CHAPTER IV

Scope & objectives (Future perspectives of the present work)

Cycloaddition reactions (mainly 1,3-dipolar cycloaddition reactions) have made organic synthesis much more attractive than any other reactions. These reactions are regarded as feathers in modern organic synthesis due to its wide range of applicability[1,2]. The five membered oxygen-nitrogen heterocycles developed via these reactions are not only have excellent synthetic potentials due to their further convertions into new molecules (e.g, β-amino alcohols & ketons)[3] but also capable of exhibiting marvelous broad spectrum biological (anticancer, antimicrobial, anticonvulsant & antitubercular) activities[4,5]. We have come across with these activities & properties of isoxazolidine and isoxazoline derivatives from the research articles contributed by brilliant researchers in this field. Some of them are: Padwa A & his coworkers[1], Kobayashi S & coworkers[2], Huisgen R & coworkers[3], Opplozer W & coworkers[6], Tufariello J J & coworkers[7], Grigg R & coworkers[8], Deshong P & coworkers[9], Ali S & coworkers[10], Fisera L & coworkers[11] and Aggarwal V & coworkers[12]. Our country also was not far behind from these eminent scientists for their contribution in this field as well[13-16].

Selectivity has been always a focus or point of attraction in cycloaddition reactions. The identification & implementation of regioselective cycloaddition reactions was made possible due the great efforts rendered by K.N Houk & his group workers[17]. The chemistry of fluoro[18] & chloro nitrone[19] and their 1,3-dipolar cycloaddition reactions generating fluoro & chloro cycloadducts with high synthetic potential also enlighted us to focus our aim in this synthesis. Using the electron withdrawing effects of chlorine how a nitrone can be made highly reactive at room temperature was first shown by Eschenmoser A & coworkers[19] by introducing α-chloro nitrone. Introduction of intramolecular cycloaddition reaction was also a big success in this chemistry and this concept was first reported by two eminent researchers in this chemistry Albert Padwa[1] & Wolfgang Oppolzer & their coworkers[6] Using the versatile synthetic potentials of chloro nitrone & fluoro nitrone a variety of biologically active molecules (fluoro & chloro isoxazolidine, isoxazoline derivatives) have been synthesized & reported[1].

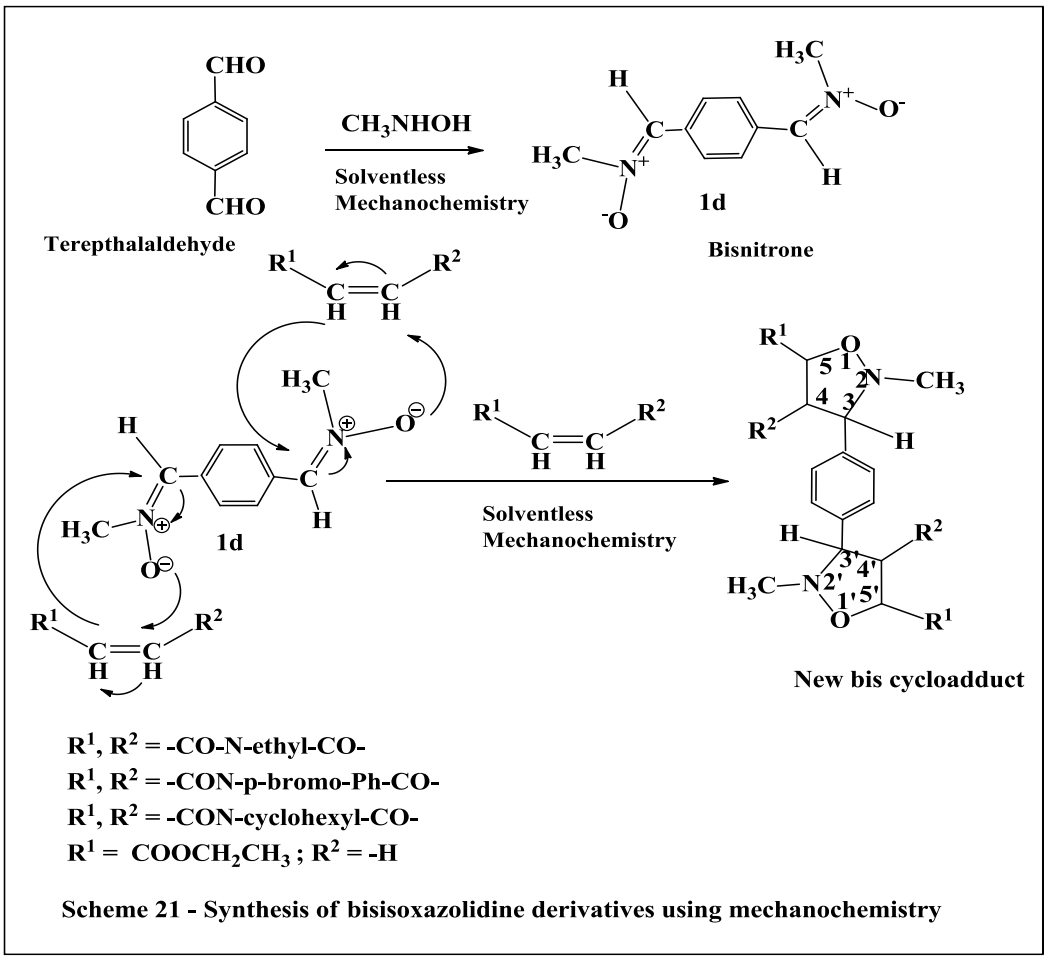
The nitrone chemistry became highly enriched in the year 2000 when Heaney F & her coworkers first reported the synthesis of stable bis-nitrone (a dinitrone) from terepthalaldehyde. They also successfully performed simultenous double 1,3-dipolar cycloaddition reactions with active olefins for the first time in this chemistry[20]. This challenging cycloaddition reaction has been further developed and repoted with more applications later by various eminent researchers[21-23].

