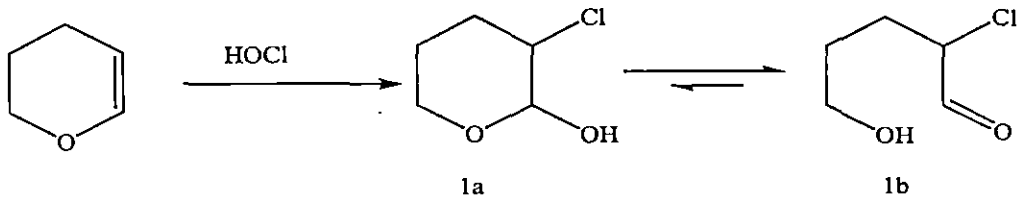
CHAPTER III

Results and Discussion

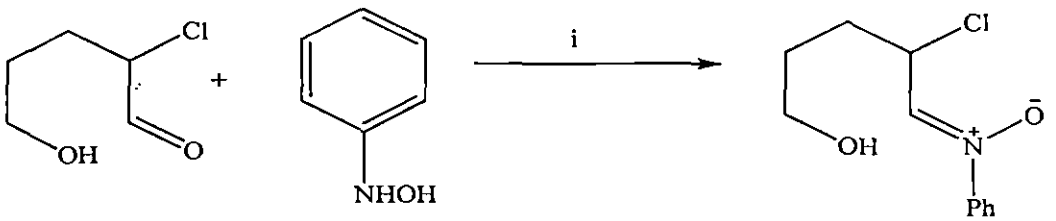
The present study reports about the synthesis, cycloaddition reaction and applications of α-chloro and α-amino nitrones[1-15]. Eschenmoser et al. have shown the synthetic potentiality of α-chloro nitrone in 1,4-dipolar cycloaddition reactions with inactivated double bonds[16]. We have reported an application 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



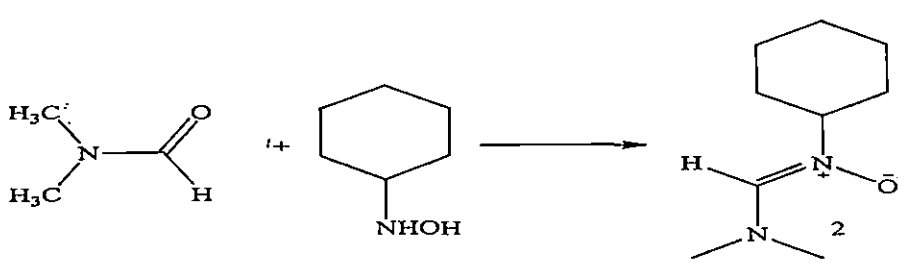
Preparation of *N*-phenyl-α-chloronitrone

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.

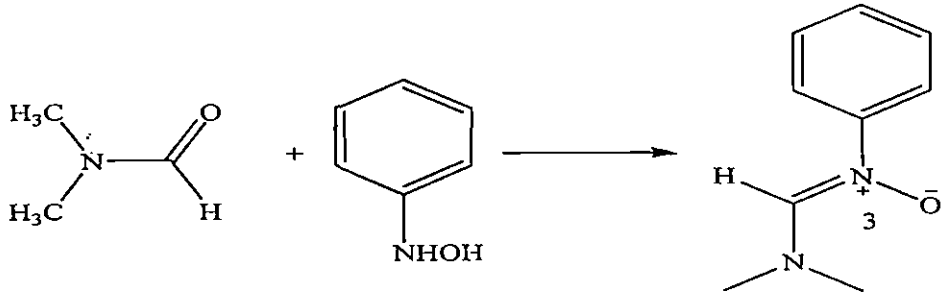


Preparation of *N*-cyclohexyl-α-aminonitrone (**2**)

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.

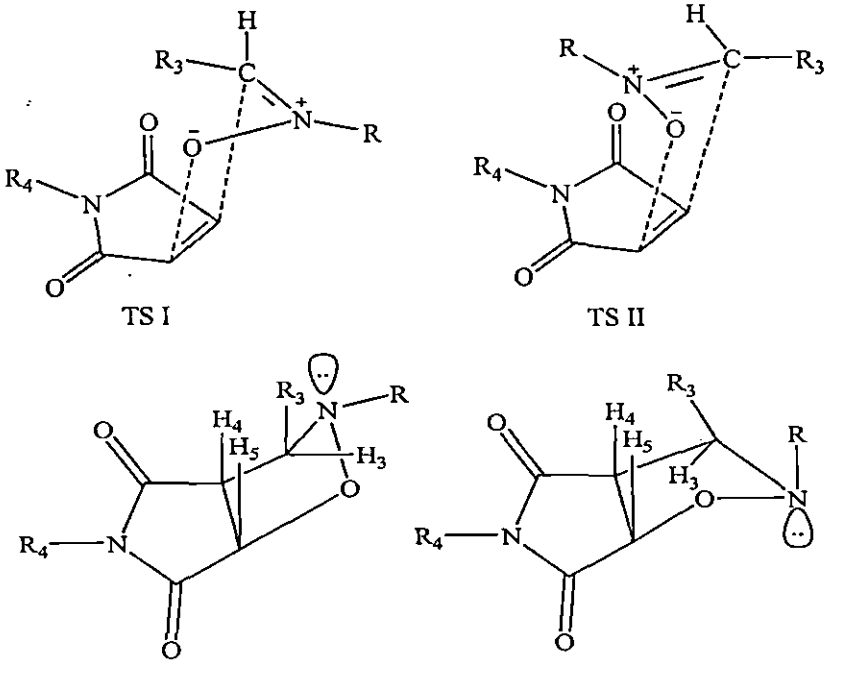
In the case of α-chloro nitrone, the reactions were found to be highly stereoselective to form diastereomeric cycloadducts with the predominance of one of the isomers in case of *N*-phenyl maleimide, *N*-methyl maleimide, *N*-cyclohexyl maleimide, acenapthylene etc. while regioselective cycloadducts 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.



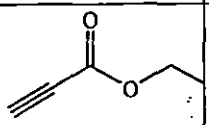
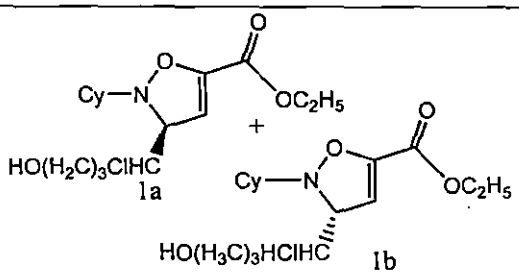
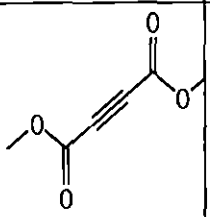
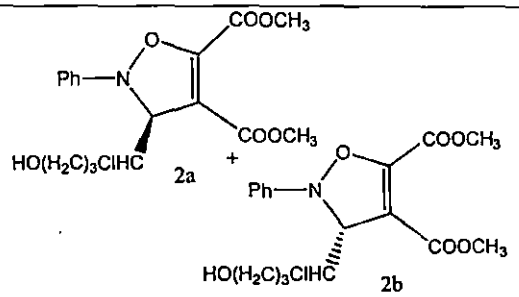
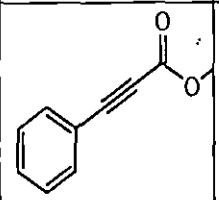
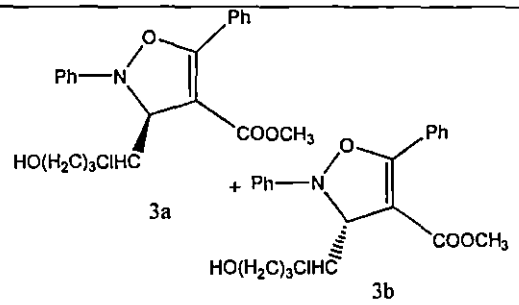
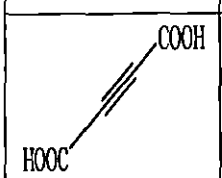
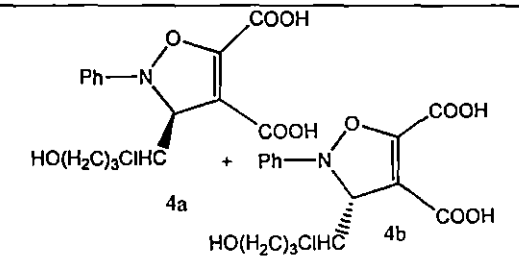
R_3 = $CHCl(CH_2)_3OH$; R_4 = Ph; Me; Cy

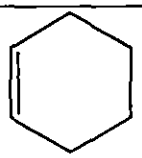
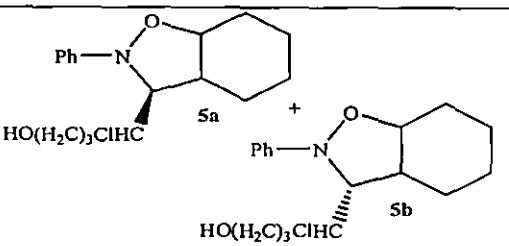
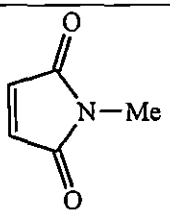
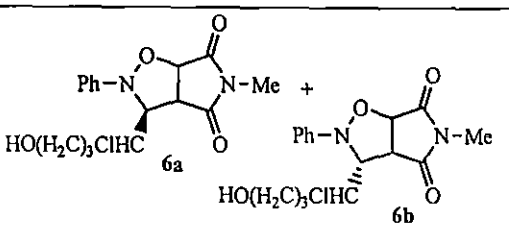
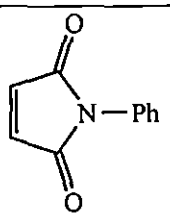
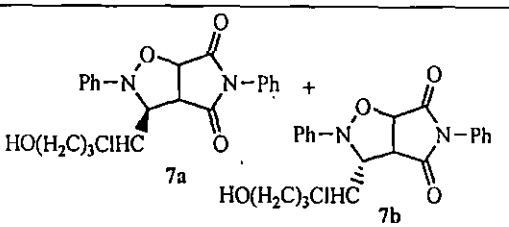
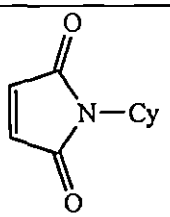
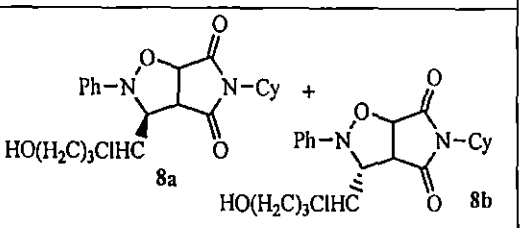
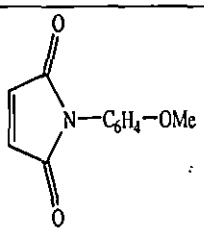
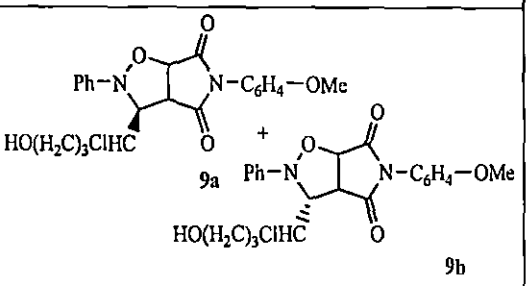
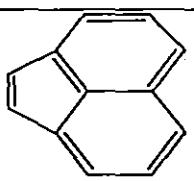
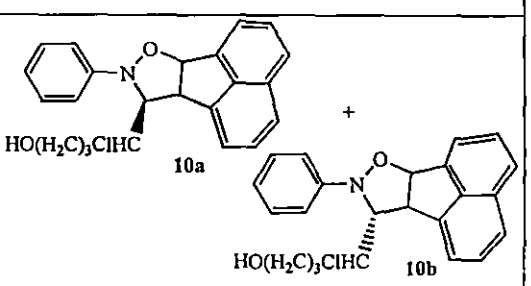
Fig. 1

