

Chapter III

Results and Discussion

The present study reports the synthesis, cycloaddition reaction and applications of α -chloro nitron. ^{1,2,3} Eschenmoser et al have shown the synthetic potentiality of α -chloro nitron in 1,4-dipolar cycloaddition reactions with un-activated olefinic double bonds ^{4,5} We have reported an application of α -chloro nitron in 1,3-dipolar cycloaddition reactions with different dipolarophiles. *N*-phenyl- α -chloro nitron was synthesized from a mixture of chlorohydrin and its tautomer with *N*-phenylhydroxylamine ⁶⁻¹⁵ in dry ether and anhydrous magnesium sulphate with constant stirring for 8-10 hour under nitrogenous atmosphere at room temperature. Literature survey reveals that this is the first ever report of nitron synthesis using chlorohydrin and *N*-phenylhydroxylamine. Earlier report of nitron synthesis using chlorohydrin had already been reported from this laboratory ¹⁶. Along with conventional method of synthesis in traditional solvents, α -chloro nitron has also been synthesized in aqueous phase ⁴ and Synthesis of *N*-phenyl- α -chloro nitron from chloral has also been reported ¹⁷.

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

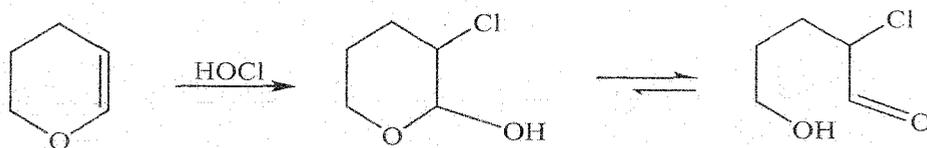
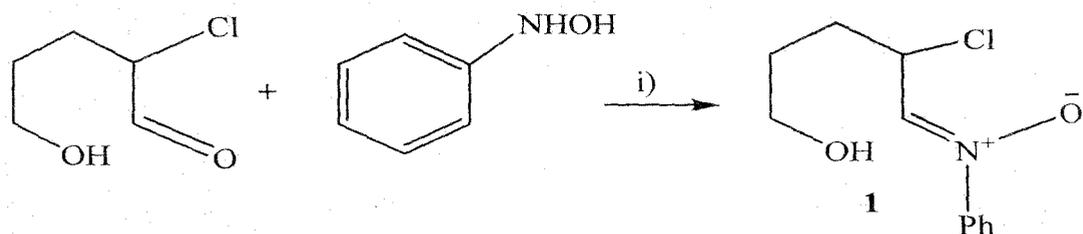


Fig 1

Greenish gummy liquid; 74.6 %; IR (CHCl₃): 3600 – 3200 (br), 2920 (s), 1720 (s), 1440 (m), 1380 (s), 1340 (m), 1284 (s) cm⁻¹; ¹H NMR (CDCl₃): δ 9.75 (1H, CHO), 5.06 (d, 1H, *J* = 6 Hz, -OCH), 5.23 – 4.96 (br, 1H, -OH, exchanged in D₂O), 4.10 – 3.93 (dt-m, 1H, CHCl), 3.80 – 3.4 (m, 4H, CH₂); MS; *m/z*: 136 (M⁺), 118, 108, 102, 78, 69.

I. Synthesis of *N*-phenyl- α -chloro nitrone (1) from Pyran



i) anhydrous MgSO_4 , RT, 12 hour, N_2 environment

Fig 2

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, $\text{CH}=\text{N}^+$), 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 ($\text{CH}=\text{N}^+$), 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 $\text{C}_{11}\text{H}_{14}\text{O}_2\text{NCl}$, (M), 225.0864, found M^+ , 225.0852.

N-phenyl- α -chloro nitrone has also been synthesized from dihydrofuran with hypochlorous acid followed and *N*-phenylhydroxylamine and it was found to be almost identical in all respects including 1,3-dipolar cycloaddition reactions. This is shown as follows.

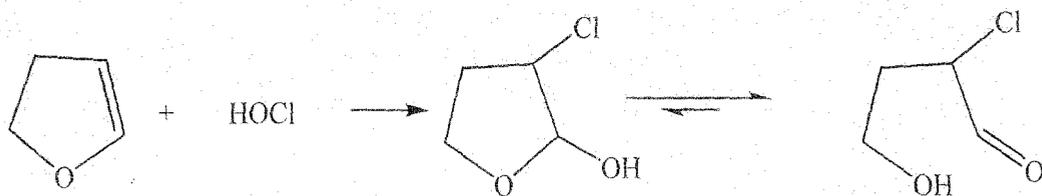


Fig 3

Greenish gummy liquid; 74.6 %; IR (CHCl_3): 3560 – 3450 (br), 2910 (s), 1730 (s), 1444 (m), 1370 (s), 1340 (m), 1280 (s) cm^{-1} ; ^1H NMR (CDCl_3): δ 9.82 (1H, CHO), 5.20 (d, 1H, $J = 7.20$ Hz, $-\text{OCH}$), 5.12 – 4.90 (br, 1H, $-\text{OH}$, exchanged in D_2O), 3.90 – 3.78 (dt-m, 1H, CHCl), 2.94 – 2.64 (m, 4H, CH_2); MS: m/z 121 (M^+), 104, 93, 87, 78, 35, 29.

II. Synthesis of *N*-phenyl- α -chloro nitron (2) from Furan

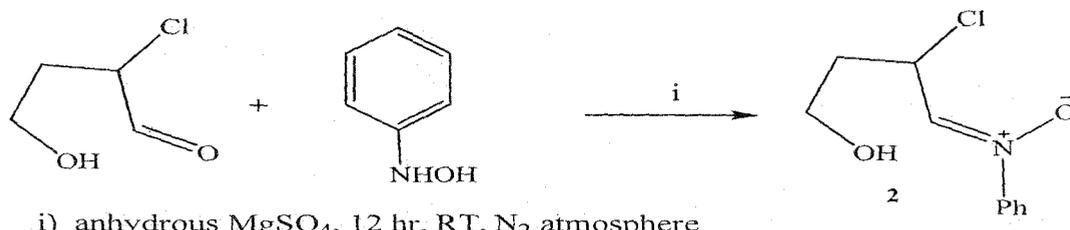


Fig 4

IR (CHCl_3): 3510 - 3432 (br), 1610 (s), 1430 (m), 1165 (s), 780 (s) cm^{-1} ; ^1H NMR (CDCl_3): δ 7.44 - 7.32 (m, 5H, C_6H_5), 6.96 (d, 1H, $J = 6.28$ Hz, $\text{CH}=\text{N}^+$), 5.20 - 5.12 (br, 1H, CH_2OH , exchanged in D_2O), 4.62 (dt-m, 1H, CHCl), 2.70 - 2.54 (m, 4H); ^{13}C NMR (CDCl_3): δ 141.40 ($\text{CH}=\text{N}^+$), 131.00, 130.10, 128.60, 127.00 (aromatic carbons), 93.70 (CHCl), 23.54, 21.80 (2 CH_2 carbons); MS m/z : 212 (M^+); HRMS - EI: Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{NCl}$, (M), 212.5750, Found; M^+ , 212.5732.

III. Synthesis of *N*-phenyl- α -chloro nitron (3) from chloral

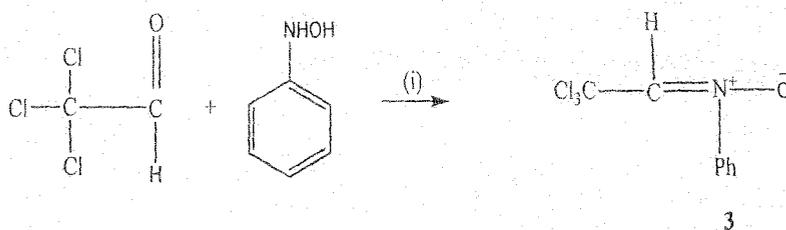


Fig 5

IR (CHCl_3): 2900 (s), 1680 (s), 1610 (s), 1260 (m), 765 (s); ^1H NMR (CDCl_3): δ 7.63 - 7.50 (m, 5H, C_6H_5), 7.20 (s, 1H, $\text{CH}=\text{N}^+$ <); ^{13}C NMR (CDCl_3): δ 142.50 ($\text{CH}=\text{N}^+$ <), 133.24, 131.50, 130.00, 128.00 (aromatic carbons), 29.00 (CCl_3); HRMS: Calcd. For $\text{C}_8\text{H}_6\text{ONCl}_3$ (M), 238.4540; Found; (M^+) 238.4525.

In the case of conventional solvents the reactions are 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, Acenaphthylene etc while regioselective cycloadducts are formed in case of methyl vinyl ketone, acrylonitrile, styrene etc respectively. The regioselectivity in these reactions are rationalized by the use of frontier orbital theory^{18,19}. The α -chloro nitron have considerably higher ionization potential than

normal nitrones due to the electron withdrawing effect of chlorine. Therefore nitrone (LUMO)-dipolarophile (HOMO) interactions are so important that it completely dominates the reaction and lead to the formation of only five substituted adducts¹⁸. One of the most important features of these cycloaddition reactions are the introduction of three to four asymmetric centres in a single step. In these cycloaddition reactions, the C-C and 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 C₃ and C₄ respectively²⁰

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 reportedly takes 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 electrophilic 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^{21,22}. 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, CH₂Cl₂ (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. 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 FMOs are only slightly affected by hydrogen bond interactions and lead to a reduction of the energy gap between the interacting FMOs (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 yield²³.

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^{21,22}. These results can be rationalized by an *exo* approach of the nitron **1** for the major cycloadducts which have the *Z* configuration (transition state **I**). The minor cycloadducts are formed by the *endo* approach of *Z* nitron (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 (*J*). The most significant differences in the ¹H 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 $J_{3,4} \sim 9.16$ 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 6**). The diastereomeric isoxazolidines were separated by column chromatography and obtained in analytically pure form²³. The *endo/exo* stereochemistry mentioned above is based on extensive NMR investigations. Most relevant are the coupling constants ($J_{\text{H3, H4}}$) 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-4²⁴. 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 theory²⁰ and ¹H NMR experiments. Since α -chloro nitron exist exclusively in *Z* configuration, the cycloadducts were formed from *Z* nitrons 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 water²¹. The reactions were found to be highly regioselective to form solely 5 substituted isoxazolidines respectively. Nitron **1** has considerably higher ionization potential than normal nitrons due to the electron withdrawing effect of chlorine. Therefore nitron (LUMO)-dipolarophile (HOMO) interactions were so important that it completely dominates the reaction and leads to the formation of only 5 substituted adducts²⁵. Considering the ¹H 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 ^1H 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 ($J_{\text{H}_4, \text{H}_5} = 6 - 8.4 \text{ Hz}$; $J_{\text{H}_4, \text{H}_3} = 6.2 - 7.6 \text{ Hz}$)^{24,26}. 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.

