3$): 169, 168 (carbonyl carbons), 134-126 (6 aromatic carbons), 95 (CHCl), 88.5 (C_5), 74(C_3), 56 (C_4), 44, 42, (OCH_3), 36, 35, 30 (3 CH_2 carbons). MS :m/z: 370 (M^+), 311, 293, 262, 234, 204, 108, 77, 59, 31. HRMS- EI. [Found : (M^+) 369.5822 $C_{17}H_{20}ClO_6N$ requires M, 369.5840].

Ethyl propiolate cycloadduct

Diastereoisomer **1a** : liquid, IR ($CHCl_3$): 3560-3490, 2945, 1770, 1680, 1430, 1260, 780. ^1H NMR ($CDCl_3$): 7.02-6.92 (m, 5H, C_6H_5), 5.10-5.02 (br, 1H, OH, exchanged in D_2O), 4.80-4.64 (t, 1H, J=9.26, 6.08 Hz, C_3H), 4.26-4.12 (d, 1H, J=9.24, 6.06 Hz, C_4H), 3.82-3.50 (dd, 1H, J=6, 9.28 Hz, CHCl), 3.35-3.16 (dd, 2H, $COOCH_2CH_3$), 3.08-2.92 (t, 3H, $COOCH_2CH_3$), 1.40-1.24 (m, 3 CH_2 protons). ^{13}C NMR ($CDCl_3$): 168.4 (carbonyl carbon), 133-126 (6 aromatic carbons), 93 (CHCl), 86 (C_5), 78 (C_3), 55 (C_4), 32, 30 ($COOCH_2CH_3$), 26, 25, 23 (3 CH_2 carbons). MS :m/z: 326 (M^+), 295, 253, 249, 219, 108, 77, 73. HRMS-EI. [Found : (M^+) 325.5932 $C_{16}H_{20}ClO_4N$ requires M, 325.5944].

Diastereoisomer **1b**: liquid, IR ($CHCl_3$): 3550-3480, 2955, 1760, 1680, 1440, 1265, 770. ^1H NMR ($CDCl_3$): 7.04-6.94 (m, 5H, C_6H_5), 5.14-5.02 (br, 1H, OH, exchanged in D_2O), 4.83-4.62 (t, 1H, J=2.26, 4.08 Hz, C_3H), 4.22-4.10 (d, 1H, J=2.24, 4.06 Hz, C_4H), 3.80-3.52 (dd, 1H, J=4, 2.28 Hz, CHCl), 3.38-3.22 (dd, 2H, $COOCH_2CH_3$), 3.10-2.94 (t, 3H, $COOCH_2CH_3$), 1.46-1.20 (m, 3 CH_2 protons). ^{13}C NMR ($CDCl_3$): 168 (carbonyl carbon), 134-127 (6 aromatic carbons), 95 (CHCl), 86.5 (C_5), 76 (C_3), 55.5 (C_4), 31, 30 ($COOCH_2CH_3$), 28, 26, 24 (3 CH_2 carbons). MS :m/z: 326 (M^+), 295, 253, 249, 219, 108, 77, 73. HRMS - EI. [Found : (M^+), 325 5930

$C_{16}H_{20}ClO_4N$ requires M, 325.5944].

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References

1. B. Chakraborty and M.S. Chhetri, *Indian J. Heterocyclic Chem.*, **17** (2008), 213.
2. B. Chakraborty and M.S. Chhetri, *Indian J. Chem.*, **47B** (2008), 485.
3. B. Chakraborty, *Indian J. Heterocyclic Chem.*, **17** (2008), 293.
4. B. Chakraborty and A.R. Ghosh, *Indian J. Chem.*, **33B** (1994), 1113.
5. B. Chakraborty and A.R. Ghosh, *Indian J. Heterocyclic Chem.*, **5** (1995), 99.

2443/08

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SYNTHESIS AND 1,3 DIPOLAR CYCLOADDITION REACTIONS OF N-CYCLOHEXYL α-AMINO NITRONE IN WATER. A NEW APPROACH

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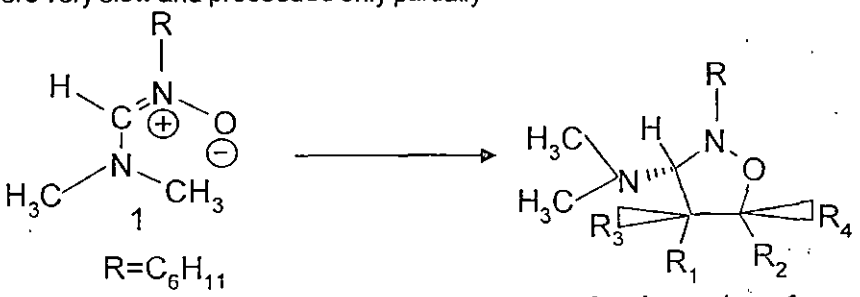
N-Cyclohexyl-α-N,N-dimethyl amino nitrone has been synthesized from N-N dimethyl formamide & 1,3-dipolar cycloaddition reactions of 1 with alkenes have been studied in water.

The 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is an efficient method for the synthesis of the isoxazoline ring system[1]. Further more the cycloadducts have found numerous applications in synthesis through reductive cleavage of N-O bond[2]. More recently, advances have been made in the use of water as solvent to influence the rate and yield in various organic synthesis because it is readily available, economical and environmentally benign[3].

In the present study, we have reported excellent yield in a much lesser time in aq phase synthesis of isoxazolidines using 1,3 dipolar cycloaddition reaction of N-cyclohexyl α-N,N-dimethyl amino nitrone **1**. (Table-1). The reactions are very clean and high yielding. Almost all the reactions of nitrone **1** in water are very fast (5 -6 hr) compared to the reaction of N-phenyl α-amino nitrone in organic solvents like THF, CH_2Cl_2 which were reported to take longer periods (26-30 hr)[4]. No catalyst or co-organic solvent is required. It was observed that the reactions in common organic solvents such as THF or methylene chloride under identical experimental conditions were very slow and proceeded only partially even after 10-15 hr. Hence this is a very simple and greener procedure for cycloaddition reaction in the isoxazolidine synthesis. The amount of water used in the reaction did not have any significant influence on the overall rate of the reaction and yield of the products. It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β-unsaturated carbonyl compounds (maleimides) and thereby increasing the eletrophilic character at the β-carbon which is attacked by nucleophilic oxygen atom of the nitrone[5]. Thus, water activatives the alkene (maleimides) and thereby greatly facilitates the reaction.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 79.5 MHz. IR spectra were obtained on a Perkin-Elmer RX 1-881 machine. MS spectra were recorded



1

R=C_6H_{11}

2a, b, c, d, e, f

2a : R_1, R_2=-CONPhCO; R_3=R_4=H
2b : R_1, R_2=-CONC$_6$H$_{11}$CO; R_3=R_4=H
2c : R_1, R_2=-CONMeCO; R_3=R_4=H
2d : R_1=H, R_2=C_6H_5; R_3=R_4=H
2e : R_1, R_2=napthalene ring; R_3=R_4=H
2f : R_1=R_2=R_3=R_4=Cl

Table-1
Characterization of compounds prepared

Nitrone	Dipolarophile	Yield (%)	R_f	M.P. (°C)	Time (hr)
Nitrone 1		92	0.32	48	8
2a	N-phenyl maleimide	93	0.42	114	6
2b	N-cyclohexyl maleimide	90	0.40	106	5
2c	N-methyl maleimide	94	0.39	83	5
2d	Styrene	82	0.33	74	14
2e	Acenaphthene	79	0.40	122	14
2f	Tetrachloroethylene	77	0.34	-	16

on a Jeol SX-102 (FAB) instrument. Elemental analyses (C,H,N) were performed on a Perkin-Elmer 2400 series CHN analyzer. TLC was carried out on Fluka silica gel TLC cards.

Preparation of nitrone and cycloadducts

N-Cyclohexyl hydroxylamine[5] (8.7 mmol) was added to N,N-dimethyl formamide (9 ml, 1 equivalent and anhyd $MgSO_4$). The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 hr. The formation of the nitrone was monitored by TLC having R_f=0.32. The nitrone was isolated by extraction with ether and washed with brine and finally obtained under reduced pressure as pale yellow crystalline solid (m.p. 48°).

In a 50 ml conical flask, nitrone **1**[5] (1 mmol), N-methyl maleimide (1 mmol) and water (10 ml) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored on TLC. After completion of the reaction, the product was extracted with ether (2x25 ml), the organic layer was washed with brine (2x15 ml), dried over anhyd Na_2SO_4 and concentrated. The product was purified and crystallized from ethyl acetate-hexane and was obtained as white crystals (Scheme-1). This procedure was followed for all the products listed in Table-1.

Spectral data

2a: IR ($CHCl_3$): 3550, 2800, 1760; 1660; 1470, 1320, 775 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.55-7.44 (m, 5H, C_6H_5); 4.90-4.82 (d, 1H, J=6.06 Hz, Hz, C_5H); 4.46-4.35 (d, 1H, J=6.08 Hz, C_3H), 3.90 -3.76 (t, 1H, J=6.06, 6.08 Hz, C_4H); 3.22-3.10 (m, 1H, N-CH), 2.90-2.78 (br, 6H, N-Me), 2.20-1.82 (m, 10H, cyclohexyl). ^{13}C NMR ($CDCl_3$): 168, 166 (carbonyl carbons); 136-126.5 (6 signals, 6 aromatic carbons), 87.5 (C_5), 76 (C_3), 59.4 (C_4), 37, 36 (2 methyl carbons), 30-22 (6 signals, 6 cyclohexyl carbons). MS : (m/z): 343 (M^+), 328, 313, 299, 266, 260, 190, 183, 153, 111, 83, 77, 51, 44, 30. HRMS - EI.$C_{19}H_{25}O_3N_4$ (M), 343.4270, M^+ 343.4261.

2b: IR ($CHCl_3$): 3150, 2920, 1770, 1680, 1440, 1260, 1130. ^1H NMR ($CDCl_3$): 5.10-5.02 (d, 1H, J=6.10 Hz, C_5H), 4.80-4.64 (d, 1H, J=6.08 Hz, C_3H), 4.26-4.12 (t, 1H, J=6,6.06 Hzs, C_4H), 3.82-3.20 (m, 2x1H, N-CH), 2.84-2.73 (br, 6H, N-CH_3), 2.20-1.05 (m, 20H, cyclohexyl). ^{13}C NMR ($CDCl_3$), 168.4, 166.3 (carbonyl), 86 (C_5), 78 (C_3), 55 (C_4), 39, 38 (2 methyl), 33-18 (12 signals, cyclohexyl). MS (m/z): 349 (M^+), 319, 305, 266, 251, 196, 183, 153, 111, 83, 44, 30. HRMS - EI. $C_{19}H_{31}O_3N_3$ (M), 349.4750, M^+, 349.4745.

Acknowledgment

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References

1. A. Padwa, *"Synthetic application of 1,3-dipolar Cycloaddition Chemistry toward Heterocycles and Natural products"*, (Pearson, W.H. Eds, Wiley and sons: Hoboken, New Jersy, 2003).
2. Q. Cheng, W. Zhang, Y. Tagami, T. Oritani. *J. Chem. Soc., Perkin Trans,* **1** (2001), 452.
3. C.J. Li, T.H. Chang, *Organic Reactions in Aqueous Media*; Wiley: New York (2007) & (1997).
4. B. Chakraborty and M.S. Chhetri, *Indian J. Heterocyclic Chem.*, **17** (2008), 213.
5. B. Chakraborty and A.R. Ghosh, *Indian J. Chem.*, **33B** (1994), 1113.

2411/08

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AN EXPEDIENT ROUTE TO ISOXAZOLIDINE SYNTHESIS FROM N-PHENYL α-CHLORO NITRONE IN WATER. A NEW APPROACH

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The addition of N-phenyl α-chloro nitrone to alkenes (maleimides) has been carried out in water at room temp very efficiently without any catalyst. Significant rate acceleration and high yield of these reactions are observed in water compared to organic solvents.

In continuation of our earlier work[1-3], we now wish to report our studies on the synthesis and 1,3-dipolar cycloaddition reaction of N-phenyl α-chloro nitrone (**1**) with alkenes in water along with organic solvents. A comparison of isoxazolidine synthesis in traditional method with those in water is reported in Table-1. The amount of water used in the reaction did not have any significant influence on the overall rate of the reaction and yield of the products. N-phenyl α-chloro nitrone (**1**) is a white crystalline solid, m.p. 58° (uncorrected) and is stable. The structure of the nitrone 1 and all the cycloadducts are confirmed by ^1H, ^{13}C NMR, IR, Mass HRMS spectral data. Without water, the neat reactions at room temp are very inconsistent. It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β-unsaturated carbonyl compounds (maleimides) and thereby increasing the electrophilic character at the β-carbon which is attacked by nucleophilic oxygen atom of the nitrone. Thus water activates the alkene and thereby greatly facilitates the reaction.

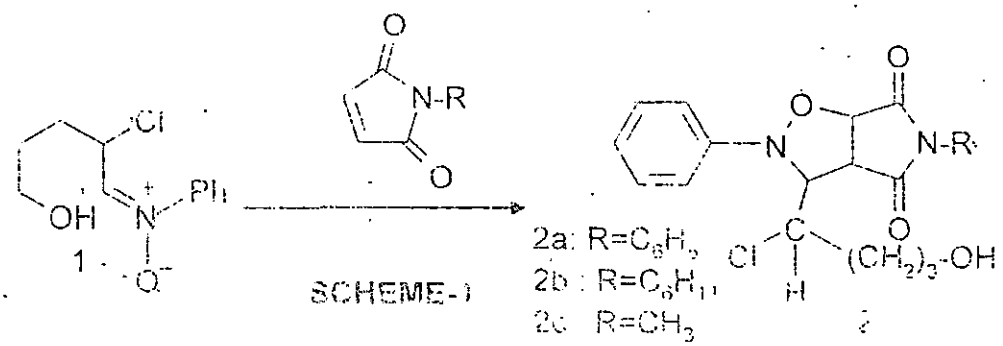
Experimental

Hand drawn silica gel (E. Merck) plates of 0.5-0.7 mm thickness were used for TLC. Silica gel (Qualigen) 60-200 mesh was used for column chromatography. Melting points are determined in open capillary tubes and are uncorrected. IR spectra were recorded as film or in solution on a Perkin-Elmer (RX 1) 881 machine. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz, FT NMR) spectrometer. MS spectra were recorded on a Jeol SX-102 (FAB) spectrophotometer. Chemical analysis were carried out on Carlo-Erba EA 1108 elemental analyzer.

Preparation of nitrone 1 and cycloadducts 2

N-Phenyl α-chloro nitrone was prepared following the same methodology as already reported for N-cyclohexyl α-chloro nitrone[4] where the formation of chlorohydrin from dihydropyran has been also described. N-Phenyl hydroxylamine (2.20 mmol), chlorohydrin (1 equivalent) and dry ether (100 ml) was taken in a 250 ml conical flask along with anhyd $MgSO_4$. The reaction mixture was kept at room temp with constant stirring with a magnetic stirrer under N_2 atmosphere for 12 hr. The formation of the nitrone was monitored by TLC having R_f=0.32 (silica gel ethyl acetate: benzene=1:10). The nitrone was isolated under reduced pressure as white crystalline solid (m.p. 58°, 93%).

In a 50 ml conical flask, nitrone **1** (1 mmol), N-phenyl maleimide (1 mmol) and water (10 ml) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere. The progress of the reaction was monitored



SCHEME-1

Table-1
Characterization of isoxazolidines (2) prepared

Dipolarophile	Solvent	Time (hr)	Yield (%)	M.P. (°C)
N-Phenyl maleimide	Water	4	94	126
N-Cyclohexyl maleimide	Water	5	92	106
N-Methyl maleimide	Water	4	93	95
N-Phenyl maleimide	THF	18,48	33,52	122
N-Cyclohexyl maleimide	THF	14,48	37,58	90
N-Methyl maleimide	THF	18,48	31,54	98

by TLC. After completion of the reaction, the product was extracted with ether (2x25 ml), the organic layer was washed with brine (2x15 ml), dried over anhyd Na_2SO_4 and concentrated. The product was purified and crystallized from ethyl acetate-hexane and was obtained as yellow crystals. Same procedure was followed for other maleimides (Scheme-1).

For the traditional cycloaddition reaction, nitrone 1 (1 mmol), N-phenyl maleimide (1 mmol), 10 ml THF were taken in a 50 ml conical flask and stirred at RT with a magnetic stirrer under N_2 atmosphere for 48 hr. The formation of the cycloadduct was monitored by TLC. The solvent was evaporated under reduced pressure and the product was purified by column chromatography using pet ether (60-80°)-methanol as eluent (Scheme-1). Same procedure was followed for other maleimides.

Spectral data

Nitrone 1

IR ($CHCl_3$): 3640-3440, 1660, 1600, 1360, 1310, 770 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.22 (s, 1H, CH=N⁺); 7.10-6.95 (m, 5H, C_6H_5); 5.10-5.02 (br, 1H, OH exchanged in D_2O), 4.30-4.15 (dd, 1H, J=6.16 Hz, CHCl); 2.20-1.96 (m, 6H, CH_2 protons). ^{13}C NMR ($CDCl_3$) : δ 142.6 (CH=N⁺); 136-126 (6 signals, 6 aromatic carbons); 54 (CHCl); 43, 40, 37 (3 CH_2 carbons). HRMS-EI : M, 227.8158 $C_{11}H_{14}ClO_2N$ requires M⁺, 227.8173%.

2a: IR ($CHCl_3$): 3550-3480, 2800, 1760, 1660, 1470, 1320, 775. ^1H NMR ($CDCl_3$): 7.55-7.40 (m, 2x5H, C_6H_5 protons); 5.05-4.95 (br, 1H, OH, exchanged in D_2O), 4.90-4.82 (d, 1H, J=6.06 Hz, C_5H), 4.46-4.35 (t, 1H, J=6.08 Hz, C_3H), 3.90-3.76 (t, 1H, J=6.06, 6.08 Hz, C_4H), 3.22-3.10 (dd, J=6,6.06 Hz, CHCl), 2.20-2.05 (m, 6H, CH_2 protons). ^{13}C NMR ($CDCl_3$): 168, 167 (carbonyl carbons); 138-124 (12 aromatic carbons); 87.5 (C_5), 76 (C_3), 59.4 (C_4), 47 (CHCl), 36, 34, 30 (3 CH_2 carbons). MS (m/z) : 401 (M^+), 370, 342, 324, 294, 247, 211, 190, 154, 108, 77, 59, 31. HRMS-EI: (M) 400.9664 $C_{21}H_{21}ClO_4N_2$ requires M⁺, 400.9673%.

2b: IR ($CHCl_3$): 3620-3530, 2920, 1770, 1680, 1440, 1260, 780. ^1H NMR ($CHCl_3$): 7.02-6.92 (m, 5H, C_6H_5) 5.10-5.02 (br, 1H, OH, exchanged in D_2O); 4.95-4.88 (d, 1H, J=6.12 Hz, C_5H), 4.80-4.64 (t, 1H, J=6.08 Hz, C_3H), 4.26-4.12 (t, 1H, J=6,6.06 Hz, C_4H), 3.82-3.20 (dd, 1H, J=6,6.08 Hz, CHCl), 2.75-2.56 (m, 1H, N-CH proton), 2.40-2.24 (m, cyclohexyl and CH_2 protons). ^{13}C NMR ($CDCl_3$): 168.4, 168 (carbonyl carbons); 133-126 (6 aromatic carbons); 86 (C_5), 78 (C_3), 55 (C_4), 39 (CHCl), 32-20 (cyclohexyl and CH_2 carbons). MS (m/z): 407(M^+), 348, 330, 324, 299, 211, 196, 108, 83, 77, 59. HRMS-EI: (M)407.0424 $C_{21}ClH_{27}O_4N_2$ requires M⁺ 407.0430.

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References

1. B. Chakraborty and M. Chhetri, *Indian J. Chem.*, **47B** (2008), 485.
2. B. Chakraborty and M. Chhetri, *Indian J Heterocyclic Chem.*, **17** (2008), 213
3. B. Chakraborty, *Indian J Heterocyclic Chem* **17** (2008), 293.
4. B. Chakraborty and A.R. Ghosh *Indian J Heterocyclic Chem* . **5** (1995), 99

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Note

Synthetic potentiality of α-chloronitrone in aldehyde synthesis: A new approach

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N-Phenyl-*N*-cyclohexyl-α-chloronitrones have been synthesized and a new method of synthesis of aldehyde has been discovered involving SN^i and SN^2 reactions with benzyl chloride.

Keywords: *N*-Phenyl-*N*-cyclohexyl-α-chloronitrone, SN^2 reaction, aldehyde synthesis

The synthesis of *N*-phenyl-*N*-cyclohexyl-α-chloronitrones[1] **1a,b** and their 1,3-dipolar cycloaddition reaction with different dipolarophiles have been already established. Existing reports[2-7] already describe the general method of the synthesis of the said nitrones and the cycloaddition reaction to form isoxazolidines. In the light of Eschenmoser's chloronitrone[8] and considering the synthetic potentiality of *N*-phenyl-*N*-cyclohexyl-α-chloronitrones[1], SN^2 reaction of the nitrones with benzyl chloride have been studied. SN^2 reaction of *N*-cyclohexyl-α-amino nitrone with benzyl chloride and isopropyl bromide has been already reported[9]. The present paper reports a new method of synthesis for aldehydes using *N*-phenyl-*N*-cyclohexyl-α-chloronitrones[1]. This is completely a new approach of aldehyde synthesis using nitrone as a reactive intermediate. Both the nitrones **1a,b** are synthesized from a mixture of chlorohydrin and its tautomer with *N*-phenyl-*N*-cyclohexyl hydroxylamines respectively with constant stirring for 24 hr with magnetic stirrer under N_2 atmosphere at RT.where ethanol and dry ether are used as solvents. Chlorohydrin and its tautomer are obtained when 2,3-dihydro-4*H*-pyran is subjected to chlorohydrination with HOCl[10]. *N*-Phenyl-α-chloronitrone is a yellowish white crystalline solid, m.p. 44°C, while *N*-cyclohexyl-α-chloronitrone is a white crystalline solid, m.p. 58°C. Both the nitrones are highly unstable and hence they are used immediately after their formation for the SN^2 reaction with benzyl chloride (*in situ* reaction).

The most remarkable feature of both the nitrones **1a,b** is that they undergo SN^2 reaction with benzyl chloride leading to the formation of benzaldehyde, a significant reaction in nitrone chemistry which proceeds through SN^i reaction initially and forms transient nitrones **2a,b**. A new mechanistic pathway has been suggested for the synthesis of aldehyde (**Scheme I**).

