Abstract

Introduction

Nitrones are versatile synthetic intermediates and excellent spin trapping reagents. Nitrones are prepared either by condensation of aldehyde and ketones with hydroxyl amines or by oxidation of the corresponding *N,N*-disubstitutedhydroxylamines[1]. The 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is an efficient method for the synthesis of the isoxazolidine ring system[2]. 1,3-dipolar 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 synthesis of novel isoxazolidine, isoxazoline derivatives and their further applications have been widely illustrated. The 1,3-dipolar cycloaddition reaction has a singular capability of establishing large number of stereo-chemical centres in one synthetic step.

The present work entitled **"*Greener approach to the synthesis of some novel class of Isoxazolidine and Isoxazoline derivatives using N-methyl & N-phenyl-α-chloro nitrones*"** reports newly synthesized *N-methyl & N-phenyl-α-chloro nitrones*[3] from chlorohydrin and their cycloaddition reactions with different olefins, alkynes leading to the formation of *regio and stereoselective* cycloadducts following *green chemistry* methodologies. The dissertation also reports about the synthesis of *α*-chloro nitrone synthesized from dry distilled chloral and cycloaddition reactions leading to the formation of regio and stereoselective cycloadducts. Majority of the reactions have been carried out in water and under microwave irradiation. High yield of *cycloadducts* (both isoxazolidine and isoxazoline derivatives) have been reported compared with the reactions performed in conventional solvents and thereby applications of *green chemistry methodology of nirone-cycloaddition reactions have been achieved*[4,5]. *N-methyl & N-phenyl-α-chloro nitrones* have been also used successfully as *potential oxidizing reagents* for the synthesis of aldehyde and ketones with unexpected high yields and the *side products* of the reaction are also effectively used as *new dipolarophiles* for the synthesis of *spiro* cycloadducts[6,7,8].Most of the cycloadducts have been screened for biological activities and found to have good antibacterial activities[9].

General nature of cycloaddition reaction and review of earlier work

1,3-dipolar cycloaddition reactions of *N-methyl & N-phenyl-α-chloro nitrones* are not only regioselective but also stereoselective. The relative configurations of C_3, C_4, C_5 (asymmetric centres) protons of the cycloadducts are *syn* in most of the cases since most of the nitrones

exist exclusively in the *Z* configuration. Therefore the cycloadducts are formed from *Z* nitrone through an *exo*-transition state geometry. The C-C bond of the isoxazolidine ring is more developed in the transition state then C-O bond. In the 1,3-dipolar cycloaddition reaction of nitrone with alkenes, the latter approaches the nitrone exclusively from the side opposite to the C_3-substituent. This approach controls stereochemistry at C_3 position.

A comprehensive review on nitrone cycloaddition reactions was conducted as a part of our present research work in this dissertation. This review work was needed to understand the gravity of nitrone cycloaddition reactions and their applications, contributions to the fraternity of synthetic organic chemists. This review work also helped us to define and understand the work undertaken for this dissertation and especially how to reach the final target.

From the review work it has been found that in the majority of the publications nitrones are generated *in situ*. Because of their instability, 1,3-dipolar cycloaddition reactions are carried out mainly by trapping the nitrones with suitable dipolariphiles at the time of their generation. Dimerization of the nitrone can be controlled in this fashion and the yield of the cycloadducts are also extremely high.

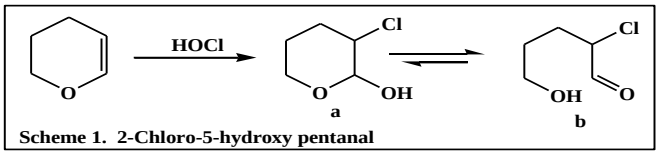
In this dissertation, we have employed the following methodologies of "*Green Chemistry Techniques*".

- *Aqueous phase 1,3-dipolar cycloaddition reactions*
- *Microwave assisted (solid phase) synthesis of nitrones and cycloaddition reactions*
- *To utilize side products in further reactions (atom efficiency)*

In majority of the reactions, mild reaction conditions (room temperature, short reaction times, avoiding oil bath heating etc), easy work up and isolation of the compounds has made these protocols more attractive.

