Abstract

Introduction

"*Nitrones*" are best known as versatile synthetic intermediates and excellent spin trapping reagents. They may be prepared either by condensation of aldehyde or ketones with hydroxyl amines and also by oxidation of the corresponding *N,N*-disubstitutedhydroxylamines[1]. 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is an important widely known method for the synthesis of the isoxazolidine ring system[2]. These cycloaddition reactions are an integral and weighty part of organic chemistry in pedagogy and research as well. The wealthy literature on cycloaddition reactions of nitrone and for the syntheses of novel isoxazolidine, isoxazoline derivatives and also their further applications has been widely illustrated. The 1,3-dipolar cycloaddition reaction is capable of establishing large number of stereo-chemical centres in one synthetic step.

The present work entitled "*Synthesis, Characterization and Inclusion Complexation of some Isoxazolidine and Isoxazoline derivatives for Advanced Applications Explored by Physicochemical Approach"* reports synthesis and cycloaddition reactions of furfuryl nitrone as well as inclusion complexation followed by advanced applications. The entire work (synthesis & cycloaddition) has been conducted following green chemistry (ball-milling) methodology. Inclusion complexation studies with few molecules (synthesized cycloadducts) have been also studied successfully and has attracted a new dimension in this chemistry as well! Evidence of stereoselectivity and regioselectivity was observed in the 1,3-dipolar cycloaddition reactions of *N-substituted furfuryl nitrone and N-substituted dihydrofuran derived nitrones* with olefins and alkynes. Majority of these reactions have been carried out in solvent free ball-milling procedure. High yield and short reaction time was the major advantage in this protocol of synthesis of *cycloadducts* compared with the reactions performed in conventional solvents[2]. Few newly synthesized cycloadducts have been also successfully converted into synthetically more important cross-coupling products[4]. This may be considered as one of most important applications in this chemistry. The newly synthesized nitrones may be used as potential oxidizing reagents in the synthesis aldehyde and ketones[3]. Majority of the cycloadducts have been screened for biological activities and are found to have good to excellent potential biological activities (anticancer activities)[5].

General nature of cycloaddition reaction and review of earlier work

1,3-dipolar cycloaddition reactions of *nitrones* are both regioselective and stereoselective in nature. The configurations of C_3, C_4, C_5 (*asymmetric centres*) protons of

the isoxazolidine rings are *syn* in most of the cases because most of the nitrones exist exclusively in the *Z* configuration. Therefore, the isoxazolidines are developed from *Z* nitrone via an *exo*-transition state geometry. The stereochemistry of the isoxazoline derivatives are difficult to define due to the absence of hydrogen atoms at C_4, C_5 positions. The C-C bond of the isoxazolidine ring is developed more in the transition state then C-O bond. During 1,3-dipolar cycloaddition reactions of nitrone with an olefin, the latter approaches the nitrone exclusively from the opposite side to the C_3-substituent. This kind of approach controls stereochemistry at C_3 position.

A comprehensive review on nitrone cycloaddition reactions has been conducted as a part of our present research work in this dissertation. This review work was conducted to understand the gravity of nitrone cycloaddition reactions and their applications, importance to the synthetic organic chemistry community. The review work also helped us to define and understand the work undertaken and to be presented in this dissertation and especially how to reach the final goal.

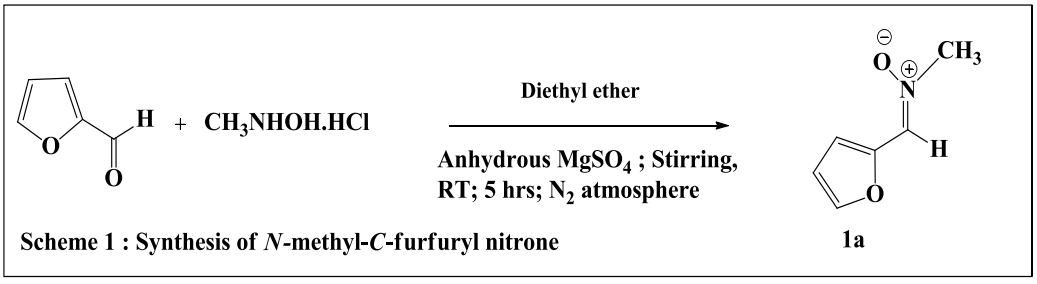
From the review work, we have found that probably *inclusion complexation* in this chemistry will find a new application. 1,3-dipolar cycloaddition reactions have been carried out mainly by trapping the nitrones with suitable dipolariphiles at the time of their generation. We may control dimerization of the nitrone in this fashion and the yield of the cycloadducts may also be extremely high.