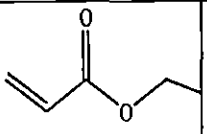
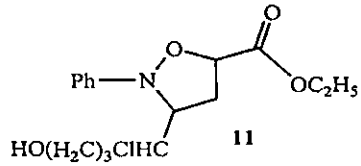
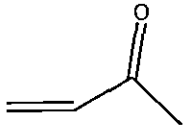
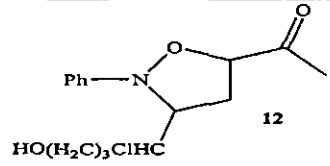
In general the reactions are very clean and high yielding compared to usual cycloaddition reactions of nitrones. The products were characterized from their spectroscopic (IR, ^{1}H NMR, HRMS, ^{13}C NMR) data. No catalyst or co-organic solvent was required. The exact stereochemistry at the asymmetric 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%	

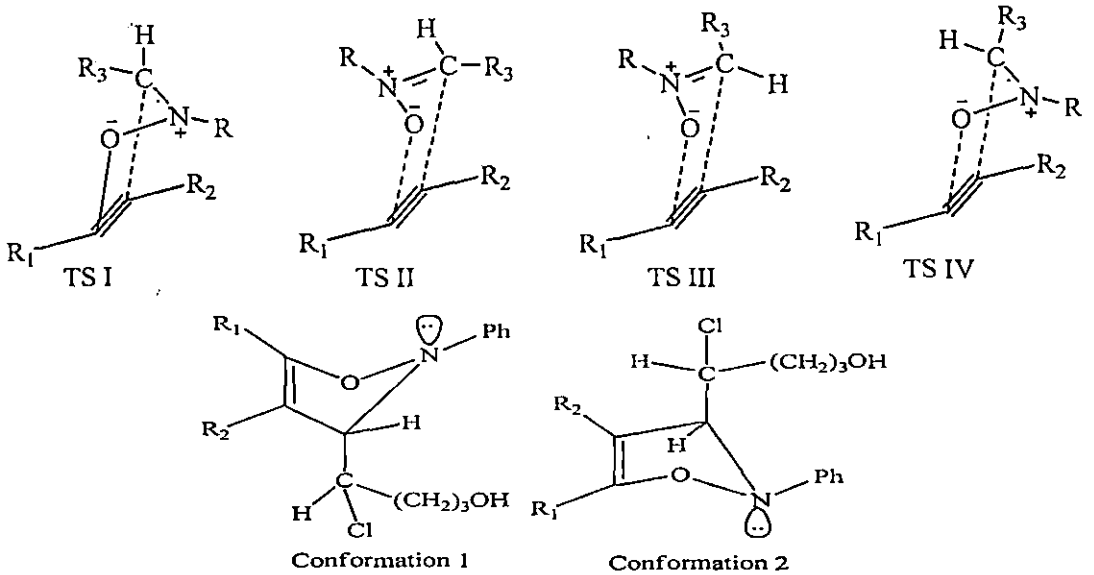
Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Water; RT; Time = 14 hr	Reddish gummy liquid	5a: 60%, 5b: 28%	
	Water; RT; Time = 4 hr	white solid	6a: 75.6%, 6b: 20.4%	
	Water; RT; Time = 4 hr	Yellowish white solids	7a: 70.8%, 7b: 23.2%	
	Water; RT; Time = 5 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.



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

$R_1 = COOC_2H_5$; $R_2 = H$

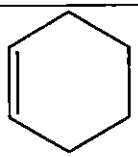
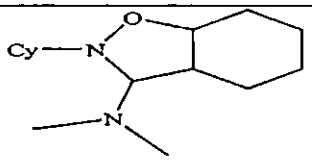
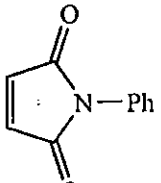
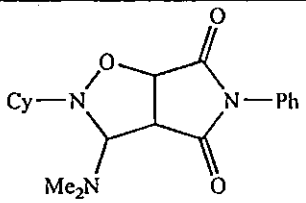
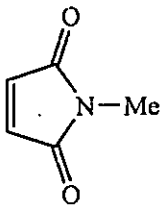
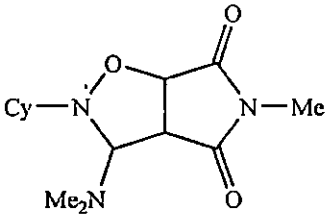
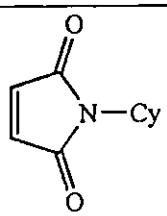
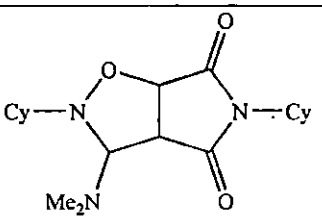
Fig. 2

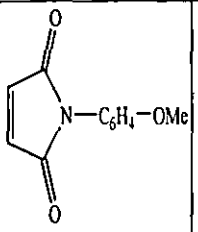
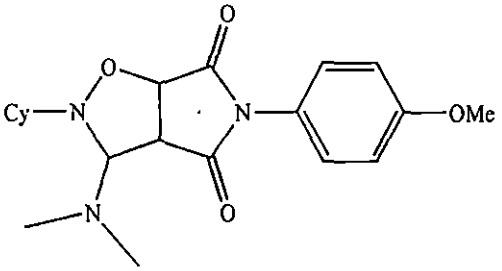
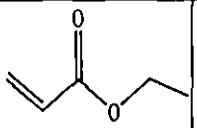
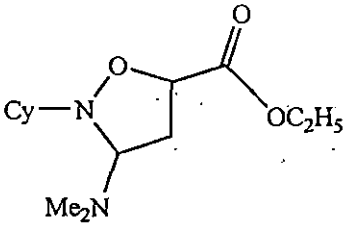
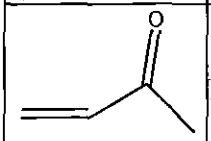
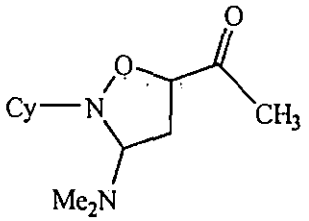
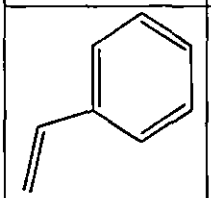
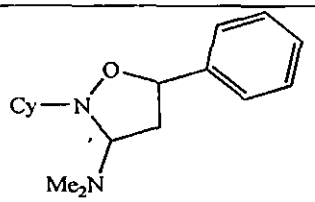
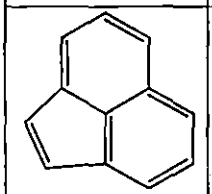
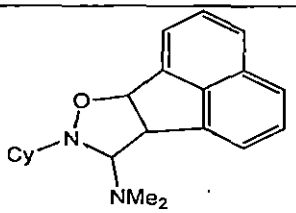
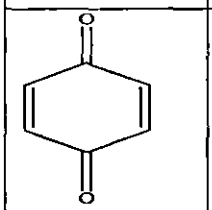
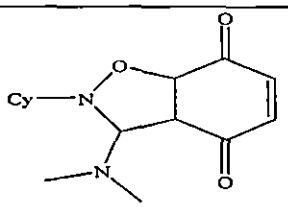
Another important aspect of the cycloaddition reactions are the *exo* addition over *endo* addition. In the majority of the cases *exo* addition were preferred since α-chloro nitrone exist exclusively in the *Z* configuration. Houk et al[21] proposed that preference for the *endo* transition state will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

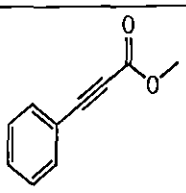
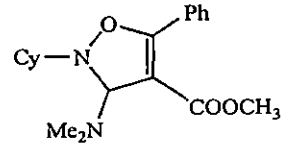
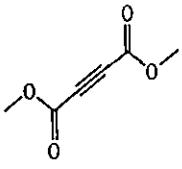
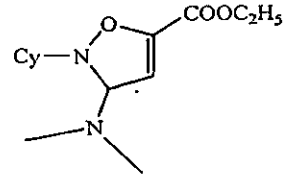
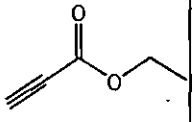
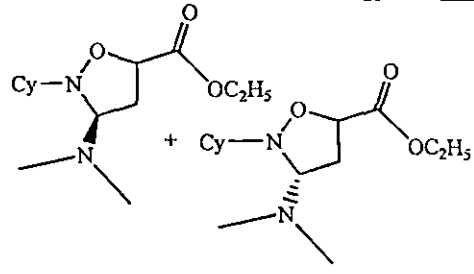
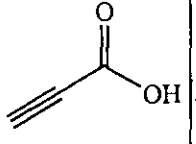
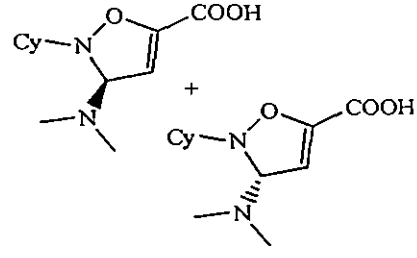
dipole (LUMO) – dipolarophile (HOMO) interactions will be important and are in accordance with P. Deshong et al[25].

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%	

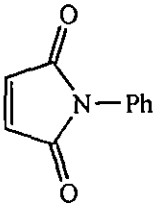
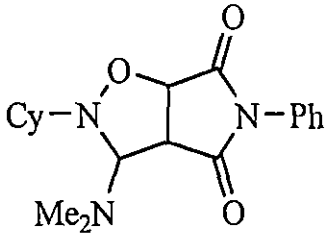
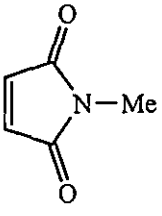
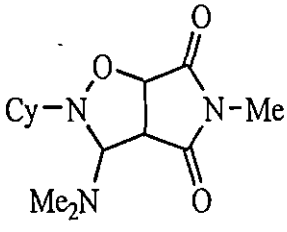
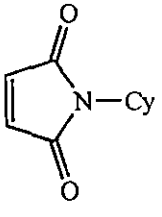
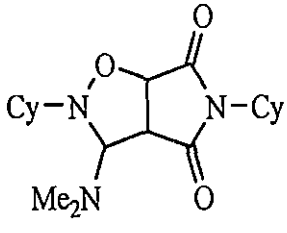
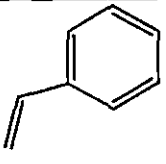
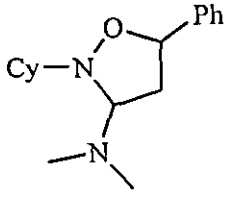
Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Solventless RT, Time = 14 hr	Colourless gummy liquid	96 %	
	Solventless RT, Time = 18 hr	Red liquid	92 %	
	Solventless RT, Time = 6 hr	Red gummy liquids	70 %, 22 %	
	Solventless RT, Time = 11 hr	colourless liquids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