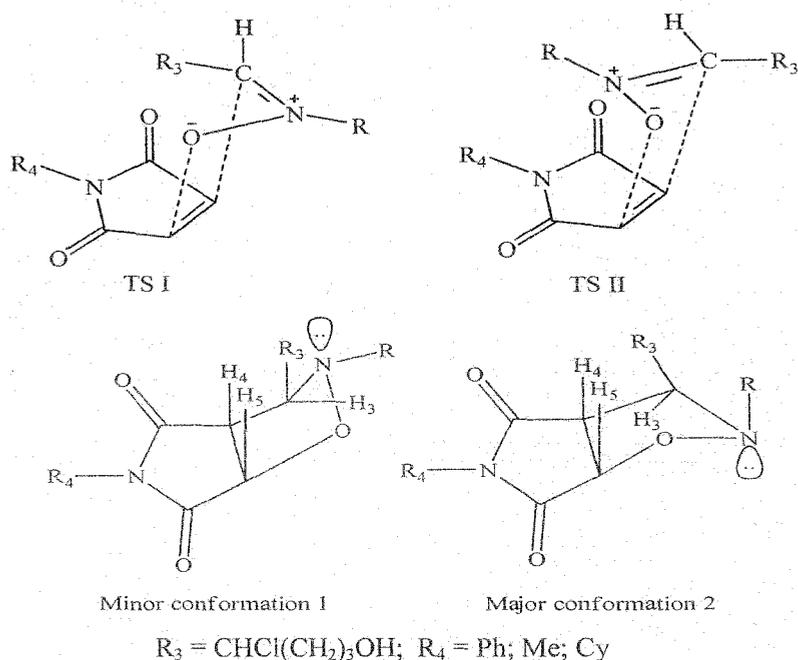
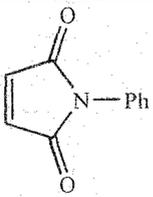
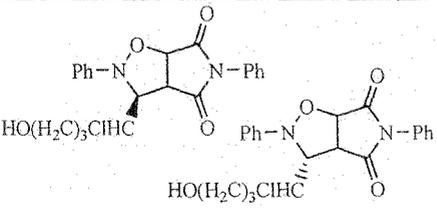
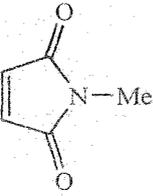
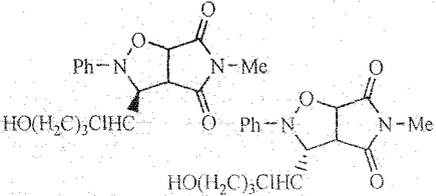
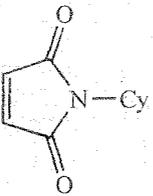
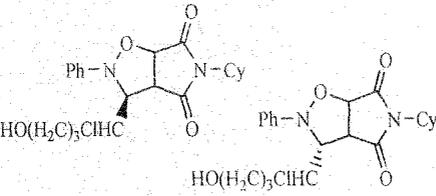
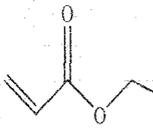
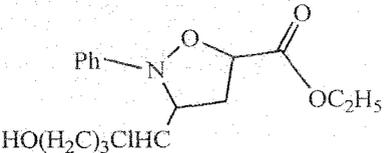
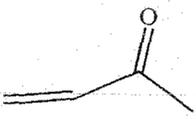
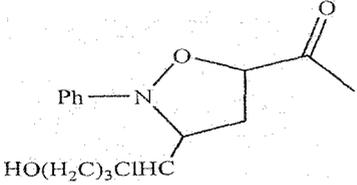


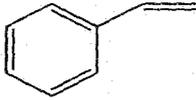
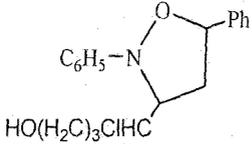
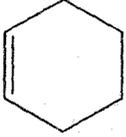
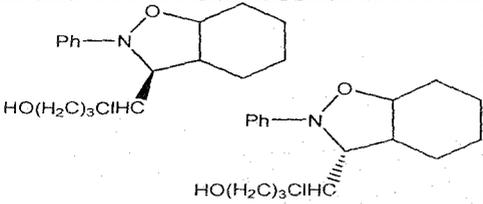
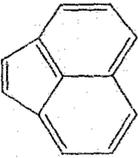
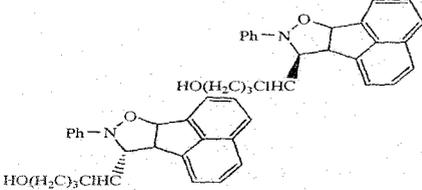
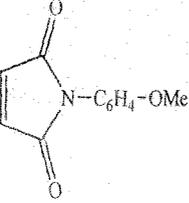
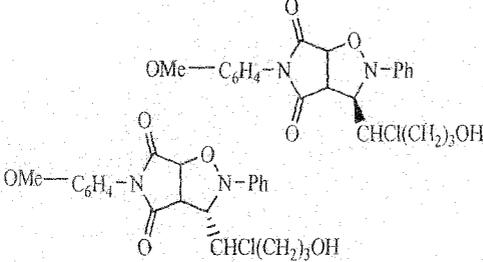
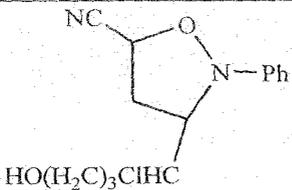
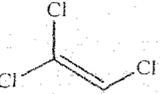
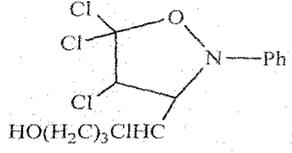
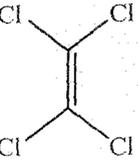
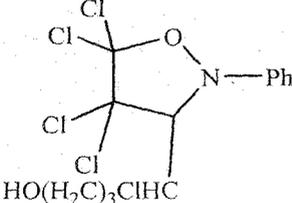
Fig. 6

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, ^1H 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 $\text{M}^+ + 2$ ion peaks obtained in most of the diastereomers and regioselective cycloadducts as the peak of highest m/z value. These can be explained as $\text{M}^+ + 2$ isotopic peaks due to the presence of isotopic abundance of

Cl³⁷ atom in these compounds. In addition, mass fragmentation peaks of different value are also obtained for diastereomers of a particular cycloadduct. The 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: Cycloadducts developed from nitron 1

Dipolarophile	Solvent/ Reaction condition	Nature of product & Yield	Structure of product(s)
	RT, 10 hr, Nitrogen atmosphere Diethyl ether	white solids, 70.8%, 23 %	
	RT, 8 hr, Nitrogen atmosphere Diethyl ether	white solid, 75.6 %, 20 %	
	RT, 10 hr, Nitrogen atmosphere Diethyl ether	Dark yellow crystals, 68%, 27 %	
	RT, 8 hr, Nitrogen atmosphere Diethyl ether	white gummy liquid, 93%	
	RT, 8 hr, Nitrogen atmosphere Diethyl ether	pale yellow oil, 91%	

	RT, 14 hr, Nitrogen atmosphere Diethyl ether	White solid, 93 %	
	RT, 14 hr, Nitrogen atmosphere Diethyl ether	Reddish yellow gummy liquid, 60%, 20%	
	RT, 7 hr, Nitrogen atmosphere Diethyl ether	bright yellow crystals, 73%, 23%	
	RT, 11 hr, Nitrogen atmosphere Diethyl ether	White solid, 70.8%, 25.8 %.	
	RT, 13 hr, Nitrogen atmosphere Diethyl ether	colourless oily liquid, 82%	
	RT, 10 hr, Nitrogen atmosphere Diethyl ether	colourless oily liquid, 80%	
	RT, 12 hr, Nitrogen atmosphere Diethyl ether	colourless gummy liquid, 75%	

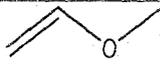
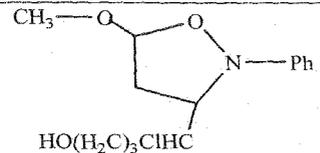
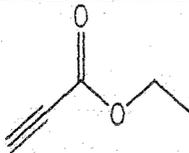
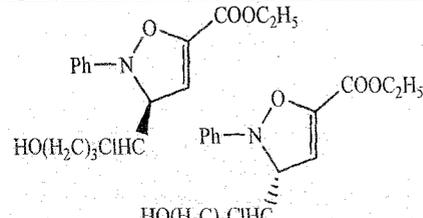
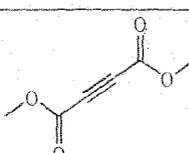
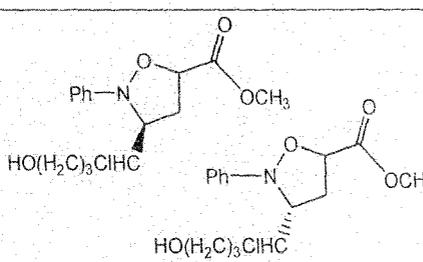
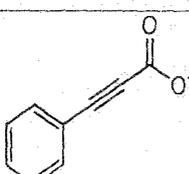
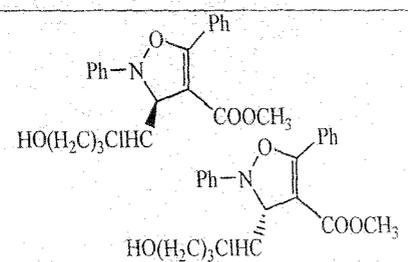
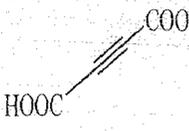
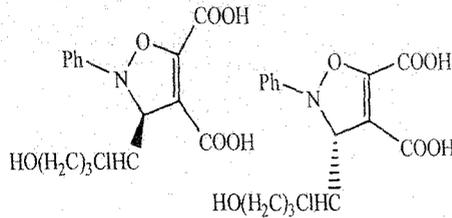
	RT, 13 hr, Nitrogen atmosphere Diethyl ether	colourless liquid, 79%	
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Table 2: Cycloadducts developed from nitron 1 (triple bonded)

Dipolarophile	Solvent/Reaction condition	Nature of product & Yield	Structure of product(s)
	Dry ether, RT, 12 hr, Nitrogen atmosphere	white viscous liquid, 70 %, 22 %	
	Dry, ether RT, 10 hr, Nitrogen atmosphere	white viscous liquid, 69% , 27 %	
	Dry ether, RT, 13 hr, Nitrogen atmosphere	white viscous liquid, 75%, 24 %	
	Dry ether, RT, 14 hr, Nitrogen atmosphere	colourless viscous liquid, 73 %, 24 %	

In case of alkynes, we examined the reactions in diethyl ether since there are less possibilities of the formation of hydrogen bonding between the nitron 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 temperatures. 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)²⁷. 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 theory²⁰. 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 -chloronitronone (**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**)²⁸. The minor cycloadduct is formed by the *endo* approach of *Z* nitrone (transition state **II**)²⁹. 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 ($J_{H_3, CHCl}$; J_{H_3, H_4}) 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 ($J_{H_3, CHCl}$) is 2.5 to 2.58 Hz which implies a *trans* relationship between H_3 and $CHCl$ (Ref 15). Comparing the ¹H NMR spectrum of isoxazolines, we suggest the major and minor conformers of cycloadducts which are conformationally mobile isoxazoline ring system (**Fig 7**) 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 XI & XII** in Mass spectra). Since C_4 and C_5 protons are absent in dimethyl acetylene dicarboxylate, phenyl methyl propiolate, acetylene dicarboxylate cycloadducts therefore the coupling constant values could not be calculated.