In this dissertation, for the synthesis and 1,3-dipolar cycloaddition reaction of furfuryl nitone and their applications we have adopted in aqueous phase while for dihydrofuran derived nitrone it was microwave induced reactions as "*Green Chemistry Techniques*". In addition ball-milling techniques have been employed in other reactions.

In majority of these undertaken reactions, mild reaction conditions (short reaction times, avoiding oil bath heating etc), easy work up procedure in isolation of the compounds have made these protocols more attractive in practice.

Laboratory experimental work with results

Synthesis of N-Methyl furfuryl nitrone at room temperature

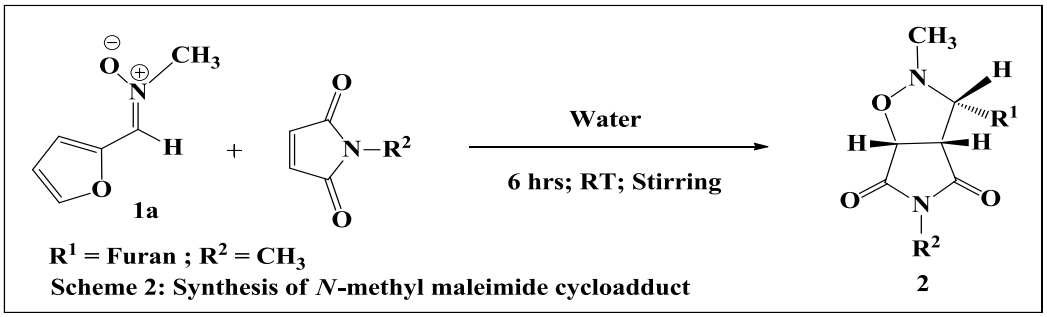


Scheme 1 : Synthesis of *N*-methyl-*C*-furfuryl nitrone

***Spectral data of N-methyl-C-furfuryl nitrone*:**

White crystalline solid (m.p 82^{0}C, uncorrected). UV λ_{max} 236 nm; IR (KBr): υ_{max} 3020 (m), 2230 (m), 1684 (m), 1620 (s), 1440 (m), 1150 (m), 786 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.87-7.25 (m, 3H, furan protons), 6.94 (s, 1H,-CH=N$^+$), 3.38 (s, 3H, CH_3); ^{13}CNMR ($CDCl_3$): δ 142.10 (CH=N$^+$), 134.80, 134.33, 134.15, 133.97 (furan carbons), 30.50 (CH_3).

General procedure for the synthesis of isoxazolidine derivatives using N-methyl-C-furfuryl nitrone



Scheme 2: Synthesis of *N*-methyl maleimide cycloadduct

In a 100mL RB flask a solution of nitrone **1a** (1 mmole), 20 mL water & dipolarophiles were added (1 equivalent) at RT under nitrogen atmosphere. The reaction mixture was stirred for 6 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the cycloadducts were extracted with ether (2x25 mL), the organic layer was washed with saturated brine (2x15 mL), dried over anhydrous Na_2SO_4 & concentrated to afford crude isoxazolidine derivative as white crystals (95%). The product was purified by column chromatography using ethyl acetate-hexane (1:6) to afford the desired cycloadduct **2**. Same methodology was adopted for the synthesis of other isoxazolidine derivatives.