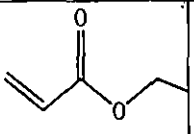
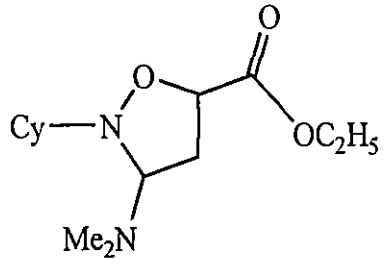
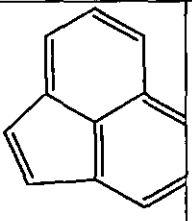
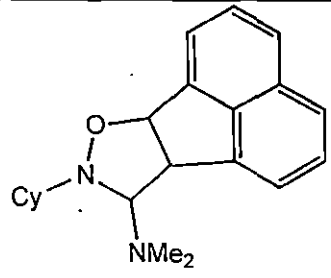
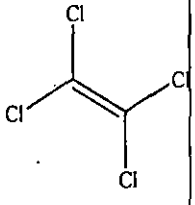
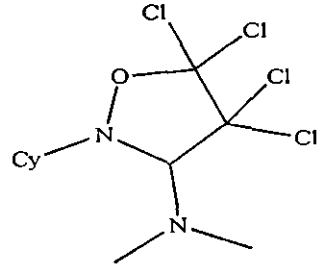
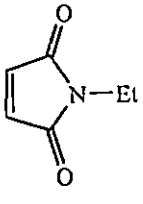
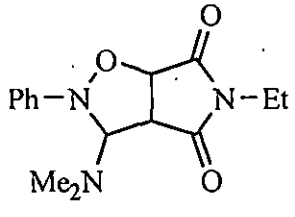
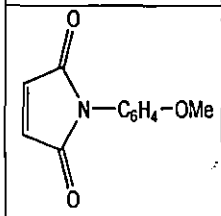
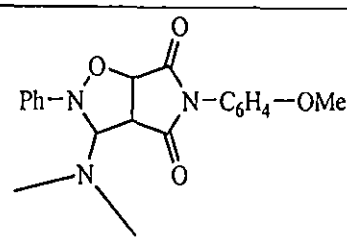
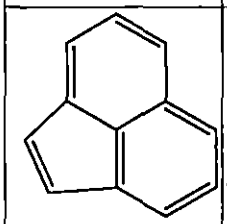
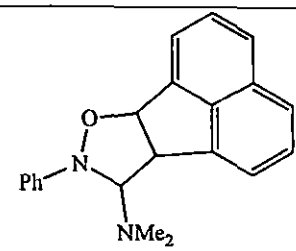
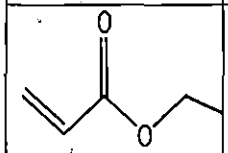
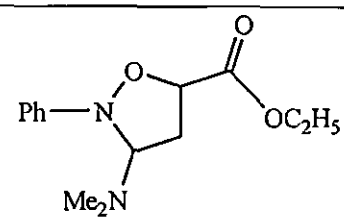
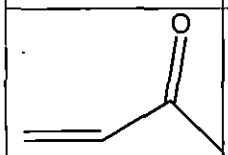
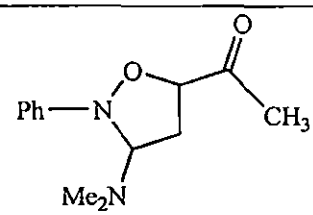
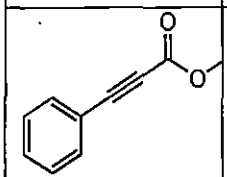
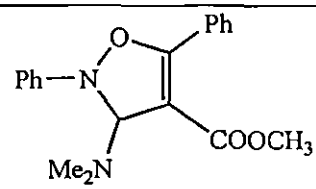
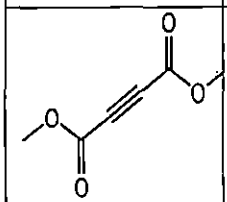
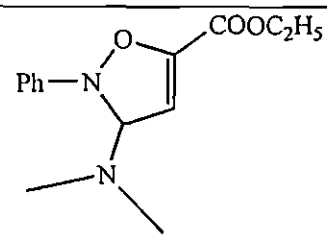
Dipolarophile	Solvent / Reaction condition	Nature of product	Yield	Structure of product/s
	Water; RT, Time = 5 hr	Colourless liquid	92 %	
	Water; RT, Time = 5 hr	Bright yellow crystalline solid	94 %	
	Water; RT, Time = 5 hr	Pale yellow oily liquid	96 %	

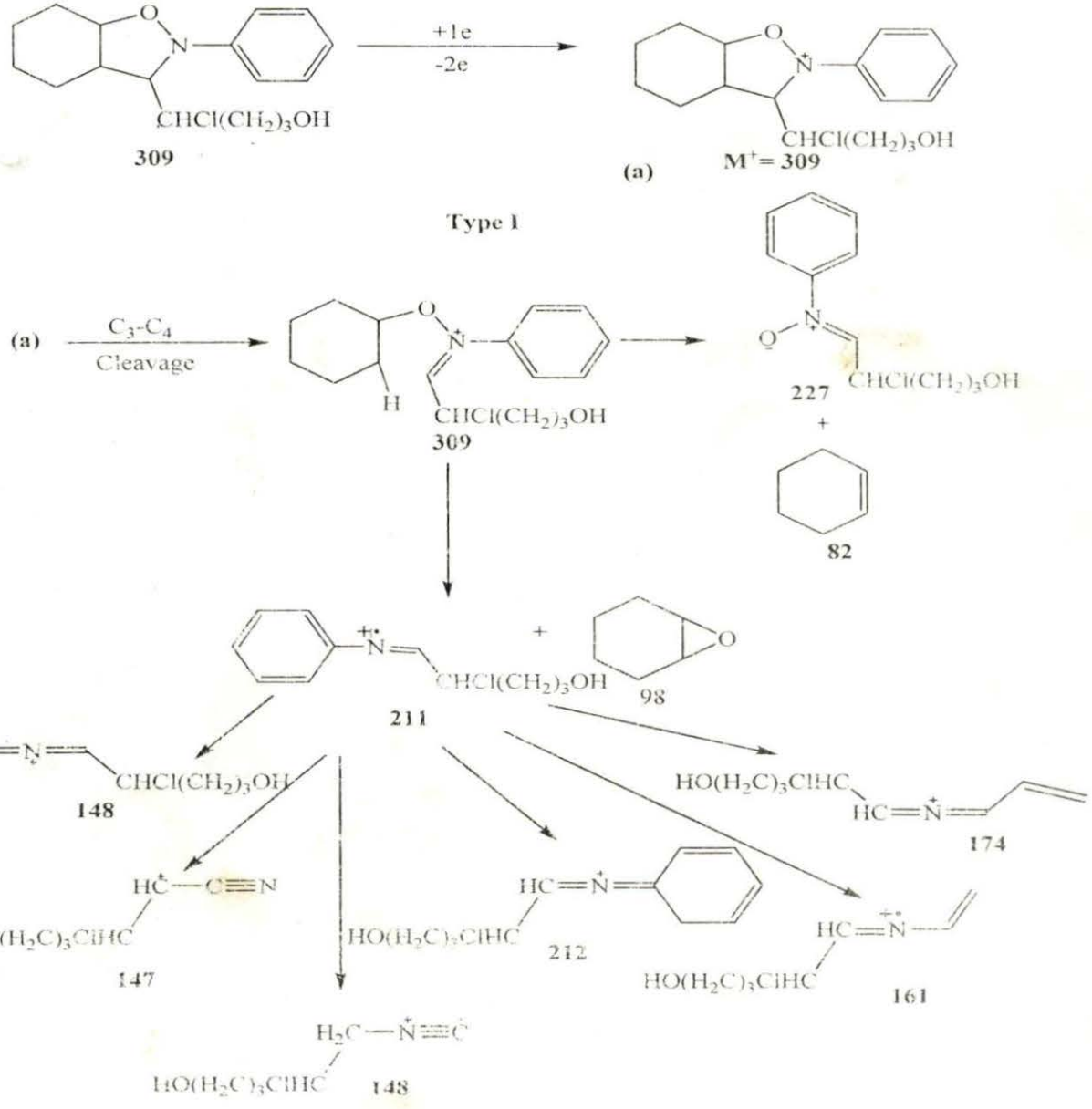
Table 3: (Reaction of nitrone 3 with different dipolarophiles in solvent less condition)

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

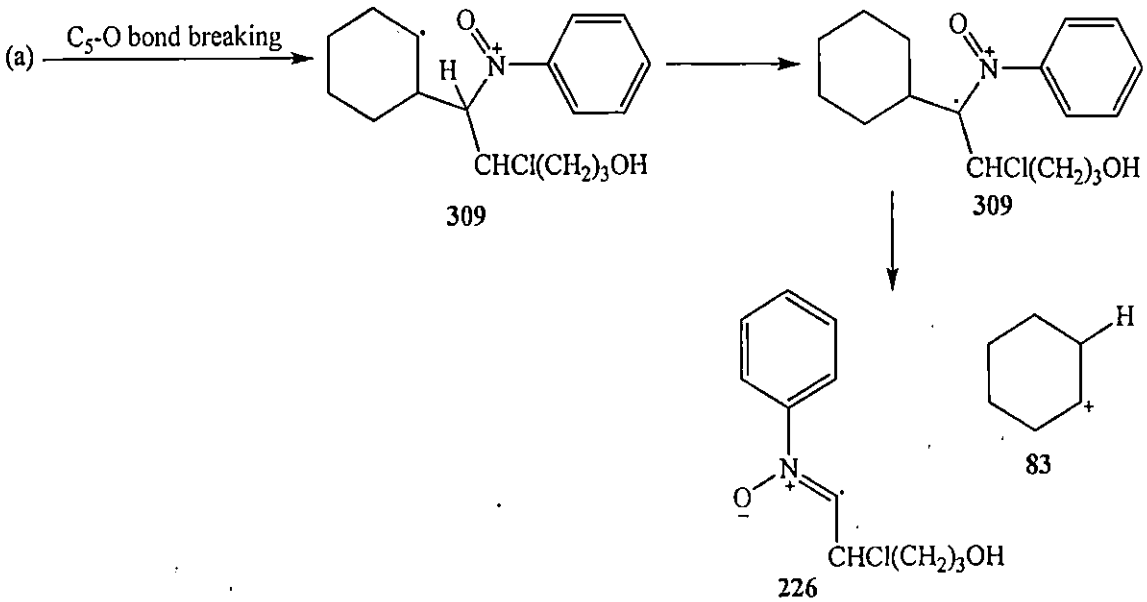
Dipolarophile	Solvent/Reaction condition	Nature of product	Yield	Structure of product/s
	Water, RT, Time = 5 hr	Dark yellow crystals	94 %	
	Water, RT, Time = 5 hr	Yellow crystals	89 %	
	Water, RT, Time = 5 hr	White gummy liquid	93 %	
	Water, RT, Time = 8 hr	Pale yellow oil	91 %	
	Dry ether, RT, Time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

Interpretation of mass spectra

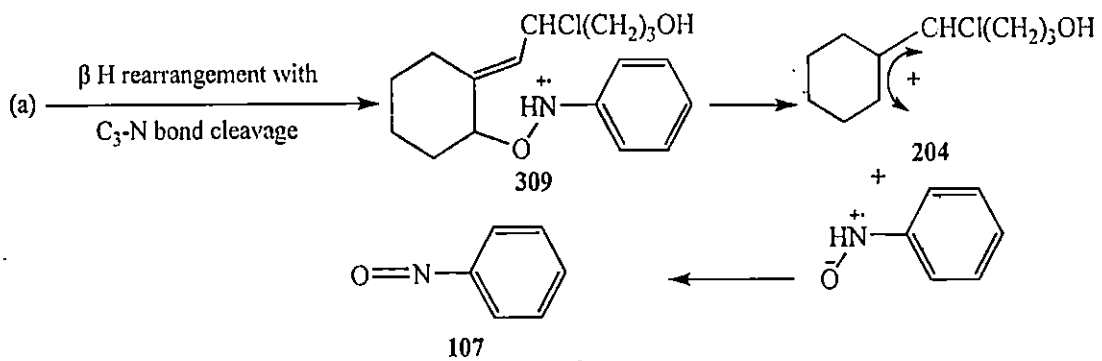
In the case of *N*-phenyl-α-chloronitrone, all the cycloadducts formed possess 2-phenyl-3-chloro butanol-1,2-isoxazolidine moiety in common. Therefore it was very usual to expect same rationalization in the mass fragmentation pattern. On electron impact mass fragmentation of a molecule would generate 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.