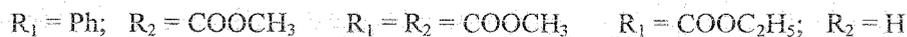
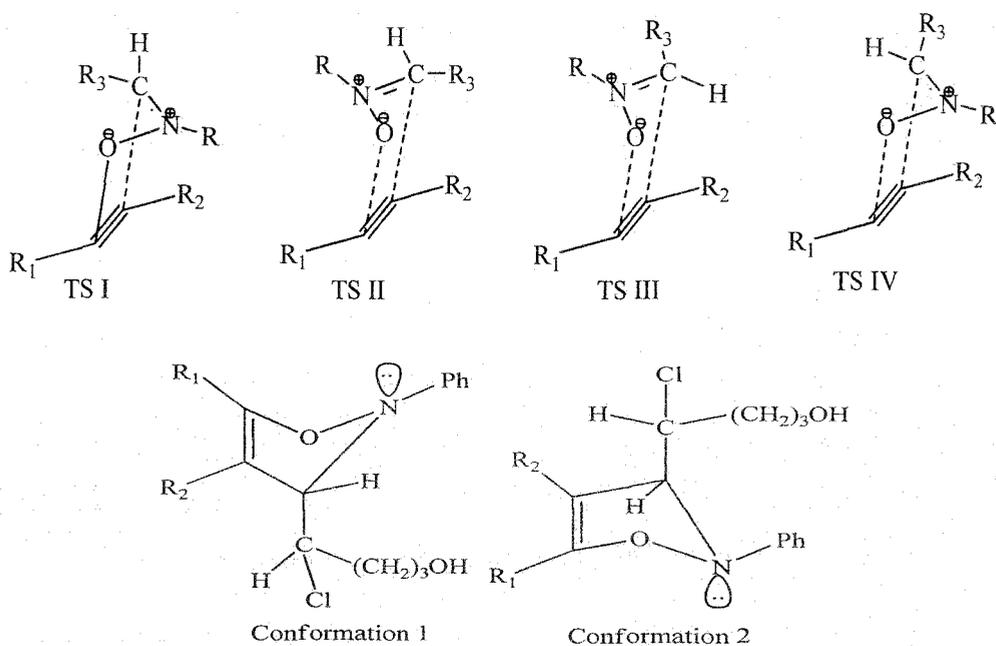


Fig 7

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 nitronium exist exclusively in the *Z* configuration. Houk et al²⁵, 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 al²⁴.

Table 3: Cycloadducts developed from nitronium 2

Dipolarophile	Solvent/Reaction condition	Nature of product & Yield	Structure of product(s)
	CH ₂ Cl ₂ , RT, 10 hour, N ₂ atmosphere	white solids, 63%, 36%	

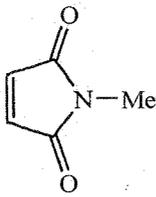
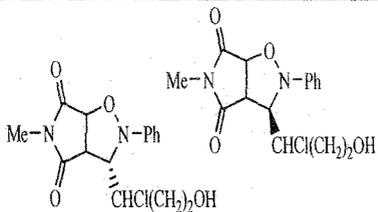
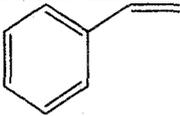
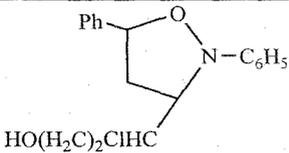
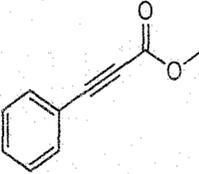
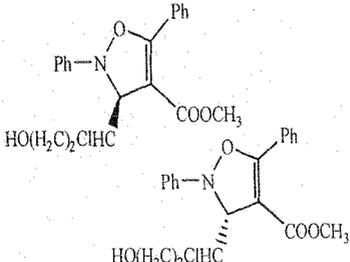
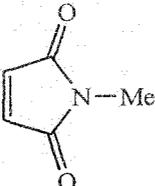
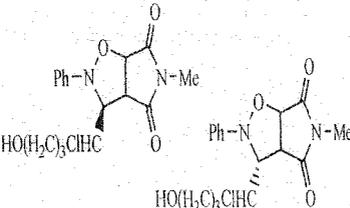
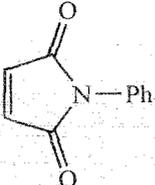
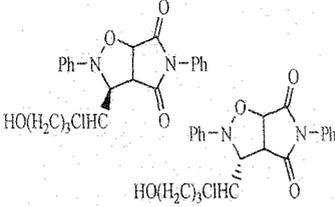
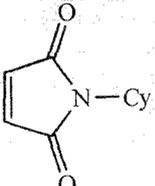
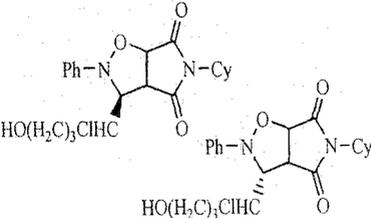
	CH ₂ Cl ₂ , RT, 12 hour, N ₂ atmosphere	white solids, 68%, 30%	
	CH ₂ Cl ₂ , RT, 14 hour, N ₂ atmosphere	white solid, 93 %	
	CH ₂ Cl ₂ , RT, 8 hour, N ₂ atmosphere	Red liquid, 66%, 32%	

Table 4: Cycloadducts developed from nitrone 1 in aqueous medium

Dipolarophile	Solvent/Reaction condition	Nature of product & Yield	Structure of product(s)
	Water, RT, 4 hr, N ₂ atmosphere	white solid, 75,6%, 20,4%	
	Water, RT, 4 hr, N ₂ atmosphere	yellowish white solids, 70,8%, 23,2%	
	Water, RT, 5 hr N ₂ atmosphere	dark yellow crystals, 68%, 27%	

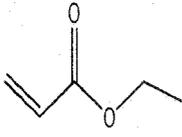
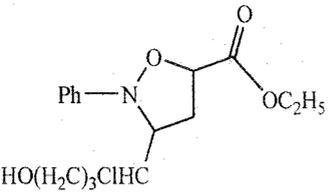
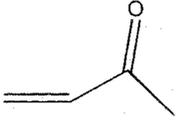
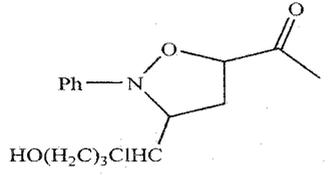
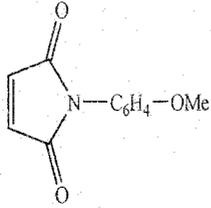
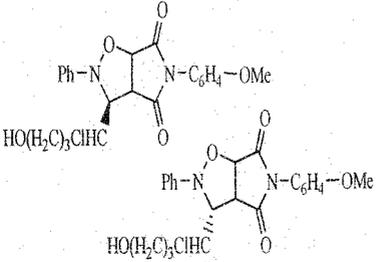
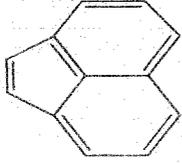
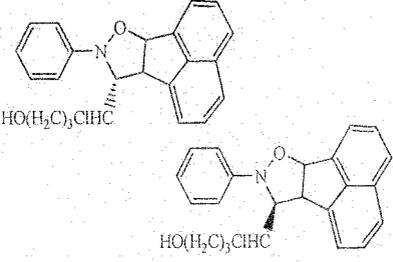
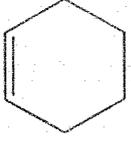
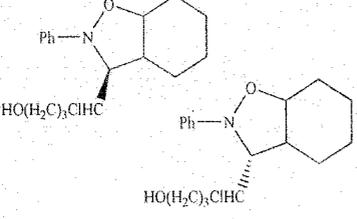
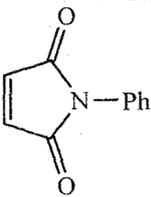
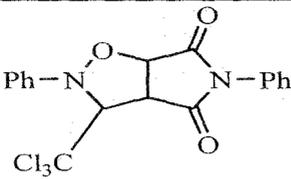
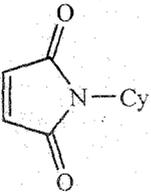
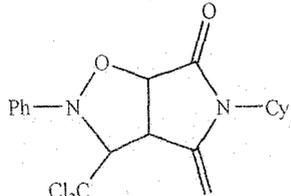
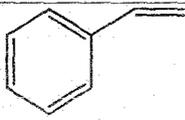
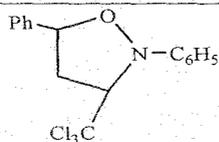
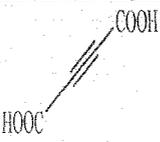
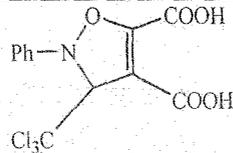
	Water, RT, 5 hr, N ₂ atmosphere	white gummy liquid, 93%	 HO(H ₂ C) ₃ CHC
	Water, RT, 8 hr, N ₂ atmosphere	pale yellow oil, 91%	 HO(H ₂ C) ₃ CHC
	Water, RT, 5hr, N ₂ atmosphere	white solids, 70.8%, 21.2%	 HO(H ₂ C) ₃ CHC
	Water, RT, 7 hr, N ₂ atmosphere	bright yellow crystals, 73 %, 23%	 HO(H ₂ C) ₃ CHC
	Water, RT, 14 hr, N ₂ atmosphere	reddish gummy liquid, 60%, 28%	 HO(H ₂ C) ₃ CHC

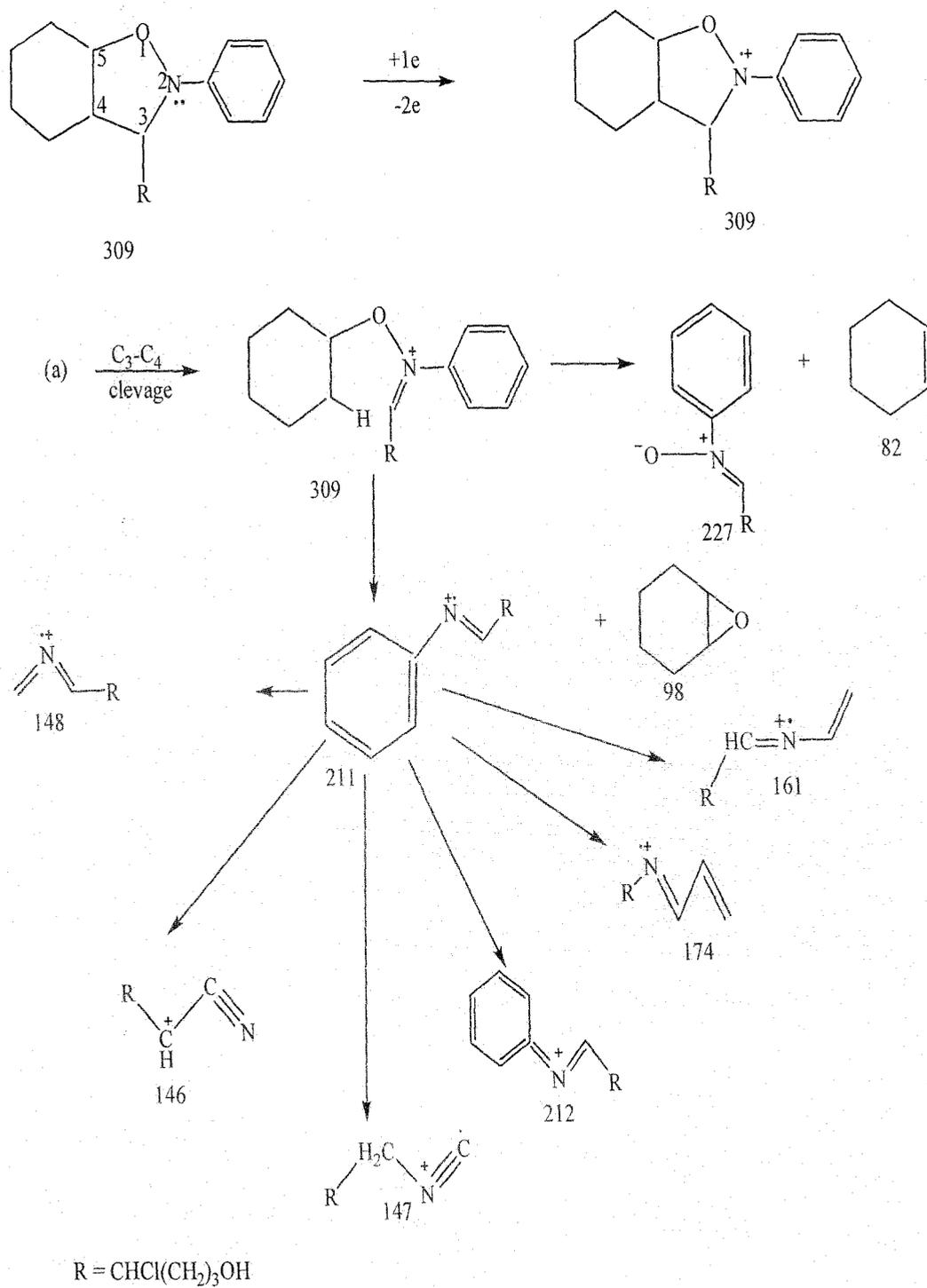
Table 5: Cycloadducts developed from nitron 3

