CHAPTER V

Scope and objectives

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

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

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

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

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

ii) The nitrones are having tremendous synthetic potentiality.

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

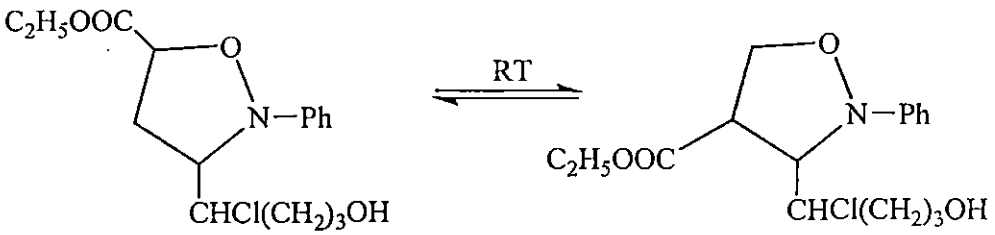
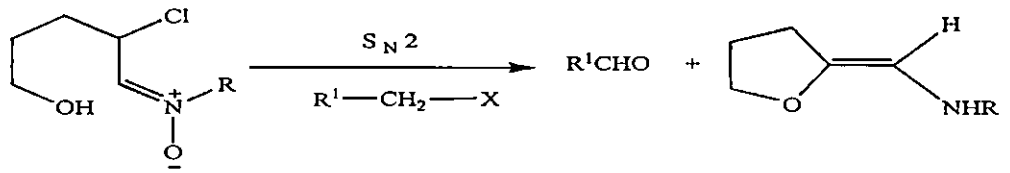


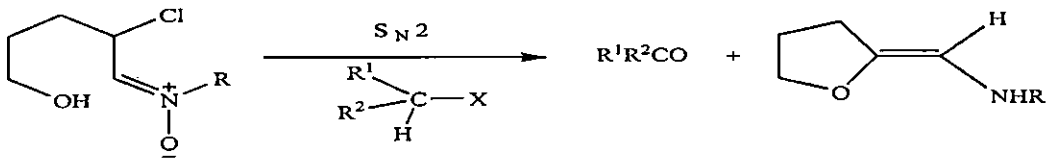
Fig. 1

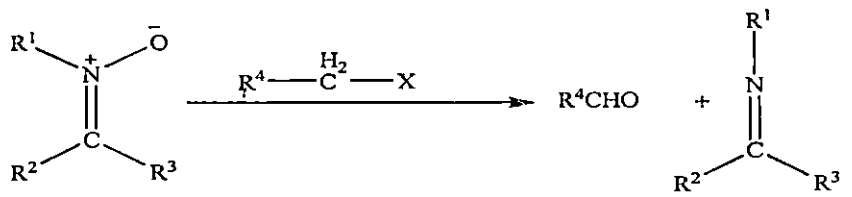
Excellent diastereofacial selectivity has been observed in nitrone additions to dipolarophiles when water, is used as a solvent. In case of maleimides and cyclohexenes mixture of diastereoisomers in the ratio of 2:1 are reported with asymmetric induction at *C*-3, *C*-4, *C*-5 position in a single step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

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



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

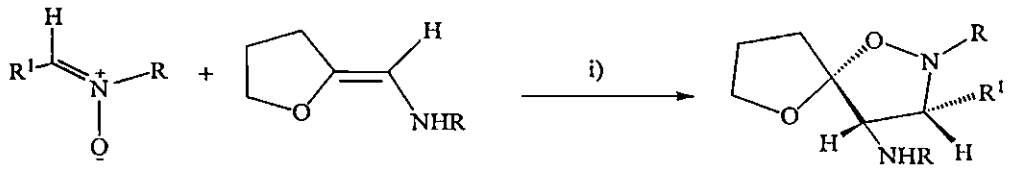




R^1 = Ph, Cy; R^2 = NMe_2; R^3 = H and R^1 = Ph,Cy; R^2 = NH_2; R^3 = H

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

Scheme 1



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

Scheme 2

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

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

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

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

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

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

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