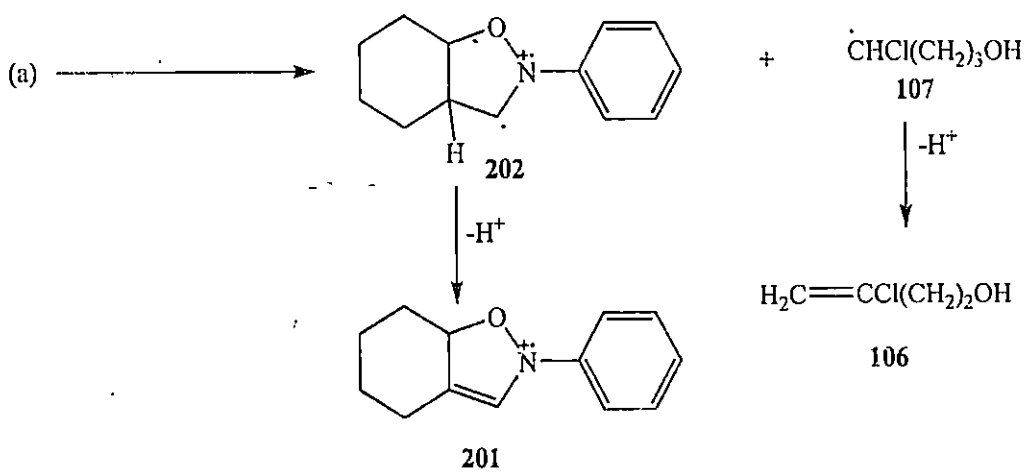
Type II



Type III



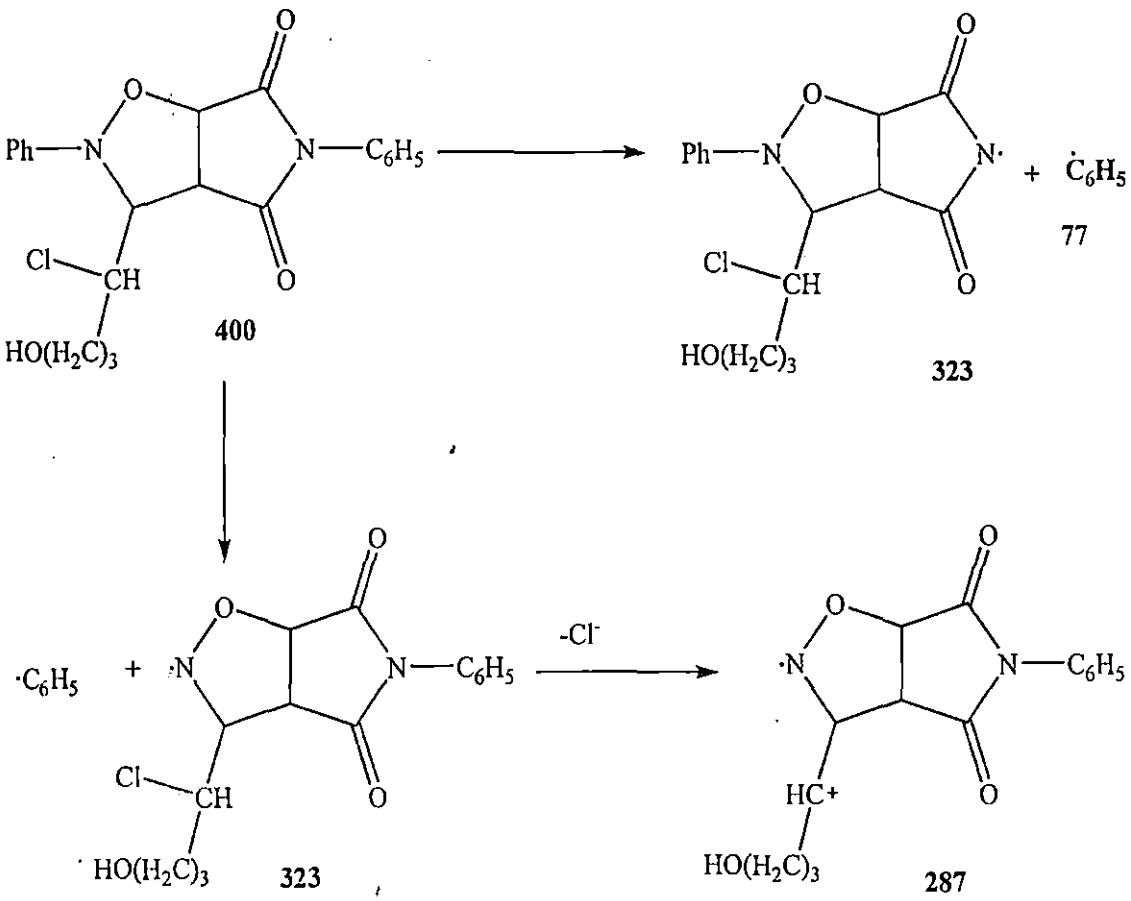
Type IV



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.

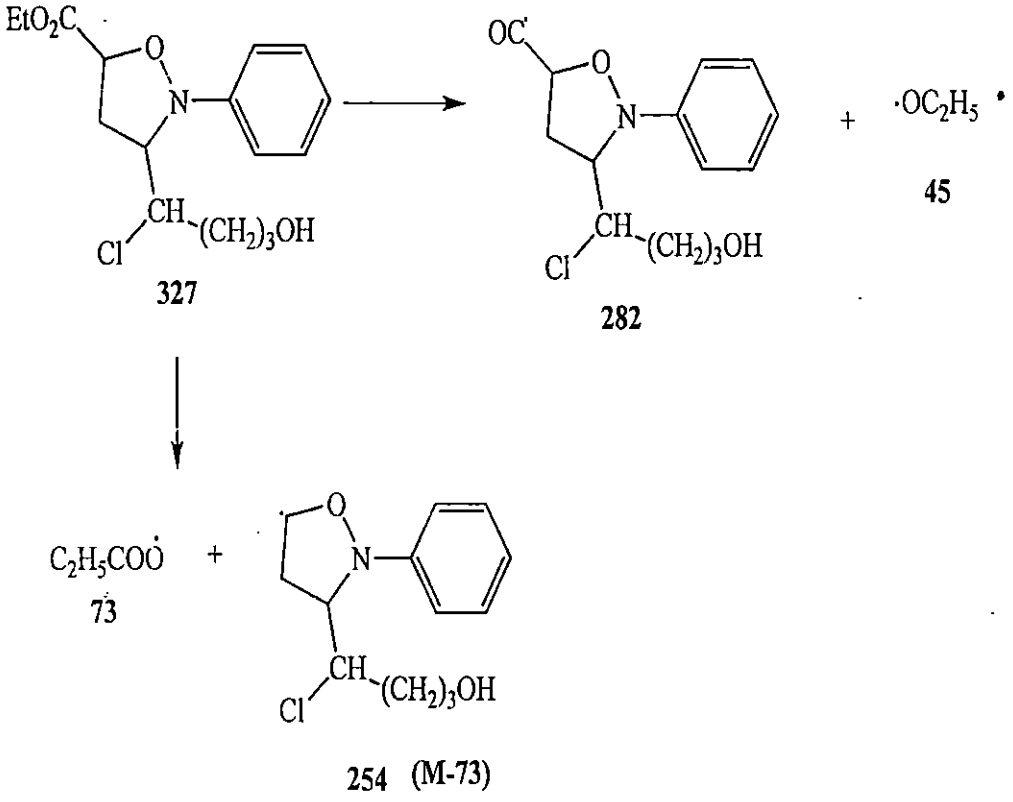
In the mass fragmentation pattern of maleimides (*N*-phenyl, *N*-cyclohexyl, *N*-methyl etc.) both the nitrones in addition to the common expected fragments, other prominent peaks at *m/e* = 77, 83, 15 for phenyl, cyclohexyl, methyl were also obtained.

Type V



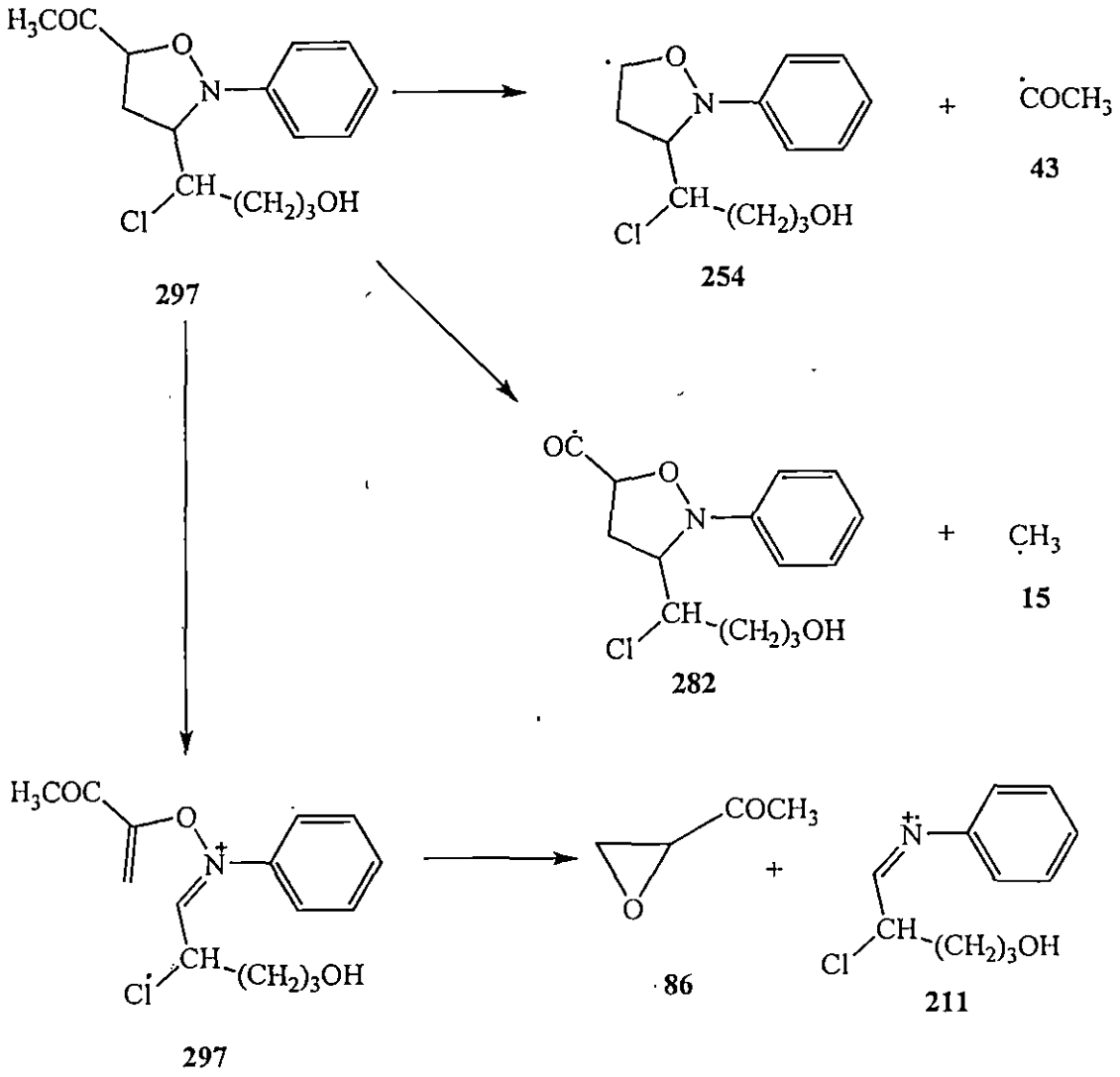
The fragmentation pattern of ethyl acrylate cycloadduct followed the general pattern with some typical peaks *i.e.* CH_3-CH_2-O (45), CH_3-CH_2-COO (73) shown in **Type VI.**

Type VI



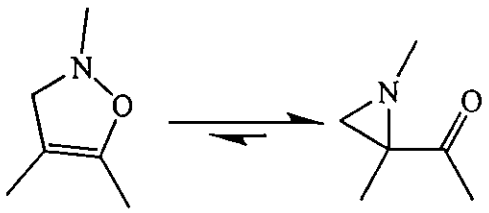
The fragmentation pattern of methyl vinyl ketone shows some special peaks in addition to the general pattern **(Type VII)**