Dipolarophile	Solvent/Reaction condition	Nature of product & yield	Structure of product(s)
	CHCl ₃ , 0-5 ⁰ C, N ₂ atmosphere, 6 hour	White solid, 82%	
	CHCl ₃ , 0-5 ⁰ C, N ₂ atmosphere, 8 hour	White solid, 78%	
	CHCl ₃ , 0-5 ⁰ C N ₂ atmosphere, 10 hour,	white crystals, 93%	
	CHCl ₃ , 0-5 ⁰ C N ₂ atmosphere, 5 hour	oily liquid, 77%	

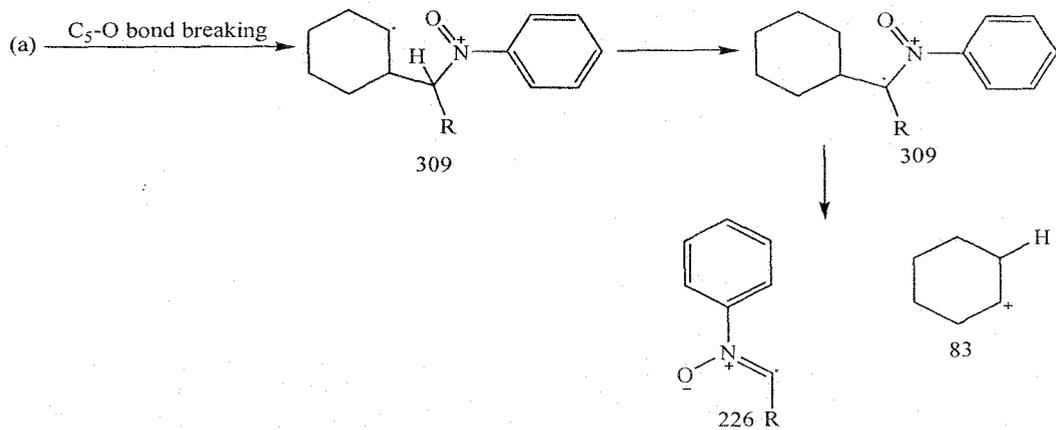
IV. Interpretation of the mass spectra

In case of *N*-phenyl- α -chloro nitrene derived from dihydropyran, furan, chloral, 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 of the compound. On electron impact (EI), mass fragmentation of a molecule would generate generally a radical ion and expectedly one of the non bonding electron of the nitrogen atom of 1,2 isoxazolidine ring would be removed as the nitrogen atom is tertiary in nature. Taking cyclohexene adduct as an example, a general scheme was formulated (**Type I – Type 11**) The fragmentation pattern of all the cycloadducts were discussed in the light of this fission pattern.

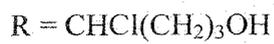
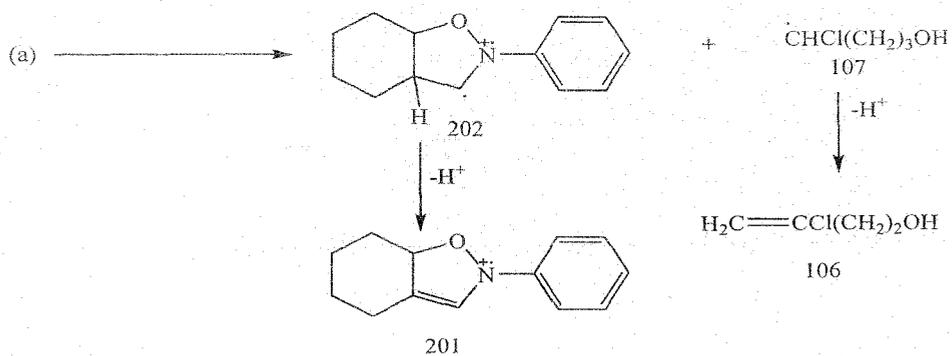
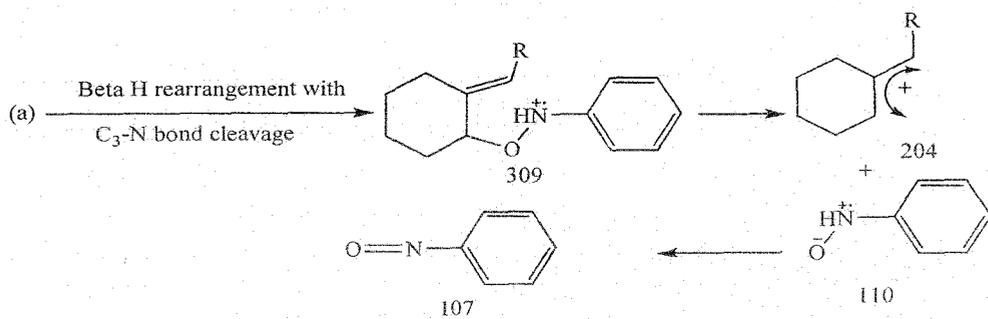
General pattern of mass fragmentation of cycloadducts



Type I

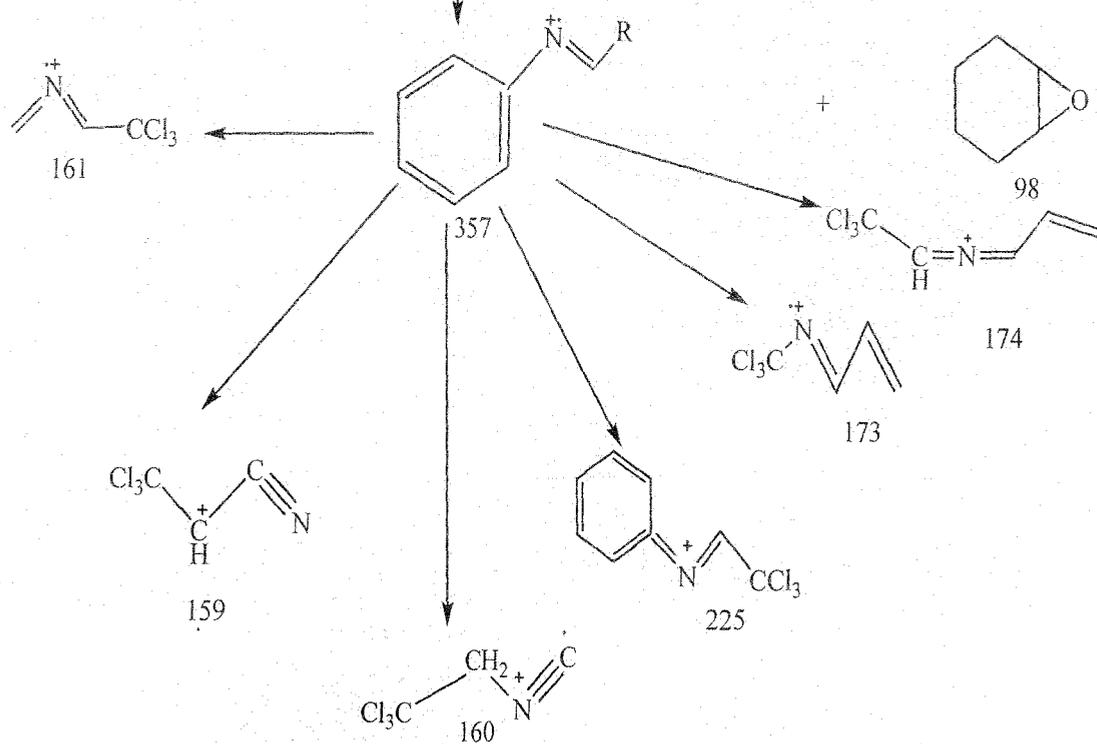
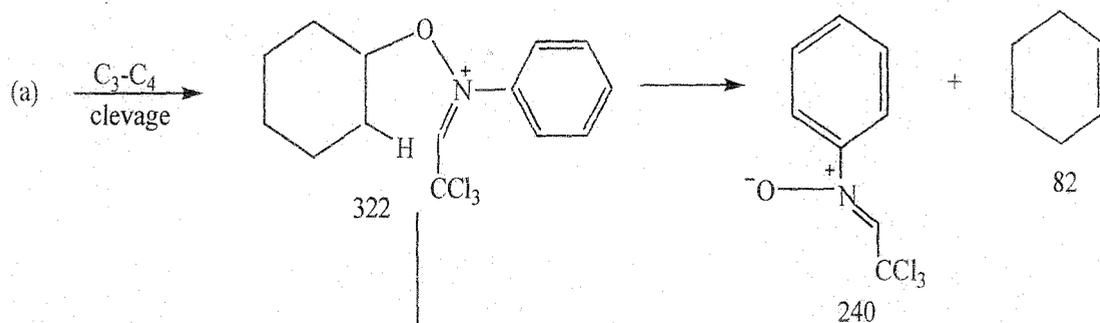
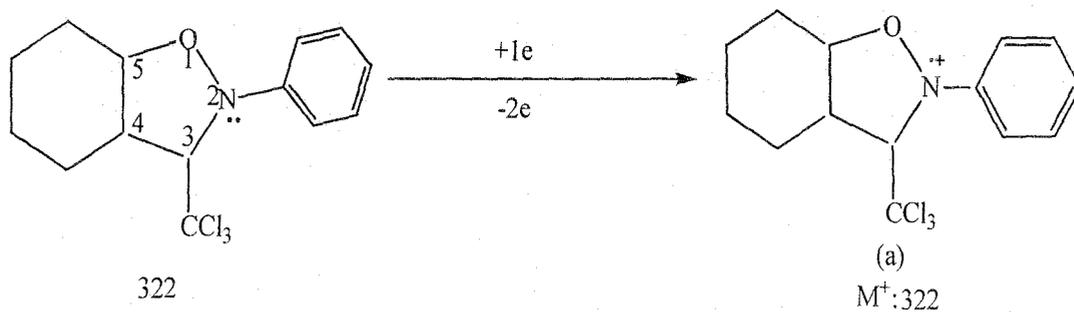


Type I (a)