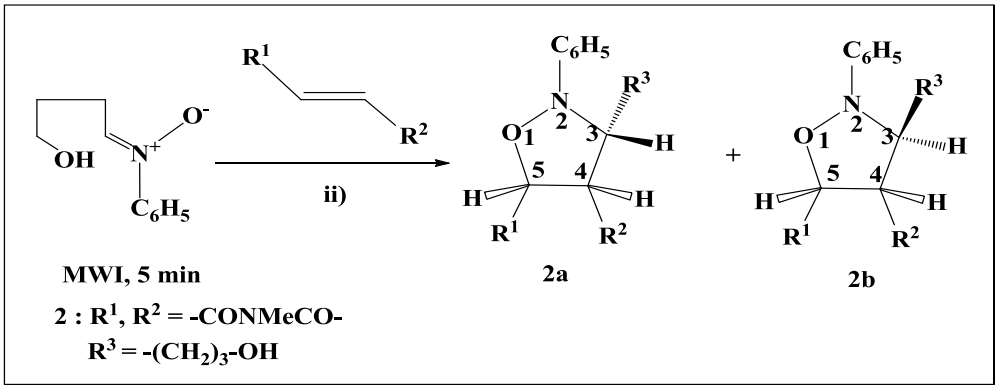
(3*S*)-2-methyl-3-furyl-dihydro-5-methyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione

White crystals. Yield 95%; R_f = 0.62; IR (KBr): υ_{max} 3030 (m), 2924 (m), 2830 (m), 1764 (s), 1680 (s), 1485 (m), 1346 (m), 805 (s), 778 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.58 – 7.24 (m, 3H, furan ring protons), 3.80 (s, 6H, 2XCH_3), 2.10 (dd, 1H, *J* = 6.06, 6.18 Hz, C_4H), 1.85 (d, 1H, *J* = 6.16 Hz, C_5H), 1.65 (d, 1H, *J* = 6.06 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 172.60, 172.42 (carbonyl carbons), 137.44, 137.34, 137.20, 137.06 (furan ring carbons), 87.46 (C_5), 76.82 (C_3), 57.62 (C_4), 30.44, 31.15 (N-CH_3 carbons); FAB-MS: *m/z* 236 (M$^+$,100%), 221, 206, 169, 168, 154 (B.P), 67; Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.10; N, 11.86%. Found: C, 55.40; H, 5.05; N,11.43.

Synthesis of isoxazolidine derivatives from dihydrofuran using microwave irradiation

A mixture of *N*-phenylhydroxylamine (250 mg, 2.29 mmole), 2,3-dihydrofuran (160 mg, 1 equivalent) was taken in a 25 mL Erlenmeyer flask and a paste was made. The reaction mixture was irradiated for 5 minutes at 30^{0}C.

The formation of nitrone was monitored by TLC (R_f = 0.42). *N*-methyl maleimide (254mg, 1 equivalent) was added *in situ* at this stage and the reaction mixture was further irradiated for 5 minutes at 30^0C. The completion of the reaction was monitored by TLC (R_f = 0.64, 70). The reaction mixture was cooled to RT and extracted with diethyl ether. The products were concentrated in a rotary evaporator and finally the mixture of diastereomers were purified and separated by column chromatography using ethyl acetate-hexane to afford pure isoxazolidine derivatives **2a** and **2b**. This general procedure was followed for the synthesis of other cycloadducts.



(*3R*,3a*S*,6a*R*)–dihydro-3-(3-hydroxypropyl)-5-methyl-2-phenyl-2*H*-furrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 2a