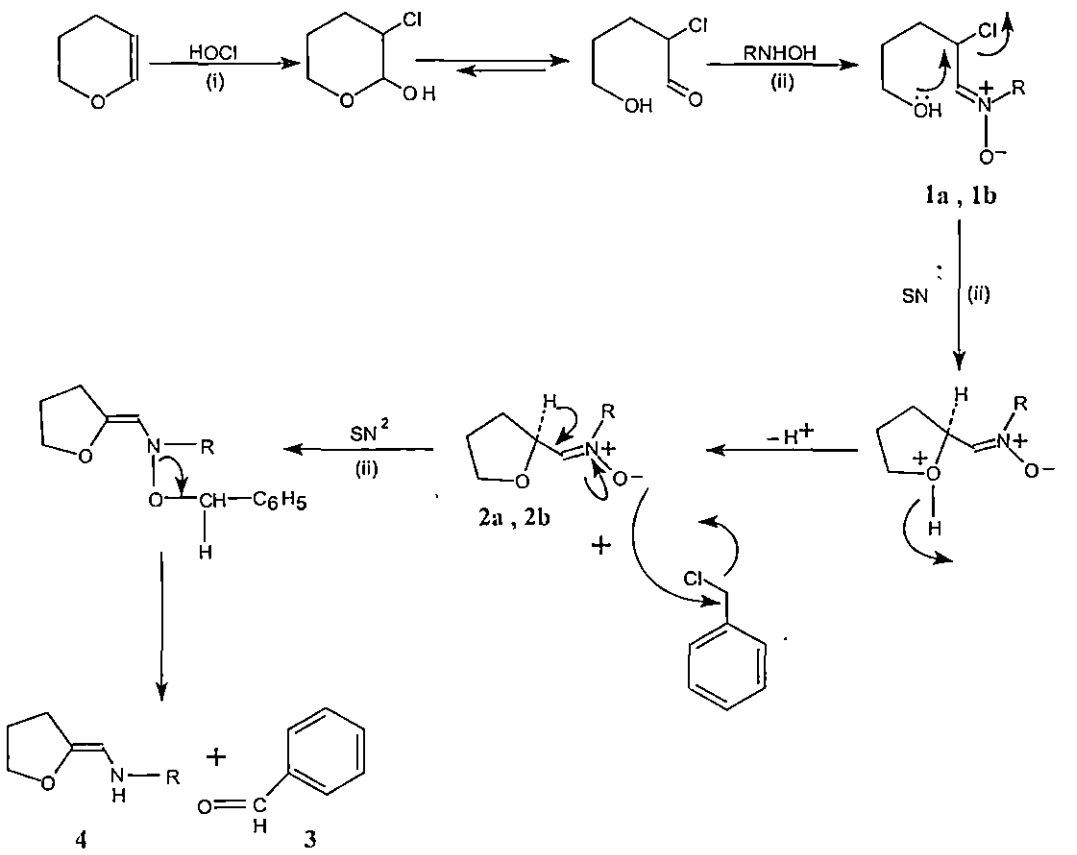
The lone pair of electrons of the OH group of the nitrones **1a,b** play the most significant role in SN^i mechanism for the formation of transient nitrones **2a,b** which reacts very quickly with benzyl chloride and results in the formation of benzaldehyde with a very good yield (72% and 63% respectively) along with furan derivative.

Experimental Section

Hand drawn silica gel (E. Merck) plates of 0.5-0.7 mm thickness are used for TLC. Silica gel (LOBA, 60-200 mesh) is used for column chromatography. Melting point is determined in open capillary tube. IR spectra are recorded as film or in solution by Perkin-Elmer 881 machine. ^1H and ^{13}C NMR spectra are recorded by Bruker WM (400 MHz, FT NMR) and 79.739 MHz spectrometers respectively. Mass spectra are recorded by Jeol D-300 (CI) spectrometers. Chemical analysis are carried out on Carlo-Erba EA 1108 elemental analyzer.

Preparation of nitrones 1a,b and benzaldehyde

N-Phenylhydroxylamine[1] (2.20 mmole) is added to a solution of chlorohydrine (1 equivalent) in dry distilled ethanol (100 mL) and is kept at RT for 24 hr with constant stirring with a magnetic stirrer under N_2 atmosphere. The formation of nitrone is monitored by TLC having R_f=0.36 (silica gel, ethyl acetate:benzene = 1:10). Benzyl chloride (1 equivalent) is added at this stage and the reaction mixture is kept for further 8 hr. Similarly *N*-cyclohexyl hydroxyl amine[11] (2.17 mmol) is added to a solution of chlorohydrine (1 equivalent) in dry ether (150 mL) and anhydrous $MgSO_4$ and is kept at RT for 24 hr with constant stirring with a magnetic stirrer under N_2 atmosphere. The formation of nitrone is monitored by TLC having R_f = 0.28 (silica gel, ethyl acetate:benzene = 1:10). Benzyl chloride (1 equivalent) is added at this stage



1a, 2a: R=C_6H_5; (i) Dry ether; (ii) Dry distilled ethanol
1b, 2b: R=C_6H_{11}; (ii) Dry ether

Scheme I

and the reaction mixture is kept for further 10 hr. During this process both the transient nitrones **2a,b** react very quickly with benzyl chloride and develop an intermediate compound which has a labile N-O bond and is easily cleaved[12] into benzaldehyde and furan derivatives. Two distinct spots are identified in TLC in both the reactions. For nitrone **1a** with benzyl chloride reaction, the R_f values are 0.40 and 0.56 respectively while for nitrone **1b** with benzyl chloride reaction, the R_f values are 0.44 and 0.60 respectively. The solvent is evaporated off in both the cases using vacuum pump and the products are distinguished by column chromatography (20 g silica gel column) using benzene-pet ether (60°-80°C) as eluent. Benzaldehyde is obtained as colourless liquid using pet ether:benzene = 60:40 ratio in case of nitrone **1a** and pet ether:benzene = 80:20 ratio for nitrone **1b** while furan derivatives are obtained as yellow gummy liquids using benzene as eluent in both the cases. The structure of the nitrones **1a,b**, benzaldehyde and furan derivatives are confirmed by ^1H and ^{13}C NMR, MS and IR spectra respectively.

Considering the spectral data of compound **3** in both the cases, the formation of benzaldehyde is confirmed. The sharp singlet signals at δ 9.76, 9.80 and δ 198.6, 198 in the NMR spectrum agrees well with the structure of benzaldehyde. The molecular ion peak at 106 and the base peak at 105 are also in support of benzaldehyde.

Spectral data

Nitrone **1a**: IR ($CHCl_3$): 3600-3530 (br), 1620 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55-7.44 (m, 5H, C_6H_5), 7.10-6.88 (d, 1H, CH=N^+), 5.40-5.30 (br, 1H, CH_2OH, exchanged in D_2O), 4.66-4.52 (q, 1H, CHCl), 3.05-2.00 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 143 (CH=N^+), 132, 130, 128, 126, 125, 122 (6 aromatic carbons), 96.5 (CHCl), 45, 41, 37 (3 CH_2 carbons). Anal. Found: C, 57.30; H, 9.55; N, 6.10. $C_{11}H_{14}ClO_2N$ requires C, 57.42; H, 9.62; N, 6.22%.

Nitrone **1b**: IR ($CHCl_3$): 3500-3450 (br), 1680 (s), 1640 (m), 1155 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.05-5.90 (d, 1H, $CH=N^+$), 5.15-5.05 (br, 1H, CH_2OH, exchanged in D_2O), 4.30-4.15 (q, 1H, CHCl), 3.70-3.50 (m, 1H, N-CH proton), 2.60-0.5 (m, 16H); ^{13}C NMR ($CDCl_3$): δ 142.6 ($CH=N^+$), 95 (CHCl), 63.2 (CH_2OH), 53 (N-CH), 50-10 (7 signals, cyclohexyl and other CH_2 carbons). Anal. Found: C, 56.50; H, 8.52; N, 5.92. $C_{11}H_{20}ClO_2N$ requires C, 56.53; H, 8.56; N, 5.99%.

Compound **3** (Obtained from the reaction between **1a** and benzyl chloride): IR ($CHCl_3$): 1695 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.76 (s, 1H, CHO), 7.50-7.40 (m, 5H,C_6H_5); ^{13}C NMR ($CDCl_3$): δ 198.6 (CHO), 137, 135, 134, 130, 126, 123 (6 aromatic carbons); MS: *m/z* 106 (M^+), 105 (B.P), 77, 51, 28.

Compound **3** (Obtained from the reaction between nitrone **1b** and benzyl chloride): IR ($CHCl_3$): 1700 (s), 780(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.8 (s, 1H, CHO), 7.60-7.44 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 198 (CHO), 136-120 (6 signals, 6 aromatic carbons); MS: *m/z* 106 (M^+), 105 (B.P), 77, 51, 28.

Compound **4** (Obtained from the reaction between nitrone **1a** and benzyl chloride): IR ($CHCl_3$): 3050 (m), 2960 (s), 1650 (s), 1470 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60-7.48 (m, 5H, C_6H_5 protons), 4.80 (s, 1H, C=CH), 2.10-1.72 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 138, 136, 134, 130, 128, 126 (6 aromatic carbons), 112, 110 (double bonded carbons), 42, 37, 29 (3 CH_2 carbons); MS: *m/z* 175 (M^+), 98, 92, 83, 77.

Compound **4** (Obtained from the reaction between nitrone **1b** and benzyl chloride): IR ($CHCl_3$): 3060-3020 (br), 2980 (m), 1650(s), 1486 (m), 1245 (s) cm^{-1}: ^1H NMR ($CDCl_3$): δ 4.88 (s, 1H, C=CH), 3.82-3.70 (m, 1H, N-CH proton), 2.86-1.10 (m, 16H); ^{13}C NMR ($CDCl_3$): δ 139, 112 (2 signals, double bonded carbons), 70-16 (8 signals, cyclohexyl and furan ring carbons); MS: *m/z* 181 (M^+), 97, 84, 83.

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References

1 Chakraborty B, Ph.D. Dissertation, University of North Bengal, Darjeeling, **1996**.

2 Chakraborty B & Ghosh A R, *Indian J Chem*, 33B, **1994**, 1113.

3 Chakraborty B & Ghosh A R, *Indian J Heterocyclic Chem*, 5, **1995**, 99.

4 Chakraborty B & Ghosh A R, Indian *J Heterocyclic Chem*, 6, **1996**, 75.

5 Chakraborty B, *Indian J Heterocyclic Chem*, 2007 (in press).

6 Chakraborty B, *Indian J Heterocyclic Chem*, 6, 1997, 231.

7 Chakraborty B, *Indian J Heterocyclic Chem*, 6, 1997, 233.

8 Eschenmoser A, Kemp U M, Blatt K, Gygax P & Dasgupta T K, *Helv Chim Acta*, 55, **1972**, 2187.

9 Chakraborty B, *Indian J Heterocyclic Chem*, 9, 1999, 79.

10 Fieser L F & Fieser M, *Reagents for Organic Synthesis* (John Wiley and Sons Inc, New York), **1967**, 487.

11 Ghosh A R, *Indian J Chem*, 23B, **1984**, 449.

12 Noguchi M, Okada H, Nishimura S & Yamagata Y, *J Chem Soc Perkin Trans 1*, **1999**, 185.

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SYNTHESIS AND 1,3-DIPOLAR CYCLOADDITION REACTION OF N-PHENYL-α-N,N-DIMETHYL AMINO & N-PHENYL-5-HYDROXY NITRONES WITH N-SUBSTITUTED MALEIMIDES

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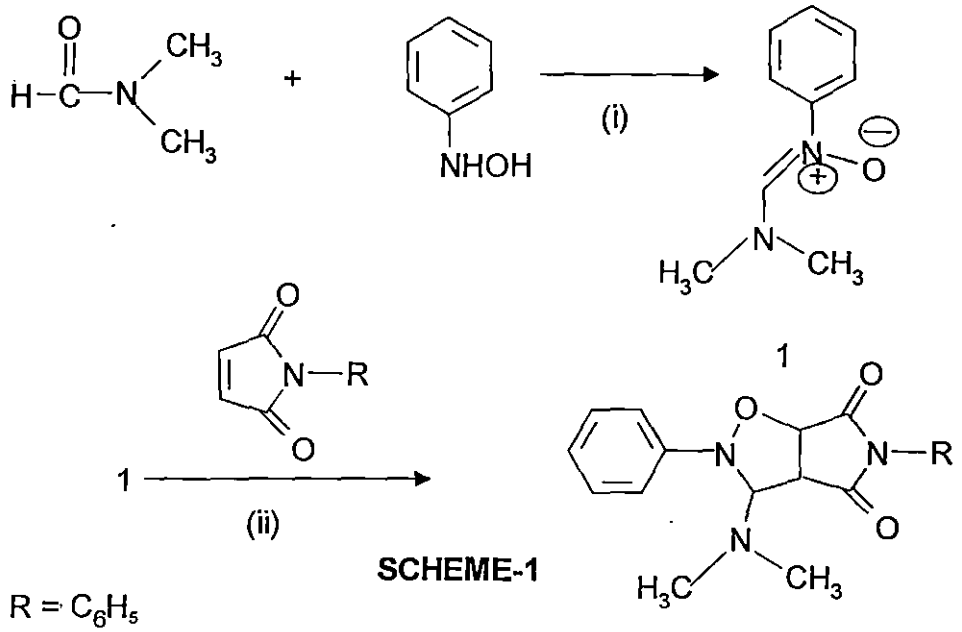
N-Phenyl-α-dimethyl amino nitrone (**1**) & N-phenyl-5-hydroxy nitrone (**3**) have been synthesized from N,N-dimethyl formamide & dihydropyran respectively using N-phenyl hydroxylamine and 1,3-dipolar cycloaddition reaction of the nitrones have been studied with N-substituted maleimides.

In continuation of our earlier work[1-9] we now wish to report our studies on the synthesis and 1,3-dipolar cycloaddition reaction of nitrone (**1**) and (**3**) with N-substituted maleimides. Between the two nitrones, N-phenyl-α-N,N-dimethyl amino nitrone (**1**) is highly unstable and upon isolation decomposes quickly at room temp having melting point 38° (uncorrected). Hence for 1,3-dipolar cycloaddition reaction, nitrone (**1**) was trapped *insitu* by different maleimides to afford cycloadducts in satisfactory yields (Scheme-1, Table-1).

On the other hand, N-phenyl-5-hydroxy nitrone (**3**) is a white crystalline solid, comparatively stable having melting point 52° (uncorrected). For the cycloaddition reaction usually the nitrones are not isolated and are trapped *insitu* by different dipolarophiles to afford cycloadducts (Scheme-2). This procedure is followed in our study for both nitrone (**1**) and (**3**). The most important advantage of this procedure is that dimerization of nitrones can be controlled and the yield of the cycloadducts (isoxazolidines) are also high. The concerted nature of this cycloaddition reaction with nitrone as 1,3 dipole has been generally accepted[10]. Both nitrone (**1**) and (**3**) react smoothly with N-substituted maleimides to afford cycloadducts (isoxazolidines) in satisfactory yields (Scheme-1,2, Table-1). The structure of the nitrone (**3**) and all the cycloadducts are confirmed by ^1H, ^{13}C NMR, IR, Mass spectral data. Like most of the nitrones (as observed from review work), nitrone (**1**) and (**3**) also exist exclusively in **Z** configuration and *syn* cycloadducts are formed from **Z** nitrone through exo transition state geometry[11]. another important feature of these cycloaddition reactions is the introduction of chirality by a single step reaction. Three new chiral centers are developed in the newly formed cycloadducts (isoxazolidines) at C_3, C_4, C_5 positions. The relative configurations of C_3, C_4, C_5 protons of the cycloadducts **2**a-c and **4**a-c are *syn*, as evidenced by their coupling constant (J=6.06-6.18 Hz, for C_4-C_5 and J=6.02 -6.18 Hz, for C_3-C_4) values[12]. Nitrone cycloadditions are believed to be a process with similarity of LUMO and HOMO energies in dipole and dipolarophile. As such both HOMO (dipole)-LUMO (dipolarophile) and LUMO (dipole) - HOMO (dipolarophile) interactions are important in determining reactivity and regiochemistry[13]. In these cycloaddition the C-C & C-O bond formation in the transition state may not happen in a synchronous manner. The C-C bond of isoxazolidine ring is more developed in the transition state than C-O bond. This process would afford products having *syn* configuration at C_3 & C_4 respectively[11]. Expected fragmentation peaks are obtained in mass spectra which gives strong evidence in favour of the structure of the isoxazolidines. ^{13}C NMR spectra also agreed well with the assigned structures of nitrone (**3**) and cycloadducts[12].

Experimental

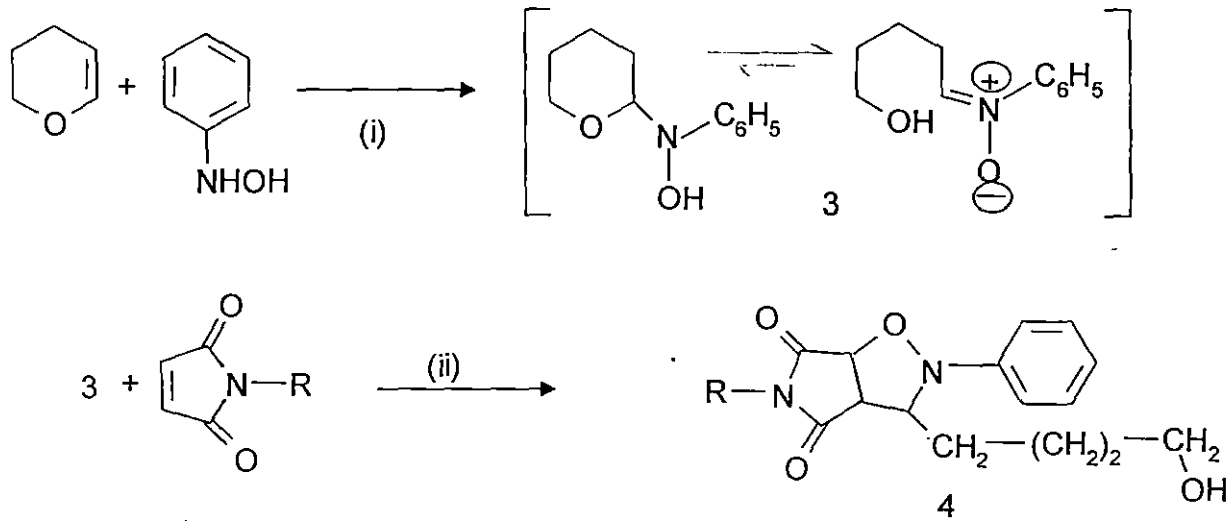
Hand drawn silica gel (E. Merck) plates of 0.5-0.7 mm thickness were used for TLC studies. Silica gel (LOBA) 60-200 mesh was used for column chromatography. Melting points are determined in open capillary tubes and are uncorrected. IR spectra were recorded as film or in solution on a Perkin-Elmer 881 machine. PMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM (400 MHz, FT NMR) and



SCHEME-1

2a, R = C_6H_5
b, R = C_6H_{11}
c, R = *p*-OCH_3-C_6H_4

(i) Anhy $MgSO_4$, N_2 atmosphere, R.T. 24 hr
(ii) Anhy $MgSO_4$, N_2 atomsphere, R.T. 48 hr



i) THF, reflux, 24 hr
ii) Again 24 hr, reflux

SCHEME-2

4a, R = C_6H_5
b, R = C_6H_{11}
c, R = *p*-OMe-C_6H_4

79.739 MHz spectrophotometers respectively. MS spectra were recorded on a Jeol D-300 (CI) spectrophotometer. Chemical analysis are carried out on Cario-Erba EA 1108 elemental analyzer.

Preparation of nitrone (1) and cycloadducts

N-Phenyl hydroxyl amine (0.516g, 4.7mmol) was added to dry distilled N,N-dimethyl formamide (9 ml) and anhyd $MgSO_4$. The reaction mixtures was kept at room temp with constant stirring under N_2 atmosphere for 24 hr. The reaction was monitored by TLC (Silica gel; ethyl acetate: benzene=1:10). N-phenyl maleimide was added at this stage (1 equivalent) and the reaction mixture was kept at room temp for further 48 hr with constant stirring under same environment. Crude product was isolated by extraction with ether and washed with brine water twice. The cycloadduct was purified by column chromatography using benzene-pet ether (60-80°) as eluent. Same procedure was followed for N-cyclohexyl & *p*-OMe-N-phenyl maleimides.

Spectral characteristics of the cycloadducts

2a : IR ($CHCl_3$): 3100, 1760, 1660, 1420, 1300, 770 cm^{-1}. MS (m/z), 337 (M^+), 293, 260, 216, 183, 139, 77. PMR ($CDCl_3$): δ 7.60-7.44 (m, 2x5H, C_6H_5 protons); 5.20-5.10 (d, 1H, J=6.06 Hz, C_5H); 4.35-4.26 (d, 1H, J=6.16, C_3H); 3.70 -3.55 (t, 1H, J=6.12 Hz, C_4H); 2.45-2.30 (br, m, 6N-methyl protons). ^{13}C NMR ($CDCl_3$): 168.5, 167.0 (Carbonyl Carbons), 128.5, 126 (2xC_6H_5 Carbons), 85 (C_5), 74(C_3), 56 (C_4), 26, 25 (2xCH_3 carbons).

2b: IR ($CHCl_3$): 2900, 1760, 1680, 1390, 760. MS (m/z): 343 (M^+), 266, 260, 183, 83, 77, 44. PMR ($CDCl_3$): 7.46-7.30 (m, 5H, C_6H_5); 5.00-4.86 (d, 1H, J=6.08 Hz, C_5H); 4.50-4.25 (d, 1H, J=6Hz, C_3H); 3.56-3.40 (t, 1H, J=6.08 Hz, C_4H); 2.40-2.30 (br, m, 6N-Me protons); 2.00-0.8 (m, 10H, 5xCH_2); 2.20-2.10 (br, m, 1H, N-CH proton). ^{13}C NMR ($CDCl_3$): 168.7, 168. (Carbonyl carbons), 129 (C_6H_5), 83 (C_5); 73 (C_3); 58 (C_4); 54 (N-CH carbon); 50-32 (6 Signals, Cyclohexyl C-atoms); 26, 24 (2xCH_3 carbons).

2c: IR ($CHCl_3$): 3020, 1760, 1660, 1440, 1320, 765 cm^{-1}. MS (m/z): 367 (M^+), 336, 323, 290, 216, 107, 77, 31. PMR ($CDCl_3$): 7.20-6.90 (m, 9H, aromatic protons); 5.28-5.16 (d, 1H, J=6Hz, C_5H); 4.24-4.16 (d, 1H, J=6Hz, C_3H); 3.80 (s, 3H, -OCH_3); 3.58-3.42 (t, 1H, J=6.18 Hz, 6Hz, C_4H); 2.33-2.24 (br, m, N-CH_3 protons). ^{13}C NMR ($CDCl_3$): 169, 168 (Carbonyl carbons); 132, 129 (2xC_6H_5 carbons); 87 (C_5); 73 (C_3); 58 (C_4); 55 (OCH_3); 26, 25 (2xCH_3 carbons).