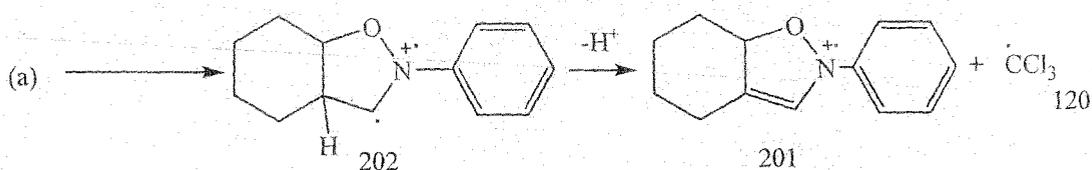
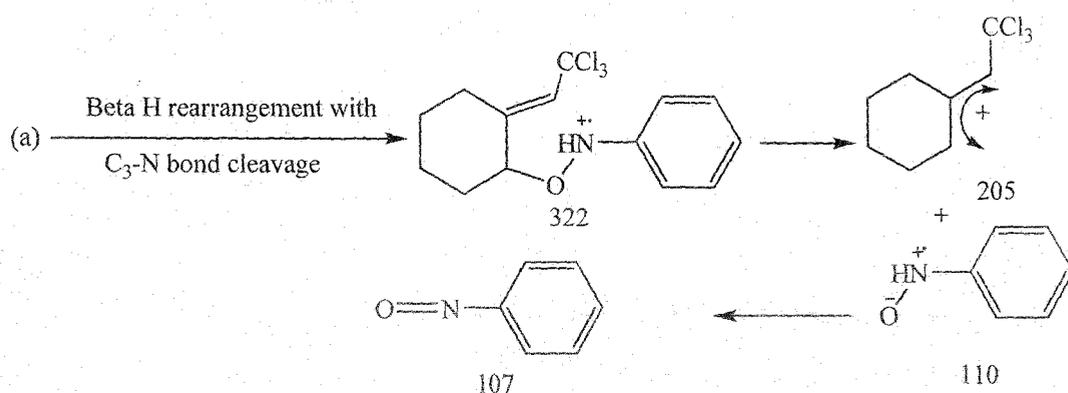
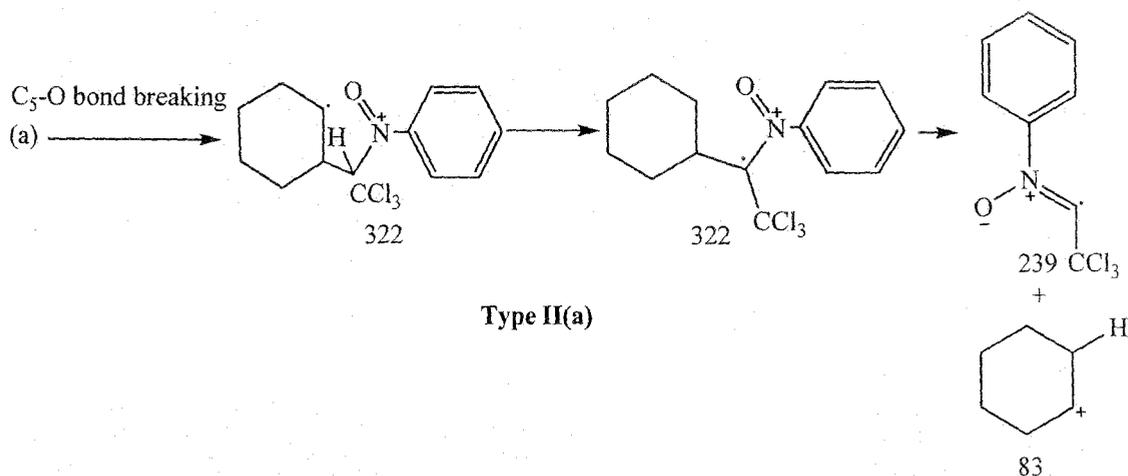


Type I (b)

(Cycloadducts formed from Chloral)

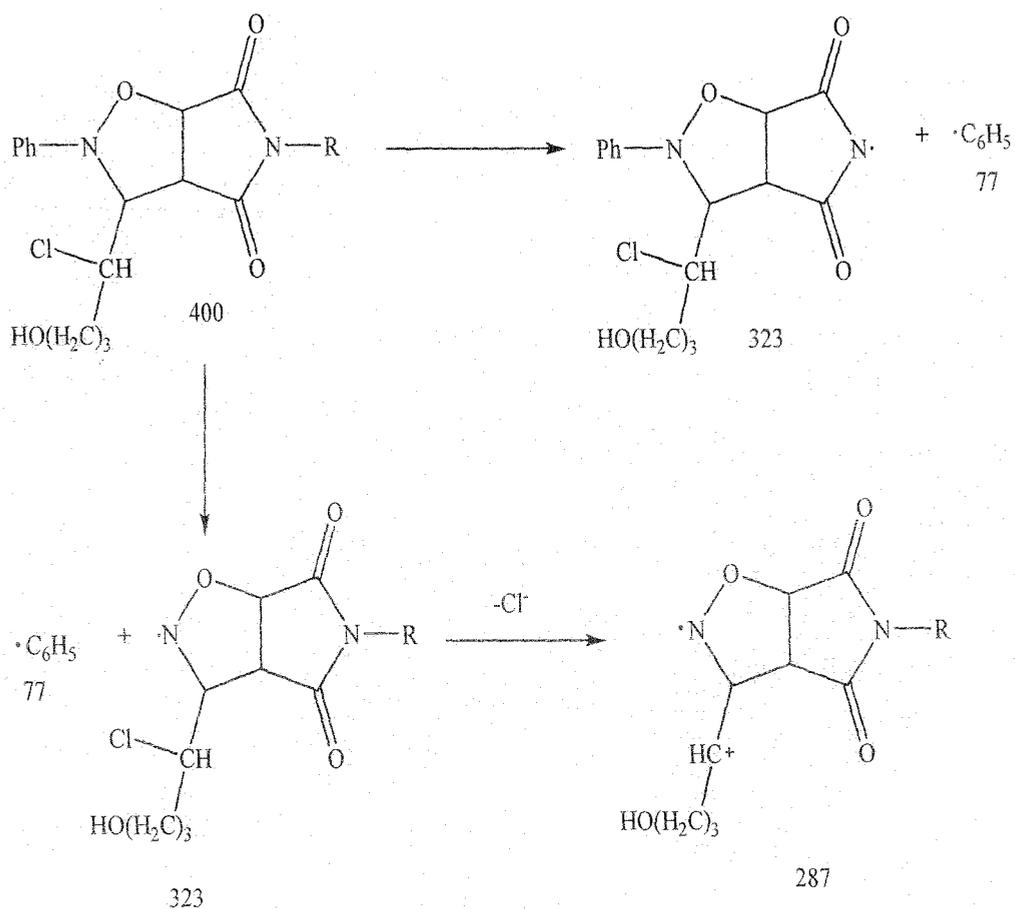


Type II



In the case of cycloadducts formed from α -chloro nitronium, the major fission pattern is molecular ion due to α -cleavage. Among the probable mode for α -cleavage i.e. $\text{C}_3\text{-C}_4$ and $\text{C}_6\text{-C}_7$, the latter cleavage was not possible because this leads to highly substituted bond cleavage. Another type of bond cleavage is $\text{C}_5\text{-O}$ 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.

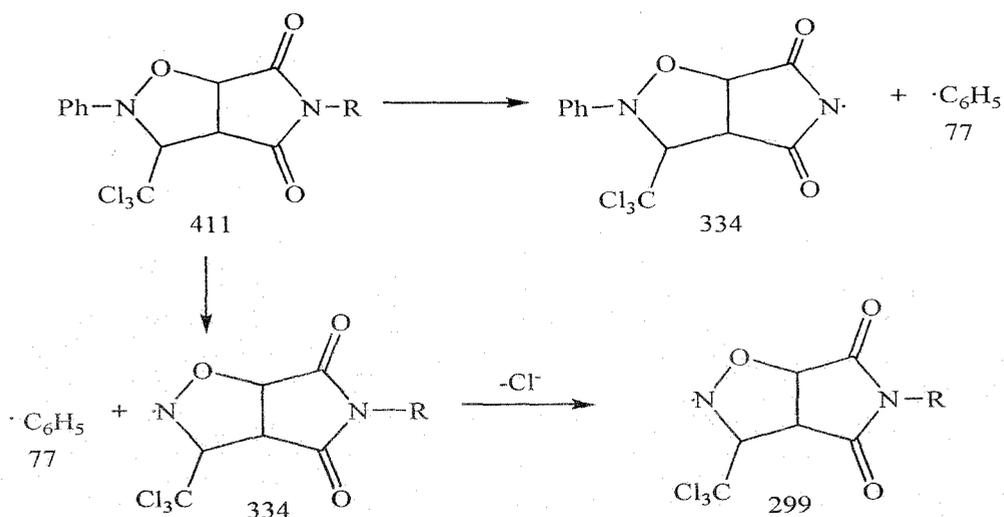
In the mass fragmentation pattern of maleimide cycloadducts (*N*-phenyl, *N*-cyclohexyl, *N*-methyl etc.), in addition to the common expected fragments other prominent peaks at *m/e* 77, 83, 15 for phenyl, cyclohexyl, methyl were also obtained (in case of both nitrene 1 & 2). Fragmentation pattern with *N*-phenyl maleimide cycloadduct may be shown as below.



Type III

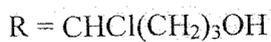
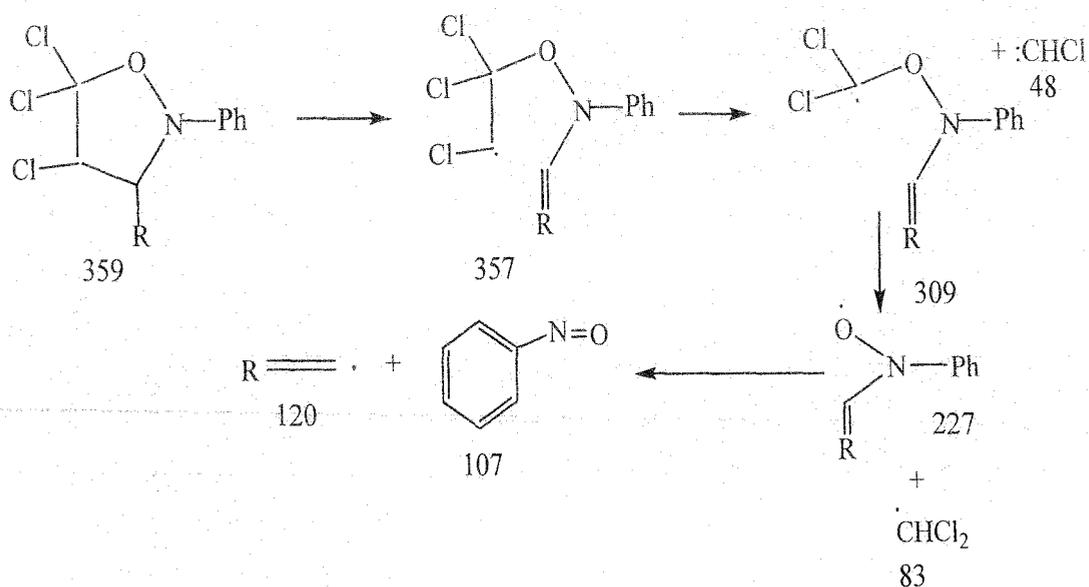
Fragmentation pattern of other maleimide cycloadducts were found to follow the same pattern as **Type III**.

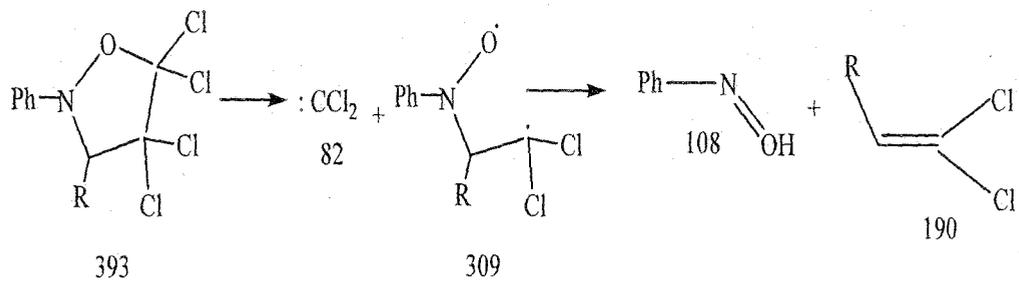
Mass fragmentation pattern of *N*-phenyl, *N*-methyl maleimide cycloadducts (developed from chloral) may be shown in the following way taking *N*-phenyl maleimide cycloadduct as example.