Type VIII

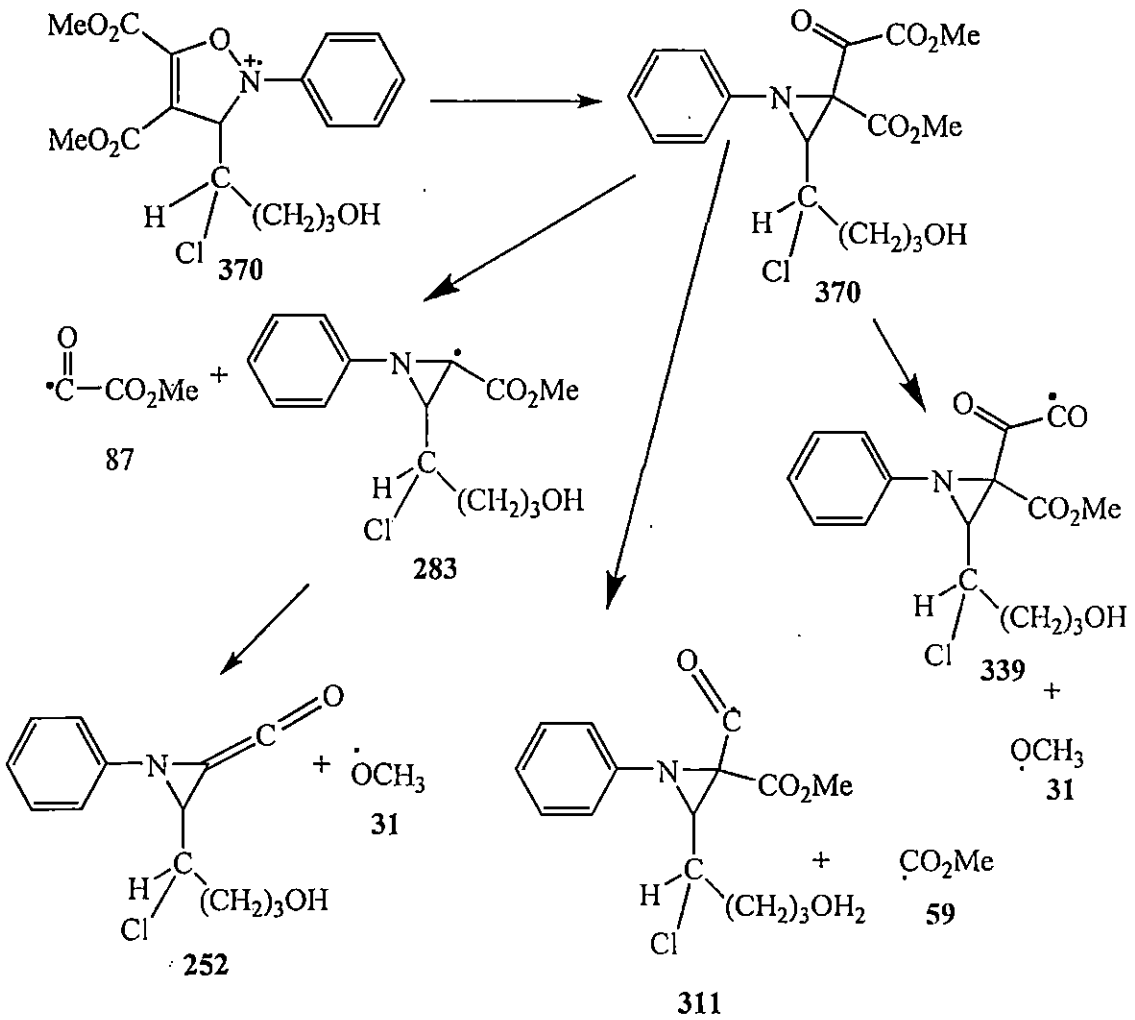


The fragmentation pattern of acetylene adducts are completely different and are explained in **Type IX**.

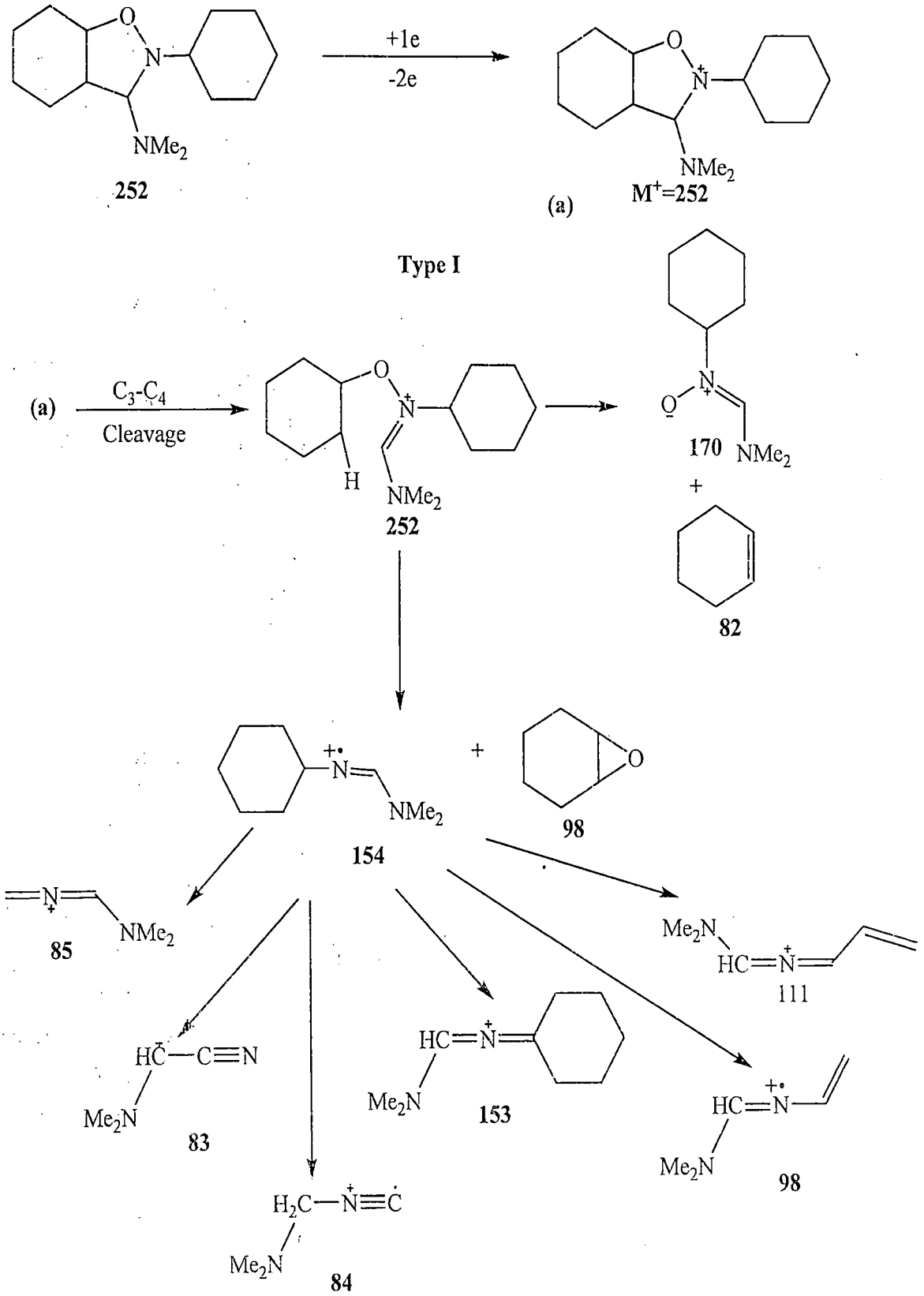
Type IX



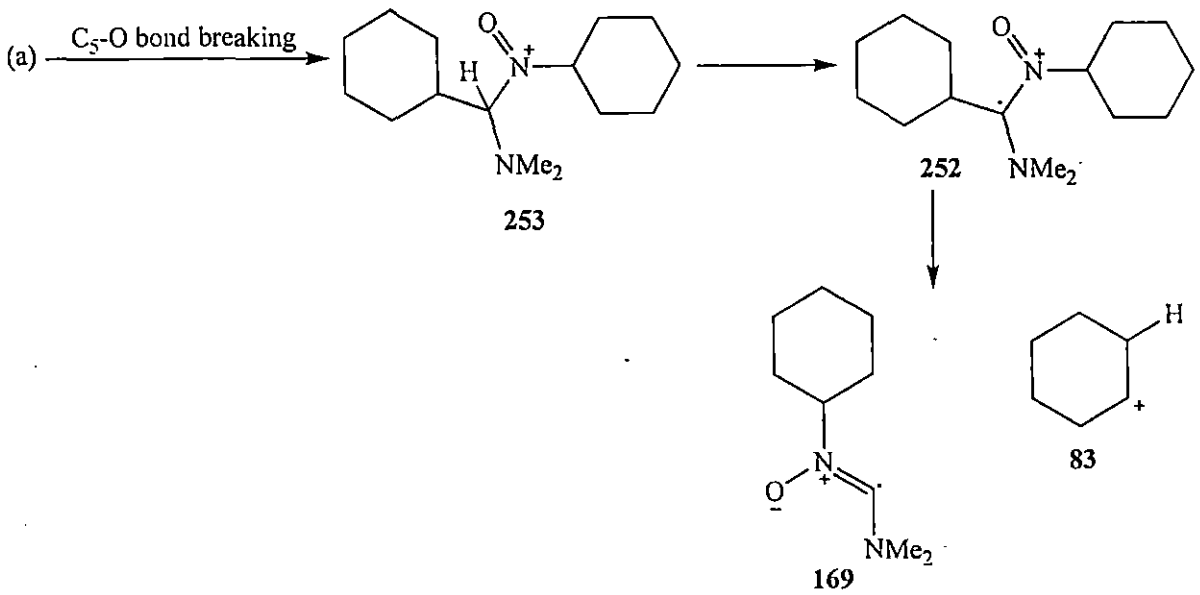
Example with $H_3COOC-C\equiv C-COOCH_3$ adduct



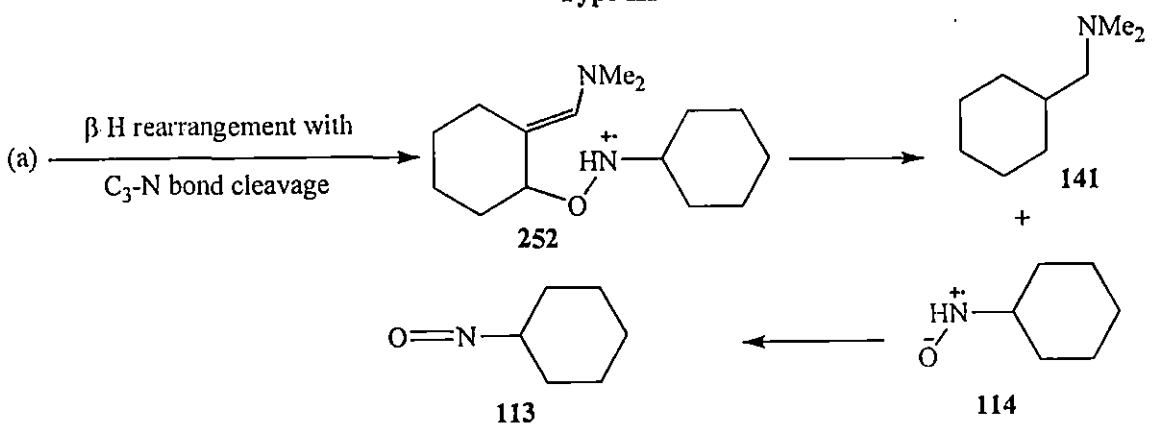
Similarly mass fragmentation pattern of the cycloadducts formed by the reaction of α-amino nitrone with different dipolarophiles can be understood. A general scheme is discussed as below (taking cycloadduct formed from the reaction of *N*-cyclohexyl-α-amino nitrone with cyclohexene as an example).