All the compounds gave satisfactory elemental analysis data.

Preparation of nitrone (3) and cycloadducts

N-Phenyl hydroxyl amine (2.17mmol) was added to a solution of 2,3-dihydro-4*H*-pyran (1 equivalent) in THF (20 ml) under N_2 atmosphere and the reaction mixture was refluxed for 24 hr. The formation of nitrone was monitored by TLC (Silica gel; ethyl acetate: benzene=1:10). N-phenyl maleimide was added at this stage (1 equivalent) and the reaction mixture was further refluxed for 24 hr. The solvent was evaporated under reduced pressure and the cycloadduct was isolated by column chromatography using benzene-pet ether (60=80°) as eluent. Same procedure was followed for N-cyclohexyl and *p*-OMe-N-phenyl maleimides.

Spectral characteristics of the nitrone & cycloadducts

Nitrone (**3**) : IR ($CHCl_3$): 3550; 1920, 1680, 1600, 1340, 780. PMR ($CDCl_3$): 7.60-7.44 (m, 5H, C_6H_5); 3.44-3.32 (t, 1H, CH=N^+), 3.10-2.94 (t, 2H, CH_2OH, exchangeable with D_2O), 2.00-1.20 (br, m, 6H). ^{13}C NMR ($CDCl_3$): 141 (-CH=N^+), 128, 127, 125, 125.5, 124, 124.6 (C_6H_5 carbons); 39 (CH_2OH carbon); 32, 30, 27 (3 signals for CH_2 carbons).

4a: IR ($CHCl_3$), 3550, 2920, 1760, 1660, 1400, 760. MS (m/z), 366(M^+), 293, 289, 216, 212, 154, 77, 73, 31. PMR ($CDCl_3$): 7.60-7.45 (m, 2x5H, C_6H_5 protons), 5.15-5.05 (d, 1H, J=6.06 Hz, C_5H), 4.45-4.32 (t, 1H, J=6.06 Hz, 6.16Hz, C_4H), 3.58-2.35 (dd, 1H, J=6 Hz, C_3H); 2.45-2.32 (t, 2H, CH_2OH, exchangeable with D_2O); 2.20-1.90 (br, m, 6H). ^{13}C NMR ($CDCl_3$): 168.6, 168 (Carbonyl carbons), 134-123 (2xC_6H_5 carbons), 86 (C_5), 76(C_3), 56 (C_4), 36 (CH_2-OH carbon), 28, 26, 25 (3xCH_2 carbons).

4b: IR ($CHCl_3$): 3600-3540, 2900, 1760, 1680, 1660, 1440, 770. MS (m/z), 372(M^+), 341, 299, 295, 289, 212, 160, 83, 77, 31. PMR ($CDCl_3$): 7.52-7.46 (m, 5H, C_6H_5); 5.05-4.86 (d, 1H, J=6.08 Hz, C_5H), 4.90-4.78 (dd, 1H, J=6 Hz, 6.16Hz, C_3H), 3.80-3.66 (t, 1H, J=6Hz, 6.08 Hz, C_4H); 2.62-2.52 (t, 2H, CH_2OH exchangeable with D_2O), 2.46-2.32 (br, m, 1H, N-CH); 1.96-1.20 (br, m, 16H, 8xCH_2 protons). ^{13}C NMR ($CDCl_3$): 167, 166 (Carbonyl carbons), 129-124 (6 signals, C_6H_5 carbons), 84 (C_5), 73 (C_3), 59 (C_4), 55 (N-CH carbon), 38 (CH_2-OH carbon), 32-20 (8 signals, cyclohexyl & CH_2 carbon).

4c: IR ($CHCl_3$): 3550-3450, 2880, 1740, 1660, 1600, 1440, 770. MS (m/z): 396(M^+), 365, 323, 319, 289, 212,

Table-1

Nitrone	Dipolarophile	Time (hr.)	Yield (%)	R_f	M.P. (°C)
Nitrone (3)		24	72	0.30	52
Nitrone (3)	N-phenyl maleimide	24	66	0.38	70
Nitrone (3)	N-cyclohexyl maleimide	24	54	0.42	59
Nitrone (3)	*p*-methoxy-N-phenyl maleimide	24	79	0.46	88
Nitrone (1)	N-phenyl maleimide	48	72	0.40	122
Nitrone (1)	N-cyclohexyl maleimide	48	54	0.33	108
Nitrone (1)	*p*-methoxy-N-phenyl maleimide	48	62	0.36	92

107, 77, 31. PMR ($CDCl_3$): 7.20-6.90 (m, 9H, aromatic protons), 5.35-5.20 (d, 1H, J=6.06 Hz, C_5H); 4.40 -4.22 (dd, 1H, J=6Hz, 6.16 Hz, C_3H), 3.90 -3.77 (t, 1H, J=6.06 Hz, C_4H), 3.70 (s, 3H, $-OCH_3$), 2.80-2.66 (t, 2H, CH_2OH, exchangeable with D_2O), 2.30-1.96 (br, m, 6H, protons). ^{13}C NMR ($CDCl_3$): 168, 167 (carbonyl carbons), 133-124 (2x C_6H_5 carbons), 86 (C_5), 73 (C_3), 58(C_4), 55 (OCH_3), 36 (CH_2-OH), 29, 27, 24 (3x CH_2 carbons).

All the compounds gave satisfactory elemental analysis data.

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References

1. B. Chakraborty and A.R. Ghosh, *Indian J. Chem.*, **33B** (1994), 1113.
2. B. Chakraborty and A.R. Ghosh, *Indian J. Heterocyclic Chem.*, **5** (1995), 99.
3. B. Chakraborty and A.R. Ghosh, *Indian J. Heterocyclic Chem.*, **6** (1996), 75.
4. B. Chakraborty, *Indian J. Heterocyclic Chem.*, **6** (1996), 77.
5. B. Chakraborty, *Indian J. Heterocyclic Chem.*, **5** (1996), 317.
6. B. Chakraborty, *Indian J. Heterocyclic Chem.*, **7** (1997), 77.
7. B. Chakraborty, *Indian J. Heterocyclic Chem.*, **7** (1997), 231.
8. B. Chakraborty, *Indian J. Heterocyclic Chem.*, **6** (1997),233.
9. B. Chakraborty, *Indian J. Heterocyclic Chem.*, **8** (1999), 243.
10. R. Sustmann, *Pure Appl., Chem.*, **40** (1974), 569.
11. P. Deshong, W. Li, J.W. Kennington, H.L. Ammon, *J. Org. Chem.*, **56** (1991), 1364 and references cited therein.
12. P. Grunanger and P. Vita-Finzi, *'The Chemistry of Heterocyclic Compounds'*, Wiley, Interscience (1991), 651.
13. K.N. Houk, R. Mosses, *J. Am. Chem. Soc.*, **106** (1984), 3880.

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Introducing novel α-*N*-methyl/phenyl furan derivatives as new and efficient dipolarophiles for 1,3-dipolar cycloaddition reaction in the regioselective synthesis of spiro isoxazolidine derivatives with α-chloro and simple nitrones

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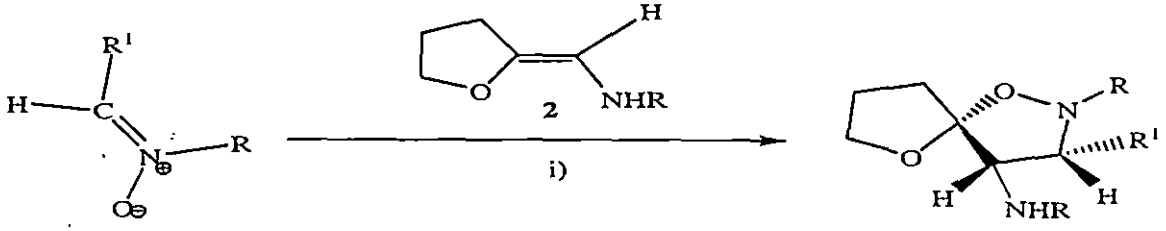
1,3-dipolar cycloaddition reaction of α-chloro and simple nitrones have been studied with novel α-*N*-methyl/phenyl furan derivatives as new dipolarophile. The reactions are found to be highly regioselective to afford single 5-spiro isoxazolidines with high yield in a short reaction time.

Keywords: α-*N*-methyl/phenyl furan derivatives as new dipolarophile, regioselectivity, spiro cycloadducts

In addition to the existing dipolarophiles available for 1,3-dipolar cycloaddition reaction of nitrones[1], we would like to incorporate for the first time some novel and efficient dipolarophiles (α-*N*-methyl/phenyl furan derivatives) which are highly reactive to afford solely 5-spiro isoxazolidines with high yield in a very short reaction time (4-6 hrs) with different nitrones at RT (Scheme 1). Detailed literature survey reveals that these type of cycloaddition reactions are generally diastereomeric in nature with the predominance of one of the isomers[2]. The novel dipolarophiles **2** (α-*N*-methyl/phenyl furan derivatives) were isolated as sideproduct and in single *E* isomeric forms (almost 20%) in all cases of the reported oxidation reaction of alkyl halides to aldehydes and ketones using α-chloro nitrones[3] (Scheme 2). The 5-spiro isoxazolidines (**3-8**) were obtained as regioselective single isomer predominantly in all the cases of α-chloro,α-amino and simple nitrones with high yields (78 – 88%) when isolated in pure condition. It could be due to the fact that nitrone (LUMO)–dipolarophile (HOMO) interactions are strong enough to dominate the reaction[4] and leads to the formation of solely 5-spiro isoxazolidines (**3-8**) via an *exo* approach of nitrone **1** (all the reported nitrones are in *Z* configuration) to the furan derivatives **2** (transition state **1**). At the outset of this work it was not sure whether the sideproducts obtained during aldehyde and ketone synthesis can be employed as efficient dipolarophile. While studying the scope of

atom efficiency in the reaction of aldehyde and ketone synthesis using α-chloro nitrones, the efficiency of the sideproducts (**2**) were confirmed. For the present study, we have used five different nitrones viz *N*-methyl-α-chloro nitrone[3], *N*-phenyl-α-chloro nitrone[5], *N*-methyl-α-amino nitrone[6], *N*-phenyl-α-amino nitrone[7] and *N*-methyl/phenyl nitrones[8] respectively in order to generalize the regioselectivity in cycloaddition reaction using novel dipolarophiles (**2**) leading to the generation of spiro cycloadducts (**3-8**).The stereochemistry of the 5-substituted regioselective spiro cycloadducts (**3-8**) in all the cases were rationalized by considering the multiplicity of the proton signals at 3-H, 4-H, CHCl (in case of α-chloro nitrones only) asymmetric centres along with their coupling constant values.[9] In the spiro isoxazolidine derivatives **3-4**, 3-H resonates around δ_H 2.50-3.50 ppm while for the 4–H around δ_H 3.00-5.85 ppm and the coupling constant is $J_{3,4}$ ~ 9.16 Hz implying a *cis* relationship between H-3 and H-4. The CHCl proton also resonates upfield around δ_H 2.20-2.60 ppm. The 3-H and CHCl protons are also *syn* as evidenced from their coupling constant values ($J_{3,CHCl}$ ~ 9.40 Hz).[9] Almost similar coupling constant values are obtained for H-3 and H-4 protons in case of other reported spiro cycloadducts (**5-8**).Cycloaddition of *Z* nitrone (all the reported nitrones are of *Z* configuration in this communication) via *exo*-transition state geometry results in the formation of *syn* spiro isoxazolidine derivatives. ^{1}H NMR spectrum of **3-8** shows significant long range coupling between H-4 with H-3' and vice versa in most of the spiro cycloadducts. In the mass spectrum, prominent base peak values are obtained in all the spiro regioselective cycloadducts and significant M+2 peaks are obtained in the spiro cycloadducts **3-4** which may be due to isotopic abundance of Cl^{37} atoms. Studies of HRMS spectra show almost exact masses for the majority of the compounds. The experimental procedure is very simple. Novel α-*N*-methyl/phenyl furan derivatives (**2**) are added to nitrone **1** in diethyl ether at RT. Smooth reaction ends with the production of regioselective spiro cycloadducts with extremely good yield in a very short reaction time. In general the reactions are very clean and high yielding compared to usual cycloaddition reactions of α-chloro & α-amino nitrones[1,5,6]. The products were characterized from their spectroscopic (IR, ^{1}H NMR, HRMS, ^{13}C NMR) data. No catalyst or co-organic solvent was required. All the spiro isoxazolidine derivatives (**3-8**) were also screened for antibacterial activity and found to be very active hence procedure described here and substrates used are very safe and useful for mankind.



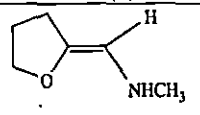
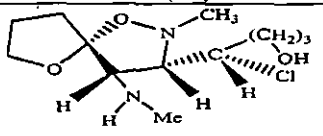
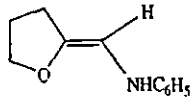
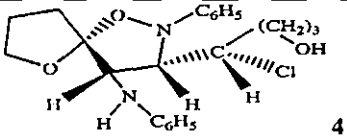
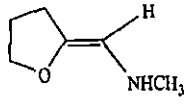
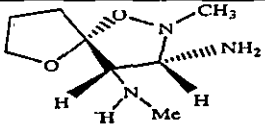
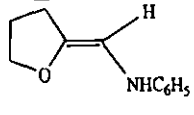
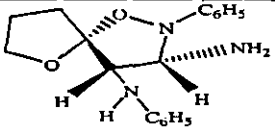
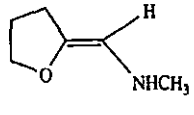
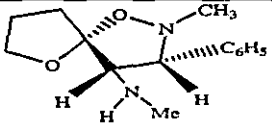
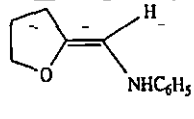
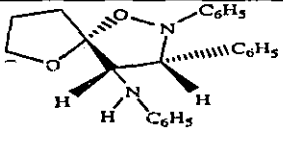
1 **Scheme - 1** 3-8

$R = CH_3$; C_6H_5

$R^1 = C_6H_5$; $CHCl(CH_2)_3OH$; NH_2

Reagents and conditions: i) Dry ether, RT, N_2 atmosphere, 4 - 6 hr

Table 1 - Cycloaddition reaction of nitrone 1 with novel dipolarophiles

Entry	Nitrone (1)	Novel dipolarophiles[a] (2)	Spiro cycloadducts[b] (3-8)	Time (hr)	Nature of products	Yield (%)[c]
1	R = Me $R^1 = CHCl(CH_2)_3OH$		 3	4	Pale yellow gummy liquid	88
2	R = Ph $R^1 = CHCl(CH_2)_3OH$		 4	5	Dark red viscous liquid	86
3	R = Me $R^1 = NH_2$		 5	5	Gray viscous liquid	84
4	R = Ph $R^1 = NH_2$		 6	6	Dark gray viscous liquid	81
5	R= Me R^1= Ph		 7	5	Colourless gummy liquid	78
6	R= R^1= Ph		 8	6	Colourless gummy liquid	78

[a]Reaction conditions: nitrone (1 mmole), furan derivative (1 equivalent),dry ether, N_2atmosphere, RT

[b]All the spiro cycloadducts were characterized by IR, ^{1}HNMR, MS, ^{13}CNMR Spectral data

[c]Isolated yield after purification

A preferential conformation for the regioselective spiro isoxazolidine derivatives may be represented in figure 1.

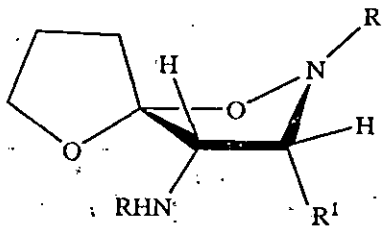
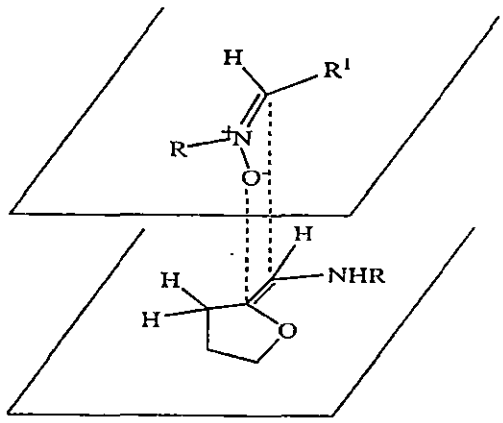


Fig 1

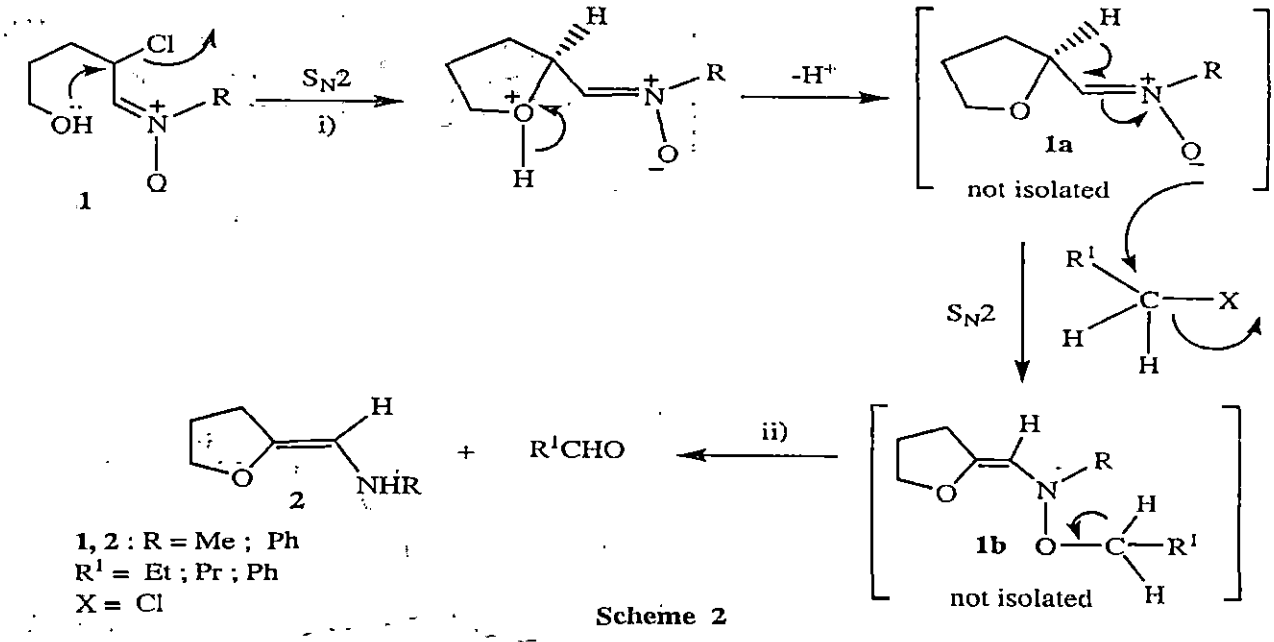
R^I = Ph, NH_2, $CHCl(CH_2)_3OH$

General conformation for the spirocycloadducts (3-8)



TS 1 for forming spiro cycloadducts (3-8)

A new mechanistic pathway for the synthesis of novel dipolarophiles (α-*N*-methyl/phenyl furan derivatives) may be represented in the following established mechanism[3] (Scheme 2).



Scheme 2

Reagents and conditions : i) Dry ether, pyridine, r.t , N_2 atmosphere
ii) Dry ether, Na_2CO_3, r.t , N_2 atmosphere

Finally, we have reported synthesis of exclusively regioselective spiro cycloadducts using some novel dipolarophiles with different nitrones in 1,3-dipolar cycloaddition reaction and

also the mechanism of synthesis of novel dipolarophiles. The formation of the desired spiro cycloadducts were obtained in good yields within a short reaction time. The newly developed side products (furan derivatives, **2**) are equally effective as dipolarophile in cycloaddition reactions like other conventional dipolarophiles used for cycloaddition reactions and may be incorporated for the general use in cycloaddition reactions as effective dipolarophile. The notable advantages offered by this method are one pot synthesis, simple operation, easy workup, mild and faster reaction conditions with high yield of products.

Experimental

^{1}H NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer (300 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q – Tof micro instrument (YA–105). TLC's were run on Fluka silica gel precoated TLC plates while column chromatography was performed with silica gel (E.Merck India) 60 – 200 mesh. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-methylhydroxylamine was purchased from Aldrich Chemical Company and was used as received. *N*-phenylhydroxylamine was prepared following standard methods available in the literature and has been used already for the synthesis of aldehydes and cycloaddition reactions involving α-amino, α-chloro nitrones in aqueous phase and in organic solvents[3,5,6,7].

General procedure for cycloaddition (for regioselective spiro cycloadducts)

To a well stirred solution of nitrone **1** (**R=Me**; 1 mmole) in diethyl ether (20 mL) taken in a 50 mL conical flask, was added α-*N*-methyl furan derivative [(*E*)-1-(dihydrofuran-2-(3H)-ylidene)-*N*-methyl methanamine)] (1 equivalent) and was stirred at RT with a magnetic stirrer under N_2 atmosphere for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.53). After completion of the reaction and work-up, the crude spiro cycloadduct was concentrated in a rotary evaporator and finally purified by column chromatography using ethyl acetate - hexane to afford pure spiro cycloadduct **3** (entry **1**, Table **1**, Scheme **1**). This procedure was followed for the reaction of nitrone **1** (**R= Me,Ph**) with α-*N*-methyl/phenyl

furan derivatives **2** [(*E*)-1-(dihydrofuran-2-(3H)-ylidene)-*N*-methyl methanamine)/(*E*)-1-(dihydrofuran-2-(3H)-ylidene)-*N*-phenyl methanamine)] listed in Table **1**.

Spectroscopic data for **2** *(R=Me; α-N-methyl furan derivative) [(E)-1-(dihydrofuran-2-(3H)-ylidene)-N-methyl methanamine)]*

IR (KBr): 3125-3054 (br), 2838 (m), 1652 (s), 1455 (m), 1210 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.81 (br, 1H, N-H), 4.56 (s, 1H, C=CH), 3.30 (N-Me), 2.50 - 2.16 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 103.00, 101.76 (double bonded carbons), 26.22, 25.30, 23.65 (3 CH_2 carbons); FAB – MS: *m/z* 113 (M^+), 98, 97; HRMS-EI: Calcd. for $C_6H_{11}ON$ (M), 113.1000, Found: M^+, 112.9876.