Type IV

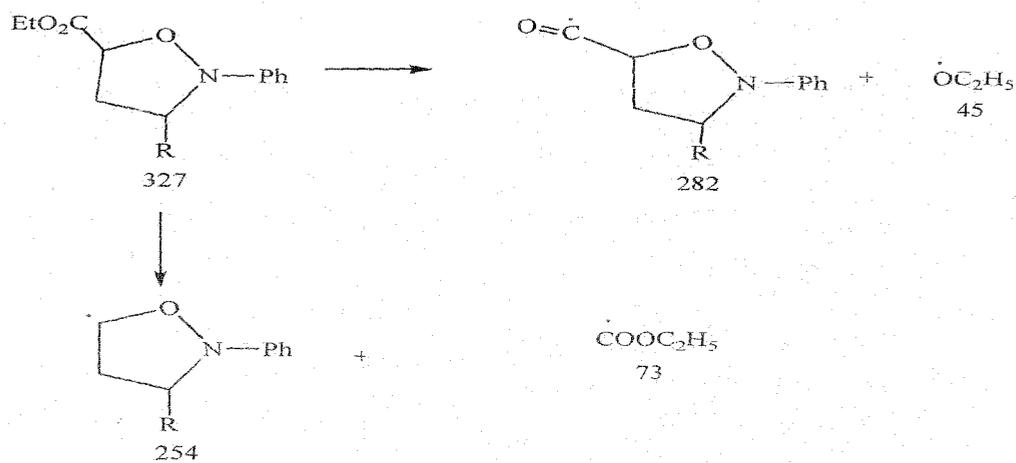
In case of trichloro and tetrachloro ethylene cycloadducts, the mass fragmentation patterns are shown as follows:





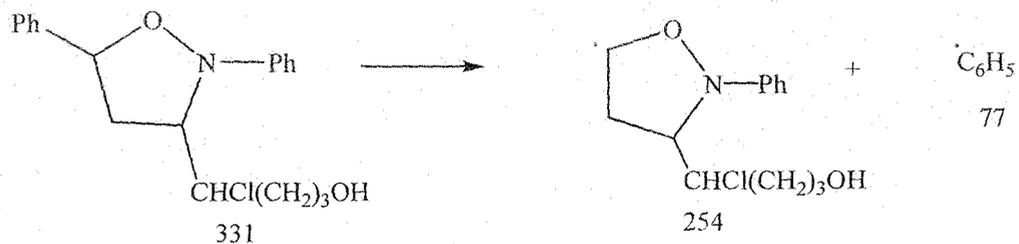
Type V

The fragmentation pattern of ethyl acrylate adduct followed the general pattern with some typical peaks of $\text{C}_2\text{H}_5\text{O}$ (45), $\text{CH}_3\text{CH}_2\text{COO}$ (73).

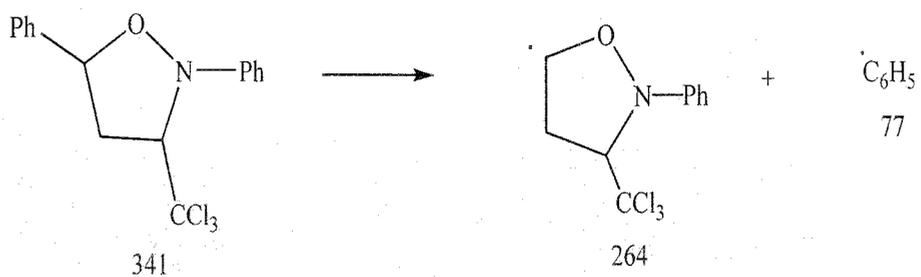


Type VI

Mass fragmentation pattern of styrene cycloadduct may be represented as follows:

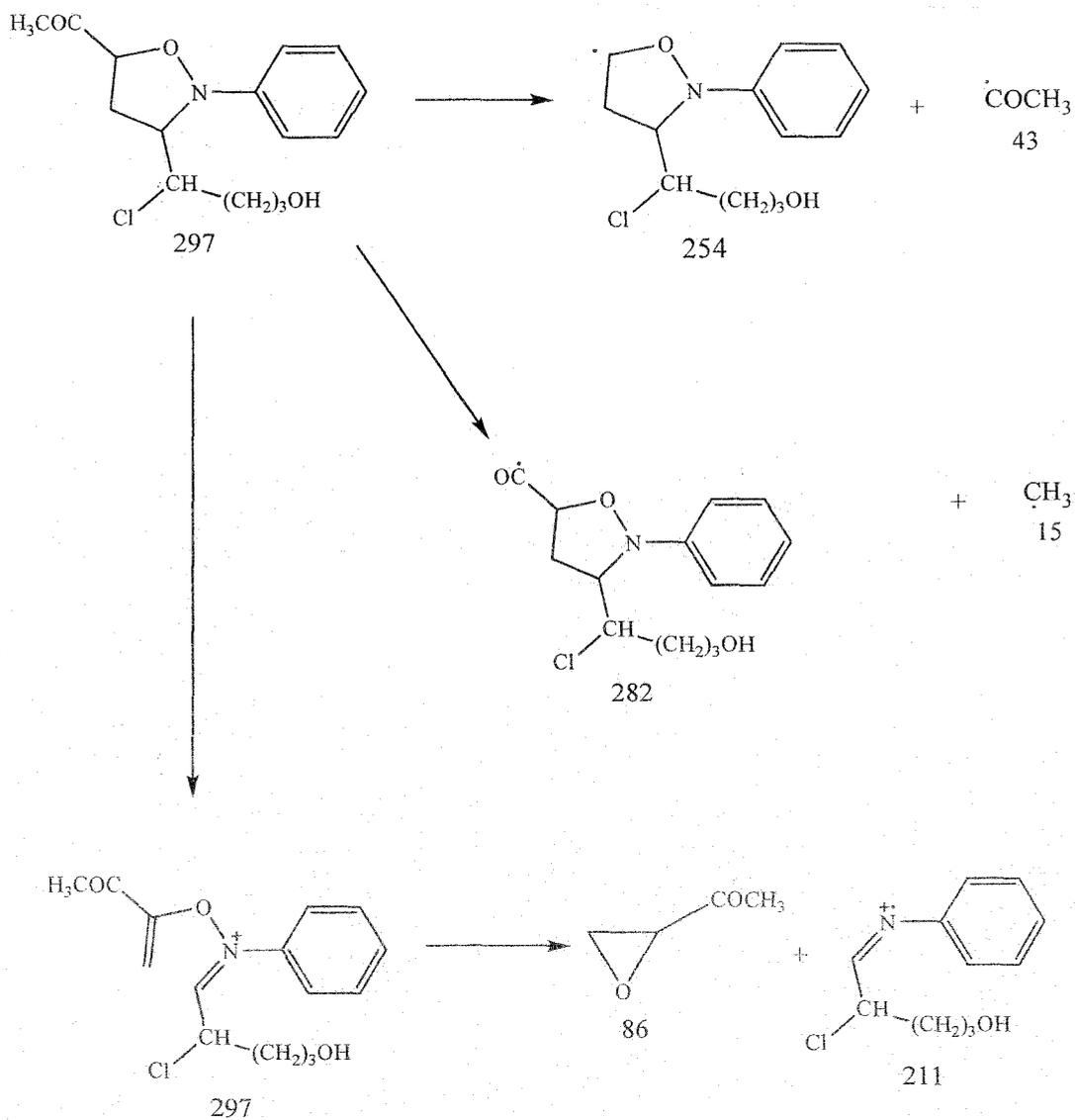


Type VII



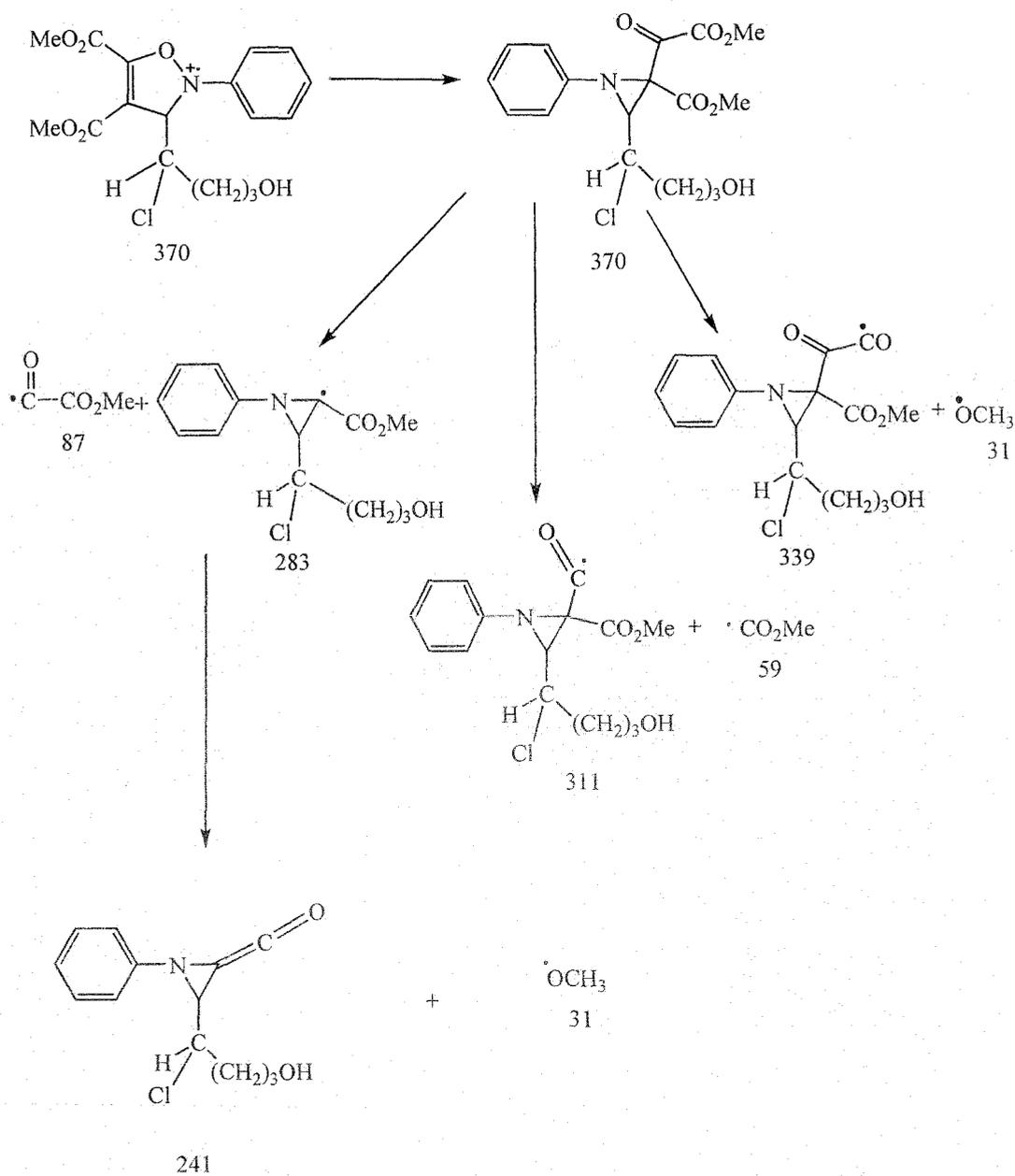
Type VIII

The fragmentation pattern of methyl vinyl ketone shows some special peaks in addition to general pattern.