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

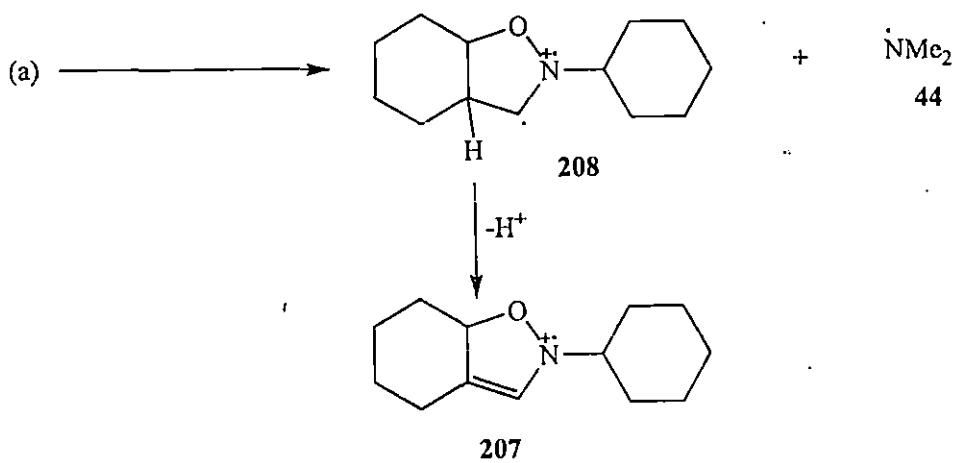
Type II



Type III



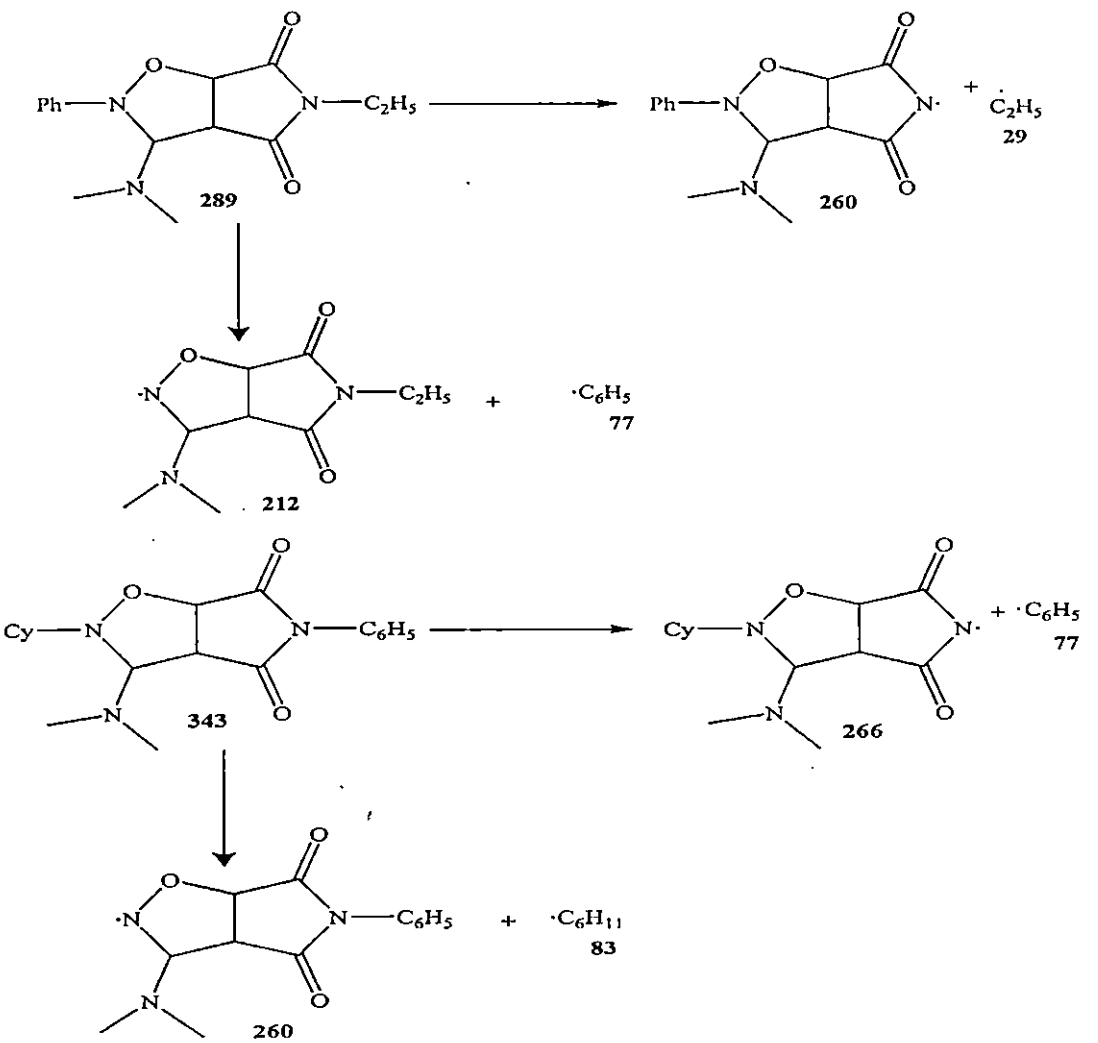
Type IV



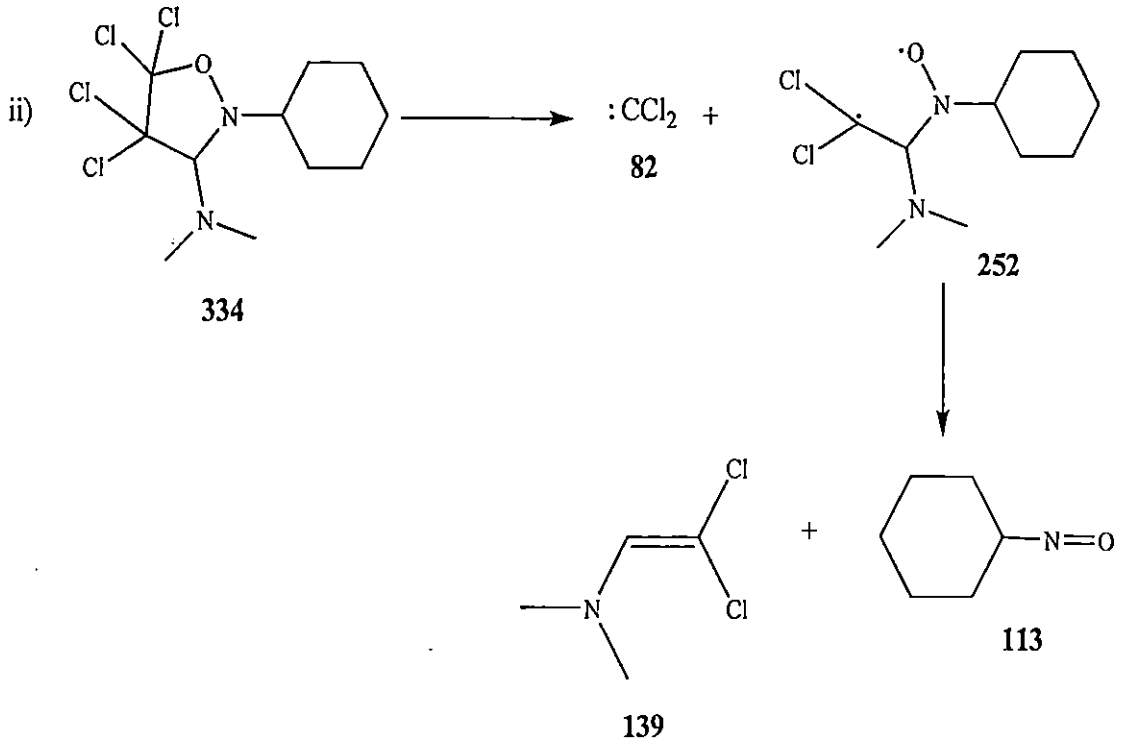
In the case of cycloadducts formed from α-amino nitrone the major fission pattern is molecular ion due to α-cleavage. Among the probable mode for α-cleavage i.e. C_3-C_4 and C_6-C_7, the latter cleavage was not possible because this leads to highly substituted bond cleavage. Another type of bond cleavage 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

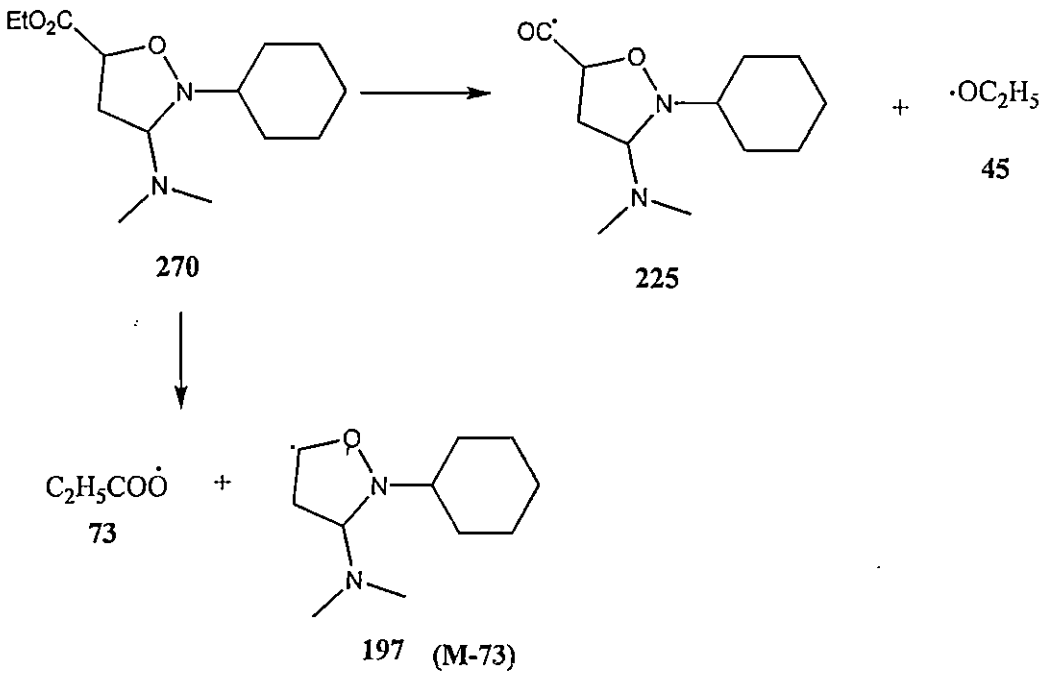


Type VI



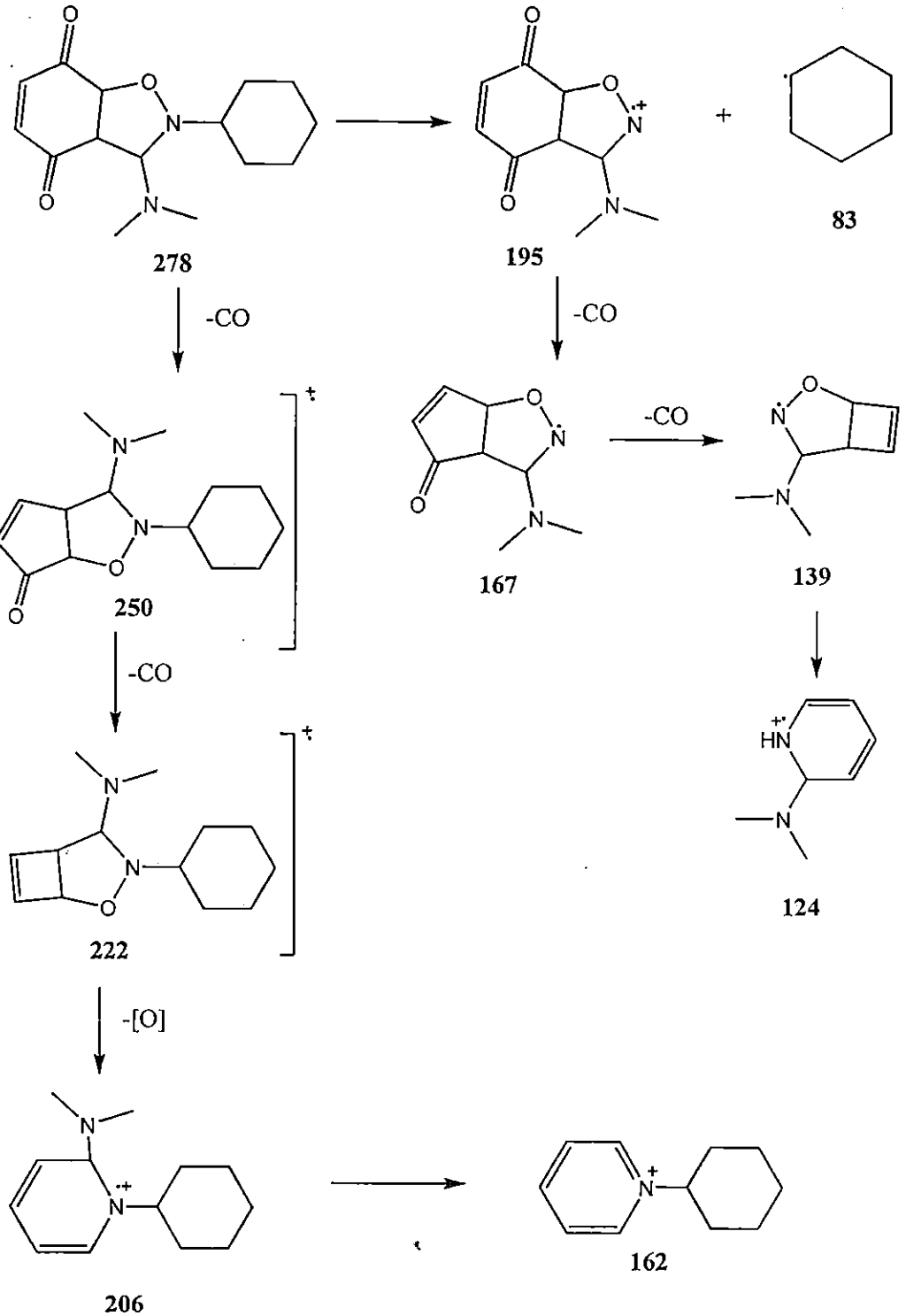
The fragmentation pattern of ethyl acrylate cycloadduct followed the general pattern with some typical peaks *i.e.* CH_3-CH_2-O (45), CH_3-CH_2-COO (73) as shown in **Type VII**.