Baldwin & his coworkers created a new dimention in nitrone-cycloaddition reactions when they were able to convert isoxazoline derivatives to synthetically more important aziridine derivatives by either mild heating or by keeping at room temperature for a period[24-26]. Therefore, it is evident that the scope of nitrone-cycloaddition chemistry is open & abundant.

In this dissertation, we have contributed some new features in this chemistry which includes synthesis & cycloaddition reactions of new *N-methyl-C-furfural nitrone(**1a**)* and *N-phenyl-4-hydroxy nitrone (**1b**)* using mechanochemistry (ball-milling) and microwave technology. We have also reported further applications of cycloadducts & nitrones in various important reactions viz, S*onogashira reaction, aziridine synthesis & synthesis of spiro-cycloadducts.* All the reported reactions do possess vast synthetic potentials and many more this kind of reactions may be performed,. Hence these procedures may enlighten future researchers in this chemistry.

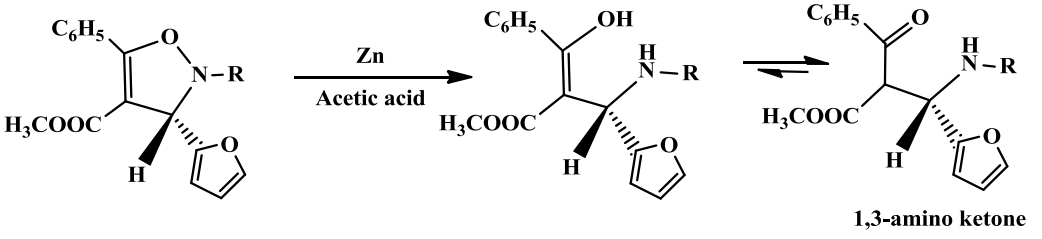
Future course of action & applications

1. Synthesis & cycloaddition reactions of bis-nitrones is attractive & challenging too. We have a plan to explore the new methodologies of synthesis & cycloaddition reactions of bis-nitrone using mechanochemistry (**Scheme21**).



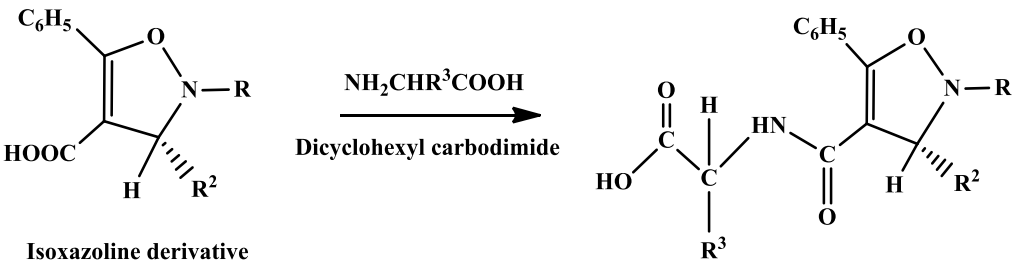
Scheme 21 - Synthesis of bisisoxazolidine derivatives using mechanochemistry

2. We have a plan to synthesize a variety of 1,3-amino ketones using newly synthesized furfuryl derived isoxazoline derivatives. Moreover, we shall also apply green chemistry methodology in this technique. Synthesis of this kind of amino ketones are going on at present (**Scheme 22**).