Spectroscopic data for **2** *(R=Ph; α-N-phenyl furan derivative) [(E)-1-(dihydrofuran-2-(3H)-ylidene)-N-phenyl methanamine)]*

IR (KBr): 3150-3060 (br), 2860 (m), 1640 (s), 1430 (m), 1140 (m), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.83 (m, 5H, C_6H_5), 6.29 (br, 1H, N-H), 2.17 (s, 1H, C=CH), 1.79 - 1.18 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 137.20, 135.65, 134.00, 132.15 (aromatic carbons), 106.24, 104.18 (double bonded carbons), 28.46, 27.10, 24.84 (3 CH_2 carbons). FAB - MS (*m/z*): 175 (M^+), 98, 97, 77. HRMS-EI: Calcd. for $C_{11}H_{13}ON$ (M), 175.0993, Found; M^+, 175.0981.

(S)-4-chloro-4-((3S,4S,5R)-2methyl-4-(methylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol **3**

3: Pale yellow gummy liquid. Yield 88%, R_f = 0.53; IR (KBr): 3460 – 3326 (br), 2948 (m), 2420 (m), 1485 (s), 1325 (m), 810 (m), 774 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.83 (br, 1H, CH_2OH, exchanged in D_2O), 4.60 (s, 1H, $NHCH_3$), 3.37 (s, 6H, 2 x N-CH_3), 3.12 (dd, 1H, *J* = 9.20, 8.32 Hz, C_3H), 2.70 (dt, 1H, *J* = 8.10, 7.88 Hz, C_4H), 2.35 (dt~m, 1H, CHCl), 1.88 – 1.42 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 93.00 (CHCl), 87.55 (C_5), 76.20 (C_3), 55.20 (C_4), 41.97 (N-CH_3), 40.24 (NH-CH_3), 33.37, 31.50, 28.68, 26.00, 25.12, 23.40 (6 CH_2 carbons); MS (*m/z*): 280 (M^++2), 278 (M^+), 263, 248, 156 (B.P), 141, 107; HRMS-EI: Calcd. for $C_{12}H_{23}O_3N_2Cl$ (M), 278.6710, Found; M^+, 278.6698.

(S)-4-chloro-4-((3S,4S,5R)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol **4**

4: Dark red viscous liquid. Yield 86%, R_f = 0.48; IR (KBr): 3485 – 3290 (br), 2962 (m), 2425 (m), 1620 (s), 1490 (s), 1260 (m), 1040 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.98 - 6.92 (m, 10H, 2 x C_6H_5), 5.84 (dd, 1H, *J* = 8.55, 8.20 Hz, C_3H), 5.00 (br, 1H, CH_2OH, exchanged

in D_2O), 3.60 (dt, 1H, J = 9.34, 7.88 Hz, C_4H), 3.40 (s, 1H, N – H proton of NHPh), 2.68 (dt~m, 1H, CHCl), 1.90 (dt, 1H, J = 6.82, 6.64 Hz, C_3·H), 1.50 – 1.12 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 138.00, 136.50, 134.30, 133.80, 131.75, 130.42, 129.46, 128.64 (aromatic carbons), 95.10 (CHCl), 86.40 (C_5), 73.75 (C_3), 53.30 (C_4), 30.20, 28.55, 27.34, 26.22, 25.73, 24.37 (6 CH_2 carbons); MS (*m/z*): 404 (M^++2), 402 (M^+), 325, 310, 309, 218 (B.P), 107, 91, 77. HRMS-EI: Calcd. for $C_{22}H_{27}O_3N_2Cl$ (M), 402.7130, Found; M^+, 402.7122.

(S)-3-amino-(3S,4S,5S)-2-methyl-4-(methylamino)-1,6-dioxa-2-azaspiroisoxazole 5

5: Gray viscous liquid. Yield 84%, R_f = 0.52; IR (KBr): 3430 - 3380 (br), 3033 (m), 2955 (m), 1773 (s), 1662 (s), 1480 (s), 1282 (m), 1178 (s), 806 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.90 (br,s, 2H, NH_2, exchanged in D_2O), 4.60 (br, 1H, $NHCH_3$), 3.36 (s, 6H, 2 x N-CH_3), 3.00 (d, 1H, J = 7.54 Hz, C_3H), 2.70 (dt, 2H, J = 6.24, 6.28 Hz, C_3'2H), 2.38 (dt, 1H, J = 7.12, 6.70 Hz, C_4H), 1.70 – 1.48 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 88.50 (C_5/C_2·), 77.12 (C_3), 56.26 (C_4), 40.94 (N-CH_3), 38.13 (NH-CH_3), 32.07, 31.22, 29.34 (3',4',5' CH_2 carbons); MS (*m/z*): 187 (M^+), 172, 157, 156 (B.P), 141. HRMS-EI: Calcd. for $C_8H_{17}O_2N_3$ (M), 187.1633, Found; M^+, 187.1613.

(S)-3-amino-(3S,4S,5S)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiroisoxazole 6

6: Dark gray viscous liquid. Yield 81%, R_f = 0.48; IR (KBr): 3436 - 3390 (br), 3030 (m), 2952 (m), 1780 (s), 1674 (s), 1480 (m), 1276 (m), 815 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.02 - 6.90 (m, 10H, 2 x C_6H_5), 5.86 (d, 1H, J = 6.30 Hz, C_3H), 5.00 (br,s, 2H, NH_2, exchanged in D_2O), 3.50 (dt, 2H, J = 6.74, 6.06 Hz, C_3' 2H), 3.38 (br,s,1H, NHC_6H_5), 2.70 (dt, 1H, J = 7.20, 6.18 Hz,C_4H), 1.52 – 1.28 (m, 4H); ^{13}C NMR($CDCl_3$): δ 137.21, 135.44, 134.00, 133.10, 130.66, 129.40, 128.32, 127.84 (aromatic carbons), 86.94 (C_5/C_2·), 74.24 (C_3), 55.70 (C_4), 27.87, 25.63, 24.00 (3',4',5' CH_2 carbons); MS (*m/z*): 311 (M^+), 295, 218, 203 (B.P), 202, 92, 77; HRMS-EI: Calcd. for $C_{18}H_{21}O_2N_3$ (M), 311.2054, Found; M^+, 311.2037.

(S)-3-phenyl-(3S,4S,5S)-2-methyl-4-(methylamino)-1,6-dioxa-2-azaspiroisoxazole 7

7: Colourless gummy liquid. Yield 78%, R_f = 0.52; IR (KBr): 3040 (m), 2965 (m), 1760 (s), 1685 (m), 1464 (s), 1290 (m), 1084 (s), 808 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.81(s,5H,C_6H_5), 4.67 (s, 1H, $NHCH_3$), 3.36 (s, 6H, 2 x N-CH_3), 3.00 (d, 1H, J = 5.74 Hz, C_3H), 2.74 (dt, 1H, J = 6.64, 6.30 Hz, C_4H), 2.30 (dt, 2H, J = 5.10, 4.92 Hz, C_3'2H), 1.80 – 1.55 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 129.05, 128.53, 128.27, 127.22 (aromatic carbons), 80.28 (C_5/C_2·), 70.36 (C_3), 59.70 (C_4), 45.17 (N-CH_3), 41.64 (NH-CH_3), 32.07, 31.22, 29.34 (3',4',5'CH_2 carbons);

MS (*m/z*):248 (M^+), 218, 171, 156 (B.P), 141, 77. HRMS-EI: Calcd. for $C_{14}H_{20}O_2N_2$ (M), 248.1862, Found; M^+, 248.1853.

(S)-3-phenyl-(3S,4S,5S)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiroisoxazole 8

8: Colourless gummy liquid. Yield 78%, R_f= 0.48; IR (KBr): 3024 (m), 2950 (m), 1772 (s), 1670 (s), 1468 (m), 1382 (m), 805 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50 - 6.62 (m, 15H, 3 x C_6H_5), 5.84 (s,1H, NHC_6H_5), 4.63 (d, 1H, J = 6.06 Hz, C_3H), 4.02 (dt, 1H, J = 6.18, 6.20 Hz, C_4H), 2.64 (dt, 2H, J = 5.28, 4.10 Hz,C_3'2H), 2.00 – 1.26 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 136.76, 136.53, 136.24, 135.15, 134.90, 134.62, 134.30, 133.78, 132.44, 132.18, 130.92, 130.37 (aromatic carbons), 83.22 (C_5/C_2'), 71.52 (C_3), 52.89 (C_4), 23.61, 22.57, 21.14 (3',4',5' CH_2 carbons); MS (*m/z*): 372 (M^+), 295, 280, 218, 203 (B.P), 92, 77; HRMS-EI: Calcd. for $C_{24}H_{24}O_2N_2$ (M), 372.2286, Found; M^+, 372.2270.

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References

1 A.Padwa & W.H.Pearson, *Synthetic application of 1,3-dipolar Cycloaddition Chemistry toward Heterocycles and Natural products (Wiley, New Jersy).*, 2003.

2 M.Cacciarini, F.M.Cordero, C.Faggi, A.Goti, *molecules,* 2000, **5**, 637 and references cited therein.

3 (a) B.Chakraborty & M.S. Chhetri, *Indian J. Chem.,* 2008, **47B**, 485; (b) B.Chakraborty, S.Kafley &.M.S. Chhetri, *J. Chem. Sci.*, 2010 (in press); (c) B.Chakraborty, *Indian J. Heterocycl. Chem.*, 2008, **17**, 293;. (d) B. Chakraborty, S. Kafley & M.S. Chhetri, P.Sharma, A.R.Ghosh, *J. Indian Chem. Soc.*, 2010 (in press); (e) B.Chakraborty, S. Kafley & M.S. Chhetri, P.Sharma, A.R. Ghosh, *Indian J. Chem, SecB*, 2009 (in press).

4 (a) K.N.Houk, J.Sims & C.R.Luskus,.*J. Am. Chem. Soc,*1973, **95**, 7302; (b) R.Newton, P.G.Savage, *Australian J. Chem*,2008,. **61**, 432 and references cited therein; (c) K.Aouadik, S.Vidal, P.J.Praly, *Synlett*, 2006, **19**, 3299 and references cited therein.

5 (a) B.Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem.*, 2009, **48B**, 447; (b) B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem., SecB,* 2010 (in press).

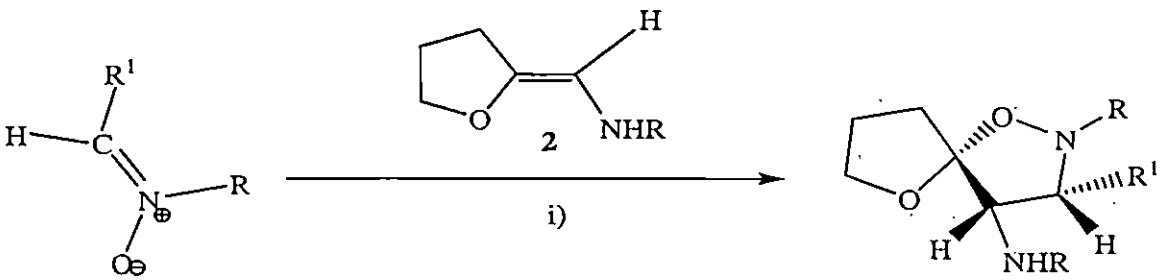
6 B.Chakraborty, N.Rai, M.S.Chhetri, *Rasayan J. Chem.,* 2010 (in press).

7 (a) B.Chakraborty, P.J.Debritto, A.R.Ghosh, *Indian J. Heterocycl. Chem.*, 1996, **6**, 77; (b) B.Chakraborty, M.S.Chhetri, *Indian J. Heterocycl. Chem.*, 2008, **17**, 213; (c) B. Chakraborty, M.S.Chhetri, *Indian J. Heterocycl. Chem.*, 2008, **18**, 201.

8 V.K. Aggarwal, R.S. Grainger, H.Adams, P.L. Spargo, *J.Org.Chem.,* 1998, **63**, 3481 and references cited therein.

9 (a) P.Deshong, W.Li, J.W. Kennington & H.L.Ammon, *J. Org. Chem.*, 1991, **56**, 1364; (b) R.Gandolfi & P. Grunanger, *The Chemistry of Heterocyclic Compounds* (*Wiley Interscience*),1999, **49 (2)**,774.

High Resolution Figures



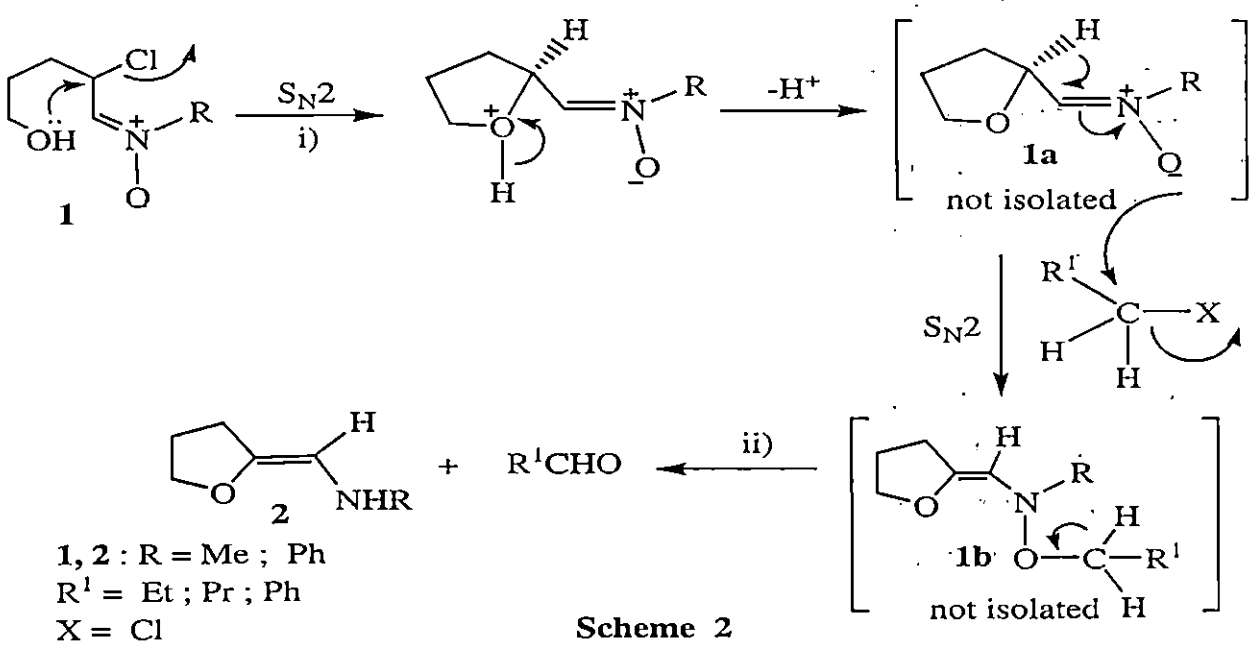
1 2 3-8

Scheme - 1

R = CH_3 ; C_6H_5

R^1 = C_6H_5 ; $CHCl(CH_2)_3OH$; NH_2

Reagents and conditions: i) Dry ether, RT, N_2 atmosphere, 4 - 6 hr



1, 2 : R = Me ; Ph

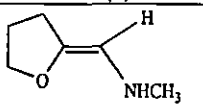
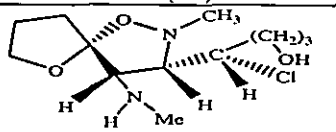
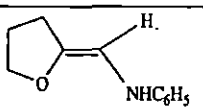
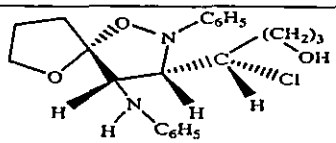
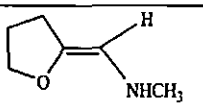
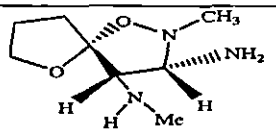
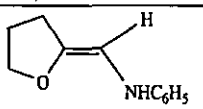
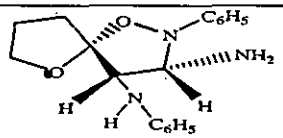
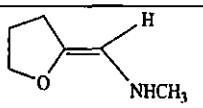
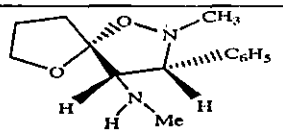
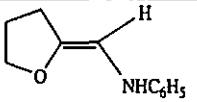
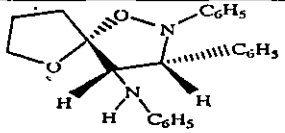
R^1 = Et ; Pr ; Ph

X = Cl

Scheme 2

Reagents and conditions : i) Dry ether, pyridine, r.t , N_2 atmosphere
ii) Dry ether, Na_2CO_3, r.t , N_2 atmosphere

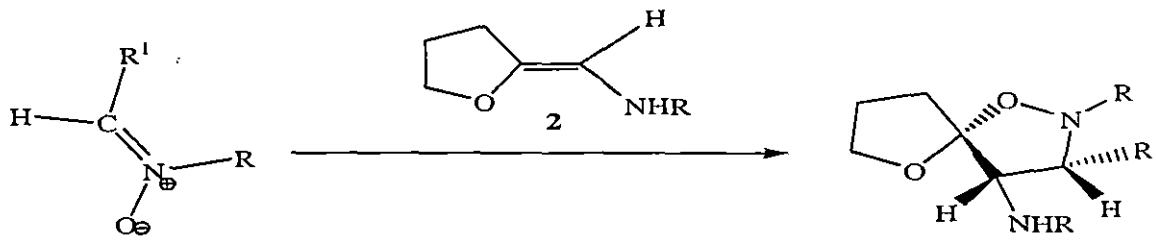
Table 1 - Cycloaddition reaction of nitrone 1 with novel dipolarophiles

Entry	Nitrone (1)	Novel dipolarophiles[a] (2)	Spiro cycloadducts[b] (3-8)	Time (hr)	Nature of products	Yield (%)[c]
1	R = Me R^{I}= $CHCl(CH_2)_3OH$		 3	4	Pale yellow gummy liquid	88
2	R = Ph R^{I}= $CHCl(CH_2)_3OH$		 4	5	Dark red viscous liquid	86
3	R = Me R^{I}= NH_2		 5	5	Gray viscous liquid	84
4	R = Ph R^{I}= NH_2		 6	6	Dark gray viscous liquid	81
5	R= Me R^{I}= Ph		 7	5	Colourless gummy liquid	78
6	R= R^{I}= Ph		 8	6	Colourless gummy liquid	78

[a]Reaction conditions: nitrone (1 mmole), furan derivative (1 equivalent),dry ether,N_2atmosphere, RT
[b]All the spiro cycloadducts were characterized by IR, ^{1}HNMR, MS, ^{13}CNMR Spectral data
[c]Isolated yield after purification

Graphical Abstract

Introducing novel α-*N*-methyl/phenyl furan derivatives as new and efficient dipolarophiles for 1,3-dipolar cycloaddition reaction in the regioselective synthesis of spiro isoxazolidine derivatives with α-chloro and simple nitrones



1 3-8

R = CH_3 ; C_6H_5
R^1 = C_6H_5 ; $CHCl(CH_2)_3OH$; NH_2

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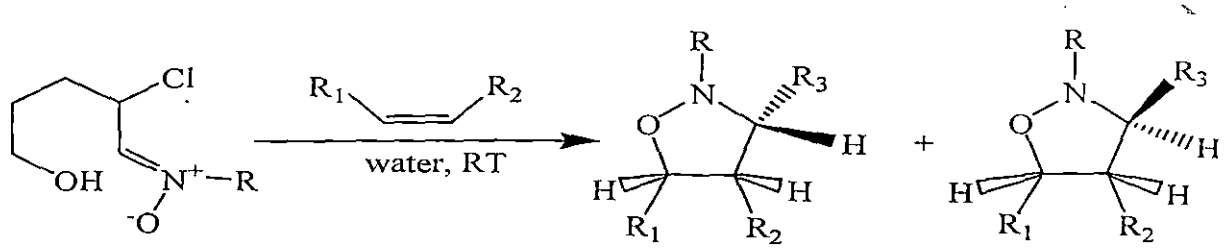
Synthesis and antibacterial activities of some novel isoxazolidine derivatives derived from N-phenyl-α-chloro nitrone in water

1,3 dipolar cycloaddition reaction of N-phenyl-α-chloro nitrone with different dipolarophiles have been studied in water for the synthesis of novel isoxazolidines. Significant rate acceleration and high yield of these reactions are observed in water with remarkable changes in stereo and regioselectivity compared to organic solvents. The structures of all compounds have been established on the basis of spectral and analytical data. All compounds have been screened for their antibacterial activity and found to be active.



R = Ph

R_3 = -$CHCl(CH_2)_3OH$

Bhaskar Chakraborty*, Manjit Singh Chhetri, Saurav Kafley & Amalesh Samanta

(SCCB-1225)
IJCB - 49B(2) (Feb), 2010, 209-215

Synthesis and antibacterial activities of some novel isoxazolidine derivatives derived from N-phenyl-α-chloro nitrone in water

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1,3 dipolar cycloaddition reaction of N-phenyl-α-chloro nitrone with different dipolarophiles have been studied in water for the synthesis of novel isoxazolidines. Significant rate acceleration and high yield of these reactions are observed in water with remarkable changes in stereo and regioselectivity compared to organic solvents. The structures of all compounds have been established on the basis of spectral and analytical data. All compounds have been screened for their antibacterial activity and found to be active.

Keywords: N-phenyl-α-chloro nitrone, 1,3 DCR, aqueous phase, stereoselectivity, regioselectivity, antimicrobial activity

The 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is an efficient method for the synthesis of the isoxazolidine ring system[1]. Furthermore, the cycloadducts have found numerous applications in synthesis through reductive cleavage of the N-O bond to give γ-amino alcohols[1]. Asymmetric induction in nitrone-olefin cycloadditions has been achieved through incorporation of chirality in both the dipole and dipolarophile[2]. More recently, advances have been made in the use of water as solvent to influence the rate, regioselectivity and stereoselectivity of the cycloaddition reactions[3]. Due to unstability of nitrones, very few examples of the isolation or detection of the nitrones have been reported and are usually trapped *in situ* by different dipolarophiles in 1,3-dipolar cycloaddition reactions to afford cycloadducts[1]. Synthesis of a stable N-phenyl-α-chloro nitrone **1** (Ref 4) for the preparation of

aldehydes[4] and novel isoxazolines[5] has already been reported.

The present paper reports the synthesis and antibacterial activity of some novel isoxazolidine derivatives derived from nitrone **1** in water with high yield and remarkable changes in stereochemistry (**Scheme I, Table I**). Organic reactions in water have received increased attention primarily because of their environmental acceptability, abundance and low cost[6]. However, water also exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents[7,8]. Thus, the development of efficient procedures for useful chemical transformations in water without any catalyst is highly appreciated. For the present study, three different maleimides, ethyl acrylate and methyl vinyl ketone (electron poor and electron rich dipolarophiles) have been used so as to study the nature of the cycloaddition reactions leading to the formation of diastereomeric and regioselective adducts. Almost all the reactions in water are very fast (4-5 hr in case of maleimides and 7-8 hr for other olefines) compared to the normal cycloaddition reactions in organic solvents which were reported to take longer periods (26-48 hrs)[1]. It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β-unsaturated carbonyl compounds, thereby increasing the eletrophilic character at the β-carbon which is attacked by nucleophilic oxygen atom of the nitrone[6]. Thus, water activates the maleimide, ethyl acrylate and methyl vinyl ketone, and thereby greately facilitates the reaction.