Type VII

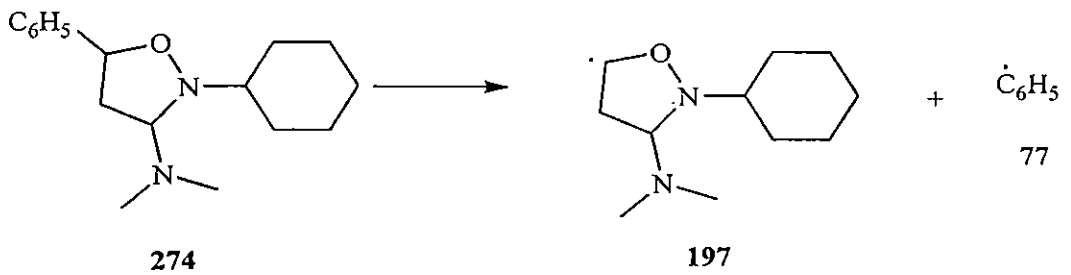


Type VIII

i)

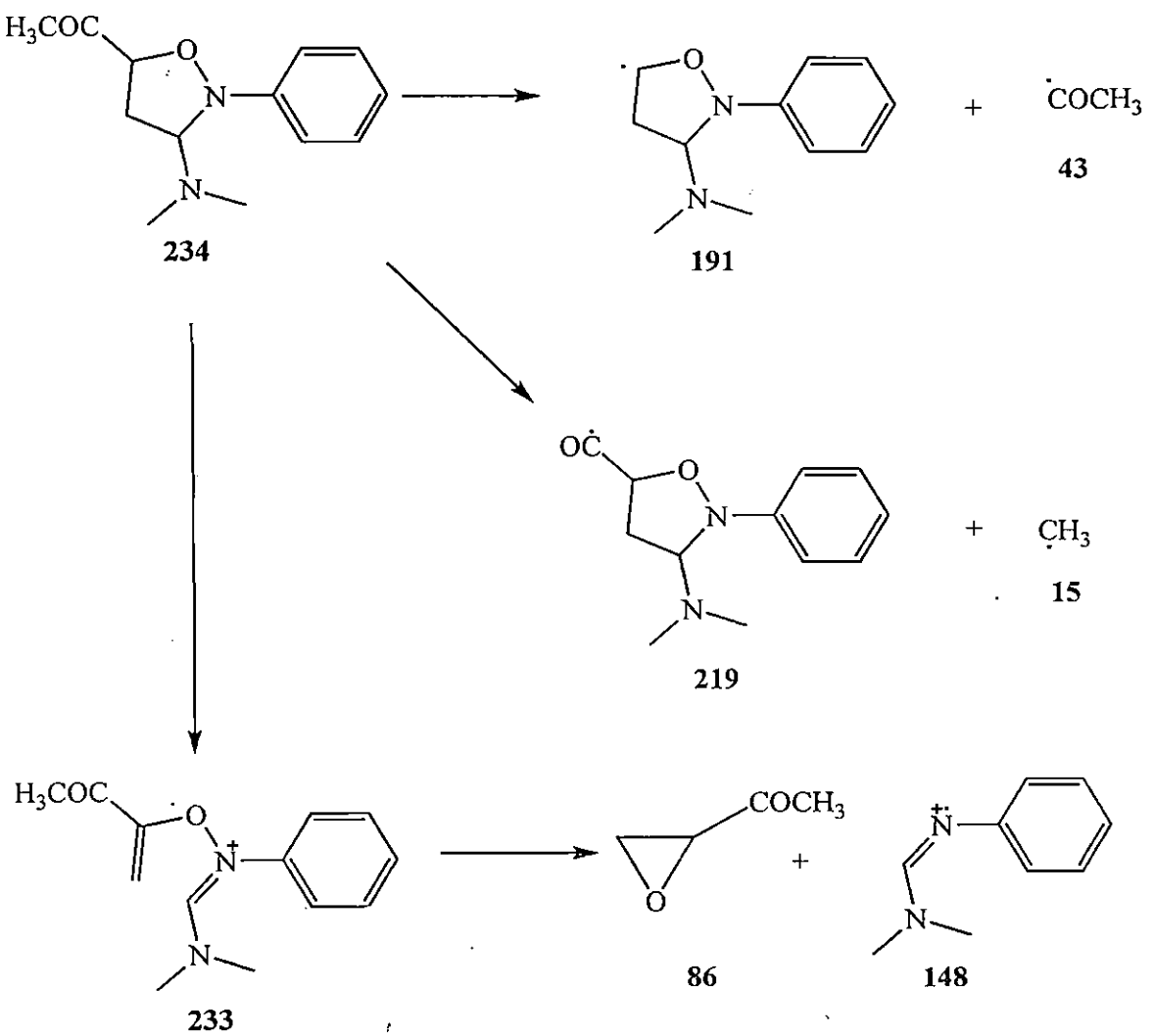


Type IX



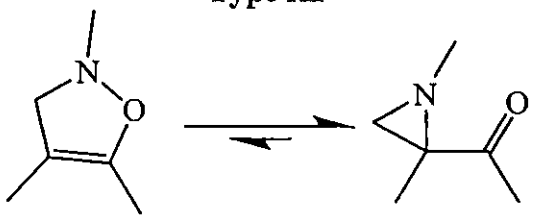
274 **197** **77**

Type X

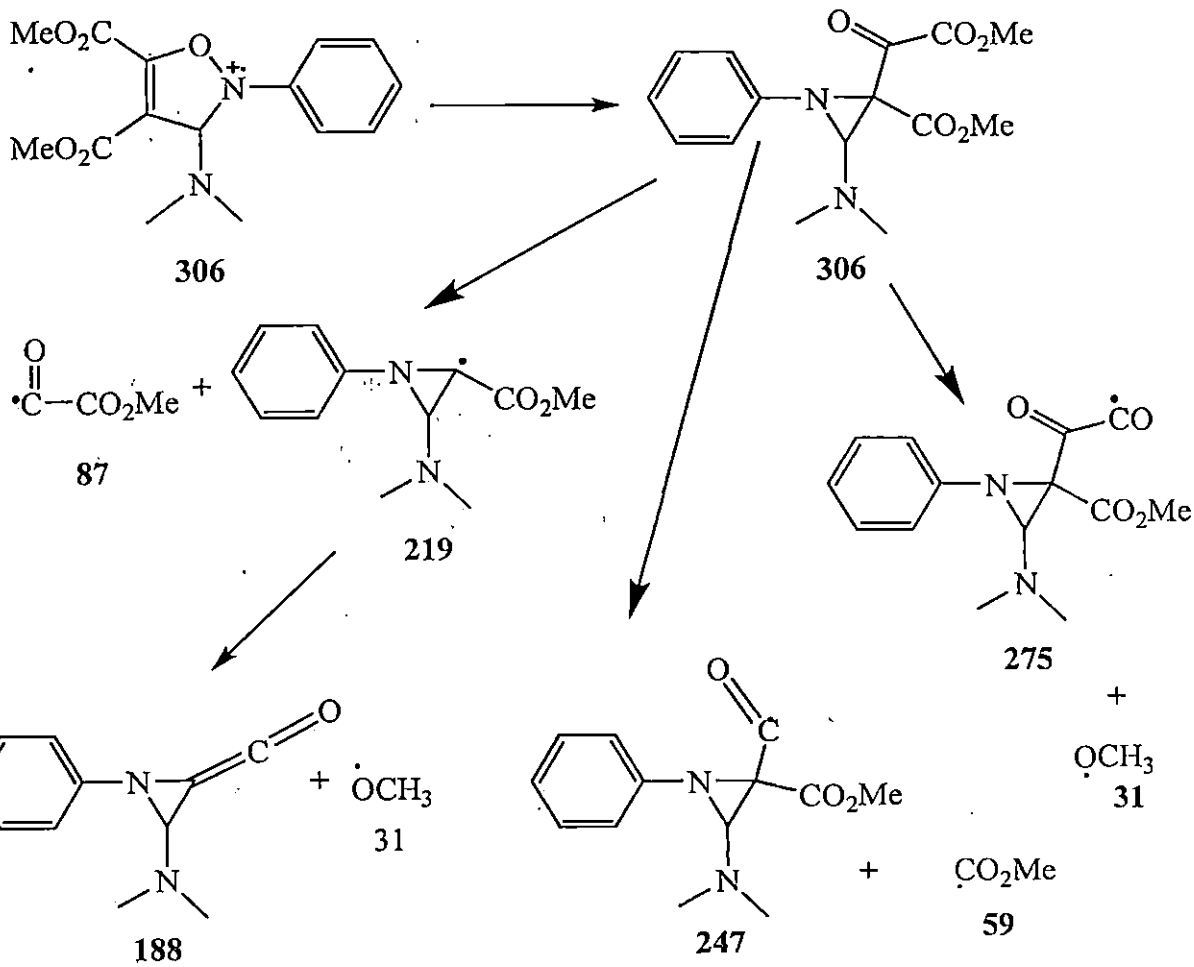


234 **191** **43** **219** **15** **233** **86** **148**

Type XI



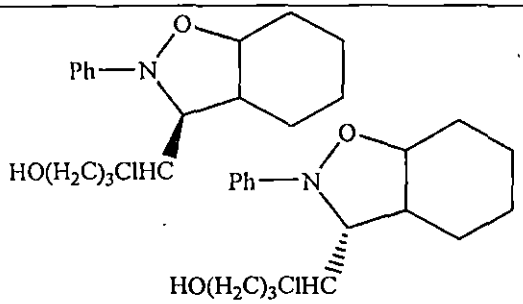
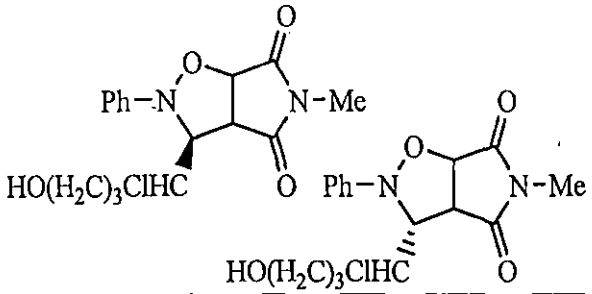
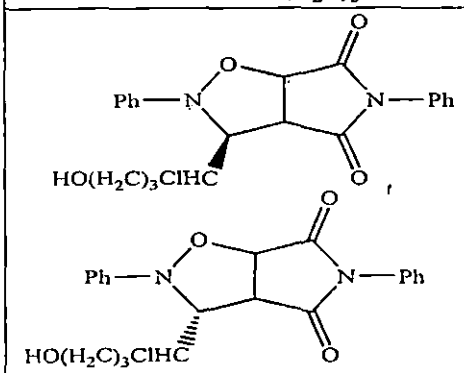
Example with $H_3COOC—C\equiv C—COOCH_3$ adduct



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)