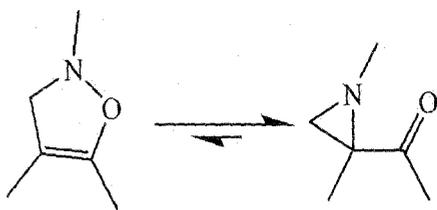


Type IX

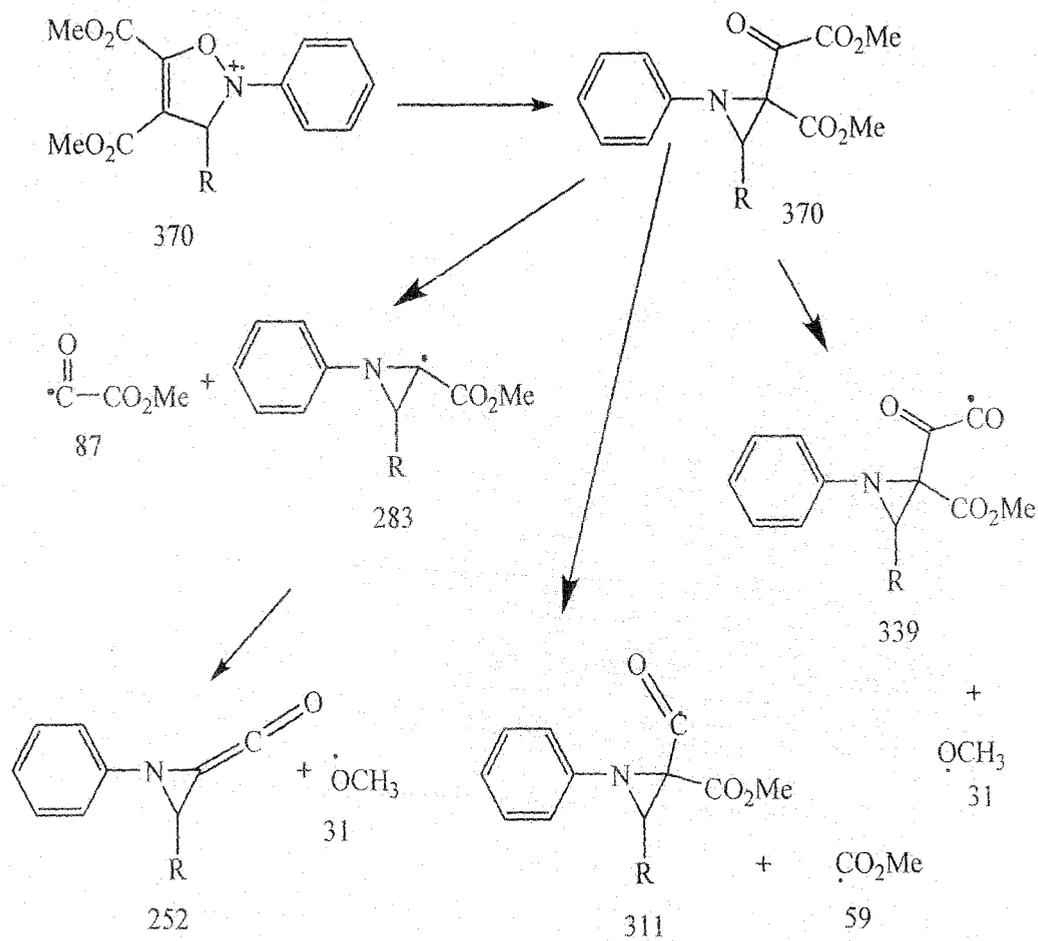
The fragmentation pattern of acetylene cycloadducts are completely different and are explained as follows:



Type X



Example with $\text{H}_3\text{COOC}-\text{C}\equiv\text{C}-\text{COOCH}_3$ adduct



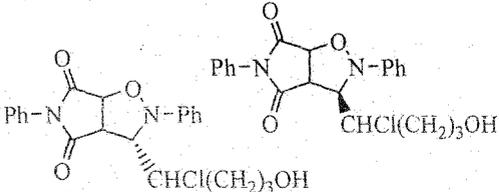
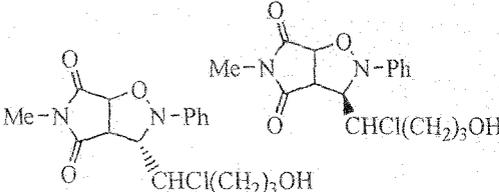
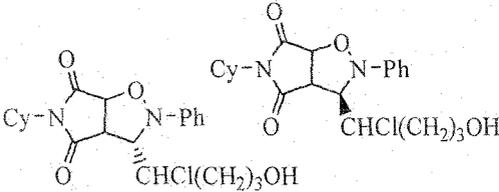
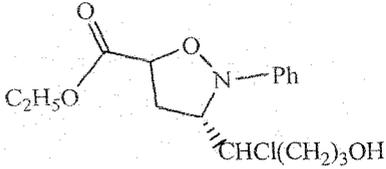
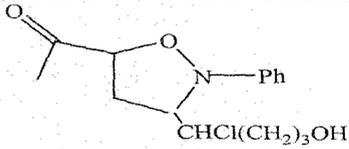
$\text{R} = \text{CHCl}(\text{CH}_2)_3\text{OH}$

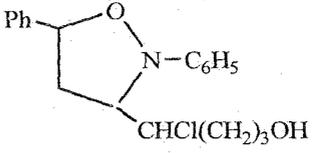
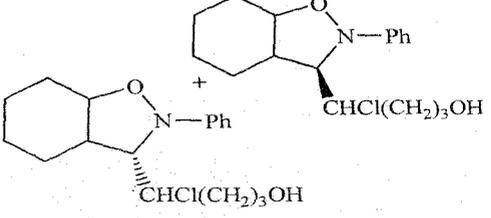
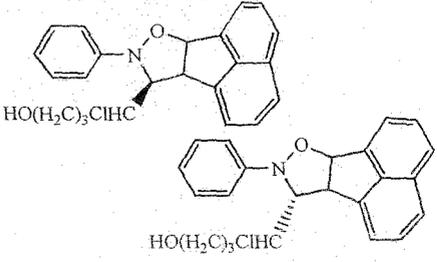
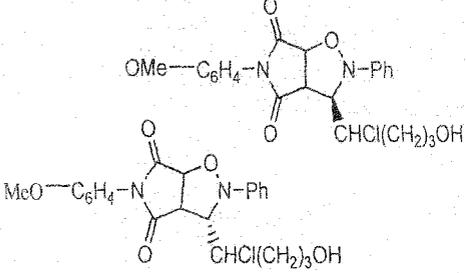
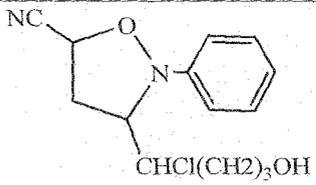
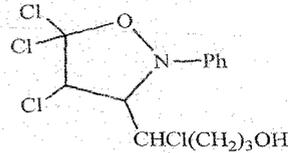
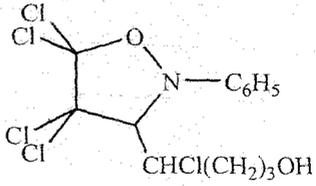
Type XI

V. Interpretation of ^1H NMR spectra

On interpretation of ^1H NMR spectra of the cycloadducts, the chemical shift and the coupling constant value determines the stereochemistry of the cycloadducts. In most of the cases, C_5 , C_4 , C_3 was asymmetric. In case of mixture of distereoisomers, the products were identified considering the multiplicity of proton signals at 3-H and 4-H along with coupling constant values. During the course of study of J values in case of the cycloadducts, the following representation gives us an idea regarding the stereochemistry of the cycloadducts. (^1H NMR values in δ ppm)

Table 6: Dihydropyran cycloadducts with C_5 and C_4 coupling constant (J values)

Cycloadducts	C_5 H (coupling constant values in parentheses)	C_4 H (coupling constant values in parentheses)
	4.39 (8.24) 5.74 (3.90)	2.89 (9.22,6.08) 3.62 (3.20, 4.80)
	5.22 (6.8) 5.26 (4.12)	3.76 (8.06,9.20) 3.60 (2.52,2.46)
	5.26 (7.22) 5.12 (8.20)	4.14 (3.22,2.08) 4.22 (2.42,2.60)
	4.11 (8.2)	3.51 (9.24,8.18)
	5.32 (7.82)	4.28 (9.48,7.10)

	5.28 (7.26)	4.24 (8.40,610)
	5.37 (8.20) 5.33 (5.42)	4.12 (9.40,7.10) 4.24 (2.60,2.55)
	5.26 (6.50) 5.30 (7.16)	3.51 (9.40,7.10) 4.28 (4.12, 3.10)
	5.28 (6.88) 5.20 (6.24)	3.86 (9.24,7.00) 3.93 (3.32,4.00)
	3.66 (8.45)	2.67 (9.30,7.50)
	-----	3.93 (8.60)
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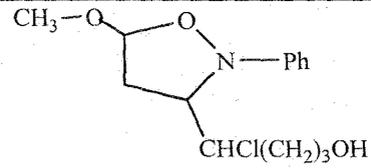
	5.18 (6.70)	3.90 (8.33,6.00)
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Table 7: Dihydrofuran cycloadducts with C_5 and C_4 coupling constant (J) values.

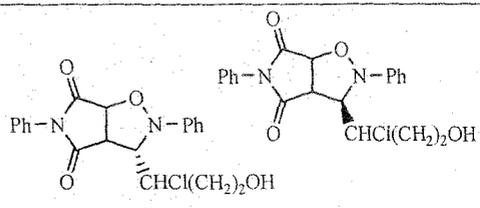
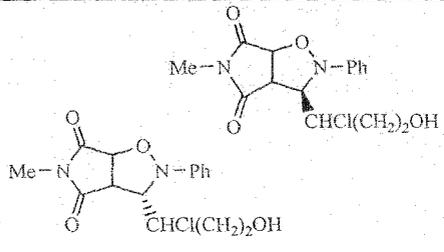
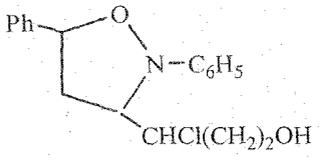
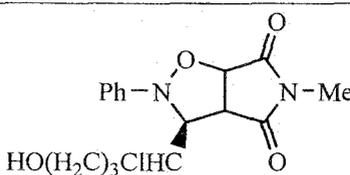
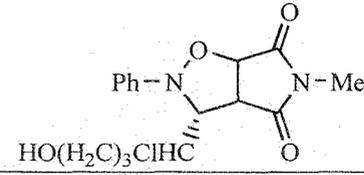
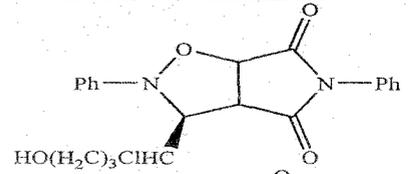
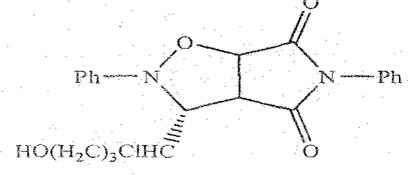
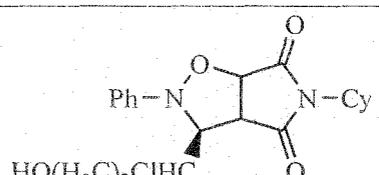
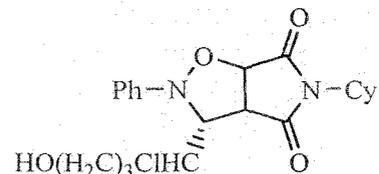
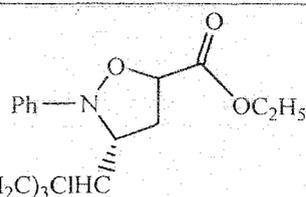
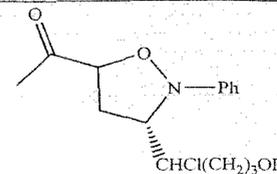
Cycloadducts	C_5 H (coupling constant values in parentheses are in Hz)	C_4 H (coupling constant values in parentheses are in Hz)
	5.35 (8.24) 5.26 (7.50)	3.70 (9.08,7.20) 3.64 (2.72,3.62)
	5.08 (8.74) 5.16 (8.12)	3.66 (8.80, 6.30) 3.63 (3.68,3.46)
	5.24 (7.60)	4.14 (9.20, 7.16)

Table 8: Dihydropyran cycloadducts with C_5 and C_4 coupling constant (J) values in aqueous phase.