Results and Discussion

Excellent diastereofacial selectivity is observed in nitrone additions in water. The addition of nitrone **1** to maleimides result in a mixture of diastereomer **2a–4a** and **2b–4b** (almost 70 : 30 ratio in all cases) and generation of as many as three to four chiral centers in a single step. Studies of organic reactions in aqueous media shows that there is a higher probability of the formation of mixture of diastereomers when water is used as solvent rather than conventional

organic solvents[7]. These results can be rationalized by an *exo* approach of nitrone **1** which has *Z* configuration for the formation of major cycloadducts **2a–4a** (transition state **I**). The minor cycloadducts **2b–4b** are formed by the *endo* approach of *Z* nitrone (transition state **II**). The mixture of diastereomers are identified by considering the multiplicity of the proton signals at 3-H and 4-H along with their coupling constant values. The most significant differences in the ^{1}H NMR data for the diastereomers are the position and multiplicity of the 3-H signal. In the minor adducts **2b–4b**, 3-H resonates upfield around δ_H 4.10 while for the same proton in major adducts **2a–4a** around δ_H 4.55 and $J_{3,4}$ ~ 9.16 Hz for major adducts whilst for minor adducts $J_{3,4}$ is ~ 2.26 Hz. These differences can be explained by considering the available isoxazolidine ring conformations. Due to the 4,5-fused pyrrolidindione, the isoxazolidine ring adopts an envelope conformation and allowing for inversion, its nitrogen atom will either extend out from the envelope, *i.e.*, minor conformation, or point inside the envelope, *i.e.*, major conformation. The minor conformer has the N-lone pair antiperiplanar and therefore, capable of shielding 3-H proton, so this conformation is assigned to the minor conformer (**Figure 1**). The diastereomeric isoxazolidines **2a–4a** and **2b–4b** were separated by column chromatography and obtained in analytically pure form[9]. The *endo/exo* stereochemistry mentioned above is based on extensive NMR investigations. Most relevant are the coupling constants ($J_{H3,\ H4}$) of the diastereomers. For **2a-4a**, this coupling constant is almost 9.2–9.4 Hz, implying a *cis* relationship between H-3 and H-4, whereas for **2b–4b**, the coupling constant is almost 2.5–4.2 Hz which implies a trans relationship between H-3 and H-4 (Ref 10). In all the diastereomers, the configurations of H-5 and H-4 are *cis* as evidenced from their coupling constant values. For ethyl acrylate and methyl vinyl ketone the regioselectivity was rationalized by using frontier orbital theory[11] and ^{1}H NMR experiments. Cycloadditions to α,β-unsaturated carboxylic acid derivatives, *e.g.*

ethyl acrylate are particularly useful because high regioselectivity is often observed in water[6]. The reactions were found to be highly regioselective to form solely 5-substituted isoxazolidines. Nitrone **1** has considerably higher ionization potential than normal nitrones due to the electron withdrawing effect of chlorine. Therefore, nitrone (LUMO)-dipolarophile (HOMO) interactions completely dominate the reaction and lead to the formation of only 5-substituted adducts[11,12]. From the ^{1}H NMR spectrum of cycloadducts **5–6**, it has been found that clear double doublet signal for H-4 protons and double triplet signal for H-3 protons are obtained in all the cases due to further coupling from vicinal hydrogens and hence is a confirmation in favour of 5-substituted adducts. From the detailed investigations on the nature of these cycloaddition reactions using TLC and ^{1}H NMR spectrum studies for the cycloadducts **5–6**, it is also confirmed that no diastereomers are formed. The relative configurations of H-3, H-4 and H-5 protons in these adducts are *syn* and the cycloadducts are in favour of *exo* transition state geometry as evidenced from their coupling constant values ($J_{H4\ ,\ H5}$ = 6–8.4 Hz; $J_{H4\ ,\ H3}$ = 6.2–7.6 Hz) (Ref 10). Similar cycloaddition reactions of nitrone with these dipolarophiles usually give both 5 and 4-substituted adducts in conventional solvents with some exceptions of either 5 or 4-substituted adducts[13,14].

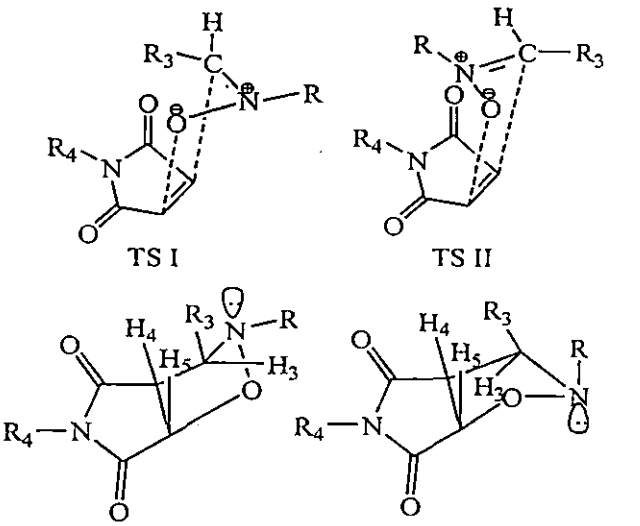


Figure 1

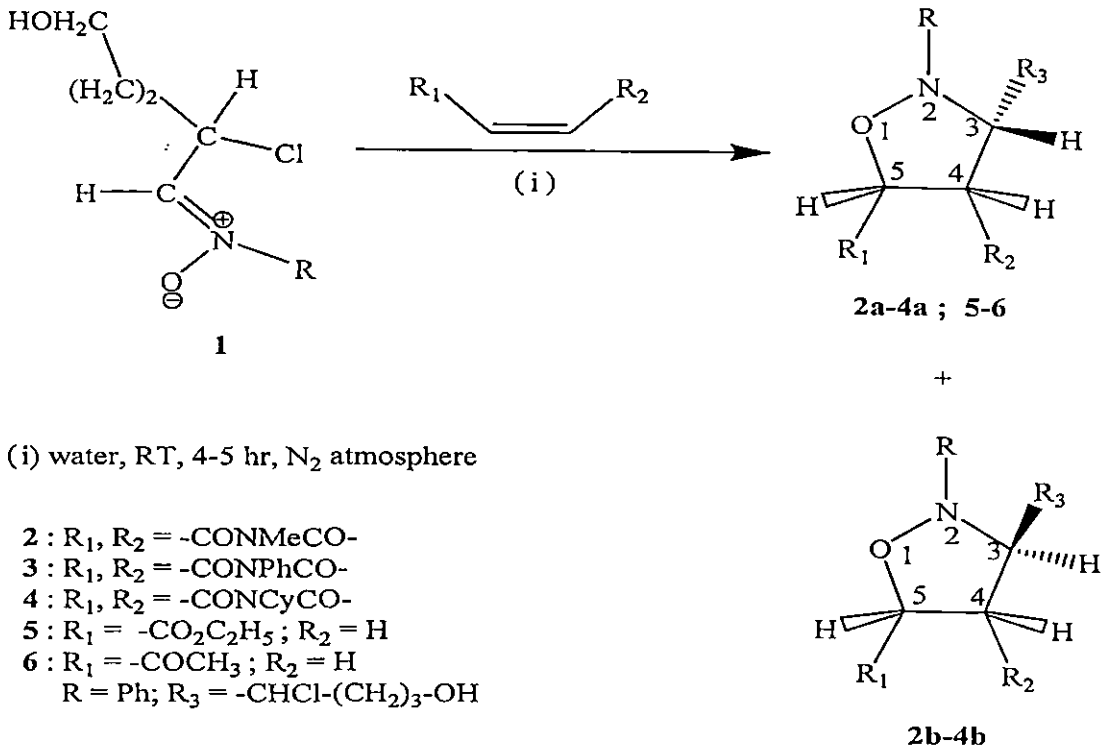
In general, the reactions are very clean and high yielding compared to usual cycloaddition reactions of nitrones. The products have been characterized from their spectroscopic (IR, ^{1}H NMR, HRMS, ^{13}C NMR) data. No catalyst or co-organic solvent are required. The structures of **2–6** have been confirmed by ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$ solution along

with MS and IR spectra. Thus, the ^{1}H NMR spectra of **2–4** indicate that these isoxazolidine derivatives are formed as a mixture of diastereomers in almost 70:30 ratio with *cis* and *trans* configurations relative to the spatial orientation of the R_3 group at C_3 with respect to the H atom at C_4 position. These diastereomers have been separated by column chromatography and recrystallized from heptane-ethyl acetate[9,15]. The ^{1}H NMR spectrum of **2a–4a** and **2b–4b** displayed different spectrum (position of signals) for the diastereomers. In contrast, the ^{1}H NMR spectrum of **5–6** displayed only one set of signals indicating that they are formed as unique cycloadducts. The exact stereochemistry at the asymmetric CHCl carbon atom of all the cycloadducts could not be determined due to multiplet signals (doublet of triplet appears almost as multiplet) obtained in the NMR spectrum and also due to freely rotating carbon centre at CHCl[4,5]. In the ^{13}C NMR spectrum, four signals were obtained in case of phenyl ring carbon atoms due to the equivalent nature of C-2 and C-6 and, C-3 and C-5 carbons. In the mass spectrum, significant M^++2 ion peak signals are obtained in most of the diastereomers and regioselective cycloadducts as the peak of highest intensity due to the presence of isotopic abundance of Cl^{37} atom in these compounds. In addition, mass fragmentation peaks of different value are also obtained for diastereomers of a particular cycloadduct. Studies of HRMS spectra shows almost exact masses in the majority of the compounds.

Antibacterial screening test

All the synthesized cycloadducts **2–4** and **5–6** were subjected to *in vitro* screening against *Vibrio parahaemolyticus*, *Klebsiella pneumoniae*, *Bacillus subtilis*, *Proteus vulgaris*, *Staphylococcus aureus*, *Shigella flexneri*, *Eschericia coli*, *Salmonella typhi* and *Vibrio cholerase*. The minimum inhibitory concentration (MIC) was determined using cup plate assay method according to the standard procedure[16]. Nutrient agar was used as a culture medium. Initially strains of desired bacteria were isolated and were suspended in normal saline. From each bacterial suspension 0.1 mL

was taken with the help of pipette and was spread on preprepared nutrient agar plate, with the help of spreader. Then cups were scooped out from each plate with the help of a cork borer and then to the respective cups different derivatives of the isoxazolidine (**2a, 3b, 4b, 5** and **6**) of concentrations (1000 μg/mL, 600, 400, 200, 100, 50, 25, 10 μg/mL) were added. The plates were incubated at 37°C for 24 hr and then results were recorded. The lowest concentration, which showed no visible growth, was taken as an end point minimum inhibitory concentration (MIC). All the compounds showed MIC 10 μg/mL except **4b** and **6**. These showed MIC 50 μg/mL against *Bacillus subtilis* and *Proteus vulgaris*. It has been observed that the derivatives of isoxazolidine (**2a, 3b, 4b, 5** and **6**) have antibacterial activity against both gram positive (*S.aureus, B.subtilis*) and gram negative (*E.coli, S.flexneri*) bacteria, hence it can be concluded that the derivatives used were broad spectrum antibiotics[17]. The MIC value obtained for isoxazolidine derivatives range from 10 μg/mL-50 μg/mL (except **5**) and are very close to the MIC values of most commonly used antibiotics like Penicillin (10 units), Sulphonamide (300 μg/mL), Nalidixic Acid (512 μg/mL), *etc.* and hence they are equally effective and can be prescribed after testing of LD_{50} (Ref 18).



(i) water, RT, 4-5 hr, N_2 atmosphere

2 : R_1, R_2 = -CONMeCO-
3 : R_1, R_2 = -CONPhCO-
4 : R_1, R_2 = -CONCyCO-
5 : R_1 = $-CO_2C_2H_5$; R_2 = H
6 : R_1 = $-COCH_3$; R_2 = H
R = Ph; R_3 = $-CHCl-(CH_2)_3-OH$

Scheme I

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. ^1H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q – Tof micro instrument (YA–105). Elemental analyses (CHN) were performed with a Perkin-Elmer 2400 series CHN Analyzer. TLC's were run on Fluka silica gel precoated TLC plates. All other reagents and solvents were purified after receiving from commercial suppliers. N-phenylhydroxylamine was prepared following standard methods available in the literature and has been used already for the synthesis of aldehydes and cycloaddition reactions involving α-amino nitrones in organic solvents[4,5].

Table I - Physicochemical data of synthesized compounds

Entry	Nitrone	Dipolarophile	Time (hr)	Cycloadduct[a] & m.p (°c) 2a-4a : *cis* ; 2b–4b: *trans*	*Cis/trans ratio*(%)	Yield[b] (%)
1	N-phenyl-α-chloro nitrone	N-methyl maleimide	4	**2a**: White solid, 104 **2b**: White solid, 120	**2a**: 76 **2b**: 20	96
2	N-phenyl-α-chloro nitrone	N-phenyl maleimide	5	**3a**: Yellow solid, 116 **3b**:Yellowish white solid, 131	**3a**: 71 **3b**: 23	94
3	N-phenyl-α-chloro nitrone	N-cyclohexyl maleimide	5	**4a**: Dark yellow crystals, 88 **4b**: Yellow crystals, 96	**4a**: 68 **4b**: 27	95
4	N-phenyl-α-chloro nitrone	Ethyl acrylate	5	**5**: White gummy liquid		93
5	N-phenyl-α-chloro nitrone	Methyl vinyl ketone	5	**6**: Pale yellow oil		91

[a]All the reactions were carried out at RT
[b]Isolated yields after purification

General procedure for cycloaddition (for diastereomers)

In a 50 mL conical flask, nitrone **1** (1 mmole), dipolarophile (1 mmole) and water (15 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 4-5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the products were extracted with ether (2 X 25 mL), the organic layer was washed with saturated brine (2 X 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate - hexane to afford cycloadducts (**Scheme I**). This procedure was followed for the substrates **1–3** listed in **Table I**.

Synthesis of (3*S*)–3-(1-chloro-4-hydroxy butyl)-5-methyl-2-phenyldihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 2a

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added N-methyl maleimide (1 mmole) at RT under nitrogen atmosphere and the reaction mixture was stirred for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.38, 0.40). The products were extracted with ether (2 X 25 mL),

the organic layers were washed with saturated brine (2 X 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate - hexane and finally obtained by removal of solvent under reduced pressure as white solids.

White solid. Yield 75.6%; R_f = 0.38; IR($CHCl_3$): 3590 - 3460 (br), 2924(m), 2840(m), 1755(s), 1660(s), 1485(m), 1340(m), 803(s), 774(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.15 – 6.98 (m, 5H, C_6H_5), 5.22 (d, 1H, J = 6.8 Hz, C_5H), 5.08 – 5.00 (br, 1H, OH, exchanged in D_2O), 4.55 (dd, 1H, J = 6.84, 9.2 Hz, C_3H), 3.76 (dd, 1H, J = 8.06, 9.20 Hz, C_4H), 3.40 (s, 3H, CH_3), 3.14 – 2.96 (m, 1H, CHCl), 1.95 - 1.52 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 174.64, 173.42 (carbonyl carbons), 134.50, 133.26, 132.00, 130.64 (aromatic carbons), 88.00 (C_5), 73.00 (C_3), 62.00 (CH_2OH), 58.00 (C_4), 52.00 (CHCl), 39.00 (CH_3), 26.00, 23.00 (2 CH_2 carbons); MS: *m/z* 340 (M^+ +2), 338 (M^+), 323, 307, 261, 247, 231, 107, 77, 59; HRMS – EI: Calcd for $C_{16}H_{19}O_4N_2Cl$ (M) *m/z* 338.1338. Found: M^+ 338.1324. Anal. Found: C, 56.57; H, 5.49; N, 8.19. $C_{16}H_{19}O_4N_2Cl$ requires C, 56.63; H, 5.60; N, 8.25%.

(3*R*)–3-(1-chloro-4-hydroxy butyl)-5-methyl-2-phenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 2b

White solid. Yield 20.4%, R_f = 0.40; IR ($CHCl_3$): 3580 – 3465 (br), 2895 (m), 1764 (s), 1660(s), 1482 (m), 1355 (m), 805 (s), 780 (s) cm^{-1} ; ^1H NMR ($CDCl_3$): δ 7.20 – 7.08 (m, 5H, C_6H_5), 5.26 (d, 1H, J = 6 Hz, C_5H), 5.10 – 4.94 (br, 1H, OH, exchanged in D_2O), 4.10 (dd, 1H, J = 2.50, 4.06 Hz, C_3H), 3.60 (dd, 1H, J = 2.52, 4.26 Hz, C_4H), 3.44 (s, 3H, CH_3), 3.22 – 3.05 (m, 1H, CHCl), 1.88 - 1.44 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.50, 171.00 (carbonyl carbons), 133.00, 132.00, 130.34, 128.60 (aromatic carbons), 88.62 (C_5), 74.00 (C_3), 61.44 (CH_2OH), 58.28 (C_4), 54.00 (CHCl), 37.00 (CH_3), 24.00, 21.00 (2 CH_2 carbons); MS: *m/z* 338 (M^+), 307, 261, 246, 231, 139, 111, 107, 77, 31; HRMS – EI: Calcd for $C_{16}H_{19}O_4N_2Cl$ (M) *m/z* 338.1338. Found: M^+ 338.1320. Anal. Found: C, 56.50; H, 5.52; N, 8.16 . $C_{16}H_{19}O_4N_2Cl$ requires C, 56.63; H, 5.60; N, 8.25%.

Synthesis of (3*S*)-3- (1-chloro-4 hydroxy butyl)- 2,5 diphenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 3a

To a stirred solution of nitrone 1 (1 mmole) in 15 mL water was added N-phenyl maleimide (1 mmole) at RT under nitrogen atmosphere and the reaction mixture was stirred for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.34, 0.42).The products were extracted with ether (2 X 25 mL), the organic layers were washed with saturated brine (2 X 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate - hexane and finally obtained by removal of solvent under reduced pressure as yellow and yellowish white solids.

Yellow solid. Yield 70.8%; R_f= 0.34; IR ($CHCl_3$): 3545 – 3480 (br), 2880 (m), 1765 (s), 1650 (s), 1472 (m), 1365 (m), 795 (s), 775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55 - 7.40 (m, 2 X 5H, C_6H_5 protons), 5.42 (d, 1H, J = 8.24 Hz, C_5H), 5.05 - 4.95 (br, 1H, OH, exchanged in D_2O), 4.46 (dd, 1H, J = 9.25, 7.28 Hz, C_3H), 3.76 (dd, 1H, J = 9.22, 6.08 Hz, C_4H), 3.22 – 3.07 (m, 1H, CHCl), 1.82 - 1.35 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 175.54, 173.68 (carbonyl carbons), 138.00, 137.00, 135.64, 134.32, 133.70, 132.00, 131.46, 130.00 (aromatic carbons), 87.50 (C_5), 76.00 (C_3), 64.52 (CH_2OH), 59.42 (C_4), 52.00 (CHCl), 28.00, 26.00 (2 CH_2 carbons); MS: *m/z* 400 (M^+), 341, 323, 246, 216, 173, 107, 77, 59, 31; HRMS – EI: Calcd. for $C_{21}H_{21}O_4N_2Cl$, (M) *m/z* 400.1494. Found: M^+ 400.1476. Anal. Found: C, 66.70; H, 5.20; N, 6.82. $C_{21}H_{21}O_4N_2Cl$ requires C, 66.84; H, 5.23; N, 6.98%.

Synthesis of (3*R*)-3- (1-chloro-4 hydroxy butyl)- 2,5 diphenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione, 3b

Yellowish white solid. Yield: 23.2%, R_f= 0.42; IR ($CHCl_3$): 3560 – 3470 (br), 2865 (m), 1760 (s), 1684 (s), 1465 (m), 1370 (m), 810 (m), 772 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35 - 7.14 (m, 2 X 5H, C_6H_5 protons), 5.24 (d, 1H, J = 7.20 Hz, C_5H), 5.00 - 4.92 (br, 1H, OH, exchanged in D_2O), 4.38 (dd, 1H, J =

3.25, 2.24 Hz, C_3H), 3.52 (dd, 1H, J = 4.42, 2.08 Hz, C_4H) , 3.37 – 3.20 (m, 1H, CHCl), 1.74 - 1.46 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 174.44, 171.86 (carbonyl carbons), 137.24, 136.48, 135.00, 134.56, 133.00, 132.80, 130.64, 129.00 (aromatic carbons), 85.00 (C_5), 72.62 (C_3), 64.56 (CH_2OH), 57.40 (C_4), 53.62 (CHCl), 28.00, 27.00 (2 CH_2 carbons); MS: *m/z* 402 (M^+ +2), 400 (M^+), 295, 246, 216, 211, 189, 154, 107, 77, 31; HRMS – EI: Calcd for $C_{21}H_{21}O_4N_2Cl$, (M) *m/z* 400.1494. Found: M^+ 400.1483. Anal. Found: C, 66.54; H, 5.14; N, 6.75; $C_{21}H_{21}O_4N_2Cl$, requires C, 66.84; H, 5.23; N, 6.98%.

Synthesis of (3*S*)-3- (1-chloro-4 hydroxy butyl)-5-cyclohexyl – 2- phenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*, 6a-*H*)-dione, 4a

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added N-cyclohexyl maleimide (1 mmole) at RT under nitrogen atmosphere and the reaction mixture was stirred for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.39, 0.44). The products were extracted with ether (2 X 25 mL), the organic layers were washed with saturated brine (2 X 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate - hexane and finally obtained by removal of solvent under reduced pressure as dark yellow and yellow crystals.

Dark yellow crystals. Yield 68%, R_f = 0.39; IR ($CHCl_3$): 3620 – 3530 (br), 2872 (s), 1770 (s), 1693 (s), 1444 (m), 1390 (m), 1260 (m), 805 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.02 – 6.92 (m, 5H, C_6H_5), 5.32 (d, 1H, J = 6.12 Hz, C_5H), 5.10 - 5.02 (br, 1H, OH, exchanged in D_2O), 4.52 (dd, 1H, J = 9.26, 6.08 Hz, C_3H), 4.26 (dd, 1H, J = 9.24, 7.06 Hz, C_4H), 3.20 – 2.94 (m, 1H, CHCl), 1.64 – 1.24 (m, 17H, cyclohexyl and CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.34, 170.26 (carbonyl carbons), 131.30, 130.55 128.63, 127.42 (aromatic carbons), 86.00 (C_5), 78.00 (C_3), 62.50 (CH_2OH), 55.00(C_4), 50.66 (CHCl), 30.00, 28.00, 26.74, 25.42, 24.36, 23.58, 22.24, 19.00 (cyclohexyl and CH_2 carbons); MS: *m/z* 406

(M^+), 375, 347, 329, 324, 222, 107, 77, 59, 31; HRMS – EI: Calcd for $C_{21}H_{27}O_4N_2Cl$ (M) *m/z* 406.1962. Found: M^+ 406.1949.