R = CH_3; C_6H_5; $C_6H_5CH_2$ **Scheme 22 - Synthesis of 1,3 amino ketones from isoxazoline derivatives**

3. Synthesis of peptide derivatives from isoxazoline derivatives is a new concept as far as the application in this chemistry is concerned. We have already undertaken this initiative and reported few synthesis in this regard[27]. Now we are in a process of synthesizing a variety of new peptide derivatives employing *N-methyl-C-furfuryl nitrone & N-phemyl-4-hydroxy nitrone* derived isoxazoline derivatives respectively (**Scheme 23**).



Isoxazoline derivative

R = CH_3; C_6H_5; $C_6H_5CH_2$ **R^2 =furfuryl ; -$(CH_2)_3$-OH** **New peptide derivative**

Scheme 23 - Synthesis of new peptides using furfuryl & furan derived isoxazoline derivatives

Application of *green chemistry methodologies (mechanochemistry, viz ball-milling technique, microwave induced reactions as well as atom efficient reactions)* are the attractive features in this dissertation. The other areas of interest of this dissertation are *Sonogashira reaction* and synthesis of *aziridine derivatives.*

Utilizing oxidizing propeties of nitrones, synthesis of aldehyde & ketones is also a new concept reported in this dissertation. The synthesis is purly an atom efficient reaction (one of the best examples of green chemistry methodology) because one can use the side-products of this reaction (imine derivatives) as efficient dipolarophiles in 1,3-dipolar cycloaddition reactions.

The highlighted features of this dissertation are:

- *Green synthesis of some new class of furfural derived isoxazolidine and isoxazoline derivatives via 1,3-dipolar cycloaddition reactions of N-methyl-C-furfural nitrone in water & on water*
- *Green synthesis of some new class of isoxazolidine derivatives synthesized from N-phenyl-4-hydroxy nitrone via 1,3-dipolar cycloaddition reactions using microwave technology*
- *Green synthesis of cross-coupling products using furfural derived isoxazolidine and isoxazoline derivatives with phenyl acetylene in ball-milling technique (Sonogashira reaction)*
- *Few special reactions leading to the synthesis of aziridine derivatives & spiro cycloadducts*
- *Synthesis of aldehydes and ketones using N-methyl-C-furfural nitrone as potential oxidizing reagent*
- *Successful re-employment of the side products (obtained during aldehyde and ketone synthesis-imines) in the synthesis of primary amines.*
- *Future scopes for the synthesis of variety 1,3- amino ketones from new isoxazolidine derivatives by the cleavage of N-O bond.*

Future course of action on "anticancer activity" of new furfural derived cycloadducts (isoxazolidine and isoxazoline derivatives)

From the preliminary studies, we have found that newly synthesized *N-methyl-C-furfuryl nitrone derived* isoxazolidine and isoxazoline derivatives have shown potential *"anticancer activities"*[28]. We have started detailed study in this most demanding area of research with many more new molecules synthesized recently in collaboration with Department of Pharmaceutical technology, Jadavpur University, Kolkata. We are sure that in due course of time we will be able to establish "*Broad spectrum*" anticancer activities of our new molecules.

Introduction of chirality and thereby developing selectivity (diastereoselectivity & regioselectivity) is always the point of interest and attraction in nitrone-cycloaddition reactions. We have also reported the synthesis of new isoxazolidine derivatives via 1,3-dipolar cycloaddition reaction in this dissertation with introduction of three (3) asymmetric centres at C-3, C-4, C-5 carbon atoms. We have also observed that diastereoselectivity in cycloaddition reactions depends on solely the chirality of C-3 & C-4 carbon atoms.

Studies on inclusion complexation using β-cyclodextrin & many more isoxazolidine and isoxazoline derivatives are going on at present and we believe more important informations in this new chemistry will be explored in near future. Also more evidences in favour of the morphological structures of inclusion complexes will be confirmed in near future using 2D-ROESY NMR spectroscopy.