Cycloadducts	C ₅ H (coupling constant values in parentheses are in Hz)	C ₄ H (coupling constant values in parentheses are in Hz)
	5.22 (6.8)	3.76 (8.06, 9.20)
	5.26 (6.0)	3.60 (2.52, 4.26)
	5.42 (8.24)	3.76 (9.22, 6.08)
	3.76 (9.22, 6.08)	3.52 (4.42, 2.08)
	5.32 (6.12)	4.26 (9.24, 7.06)
	5.26 (7.22)	4.14 (3.22, 2.08)
	4.84 (8.2)	3.88 (9.24, 8.18)
	5.32 (7.82)	4.28 (9.48, 7.10)

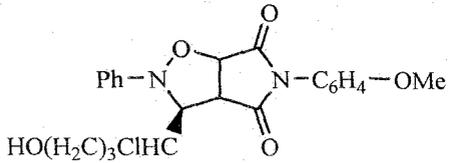
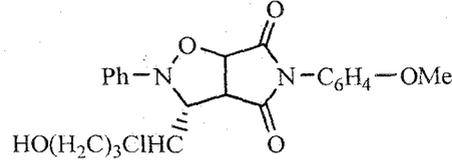
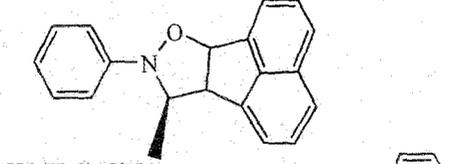
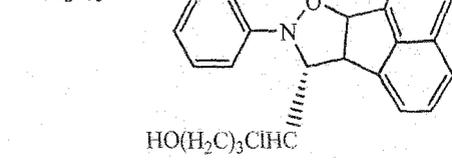
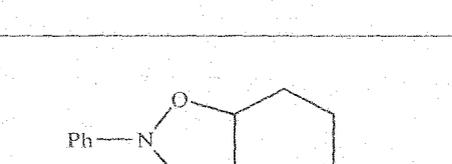
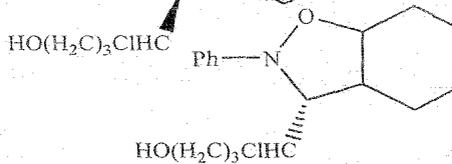
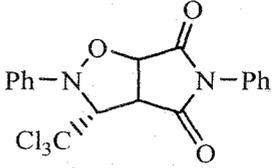
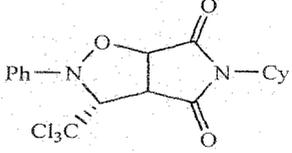
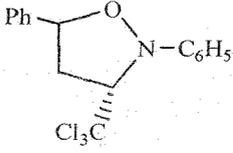
 <p>Ph-N-O HO(H₂C)₃CIHC N-C₆H₄-OMe</p>	5.28 (6.88)	3.86 (9.24, 7.08)
 <p>Ph-N-O HO(H₂C)₃CIHC N-C₆H₄-OMe</p>	5.23 (7.40)	3.54 (2.84, 3.25)
 <p>Ph-N-O HO(H₂C)₃CIHC</p>	5.26 (6.50)	4.12 (9.40, 7.10)
 <p>Ph-N-O HO(H₂C)₃CIHC</p>	5.30 (7.16)	4.28 (4.12, 3.10)
 <p>Ph-N-O HO(H₂C)₃CIHC</p>	5.37 (8.20)	4.12 (9.40, 7.10)
 <p>Ph-N-O HO(H₂C)₃CIHC Ph-N-O HO(H₂C)₃CIHC</p>	5.30 (8.20)	4.20 (2.54, 3.16)

Table 9: Cycloadducts from chloral with C_5 and C_4 coupling constant (J) values

Cycloadducts	C ₅ H (coupling constant values in parentheses are in Hz)	C ₄ H (coupling constant values in parentheses are in Hz)
	5.12 (6.90)	3.54 (7.22, 6.80)
	5.02 (8.30)	3.52 (6.08, 8.10)
	4.94 (7.50)	4.24 (6.68, 6.10)

Like nitrone 1, nitrone 2 and 3 also exists exclusively in *Z* configuration and *syn* cycloadducts are formed from *Z* nitrone through *exo* transition state geometry. Stereochemical aspects related to C₅, C₄ & C₃ protons of the cycloadducts developed from nitrone 2 & 3 are almost exactly same to that of nitrone 1 that has already been discussed. The relative configurations of C₃, C₄, C₅ protons of the cycloadducts are *syn*, as evidenced by their coupling constant ($J \sim 6.06 - 8.18\text{Hz}$, for C₄-C₅ & $J \sim 6.02 - 7.50\text{ Hz}$, for C₃-C₄) values²⁴.

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. 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(CH₂)₃OH or CHCl(CH₂)₂OH or CCl₃ group will also be at equatorial position at C-3 (**Fig 9**).

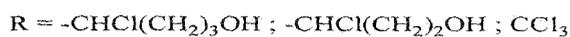
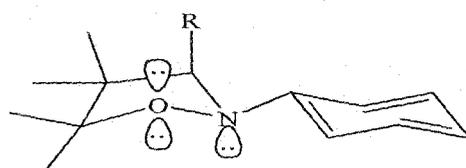


Fig 9

We have constructed the $\text{C}_5\text{-C}_4$ configurations with the corresponding dihedral angles (Fig 10)

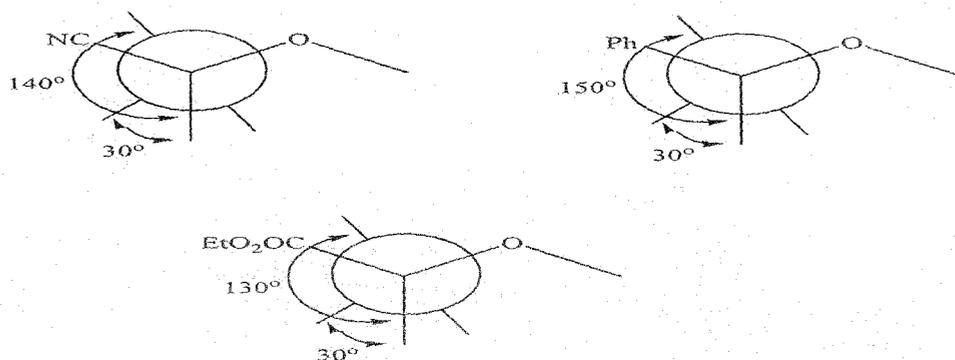


Fig 10

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-10). 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 $70\text{-}60^\circ$ 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 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 were obtained (in case of ethyl acrylate, styrene, methyl acrylate, acrylonitrile etc) due to further coupling from vicinal protons and hence confirms in favour of 5-substituted adducts. In case of the triple bonded dipolarophiles (acetylene compounds) the explanation is quite simpler since C_4

protons and C₅ protons are absent hence C₃ protons plays an important role. The stereochemistry of these cycloadducts is rationalized considering the proton signals at C₃ and CHCl protons.

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. All significant peaks in the case of methyl, ethyl acrylate are 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 signals.

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

VI. Interpretation of ¹³C NMR Spectra

On exhaustive study regarding ¹³C NMR spectra of reported cycloadducts, we have seen that 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. Although ¹³C NMR spectra cannot confirm the stereochemistry of the cycloadducts but it plays an important role in identifying the particular functional groups present in the cycloadducts.

VII. Interpretation of other spectra

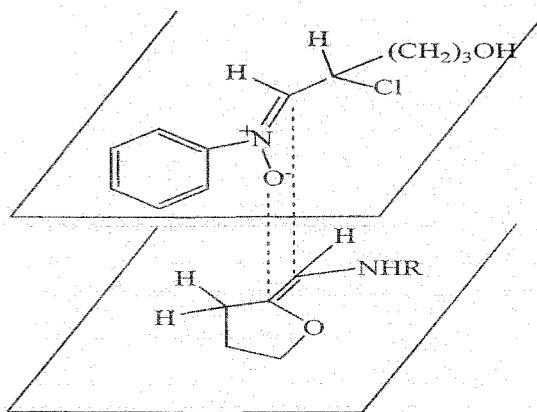
In addition to ^1H NMR and ^{13}C NMR spectrum IR, MS, HRMS and elemental analysis were most important tools for the confirmation of the cycloadducts reported in this dissertation. In the IR spectrum, absorption band at 1610 cm^{-1} and 1185 cm^{-1} represents $\text{C}=\text{N}^+$ and $\text{N}-\text{O}$ groups. Broad absorption peak at $3600\text{-}3350\text{ cm}^{-1}$ represents the absorption of hydroxyl group. Sharp singlet absorption around $750\text{-}780\text{ cm}^{-1}$ is due to phenyl $\text{C}-\text{H}$ stretching absorption. The carbonyl group absorption was obtained around $1680\text{-}1720\text{ cm}^{-1}$ depending upon the carbon functionality while $\text{C}-\text{N}-\text{H}$ stretching was generally obtained around $1240\text{-}1320\text{ cm}^{-1}$. In case of isoxazoline cycloadducts which are more 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 for α -chloro nitron. 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 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 $\text{M}^+ + 2$ ion peaks. This is due to the fact that isotopic abundance of Cl^{37} atoms are 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 for a longer period (nearly one month) and this phenomenon has been confirmed on the basis of ^1H NMR and reminds us about the brilliant work of Sk.Ali and his group²⁹. 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 nitron 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 yield³⁰. Reaction of nitrone **1** (R=Ph) with newly reported α -*N*-methyl/phenyl furan derivatives as dipolarophile are found to be highly regioselective to form solely 5-spiro isoxazolidine derivatives. 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 isoxazolidines²⁵ via an *exo* approach of nitrone **1** (in *Z* configuration) to the furan derivatives (transition state **I**). The relative configurations of H₃ & H₄ protons in the *spiro* adduct favours *exo* transition state geometry. The H₃ & H₄ protons are *syn* in these cycloadducts and their coupling constants ($J_{H_3, H_4} = 6 - 8.4$ Hzs) are also indicative of this stereochemical relationship²⁴. 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 ($J_{3, CHCl} \sim 9.40$ Hz)²⁴.



T.S.I

Similarly, the novel dipolarophiles (α -*N*-methyl/phenyl furan derivatives) were also employed for the synthesis of novel *spiro* cycloadducts with α -amino nitrones & 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*).

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