Synthesis of (3*R*)-3- (1-chloro-4 hydroxy butyl)-5-cyclohexyl – 2- phenyl dihydro-2*H* pyrrolo[3,4-*d*]isoxazole-4,6(5*H*, 6a-*H*)-dione, 4b

Yellow crystals. Yield 27%, R_f = 0.44; IR ($CHCl_3$): 3630 – 3535 (br), 2865 (s), 1760 (s), 1680 (s), 1440 (m), 1375(m), 1265 (m), 810(s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.22 – 7.04 (m, 5H, C_6H_5), 5.26 (d, 1H, *J* = 7.22 Hz, C_5H), 5.18 - 5.06 (br, 1H, OH, exchanged in D_2O), 4.43 (dd, 1H, *J* = 4.32, 3.26 Hz, C_3H), 4.14 (dd, 1H, *J* = 3.22, 2.08 Hz, C_4H), 3.38 – 3.20 (m, 1H, CHCl), 1.72 – 1.38 (m, 17H, cyclohexyl and CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 170.74, 169.86 (carbonyl carbons), 135.36, 134.50, 133.82, 132.58 (aromatic carbons), 84.34 (C_5), 75.00 (C_3), 61.64 (CH_2OH), 53.50 (C_4), 53.00 (CHCl), 27.00, 26.52, 25.46, 24.00, 23.00, 21.54, 20.55, 19.00 (cyclohexyl and CH_2 carbons); MS: *m/z* 408 (M^+ +2), 406 (M^+), 323, 216, 179, 139, 107, 83, 77, 59; HRMS – EI: Calcd for $C_{21}H_{27}O_4N_2Cl$ (M) *m/z* 406.1962. Found: M^+ 406.1943.

General procedure for cycloaddition (for regioselective cycloadducts)

In a 50 mL conical flask, nitrone **1** (1 mmole), dipolarophile (1 mmole) and water (15 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 - 6 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with ether (2 X 25 mL), the organic layer was washed with saturated brine (2 X 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography using ethyl acetate - hexane to afford pure cycloadduct (**Scheme I**). This procedure was followed for the substrates **4** and **5** listed in **Table I.**

Synthesis of (3*S*)-ethyl-3-(1-chloro-4 hydroxy butyl)-2-phenyl isoxazolidine-5-carboxylate, 5

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added ethyl acrylate (1 mmole) at RT under nitrogen atmosphere and the reaction mixture was stirred for another 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.48). The product was extracted with ether (2 X 25 mL), the organic layer was washed with saturated brine (2 X 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified and separated by column chromatography using ethyl acetate - hexane and finally obtained by removal of solvent under reduced pressure as white gummy liquid.

White gummy liquid: Yield 93%, R_f = 0.48; IR ($CHCl_3$): 3610 – 3525 (br), 2930 (s), 2856 (m), 1750 (s), 1445 (s), 795 (s), 770(s) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 7.22 - 7.14 (m, 5H, C_6H_5), 5.15 - 5.03 (br, 1H, -OH, exchanged in D_2O), 4.84 (t, 1H, J = 8.2 Hz, C_5H), 4.48 - 4.33 (dt, 1H, J = 7.22 Hz, C_3H), 4.22 (q, 2H, J = 6, 6.02 Hz, $-OCH_2CH_3$), 3.88 (dd, 2H, J = 9.24, 8.18 Hz, C_4 2H), 3.60 - 3.46 (m, 1H, CHCl), 1.84 – 1.46 (m, 6H, CH_2 protons), 1.24 (t, 3H, J = 7.52 Hz, $-OCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 167.40 (carbonyl carbon), 136.40, 134.50, 133.25, 132.60 (aromatic carbons), 88.00 (C_5), 76.00 (C_3), 63.00 (CH_2OH), 60.00 (CH_2 carbon of $-OCH_2CH_3$), 58.00 (C_4), 55.00(CHCl), 32.00, 24.00 (2 CH_2 carbons), 16.00 (CH_3 carbon of OCH_2CH_3); MS: *m/z* 329 (M^+ +2), 327(M^+), 296, 250, 219, 207, 177, 142, 108, 107, 77, 73, 31; HRMS - EI: Calcd for $C_{16}H_{22}O_4NCl$ (M) *m/z* 327.1542. Found: M^+ 327.1533.

Synthesis of 1-{(3*S*)-3-(1-chloro-4-hydroxy butyl)-2-phenyl isoxazolidin-5yl)} ethanone, 6

To a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added methyl vinyl ketone (1 mmole) at RT under nitrogen atmosphere and the reaction mixture was stirred for another 8 hr. The progress of the reaction was monitored by TLC (R_f = 0.44). The product was extracted with ether (2 X 25 mL), the organic layer was washed with saturated brine (2 X 15 mL), dried over anhydrous Na_2SO_4 and

concentrated. The crude product was purified and separated by column chromatography using ethyl acetate - hexane and finally obtained by removal of solvent under reduced pressure as pale yellow oil.

Pale yellow oil. Yield 91%, R_f = 0.44; IR($CHCl_3$): 3520 - 3380 (br), 2925 (s), 2844 (m), 1710 (s), 1440 (m), 1324 (s), 804 (m), 776 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.16 - 7.04 (m, 5H, C_6H_5), 5.32 (t,1H, J = 7.82 Hz, C_5H), 5.10 – 5.0 (br, 1H, exchanged in D_2O), 4.54 – 4.43 (dt, 1H, J = 8.30 Hz, C_3H), 4.28 (dd, 2H, J = 9.48, 7.10Hz, C_4 2H), 3.78 – 3.62 (m, 1H, CHCl), 2.12 (s, 3H, $COCH_3$), 1.86 - 1.54 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 195.22 (carbonyl carbon), 132.00, 131.55, 130.00, 128.40 (aromatic carbons), 88.00 (C_5), 78.00 (C_3), 66.00 (CH_2OH), 58.00 (C_4), 53.50 (CHCl), 24.60 ($COCH_3$), 19.00, 17.00 (2 CH_2 carbons); MS: *m/z* 297(M^+), 266, 254, 270, 212, 147, 112, 107, 77, 43, 31; HRMS-EI: Calcd for $C_{15}H_{20}O_3NCl$ (M) *m/z* 297.1437. Found: M^+ 297.1426.

Conclusions

In summary, the present procedure provides an example of green chemistry methodology for the synthesis of regio and stereoselective novel isoxazolidines in aqueous phase with high yield in a short reaction time and almost all the synthesized compounds are having significant antibacterial activity. The notable factors of this methodology are: (a) high yields (b) faster reaction (c) mild reaction conditions and (d) green synthesis avoiding use of organic solvents. Therefore, it is believed that procedure described here will find important applications in the synthesis of isoxazolidine derivatives and thereby offering greater scope for aqueous phase cycloaddition reactions.

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References

1 Padwa A & Pearson W H, *Synthetic application of 1,3-dipolar Cycloaddition Chemistry toward Heterocycles and Natural products* (Wiley, New Jersy), **2003**.

2 (a) Katagiri N, Okada M, Morishita Y & Kaneko C, *Tetrahedron*, 53, **1997**, 5725;
(b) Tejero T, Dondoni A, Rojo I, Merchan F L & Merino P, *Tetrahedron*, 53, **1997**, 3301.

3 Butler R N, Coyne A G & Moloney E M, *Tetrahedron Lett*, 48, **2007**, 3501 and references cited therein.

4 (a) Chakraborty B & Chhetri M S, *Indian J Chem*, 47B, **2008**, 485;

(b) Chakraborty B, Kafley S & Chhetri M S, *Tetrahedron Lett*, **2009** (in press).

5 Chakraborty B, Kafley S & Chhetri M S, *Indian J Chem*, **2009** (in press).

6 (a) Hayashi Y, *Angew Chem Int Ed (Engl)*, 45, **2006**, 8103; (b) Li C J & Chang T H, *Organic Reactions in Aqueous Media* (Wiley, New York), **2007**, **1997**; (c) Brogan A P, Dickerson T J & Janda K D, *Angew Chem Int Ed (Engl)*, 45, **2006**, 8100.

7 (a) Grieco P A, *Organic Synthesis in Water* (Blackie Academic and Professional, London), **1998**;

(b) Lindstrom U M, *Organic Reactions in Water*, (Blackwell Publishing, Oxford), **2007**.

8 Ranu B C & Banerjee S, *Tetrahedron Lett*, 48, **2007**, 141.

9 Najera C J M, *Angew Chem Int Ed (Engl)*, 44 , **2005**, 6272.

10 (a) Deshong P, Li W, Kennington J W & Ammon H L, *J Org Chem*, 56, **1991**, 1364;
(b) Gandolfi R & Grunanger P, *The Chemistry of the Heterocyclic Compounds* (Wiley Interscience), 49 (2), **1999**, 774.

11 Houk K N, Sims J.& Luskus C R, *J Am Chem Soc*, 95, **1973**, 7302.

12 Kranjc K & Kocevar M, *Tetrahedron*, 64, **2008**, 45 and references cited therein.

13 Chakraborty B & Ghosh A R , *Indian J Heterocycl Chem*, 6, **1996**, 75.

14 Chakraborty B & Ghosh A R , *Indian J Heterocycl Chem*, 7, **1997**, 77.

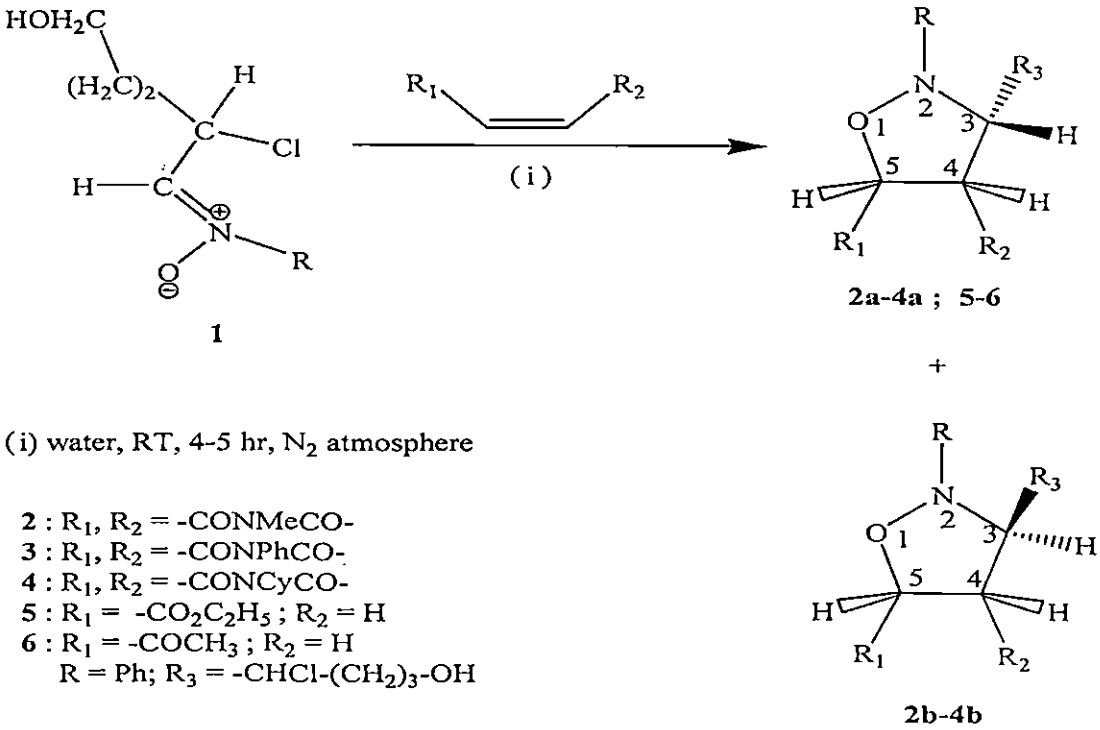
15 Heaney F, Rooney O & Cunningham D, *J Chem Soc Perkin Trans 2*, **2001**, 373.

16 Andrews J M, *J Antimicrob Chemother*, 48, **2001**, 5.

17 Chattopadhyay D, Dastidar S G & Chakrabarty A N, *Indian J Med Microbiol*, **1987**, 5 171.

18 Chakrabarty A N, Molnar J, Dastidar S G & Motohashi N, *Non Antibiotics: A New Class of Unrecognized Antimicrobics*, (NISCOM, India), **1998**.

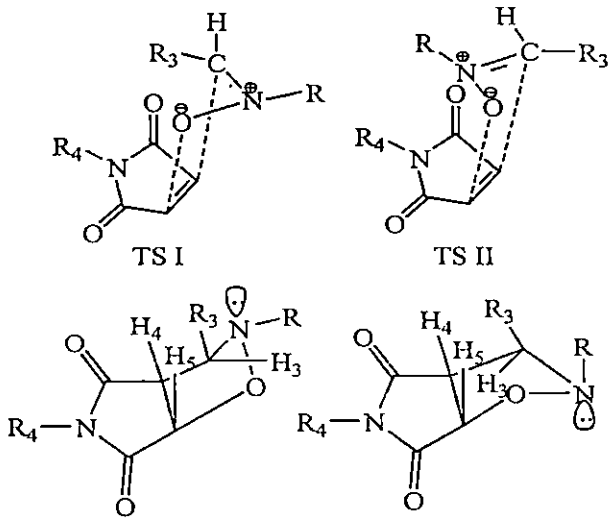
HIGH RESOLUTION FIGURE



(i) water, RT, 4-5 hr, N_2 atmosphere

2 : R_1, R_2 = -CONMeCO-
3 : R_1, R_2 = -CONPhCO-
4 : R_1, R_2 = -CONCyCO-
5 : R_1 = $-CO_2C_2H_5$; R_2 = H
6 : R_1 = $-COCH_3$; R_2 = H
R = Ph; R_3 = $-CHCl-(CH_2)_3-OH$

Scheme I



R = Ph; R_3 = $CHCl(CH_2)_3OH$; R_4 = Ph; Me; Cy

Figure 1

CONVENIENT AND NEW METHOD OF CONVERSION OF ALKYL HALIDES TO ALDEHYDES USING α-AMINO NITRONES AS OXIDIZING REAGENT

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α-amino nitrones have been used successfully as an oxidizing reagent for the synthesis of aldehydes from various alkyl halides with an excellent yield. Inaddition, hydrolysis of the side product (imines) furnishes starting material amides which are recyclable along with corresponding amines.

Conversion of alkyl halides to aldehydes using N-oxide with moderate yield has been reported long time back (Krohnke reaction). In addition to the existing methods available for the synthesis of aldehydes from alkyl halides,[1-5] we would like to incorporate an efficient methodology of synthesis of aldehydes from alkyl halides along with imines using for the first time α-amino nitrones[6,7,8] as an oxidizing reagent with an excellent yield (Scheme 1, Figure1,Table1).

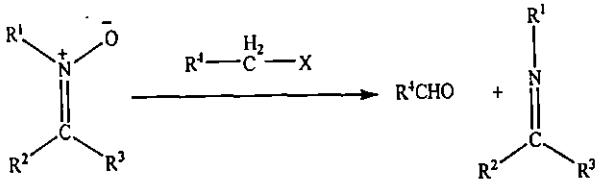


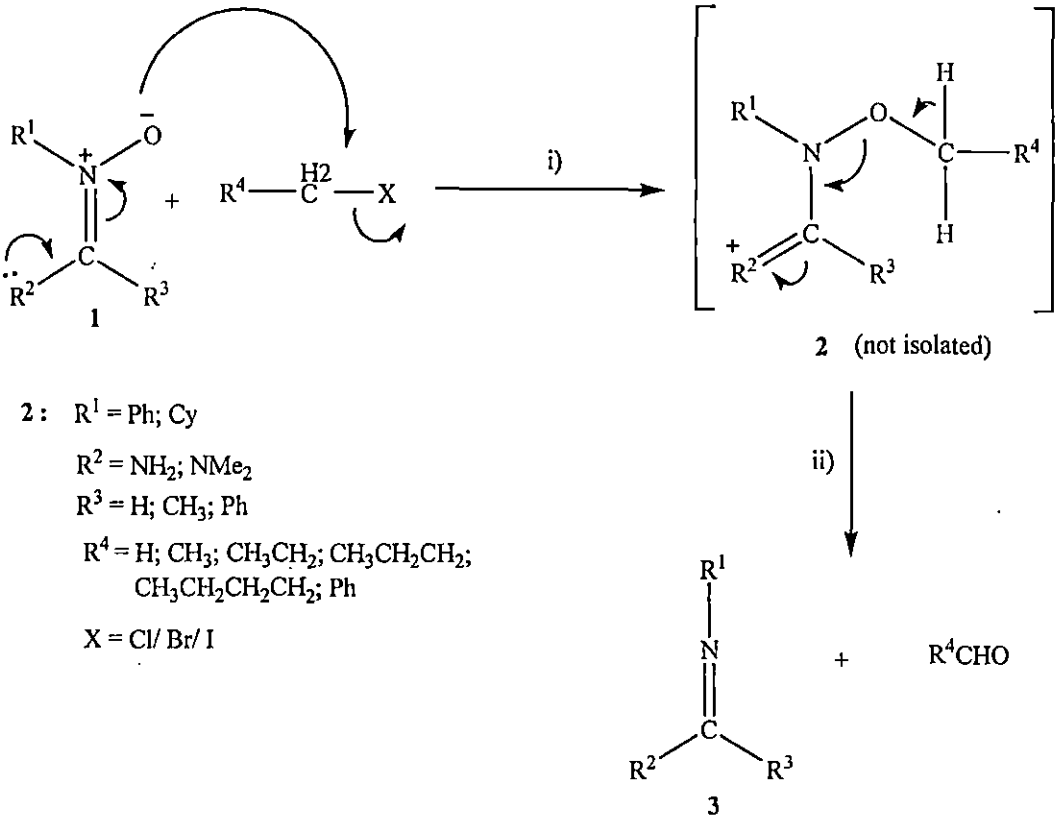
Figure 1

In addition, the side product (imines) obtained during aldehyde synthesis results starting material amide and amines upon simple hydrolysis (Scheme 2). The duly obtained amides can be successfully reused for the synthesis of nitrones while the amines can be used for further general reaction purposes. Synthesis of aldehydes from alkyl halides and recycling the side product in cycloaddition reactions using α-chloro nitrones have been already reported from this laboratory[9,10]. Literature survey reveals that aldehyde synthesis using α-amino nitrone as an oxidizing reagent has not yet reported and can be incorporated as an important application in nitrone chemistry.

The present study has been carried out using a variety of α-amino nitrones and alkyl halides

(Table 1) in order to generalize the methodology for the aldehyde synthesis. The synthesis and cycloaddition reactions of some α-amino nitrones **1** (R^1=Ph,Cy; R^2=NMe_2; R^3=H and R^1=Ph,Cy; R^2=NH_2; R^3=H) have been already reported[6,7,8] following the general methodology of α-amino nitrone synthesis from DMF and formamide[11]. The remaining α-amino nitrones (**1**) of Table 1 were prepared following the same methodology. The yield of the isolated aldehydes are extremely high (almost 80 - 88%) in a much lesser time and are much better in case of active alkyl halides compared to inactive alkyl halides while imines are obtained in almost 11 – 20% yields as side products. The results are summarized in Table 1. The products especially aldehyde, amide and amines are known compounds and spectral data of these synthesized compounds are almost identical to the values found in literature. For example, sharp singlet signals at δ 9.80 & 198 in the ^{1}H NMR and ^{13}C NMR spectrum along with molecular ion peak at 106, base peak at 105 and 77, 51 in the MS spectrum give strong evidence in favour of benzaldehyde formation. Spectral data of the imine derivatives (**3**) also agreed well with the assigned structures. For example, prominent molecular ion peak at 196 and base peak at 103 (due to the formation of PhCN) clearly indicates in favour of imine derivative **3** (entry **8**). Similarly strong evidences are also obtained from HRMS spectra in favour of the aldehyde and other known compounds formation. The proposed mechanism for the aldehyde synthesis using α-amino nitrone is very interesting. Nitrone **1** undergoes S_N2 reaction readily with alkyl halides and develops an intermediate compound (**2**) which was not isolated. The reaction rate is much more faster compared to the S_N2 reactions of α-chloro nitrones[12] due to the involvement of available electron pairs of amino or dimethyl amino group. The N-O bond of the intermediate compound (**2**) breaks[13] when the reaction mixture is stirred with solid sodium carbonate which plays an important role for the development of aldehyde and imines in a Kornblum type reaction with a very good yield (Scheme1;Table 1). The imine derivative **3**

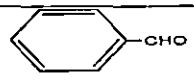
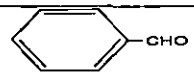
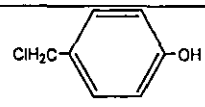
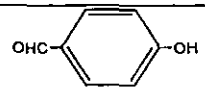
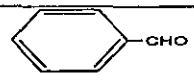
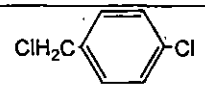
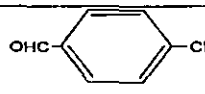
on hydrolysis results starting amide (**5**: 55–60%) and amines (**4**: 35-40%) where amides are the starting material for α-amino nitrone synthesis. In the course of the study, major difficulties were faced during isolation and identification of formaldehyde because of its volatility and GC-MS has been used to identify it (*m/z* 30, M^+ 65.52%). The products were characterized from their spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, HRMS) data. No catalyst or co organic solvent was required.