References

1. Padwa A and Pearson W H, *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Wiley: New Jersy), **2003**, 169-225**.**
2. Kobayashi , S and Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis;* Wiley- VCH:Weimheim, **2002** and references cited therin.
3. Huisgen R, *J Org Chem*, **1976**, *41,* 403 and references cited therein.
4. Martin J N and Jones R C F in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, (Eds.: A. Padwa, W. H. Pearson),Wiley, Hoboken, NJ, **2003**, pp. 1 – 80 and references cited therein.
5. Karlsson S and Hkgberg H E, *Org. Prep. Proc. Int.,* **2001**, *33*, 103 – 172.
6. a) Oppolzer W and Petrzilka M, *J Am Chem Soc,* **1978**, *61,* 2755; b) Oppolzer W and Petrzilka M, *J Am Chem Soc*, **1976**, *98,* 6722; c) Oppolzer W and Grayson J I, *J Am Chem Soc*, **1983**, *98,* 3695 and references cited therein.
7. Tufariello J J, *1,3-Dipolar Cycloaddition Chemistry*; Padwa A., Ed (Wiley-Interscience: New York, NY), **1984**; *Vol. 2*, Chapter 9, pp 83–160.
8. a) Grigg R, Heaney F and Surendrakumar S, *Tetrahedron*, **1991**, *47,* 4477; b) Grigg R, Heaney F, Surendrakumar S, and Armstrong P, *Tetrahedron*, **1991**, *47,* 4495; c) Grigg R and Allway P, *Tet Lett*, **1991**, *47,* 4495 and references cited therein
9. Deshong P, Li W, Kennington J W and Ammon H L, *J Org Chem,* **1991**, *56,* 1364.
10. a) Ali S K and Iman M Z N, *Tetrahedron*, **2007**, *63,* 9134. b) Ali S K & Wazeer M. I. M., *J Chem Soc, Perkin Trans I*, **1988,** 597 and references cited therein.
11. Hyrosova E, Fisera L, Kozisek J and Fronc M, *Synthesis*, **2008**, *8,* 1233.
12. Agarwal V K, Grainger R S, Adams H and Spargo P L, *J Org Chem,* **1998**, *63,* 3481.
13. (a) Yadav J S, Reddy B V S and Baishya G, *J Org Chem*, **2003**, *68,* 7098; (b) Yadav J S, Reddy B V S, Reddy J S S and Srinivas Rao R, *Tetrahedron*, **2003**, *59*, 1599.
14. Ghorai S, Mukhopadhyay R, Kundu A P and Bhattacharjya A, *Tetrahedron*, **2005**, *61,* 2999 and references cited therein.
15. Chatterjee A, Maiti D K and Bhattacharya P K, *Org. Lett*, **2003**, *5 (21),* 3967.
16. Basak A, Ghosh S C, Bhowmick T, Das A K and Bertolasi V, *Tet Lett*, **2002**, *43,* 5499 and references cited therein.
17. Houk K N and Moses S R, *J Am Chem Soc*, **1984**, *106,* 3880 and references cited therein.

18. (a) Chambers R D, *Fluorine in Organic Chemistry*, (Blackwell Publishing: Oxford, UK), **2004**; (b) Kirsch P, *Modern Fluoroorganic Chemistry*, (Wiley-VCH:Weinheim, Germany) **2004** and references cited therein.

19 a) Heinzer F, Saukup M and Eschenmoser A, *Helv Chim Acta*, **1978**, *61*, 2850; b) Dasgupta T K, Felix D, Kempe U M and Eschenmoser A, *Helv Chim Acta*, **1972**, *55*, 2197.

20 Heaney F, Rooney O, Cunningham D and McArdle P, *J Chem Soc. Perkin Trans. 2,* **2001**, 373 and references cited therein.

21 Cinar H, Tabatabai M and Ritter H, *Polym Int,* **2012,** *61,* 693.

22 Raspertova I, Osetska O, Gubina K and Lamika R, *Polyhedron,* **2011,** *30,* 2321.

23 Oh Seon Y, Kotani S, Sugiura M and Nakajima M, *Tetrahedron:Asymmetry*, **2010**, *21*,1834 and references cited therein.

24 Baldwin J E, Pudussery R G, Qureshi A K and Sklarz B, *J Am Chem Soc*, **1968,** *90*, 5325.

25 Sweeney J B in *Science of Synthesis;* Schaumann E and Enders D; Eds (George Thieme Verlag; Stuttgart, Germany), **2008**, vol *40a*, p 644.

26 Yudin A K, Ed. *Aziridines and Epoxides in Organic Synthesis* (Wiley-VCH, Weinheim), **2006** and references cited therin.

27 Chakraborty B, Samanta A, Luitel G P, Rai N and Mitra D, *J Heterocyclic Chem(Wiley),* **2016**, *53*, 1222 and references cited therein.

28 Chakraborty B and Chettri E, *J Heterocyclic Chem (Wiley)*, **2020,** *57*, 477.

29 Chakraborty B, Chettri M and Samanta A, *CSIR-Indian J Chem*, **2010,** *49B*, 209.

30 Chakrabarty A N, Molnar J, Dastidar S G and Motohashi N, *Non Antibiotics*: *A New Class of Unrecognized Antimicrobics*, (NISCOM, India), **1998** and references cited therein.