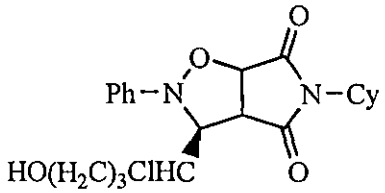
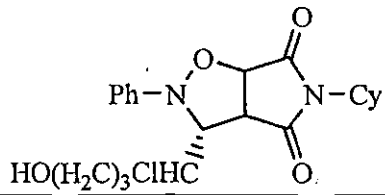
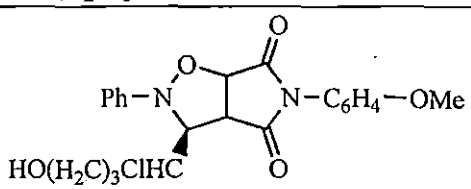
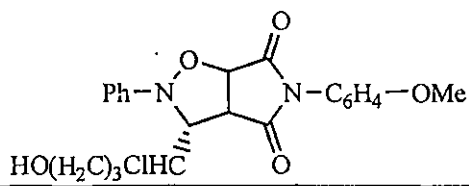
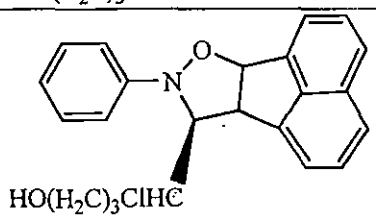
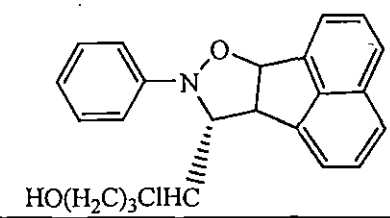
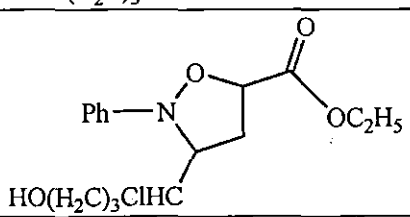
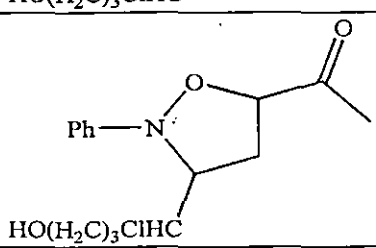
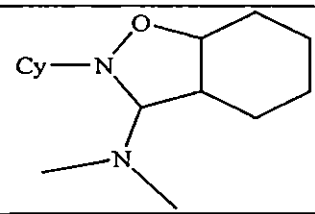
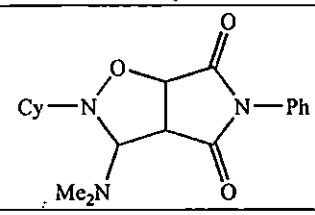
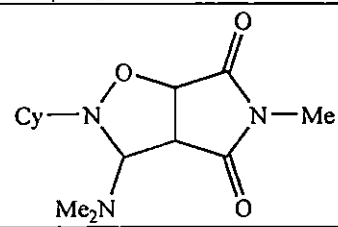
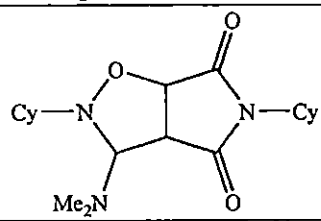
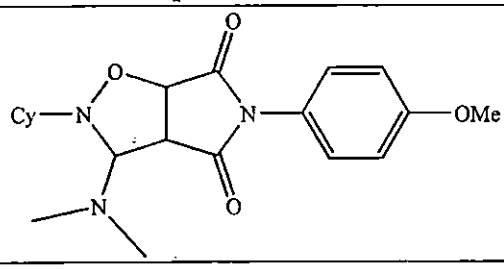
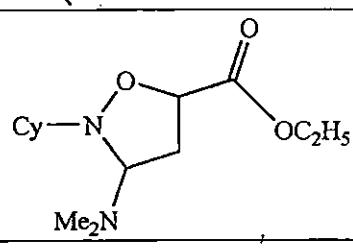
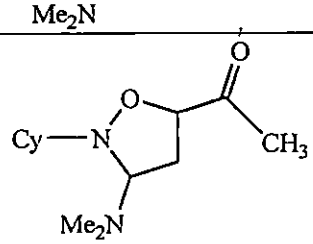
Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.32 (6.12)	4.26 (9.24, 7.06)
	5.26 (7.22)	4.14 (3.22, 2.08)
	5.28 (6.88)	3.86 (9.24, 7.08)
	5.23 (7.40)	3.54 (2.84, 3.25)
	5.26 (6.50)	4.12 (9.40, 7.10)
	5.30 (7.16)	4.28 (4.12, 3.10)
	4.11 (8.2)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

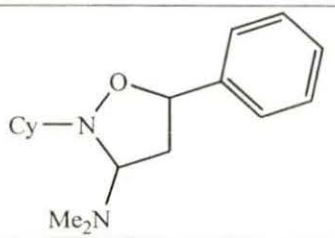
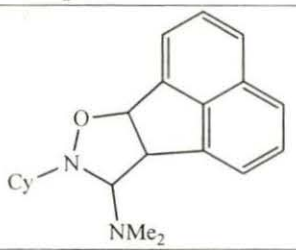
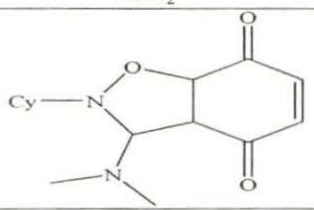
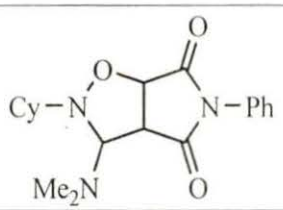
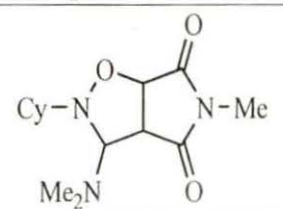
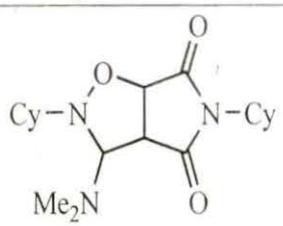
Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.10 (6.16)	3.55 (7.12, 8.10)
	4.37 (6.08)	2.89 (6.08, 6.28)
	5.24 (6.02)	3.34 (6.80, 6.88)

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)

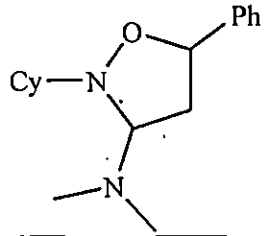
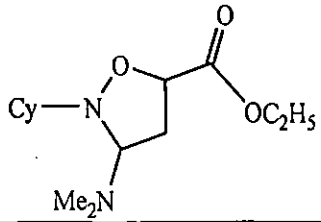
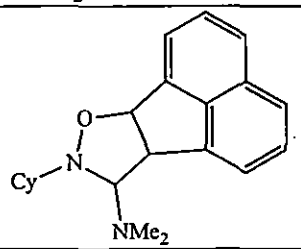
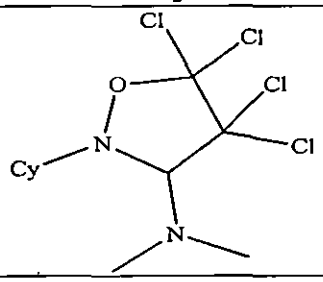
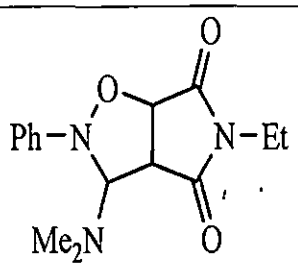
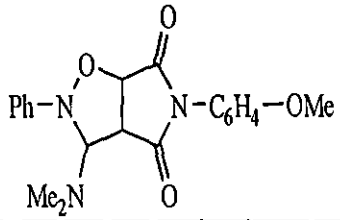
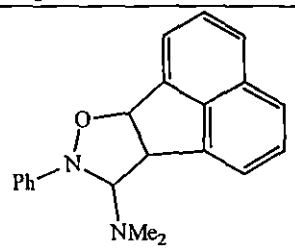
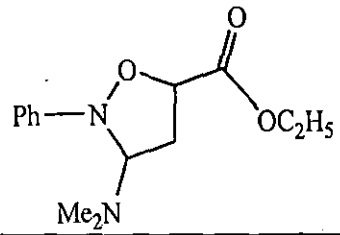
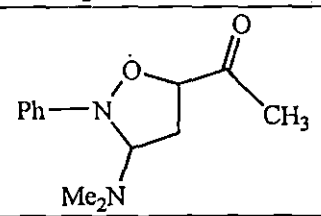
Cycloadducts	C_5 H coupling constant values in parentheses	C_4 H coupling constant values in parentheses
	5.10 (6.08)	3.70 (6.12, 6.10)
	5.20 (6.76)	3.84 (7.65, 6.62)
	5.00 (6.08)	3.56 (6.08, 6.28)
	—	—

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**).

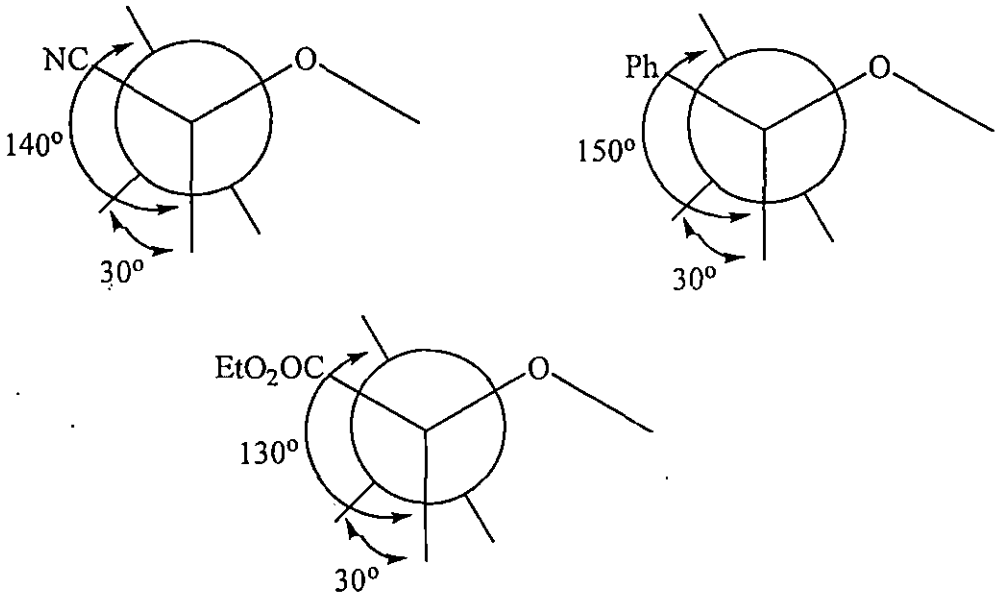
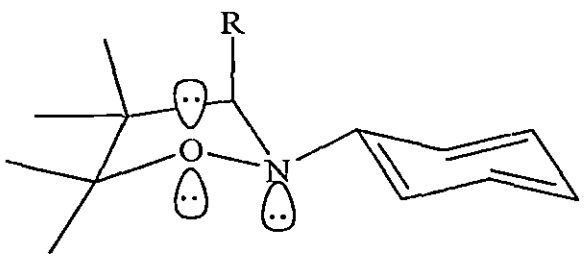


Fig. 4



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].

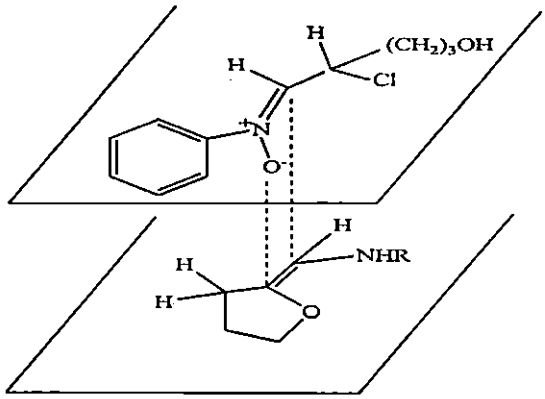


Fig. 7 (**TS I** spiro cycloadducts)

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).*

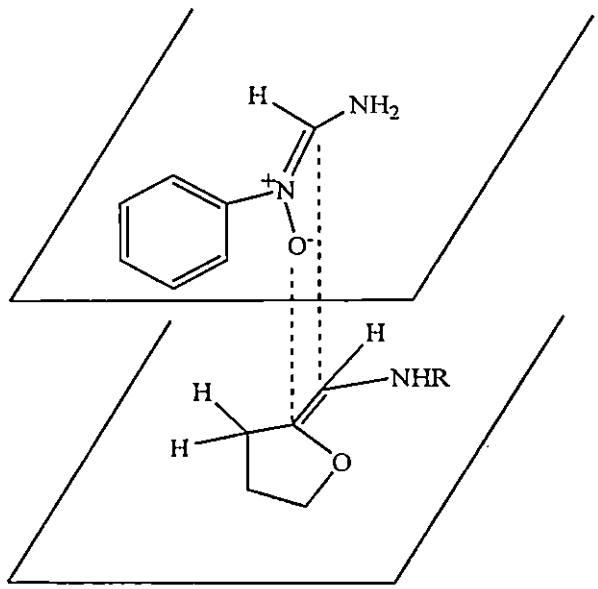


Fig. 8 (**TS - II** spiro cycloadducts)

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