2: R^1 = Ph; Cy
R^2 = NH_2; NMe_2
R^3 = H; CH_3; Ph
R^4 = H; CH_3; CH_3CH_2; $CH_3CH_2CH_2$; $CH_3CH_2CH_2CH_2$; Ph
X = Cl/ Br/ I

SCHEME 1 - Reaction condition: i) dry ether, RT, N_2 atmosphere, 1 - 2 hr
ii) dry ether, Na_2CO_3, RT, N_2 atmosphere, 3 - 4 hr

Table – 1 **Aldehyde synthesis using α-amino nitrones**

Entry	Nitrone	Alkyl halide[a]	Aldehyde[b]	Time (hr)	Yield[c] (%)
1	R^1 = Ph; R^2 = NH_2; R^3 = H	R^4 = Ph		4	86
2	R^1 = Ph; R^2 = NH_2; R^3 = H	R^4 = CH_3	CH_3CHO	5	85
3	R^1 = Ph; R^2 = NMe_2; R^3 = H	R^4 = CH_3CH_2	CH_3CH_2CHO	5	82
4	R^1 = Ph; R^2 = NH_2; R^3 = H	R^4 = H	HCHO	6	80
5	R^1 = Cy; R^2 = NH_2; R^3 = H	R^4 = Ph		4	80
6	R^1 = Cy; R^2 = NMe_2; R^3 = H	R^4 = $CH_3CH_2CH_2$	$CH_3CH_2CH_2CHO$	5	81
7	R^1 = Ph; R^2 = NH_2; R^3 = H			4	83
8	R^1 = Ph; R^2 = NH_2; R^3 = Ph	R^4 = Ph		5	88
9	R^1 = Ph; R^2 = NH_2; R^3 = Ph	R^4 = CH_3CH_2	CH_3CH_2CHO	6	84
10	R^1 = Ph; R^2 = NH_2; R^3 = CH_3			5	82

a) Reaction condition : α-amino nitrone (1 mmol), dry ether, sodium carbonate, N_2 atmosphere, RT
b) All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS spectral data.
c) Isolated yield after purification

Finally, we developed a new atom economical methodology for the aldehyde synthesis using α-amino nitrones and considered further reaction carried out by hydrolysing the imine derivatives in acid medium for the regeneration of starting material amide and corresponding amines. The isolated amide (starting material for α-amino nitrones) and amines are equally good in quality as obtained from commercial suppliers and thereby offering greater scope for the present methodology. The notable advantages offered by this method are simple operation, easy workup, mild and faster reaction conditions with high yield of products. Therefore, the present methodology may be incorporated as a general method of aldehyde synthesis from alkyl halides for extremely good yield and also as an important application of nitrones.

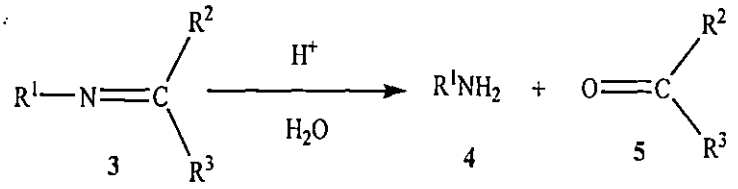
Experimental

^{1}H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q – Tof micro instrument (YA – 105). GC – MS was recorded using Clarus 500 gas chromatograph with built in MS detector Perkin – Elmer machine. TLC was carried out on Fluka silica gel TLC cards. All other reagents and solvents were purified after receiving from commercial suppliers. N-cyclohexyl, N-phenylhydroxylamines were prepared following standard methods available in the literature[14,15].

General procedure for preparation of aldehyde (benzaldehyde) and imine derivative 3 (entry 8; Table 1)

In a 100 ml conical flask, N-phenyl-α-amino nitrone[6] (500 mg, 2.3570 mmol), benzyl chloride (295.8670 mg, 1 equivalent) and diethyl ether (25 ml) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 1 hour. During this process nitrone **1** underwent S_N2 reaction very quickly with benzyl chloride and developed an intermediate compound (**2**) which was not isolated. The progress of the reaction was monitored by TLC (R_f = 0.38). 2 gms of solid Na_2CO_3 was added at this stage and the reaction mixture was stirred for further 3 hour and monitored by TLC. The N-O bond was easily cleaved[13] under basic medium in a Kornblum type mechanism and developed benzaldehyde (R_f = 0.43) and imine derivative (R_f = 0.54) respectively. The reaction mixture was filtered and concentrated on a rotary evaporator. Basic work-up followed by silica gel column chromatography using ethyl acetate – hexane results benzaldehyde as colourless liquid (706 mg, 88 %) and imine derivative (**3**) as pale yellow gummy liquid (84 mg, 11 %, Scheme 1). This general procedure was followed for all the substrates listed in Table 1.

General procedure for acid hydrolysis of imine derivative 3 (substituted formidamide / acetimidamide / benzimidamide, entry 8)



5a: R^1 = Ph; Cy
b: R^2 = NH_2; NMe_2
c: R^3 = H; CH_3; Ph

SCHEME 2 - Reaction condition: 10% HCl, hydrolysis, 30 minutes

In a 100 mL R.B flux, imine derivative **3** (70 mg), 20 mL 10% HCl was taken and refluxed in water bath for 30 minutes. The formation of the desired hydrolysed products were monitored by TLC. During the hydrolysis process, the double bond between carbon and nitrogen of the imine derivative was cleaved[16] and benzamide (**5**: R^2 = NH_2; R^3 = Ph; R_f= 0.42) and aniline (**4**: R^1 = Ph; R_f= 0.64) was developed (entry **8**). The products were extracted with ether (2 x 25 mL) when aniline passes into organic layer while benzamide remains in aqueous phase. The ether extract containing aniline was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator and finally purified by silica gel column chromatography using ethyl acetate – hexane as pale yellow liquid (24 mg, 34%). Benzamide was obtained as white crystalline solid when aqueous part of the solution was evaporated in a temperature controlled water bath and was crystallized from ethanol (42 mg, 60%; m.p. 126^{0}C; Scheme 2). This general hydrolysis procedure was followed for all the imine derivatives (**3**).

Spectral data for benzaldehyde (entry 8)

706 mg, 88 %; HRMS-EI: Calcd. for C_6H_5CHO (M),106.1240, Found ; M^+,106.1228; IR ($CHCl_3$): 2825 (s), 1695 (s), 1320 (m), 780 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.80 (s, 1H, CHO), 7.30 – 7.16 (m, 5H, C_6H_5); ^{13}CNMR ($CDCl_3$): δ 198 (CHO), 136.00, 134.00, 132.50, 131.00 (aromatic

carbons); FAB – MS: *m/z* 106 (M^+), 105 (B.P), 78, 77, 51.

Spectral data for N'-phenylbenzimidamide (imine derivative 3 ; entry 8)

84 mg, 11 %; HRMS-EI: Calcd. for $C_{13}H_{12}N_2$ (M), 196.2530, Found; M^+, 196.2519; IR($CHCl_3$): 3450 (m), 1682 (s), 780 (s) ; ^1H NMR ($CDCl_3$): δ 7.32 – 7.22 (m, 5H, C_6H_5), 6.76 – 6.63 (m, 5H, C_6H_5), 3.75 – 3.62 (br, 2H, NH_2); $^{13}CNMR$ ($CDCl_3$): δ 136.84, 135.24, 134.50, 132.80, 131.25, 130.00, 128.50, 127.45 (phenyl carbons), 87.00 (C=N); FAB – MS: *m/z* 196 (M^+), 119, 103 (B.P), 77.

Spectral data for aniline (product 4 ; entry 8)

24 mg, 34%; HRMS-EI: Calcd. for C_6H_7N (M), 93.0690, Found; M^+, 93.0682; IR($CHCl_3$): 3440(m), 3205(s), 1635 (s), 1280 (m), 910(m), 774 (s); ^1H NMR ($CDCl_3$): δ 6.88 – 6.72 (m, 5H, C_6H_5), 3.82 – 3.66 (br, 2H, NH_2); $^{13}CNMR$ ($CDCl_3$): δ 134.00, 132.50, 129.42, 128.00 (phenyl carbons); FAB – MS: *m/z* 93 (M^+).

Spectral data for benzamide (product 5 ; entry 8)

42 mg, 60%; m.p.126^{0}C; HRMS-EI: Calcd. for C_7H_7NO (M), 121.0690, Found; M^+, 121.0681; IR($CHCl_3$): 3455 (s), 1675 (s), 1630(m), 776 (s); ^1H NMR ($CDCl_3$): δ 7.14 – 7.02 (m, 5H, C_6H_5), 6.90 – 6.76 (br, $CONH_2$); $^{13}CNMR$ ($CDCl_3$): δ 177.50 (C=O), 130.50, 129.00, 128.00, 127.20 (phenyl carbons); FAB – MS: *m/z* 121 (M^+), 77.

Acknowledgements

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References

1. V. Bertini, F. Lucchesini, M.Pocci, S. Alfei S, *Tetrahedron.* , **61** (2005), 9519.
2. J. Tang, J. Zhu, Z. Shen, Y. Zhang, *Tetrahedron Letters.*, **48** (2007), 1919.
3. A.R. Katritzky, M.J. Cook, S.B. Brown, R. Cruz, G.H. Millet, A. Anani, *J. Chem. Soc. Perkin 1.*, (1979), 2493.
4. G. Cardillo, M. Orena, S. Sandri, *J. Chem. Soc. Chem. Commun.*, (1976), 190.
5. S.V. Lieberman, *J. Am. Chem. Soc.*, **77** (1954), 1114.
6. (a) B.Chakraborty, M.S.Chhetri, *Indian J. Heterocyclic Chem.*, **18** (2008), 201.

   (b) B.Chakraborty, M.S.Chhetri, *Indian J. Chem., Sect.B*, 2009 (in press; MS no: SCCB–1206).
7. B.Chakraborty, M.S.Chhetri, *Indian J. Heterocyclic Chem.*, **17** (2008), 243.
8. (a) B.Chakraborty, P.J. De Britto, A.R.Ghosh, *Indian J. Heterocyclic Chem.*, **6** (1996), 77.

   (b) B.Chakraborty, *Indian J. Heterocyclic Chem.*, **9** (1999), 79.
9. B.Chakraborty, M.S.Chhetri, *Indian J. Chem.*, **46B** (2008), 485.
10. B.Chakraborty, M.S.Chhetri, S.Kafley, *Indian J. Chem., Sect. B.*, (2009), in press; MS no: SCCB – 1300).
11. F.Heinzer, M.Saukup, A.Eschenmoser, *Helv. Chim. Acta.*, **61** (1978), 2851.
12. (a) B.Chakraborty, S.Kafley, M.S.Chhetri, *Indian J. Chem.*, **48B** (2009), 447.

    (b) B.Chakraborty, S.Kafley, M.S.Chhetri, *Indian J. Chem., Sect. B*, 2009, in the press (MS no: SCCB – 1225).

    (c) B.Chakraborty, S.Kafley, M.S.Chhetri, *Indian J. Heterocyclic Chem.*, **18** (2009), 283.

    (d) B.Chakraborty B, S.Kafley, M.S.Chhetri, *Indian J. Heterocyclic Chem.*, **18** (2008), 203.
13. W.R.Hoffmann, G.Eichler, A.Endesfelder, *Liebigs Ann. Chem.*, (1983), 2000.
14. B.Chakraborty, A.R.Ghosh, *Indian J. Chem.*, **33B** (1994), 1113.
15. F.Heaney, O.Rooney, D.Cunningham, *J. Chem. Soc., Perkin Trans 2*, (2001), 373.
16. A.I.Vogel, A.R.Tatchell, B.S.Furnis, A.J.Hannaford, P.N.G.Smith, "*Vogel's Textbook of Practical Organic Chemistry*"., 5th edition (Prentice Hall), 1996.

NOTE

New and efficient methodology of aldehyde synthesis from alkyl halide using α-chloro nitrone as a new, stable and potential oxidizing reagent

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Abstract : Consecutive SN^2 reaction of α-chloro nitrones are studied with alkyl halides and the nitrones are found to have remarkable oxidizing properties for the conversion of alkyl halides to aldehydes with high yield. In addition, the side product obtained can serve as efficient dipolarophile in 1,3 DCR to produce spiro cycloadducts in good yields.

Keywords: α-chloro nitrone as oxidizing reagent, SN^2 reaction, aldehyde synthesis, spiro cycloadduct

Introduction

Convertion of alkyl halides to aldehydes using *N*-oxide with moderate yields have been already reported (Krohnke reaction). In addition to the existing methods available for the synthesis of aldehyde from alkyl halides,[1-6] we would like to incorporate an efficient one pot synthesis of aldehyde from alkyl halides using for the first time α-chloro nitrones (**1**) as a new, stable and potential oxidizing reagent with an excellent yield (Scheme 1, Table 1). In addition, the side product (furan derivatives, **2**) obtained during aldehyde synthesis has been successfully used as dipolarophile in 1,3-DCR with nitrone (**1**) for the production of spiro cycloadducts (**3**) with high yields (almost 75 – 85% ; Scheme 2). α-chloro nitrones (**1**) are more reactive than other nitrones due to the electron withdrawing effect of chlorine and therefore can act as more powerful oxidizing agent than other nitrones.

Literature survey reveals that aldehyde synthesis using nitrone as active oxidizing reagent and further use of side products (obtained during aldehyde synthesis) as dipolarophile in cycloaddition reactions are not yet known and hence can be incorporated as an important application in nitrone chemistry. Synthesis and 1,3 dipolar cycloaddition reactions of *N*-phenyl-α-chloro

nitrone[7,8](1, R=Ph) has been already reported. Following the same methodology, novel *N*-methyl-α-chloro nitrone (1,R=Me) has been synthesized as white crystalline solid, m.p 52^{0}C (uncorrected) and used for aldehyde synthesis as oxidizing reagent.

Results and Discussion

α-chloro nitrones (1) are moderately stable and can be isolated while transient nitrone **1a** can not be isolated because of its high unstability and undergoes decomposition at room temperature. The lone pair of electron of the OH group of α-chloro nitrone facilitates intramolecular SN^2 reaction in presence of pyridine and is actually the driving force for the development of transient nitrone **1a**. Nitrone **1a** reacts very quickly with different alkyl halides (SN^2 reaction) and develops an intermediate compound (**1b**). The labile N-O bond of **1b** undergoes cleavage[9] when the reaction mixture is stirred with solid sodium carbonate which plays an important role for the development of aldehyde and furan derivative (2) as side product in a Kornblum type process (Scheme 1;Table 1). The novelty of the study is the use of α-chloro nitrone as an oxidizing reagent in aldehyde synthesis and newly developed side product as dipolarophile in cycloaddition reactions. The isolated side products (2) are equally efficient like other conventional dipolarophiles used for cycloaddition reactions and leads to the formation of regioselective 5-substituted spiro cycloadducts (3)[10,11] in 1,3-dipolar cycloaddition reaction with nitrone **1** (Scheme 2) and thereby offering greater scope for its applications. The yield of the isolated aldehydes are extremely high in a much lesser time (85 – 89%) and are much better in case of active alkyl halides compared to inactive alkyl halides. The results are summarized in Table 1. The beauty of the reaction lies in addition of pyridine at the begining to generate transient nitrone (**1a**) which is only capable of developing furan derivative (2) as side product and can be utilized as a new efficient dipolarophile in 1,3-DCR and thereby the reaction as a whole becomes atom efficient. Simple nitrones[12] (benzaldehyde derived nitrone) can also be employed as an oxidizing

reagent for aldehyde synthesis (synthesized n-butyraldehyde:yield 78%) but the side product obtained is a waste and can not be used for further reactions. At the outset of this work it was not clear about the development of transient nitrone (**1a**) but after completion of the study and spectral analysis of side product (**2**) the development of transient nitrone **1a** was confirmed. The products especially aldehydes are known compounds and spectral data of the synthesized aldehydes are almost identical to the values found in literature. For example, sharp singlet signals at δ 9.80 & 198.00 in the NMR spectrum (^{1}H, ^{13}C respectively) along with molecular ion peak at 106, base peak at 105 and peaks at 77, 51 in the MS spectrum give strong evidence in favour of benzaldehyde formation. The oxidation side product (**2**) was obtained as single isomer having *E* configuration in all the cases and the yield of the side product was almost 10 – 13 % when isolated in pure condition.The spectral data of the oxidation side products (**2**) also agreed well with the assigned structures. The spiro cycloadducts (**3**) were obtained as regioselective single isomer predominantly in 1,3-DCR of α-chloro nitrone (**1**) with side product (**2**) having high yields (70 – 85%) when isolated in pure condition. The stereochemistry of the 5-substituted regioselective spiro cycloadducts (**3**) in all the cases were rationalized by considering the multiplicity of the proton signals at 3-H, 4-H and CHCl asymmetric centres along with their coupling constant values.[13] In the spiro isoxazolidine derivatives (**3**), 3-H resonates around δ_H 3.50 to 2.50 ppm while for the 4--H around δ_H 5.80 to 3.00 ppm and the coupling constant is $J_{3,4}$ ~ 9.20 Hz implying a *cis* relationship between H-3 and H-4. The CHCl proton also resonates around δ_H 2.60 to 2.20 ppm. The 3-H and CHCl protons are also *syn* as evidenced from their coupling constant values ($J_{3,CHCl}$ ~ 9.16 to 9.40 Hz).[13] Cycloaddition of *Z* nitrone (both the reported α-chloro nitrones are of *Z* configuration in this communication) via *exo* transition state geometry results in the formation of *syn* isoxazolidine derivatives. Cycloaddition reaction using furan derivatives (**2**) with other

simple nitrones[12,14,15] are in progress using the same methodology. A preferential conformation for the spiro regioselective isoxazolidine derivatives (3) may be represented in Figure 1. Reaction of nitrone 1 with methyl iodide and ethyl bromide was also studied for the synthesis of formaldehyde and acetaldehyde respectively but no significant results were obtained because of the volatility of formaldehyde and difficulculties associated with the synthesis of acetaldehyde. These are the drawbacks of this methodology.

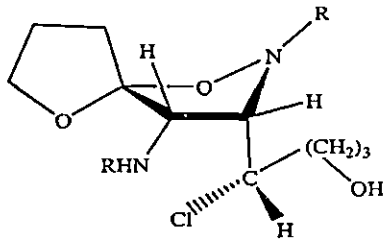
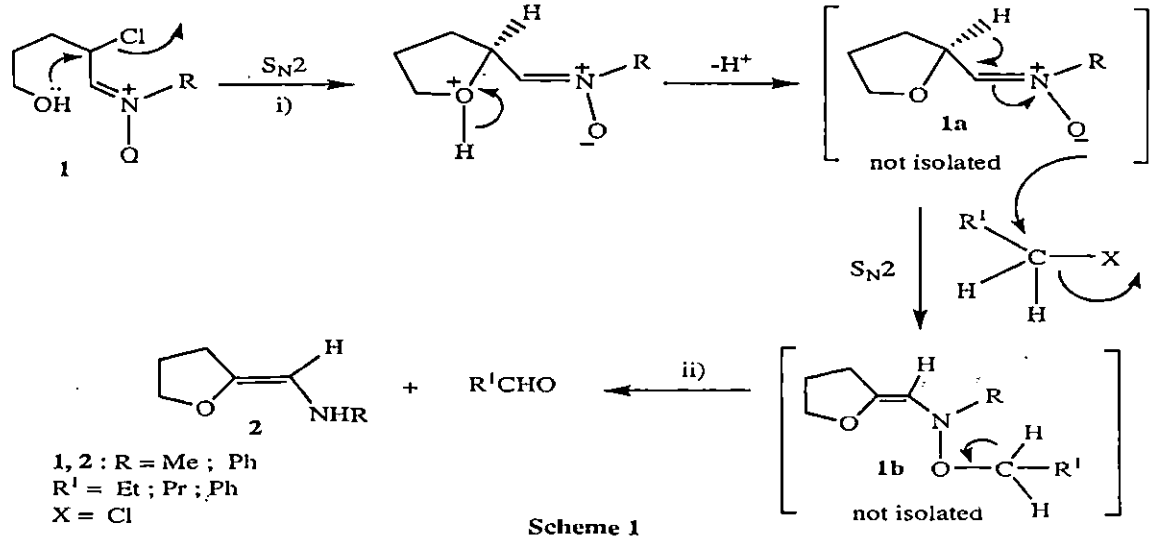


Fig. 1. General conformation for the cycloadducts **3**

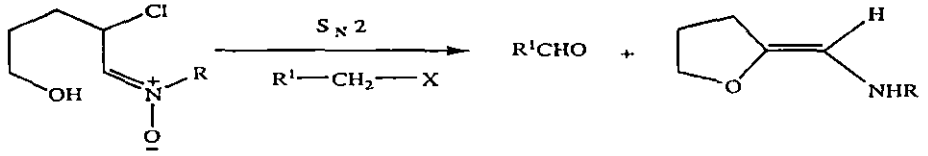


1, 2 : R = Me ; Ph
R^1 = Et ; Pr ; Ph
X = Cl

Scheme 1

Reagents and conditions : i) Dry ether, pyridine, r.t , N_2 atmosphere
ii) Dry ether, Na_2CO_3, r.t , N_2 atmosphere

Table 1. Aldehyde synthesis using α-chloro nitrones



R = Me ; Ph R^1 = Et; Pr; Ph X = Cl

Entry	Nitrone	Alkyl halide[a]	Product[b]	Time (hr)	Yield[c] (%)
1	R = Me	Benzyl chloride	Benzaldehyde	5	88
2	R = Me	1-chloro propane	Propionaldehyde	6	87
3	R = Ph	Benzyl chloride	Benzaldehyde	5	88
4	R = Ph	n-butyl chloride	n-Butyraldehyde	6	86
5	R = Me	p-hydroxy benzyl chloride	p-hydroxy benzaldehyde	4	89
6	R = Ph	p-hydroxy benzyl chloride	p-hydroxy benzaldehyde	5	89

[a] Reaction condition:α-chloro nitrone (3.0198 mmol),alkyl halide (1 equivalent),dry ether,Py, Na_2CO_3,N_2 atmosphere, RT
[b] All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS. HRMS spectral data.
[c] Isolated yield after purification.

Experimental

^{1}H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q – Tof micro instrument (YA – 105). TLC was carried out on Fluka silica gel TLC cards while column chromatography was performed with silica gel (E.Merck India) 60 – 200 mesh. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-methylhydroxylamine was purchased from Aldrich Chemical Company and was used as

received. *N*-phenylhydroxylamine was prepared following standard methods available in literature and has been used in synthesis[16,17,18].

General procedure for the synthesis of nitrone **1** (R = Me)

N-methylhydroxylamine (250mg, 5.3127 mmole) was added to chlorohydrin (720mg,1 equivalent) in dry ether (50 mL) and anhydrous $MgSO_4$. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 10 hr. The formation of nitrone was monitored by TLC (R_f = 0.34). The nitrone was isolated under reduced pressure vaccum pump as white niddle shape crystals (920mg, 94%; m.p: 52^{0}C, uncorrected).

Spectroscopic data for nitrone **1** (R = Me)

Yield: 920mg (94%); white niddle shape crystals; R_f = 0.43, m.p: 52^{0}C (uncorrected); IR (KBr): 3595 – 3470 (br), 1660(s), 1610(s), 1415 (m), 1185 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.84 (d, 1H, CH=N$^+$), 5.79 (br,1H, -OH, exchanged in D_2O), 3.51 (dt, 1H, *J* = 6.16, 6.08 Hz, CHCl), 3.31 (s, 3H, N$^+$- CH_3), 1.88 - 1.15 (m, 6H, CH_2 protons); ^{13}C NMR($CDCl_3$) : δ 141.55 (CH=N$^+$), 55.76 (CHCl), 34.84 (N$^+$-CH_3), 28.50, 27.22, 26.00 (3 CH_2 carbons); HRMS – EI: Calcd. for $C_6H_{12}O_2NCl$, (M), 165.5710, Found: M$^+$, 165.5698.