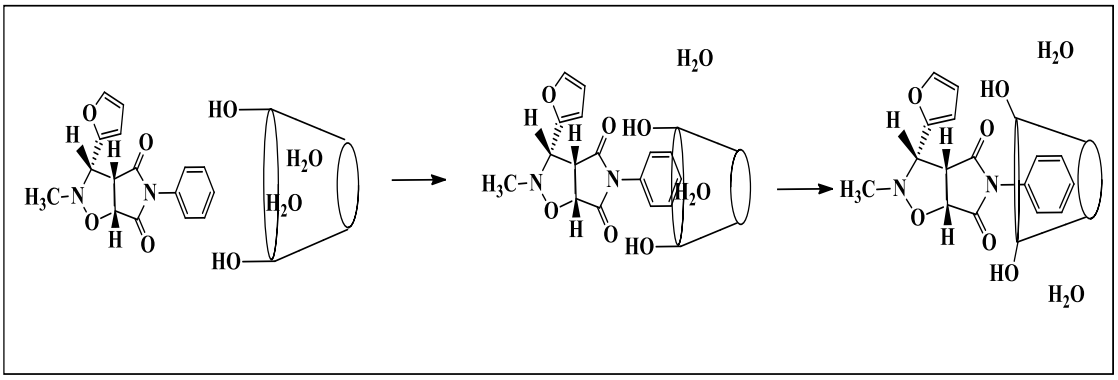
Yellow crystals. Yield 64%; R_f = 0.64; IR (KBr): υ_{max} 3623 - 3510 (br), 2915 (m), 2830 (m), 1770 (s), 1680 (s), 1430 (m), 1380 (m), 783 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.82-6.70 (m, 5H, C_6H_5), 5.06 (br, s, 1H, OH, exchanged in D_2O), 4.82 (d, 1H, *J* = 6.20 Hz, C_5H), 4.34 (dd, 1H, *J* = 6.00, 6.00 Hz, C_4H), 3.20 (s, 3H, CH_3 protons), 2.80 (dt, 1H, *J* = 6.24, 6.30 Hz, C_3H), 2.18 (dt~m, 2H, CH_2 protons of $-\underline{CH_2}-(CH_2)_2OH$), 1.70 - 1.36 (m, 4H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.43, 172.25 (carbonyl carbons), 136.45, 136.34, 136.25, 135.95 (aromatic carbons), 85.48 (C_5), 75.22 (C_3), 66.28 (CH_2OH), 58.20 (C_4), 36.18 (CH_3), 22.36, 21.87 (2 CH_2 carbons); MS: *m/z* 290 (M^+), 231, 230, 213, 212, 198, 154 (B.P), 77, 59; Anal. Found: C, 61.88; H, 6.12; N, 9.30. $C_{15}H_{18}O_4N_2$ requires C, 62.04; H, 6.24; N, 9.63%.

(*3S*,3a*S*,6a*R*)–dihydro-3-(3-hydroxypropyl)-5-methyl-2-phenyl-2*H*-furrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione, 2b

Yellow crystals. Yield 32%; R_f = 0.70; IR (KBr): υ_{max} 3615 - 3535 (br), 2933 (m), 2825 (m), 1765 (s), 1680 (s), 1440 (m), 1370 (m), 780 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.70-6.62 (m, 5H, C_6H_5), 5.10 (br, s, 1H, OH, exchanged in D_2O), 4.70 (d, 1H, *J* = 5.30 Hz, C_5H), 4.30 (dd, 1H, *J* = 3.00, 3.00 Hz, C_4H), 3.22 (s, 3H, CH_3 protons), 2.40 (dt, 1H, *J* = 2.20, 2.16 Hz, C_3H),

2.10 (dt~m, 2H, CH_2 protons of –$\underline{CH_2}$-$(CH_2)_2OH$), 1.70 - 1.28 (m, 4H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 171.20, 171.10 (carbonyl carbons), 135.50, 135.12, 134.80, 134.64 (aromatic carbons), 87.24 (C_5), 76.63 (C_3), 65.94 (CH_2OH), 58.46 (C_4), 35.00 (CH_3), 23.13, 22.68 (2 CH_2 carbons); MS: *m/z* 290 (M^+), 231, 230, 213, 212, 198, 154 (B.P), 77, 59; Anal. Found: C, 61.78; H, 6.20; N, 9.37. $C_{15}H_{18}O_4N_2$ requires C, 62.04; H, 6.24; N, 9.65%.

Cyclodextrins (CD) are cyclic oligosaccharides which consists of glucopyrasyl units linked by α-(1,4) bonds. The commonly used cyclodextrins are γ, β and γ cyclodextrins consisting of 6.7 and 8 glucopyranose units respectively. The structure of cyclodextrin molecules have a unique nature, a hydrophobic cavity and a hydrophilic surface which can form inclusion complex with a wide variety of guests[6]. The application of cyclodextrin and their derivatives for the encapsulation of bioactive compounds may protect the compounds from environmental conditions and improve the aqueous stability for increasing their capacity to functionalize the products. In some cases there is a requirement to enhance water solubility of β-cyclodextrin by adding hydroxy alkyl groups on the β-cyclodextrin surface. Molecules having suitable cavity sizes can acquire relatively small molecules within itself. When small molecules enter into the cavity of the large molecule to form a stable complex, the complex is known as the "*Host-Guest inclusion complex*"[7]. This may be illustrated as under:



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