General procedure for synthesis of aldehyde (benzaldehyde) and furan derivative **2** (*entry*1;*Table* 1)

To a stirred solution of nitrone **1** (R=Me; 500mg, 3.0198 mmol) in dry ether (25 ml) was added pyridine (1 equivalent) and stirred at RT with a magnetic stirrer under N_2 atmosphere for 1 hr while the formation of transient nitrone **1a** (not isolated) was monitored by TLC (R_f = 0.38). Benzyl chloride (292.1002mg, 1 equivalent) was added at this stage and the reaction mixture was stirred for another 3 hr till the intermediate compound **1b** (not isolated) was developed (monitorted by TLC; R_f = 0.40). 2 gms of solid Na_2CO_3 was added at this stage and the reaction mixture was stirred for further 1 hr while the progress of the reaction was again monitored by TLC (R_f = 0.43, 0.50). The reaction was typically completed when the

N-O bond was cleaved. Basic workup, removal of pyridine hydrochloride and silica gel column chromatographic purification using ethyl acetate-hexane provided desired benzaldehyde as colourless liquid (712mg, 89% ; R_f = 0.43) and furan derivative (**2**) as pale yellow gummy liquid (88mg, 10% ; R_f = 0.50). This procedure was followed for all the substrates listed in Table 1.

Spectroscopic data for benzaldehyde (*entry* 1)

Yield: 712 mg (88%); colourless liquid; R_f = 0.43; IR (KBr): 1695(s), 1320(m), 770(s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.80 (s, 1H, CHO), 7.30 – 7.16 (m, 5H, C_6H_5); ^{13}CNMR ($CDCl_3$): δ 198.00 (CHO), 136.20, 134.55, 132.60, 131.00 (aromatic carbons); FAB - MS (*m/z*): 106 (M^+), 105 (B.P), 77, 51, 28; HRMS-EI: Calcd. for C_6H_5CHO (M), 106.0417, Found; M^+, 106.0408.

Spectroscopic data for **2** (*R=Me; α-N-methyl furan derivative; entry* 1) *[(E)-1-(dihydrofuran-2-(3H)-ylidene)-N-methyl methanamine)]*

Yield: 88mg (10%); pale yellow gummy liquid; R_f = 0.50; IR (KBr): 3125-3054 (br), 2838 (m), 1652 (s), 1455 (m), 1210 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.81 (br, 1H, N-H), 4.56 (s, 1H, C=CH), 3.30 (N-Me), 2.50 - 2.16 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 103.00, 101.76 (double bonded carbons), 26.22, 25.30, 23.65 (3 CH_2 carbons); FAB – MS: *m/z* 113 (M^+), 98, 97; HRMS-EI: Calcd. for $C_6H_{11}ON$ (M), 113.1000, Found: M^+, 112.9876.

Spectroscopic data for propionaldehyde (*entry* 2)

Yield: 592mg (87%); colourless liquid; R_f = 0.50; IR (KBr): 2920 (m), 2720 (m), 1720 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.70 (t, 1H, *J* = 6.60 Hz, -CHO), 2.30 (ddd, 2H, *J* = 6.08, 6 Hz, $-CH_2$), 1.00 (t, 3H, *J* = 6.30 Hz, CH_3); ^{13}CNMR ($CDCl_3$): δ 202.40 (CHO), 44.22 (CH_2 carbon), 35.55 (CH_3 carbon); FAB – MS: *m/z* 58 (M^+), 57, 29 (B.P); HRMS-EI: Calcd. for C_3H_6O (M), 58.0417, Found: M^+, 58.0403.

Spectroscopic data for **2** (*R=Ph; α-N-phenyl furan derivative; entry* 4) *[(E)-1-(dihydrofuran-2-(3H)-ylidene)-N-phenyl methanamine)]*

Yield: 90mg (11.5%); dark yellow viscous liquid; R_f = 0.46; IR (KBr): 3150-3060 (br), 2860 (m), 1640 (s), 1430 (m), 1140 (m), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.83 (m, 5H, C_6H_5), 6.24 (br, 1H, N-H), 2.17 (s, 1H, C=CH), 1.79 - 1.18 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 137.20, 135.65, 134.00, 132.15 (aromatic carbons), 106.24, 104.18 (double bonded carbons), 28.46, 27.10, 24.84 (3 CH_2 carbons). FAB - MS (*m/z*): 175 (M^+), 98, 97, 77. HRMS-EI: Calcd. for $C_{11}H_{13}ON$ (M), 175.0993, Found; M^+, 175.0981.

Spectroscopic data for n-butyraldehyde (entry 4)

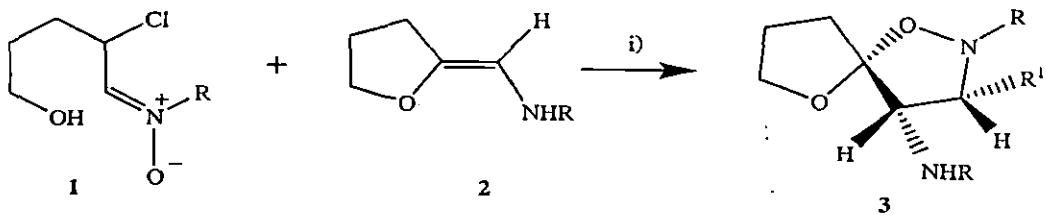
Yield: 570mg (86%); colourless liquid; R_f = 0.54; IR (KBr): 2945 (m), 2710 (m), 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.30 (t, 1H, *J* = 5.84 Hz, -CHO), 3.50 (dt, 2H, *J* = 6.50, 4.22 Hz, -C_2 2H), 1.30 (ddd, 2H, *J* = 5.50, 3.40 Hz, $C_3$2H), 0.90 (t, 3H, *J* = 4.30 Hz, CH_3); $^{13}CNMR$ ($CDCl_3$): δ 208.20 (CHO), 47.50 (C_2 carbon), 36.10 (C_3 carbon), 20.10 (C_4 carbon); FAB – MS: *m/z* 72 (M^+), 71, 57, 44 (B.P), 29; HRMS-EI: Calcd. for C_4H_8O (M), 72.0670, Found: M^+, 72.0523.

Spectroscopic data for p-hydroxy benzaldehyde (entry 5)

Yield: 776mg (89%); colourless liquid; R_f = 0.40; IR (KBr): 1690(s), 1320(m), 1210 (m), 782(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.76 (s, 1H, CHO), 7.05 - 6.93 (m, 4H, C_6H_5), 5.80 (s,1H, OH); $^{13}CNMR$ ($CDCl_3$): δ 201.64 (CHO), 134.10, 132.74, 130.40, 128.50 (aromatic carbons); FAB – MS: *m/z* 122 (M^+), 93, 92(B.P), 29; HRMS-EI: Calcd. for $C_7H_6O_2$ (M), 122.0530, Found: M^+, 122.0512.

General procedure for cycloaddition reaction of nitrone **1** *(R = Ph) with furan derivative* **2** *(R = Ph)*

To a stirred solution of *N*–phenyl-α-chloro nitrone **1** (R = Ph; 61.8375 mg, 0.2855 mmol) in 25 mL dry ether was added **2** (R = Ph, 50 mg, 0.2855 mmol, 1 equivalent) and stirred at RT with a magnetic stirrer under N_2 atmosphere for 5 hr. The progress of the reaction was monitored by TLC (R_f = 0.46). After completion of the reaction, the solvent was evaporated using a rotary evaporator to afford crude cycloadduct **3** (R=Ph) which was purified by column chromatography using



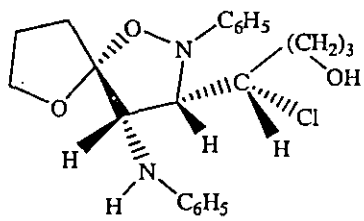
R = Me ; Ph

Scheme 2

$R^1 = CHCl(CH_2)_3OH$

i) Reaction condition : Dry ether, RT, N_2 atmosphere, 5 - 8 hr

ethyl acetate - hexane and was obtained as dark red viscous liquid **3** (R=Ph; 95 mg, 85% ; Scheme 2). This procedure was followed for the synthesis of other spiro cycloadducts **3** (R=Me).

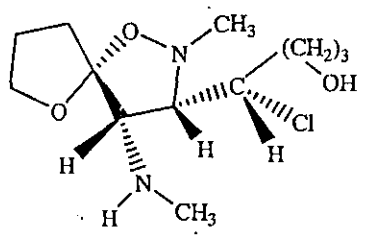


3 (R=Ph)

(S)-4-chloro-4-((3S,4S,5R)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiro[4:4]nonan-3-yl)butan-1-ol

Spectroscopic data for **3** *(R = Ph)* :

Yield: 95mg (85%); dark red viscous liquid; R_f = 0.46; IR ($CHCl_3$): 3485 – 3290 (br), 2825 (m), 2425 (m), 1620 (s), 1445 (m), 1260 (m), 1040 (m), 780 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.98 - 6.93 (m, 10H, 2 x C_6H_5), 5.84 (d, 1H, J = 9.20 Hz, C_4H), 4.96 (br, 1H, CH_2OH, exchanged in D_2O), 3.51 (dd, 1H, J = 9.34, 7.88 Hz, C_3H), 3.45 (s, 1H, N – H proton), 2.61 (dt, 1H, J = 9.44, 8.72 Hz, CHCl), 1.88 – 1.15 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 138.00, 136.50, 134.30, 133.80, 131.75, 130.42, 129.46, 128.64 (aromatic carbons), 95.10 (CHCl), 86.40 (C_5), 73.75 (C_3), 53.30 (C_4), 30.20, 28.55, 27.34, 26.22, 25.73, 24.37 (6 CH_2 carbons). MS (*m/z*): 404 (M^++2), 402 (M^+), 325, 310, 309, 218 (B.P), 107, 91, 77. HRMS-EI: Calcd. for $C_{22}H_{27}O_3N_2Cl$ (M), 402.7130, Found; M^+, 402.7122.



3 (R=Me)

(S)-4-chloro-4-((3S,4S,5R)-2methyl-4-(methylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol

Spectroscopic data for **3** (R = Me)

Yield: 91mg (83%); red gummy liquid; R_f = 0.40; IR ($CHCl_3$): 3460 – 3326 (br), 2835 (m), 2420 (m), 1440 (m), 1325 (m), 980 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.83 (br, 1H, CH_2OH, exchanged in D_2O), 4.50 (br, 1H, $NHCH_3$), 3.31 (s, 6H, 2 x N-CH_3), 2.99 (d, 1H, J = 9.16 Hz, C_4H), 2.50 (dd, 1H, J = 9.06, 7.60 Hz, C_3H), 2.19 (dt, 1H, J = 9.16, 8.50 Hz, CHCl), 1.66 – 1.60 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 93.00 (CHCl), 87.55 (C_5), 76.20 (C_3), 55.20 (C_4), 41.97 (N-CH_3), 40.24 (NH-CH_3), 33.37, 31.50, 28.68, 26.00, 25.12, 23.40 (6 CH_2 carbons). MS (*m/z*): 280 (M^++2), 278 (M^+), 263, 248, 156 (B.P), 141, 107. HRMS-EI: Calcd. for $C_{12}H_{23}O_3N_2Cl$ (M), 278.6710, Found; M^+, 278.6698.

Conclusion

Finally, we developed a new atom efficient methodology for the aldehyde synthesis using α-chloro nitrone as oxidizing reagent and considered further reaction carried out on the side product with α-chloro nitrones in 1,3-dipolar cycloaddition reaction for the development of stereochemically important 5-spiro isoxazolidines. The formation of the desired cycloadducts were obtained in good yields within a short reaction time. The newly developed side products (furan derivatives, **2**) are equally effective as dipolarophile in cycloaddition reactions like other conventional dipolarophiles used for cycloaddition reactions. The notable advantages offered by this method are one pot synthesis, simple operation, easy workup, mild and faster reaction conditions with high yield of products.

Acknowledgements

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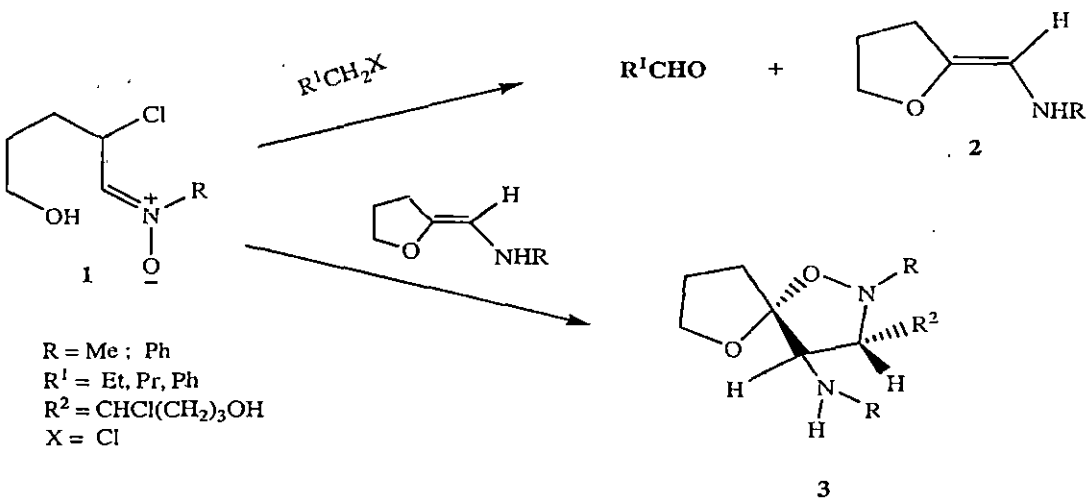
References

1. V. Bertini, F. Lucchesini, M. Pocci, S. Alfei, *Tetrahedron.*, 2005, **61**, 9519.
2. J. Tang, J. Zhu, Z. Shen, Y. Zhang, *Tetrahedron Letters.*, 2007, **48**, 1919.
3. A.R. Katritzky, M.J. Cook, S.B. Brown, R. Cruz, G.H. Millet, A. Anani, *J.Chem.Soc, Perkin I.*, 1979, 2493.
4. G. Cardillo, M. Orena, S. Sandri, *J .Chem. Soc. Chem. Commun.*, 1976, 190.
5. S.V. Lieberman, *J. Am. Chem. Soc.*, 1954, **77**, 1114.
6. W.P. Griffith, J.M. Jollife, S.V. Ley, P.D.Tiffin, K.F. Springhorn, *Syn. Commun.*, 1992, **22**, 237.
7. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem.*, 2009, **48B**, 447.
8. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J.Chem., SecB,* 2009, (in press, MS no: SCCB-1225)
9. W.R. Hoffmann, G. Eichler, A. Endesfelder, *Liebigs Ann. Chem.*, 1983, 2000.
10. R. Newton, P.G. Savage, *Australian J.Chem.*,2008, **61**, 432 and references cited therein.
11. K. Aouadik, S. Vidal, P.J. Praly, *Synlett.*, 2006, **19**, 3299 and references cited therein.
12. V.K. Aggarwal, R.S. Grainger, H.Adams, P.L. Spargo, *J.Org.Chem.*, 1998, **63**, 3481 and references cited therein.
13. P. Deshong, W. Li, J.W. Kennington, H.L. Ammon, *J. Org. Chem.*, 1991, **56**, 1364.
14. B. Chakraborty, M.S. Chhetri, *Indian J. Heterocycl. Chem.*, 2008, **18**, 201.
15. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem., SecB,* 2009, (in press, MS no: SCCB-1206)
16. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Heterocycl. Chem.*, 2008, **18**, 203.
17. B. Chakraborty, S. Kafley, M.S. Chhetri, *Indian J. Chem., SecB,*2009, (in press, MS no: SCCB-1300)
18. B. Chakraborty, M.S. Chhetri, *Indian J. Heterocycl. Chem.*, 2008, **17**, 213.

Graphical Abstract

New and efficient methodology of aldehyde synthesis from alkyl halide using α-chloro nitrone as a new, stable and potential oxidizing reagent

Consecutive SN^2 reaction of α-chloro nitrones are studied with alkyl halides and the nitrones are found to have remarkable oxidizing properties for the conversion of alkyl halides to aldehydes with high yield. In addition, the side product obtained can serve as efficient dipolarophile in 1,3 DCR to produce spiro cycloadducts in good yields.



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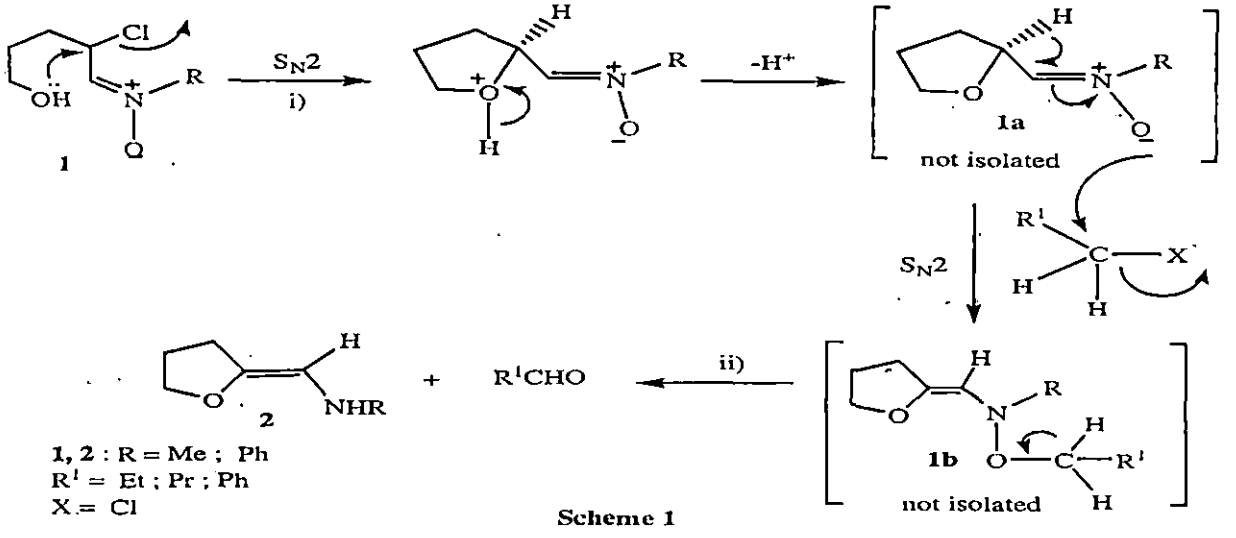
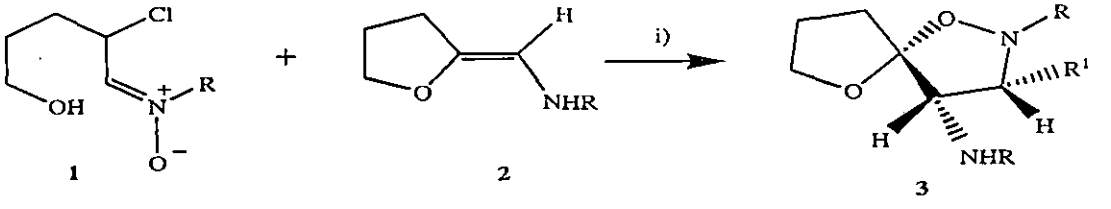
HIGH RESOLUTION FIGURES



Scheme 1

Reagents and conditions : i) Dry ether, pyridine, r.t , N_2 atmosphere
ii) Dry ether, Na_2CO_3, r.t , N_2 atmosphere



Scheme 2

i) Reaction condition : Dry ether, RT, N_2 atmosphere, 5 - 8 hr

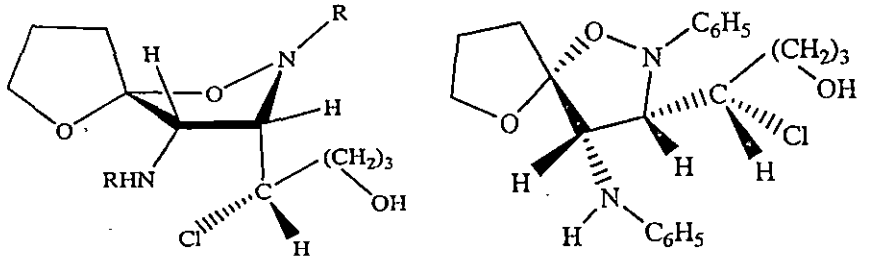
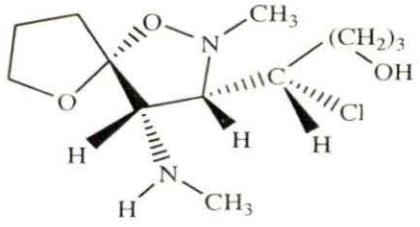
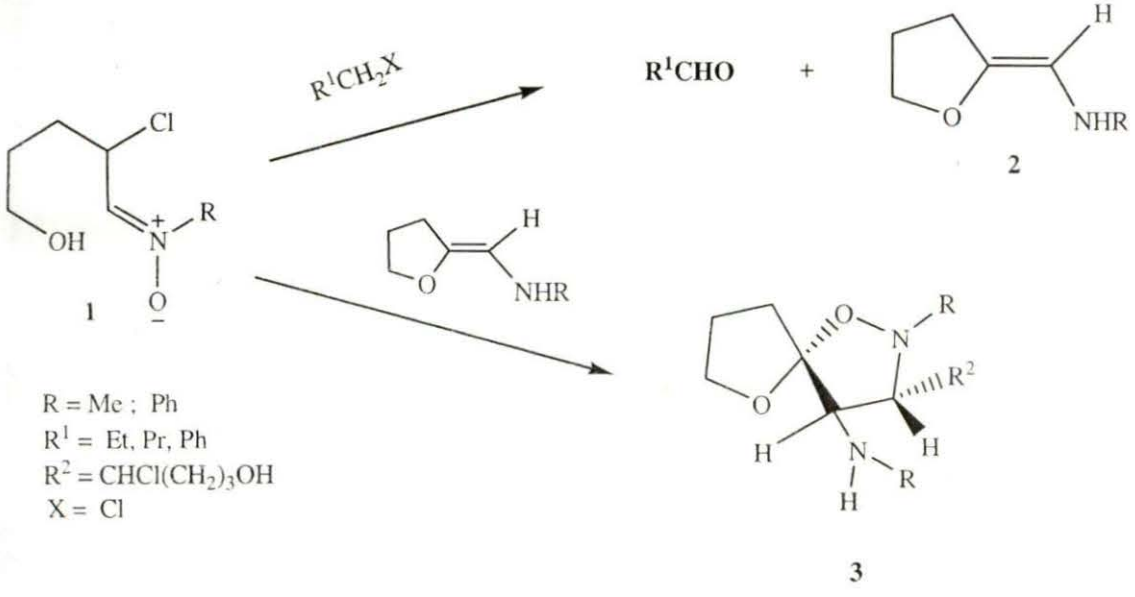


Fig. 1. General conformation for the cycloadducts **3** **3** (R=Ph)



3 (R=Me)

Graphical Abstract



R = Me ; Ph
R^1 = Et, Pr, Ph
R^2 = $CHCl(CH_2)_3OH$
X = Cl

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