Laboratory experimental work with results

Preparation of 2-Chloro-5-hydroxy pentanal (Chlorohydrin derivative)

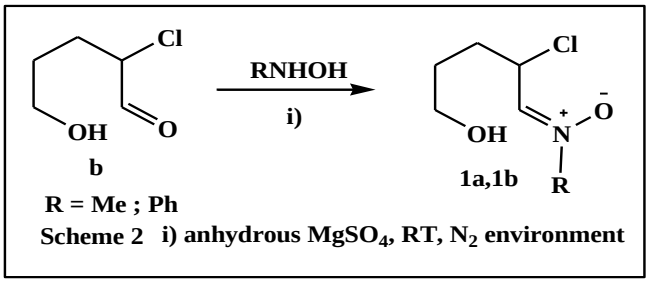


Scheme 1. 2-Chloro-5-hydroxy pentanal

Spectral data of 2-Chloro-5-hydroxy pentanal (b)

Greenish gummy liquid; Yield 74.6%; IR (KBr): υ_{max} 3600–3200 (br), 2920 (s), 1720 (s), 1440 (m), 1380 (s), 1340 (m), 1284 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.75 (1H, CHO), 5.06 (d, 1H, *J* = 6 Hz, -OCH), 5.23 – 4.96 (br, 1H, -OH, exchanged in D_2O), 4.10 – 3.93 (dt~m, 1H, CHCl), 3.80 – 3.4 (m, 4H, CH_2); MS (*m/z*): 136 (M^+), 118, 108, 102, 78, 69.

Preparation of α-chloronitrone (1a & 1b)

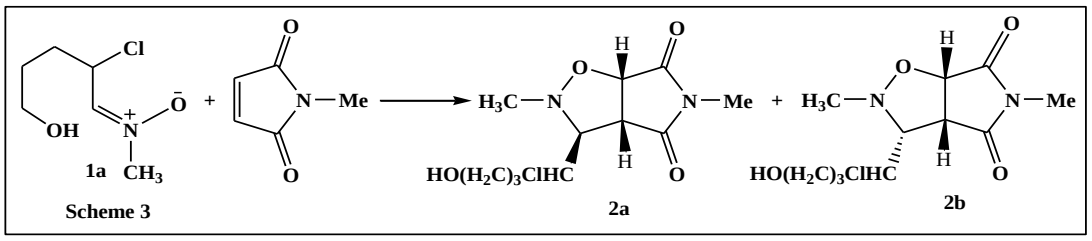


Scheme 2 i) anhydrous $MgSO_4$, RT, N_2 environment

Spectral data of (Z)-N-(2-chloro-5-hydroxypentylidene)methyl amine oxide (1a;R=Me)

White needle shape crystals; Yield: 94%; R_f = 0.36; m.p: 52^{0}C (uncorrected); IR ($CHCl_3$) : υ_{max} 3595–3470 (br), 1660 (s), 1610 (s), 1415 (m), 1185 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.84 (d, 1H, CH=N$^+$), 5.79 (br,1H, -OH, exchanged in D_2O), 3.51 (dt, 1H, *J* = 6.0, 6.0 Hz, CHCl), 3.31 (s, 3H, N$^+$- CH_3), 1.88 - 1.15 (m, 6H, CH_2 protons); ^{13}C NMR($CDCl_3$) : δ 141.5 (CH=N$^+$), 55.7 (CHCl), 34.8 (N$^+$- CH_3), 28.5, 27.2, 26.0 (3 CH_2 carbons); HRMS–EI: Calcd. for $C_6H_{12}O_2NCl$, (M), 165.0870, Found: M$^+$, 165.0861.

General procedure for the synthesis of isoxazolidine derivatives using N-methyl-α-chloro nitrone (1a) in aqueous phase (cycloaddition reaction with N-methyl maleimide)



Scheme 3

To a stirred solution of nitrone **1a** (1 mmol) in 15 mL water, was added *N*-methyl maleimide (1 equivalent) at RT under nitrogen atmosphere and the reaction mixture was stirred for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.4, 0.5). The products were extracted with ether (2x25 mL), the organic layers were washed with brine water (2x15 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate - hexane and finally obtained under reduced pressure as colourless liquids, which finally crystallized to white crystals.

2a. Spectral data of (3*S*)-3-((*R*)-1-chloro-4-hydroxybutyl)-dihydro-2,5-dimethyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6 a-*H*)-dione

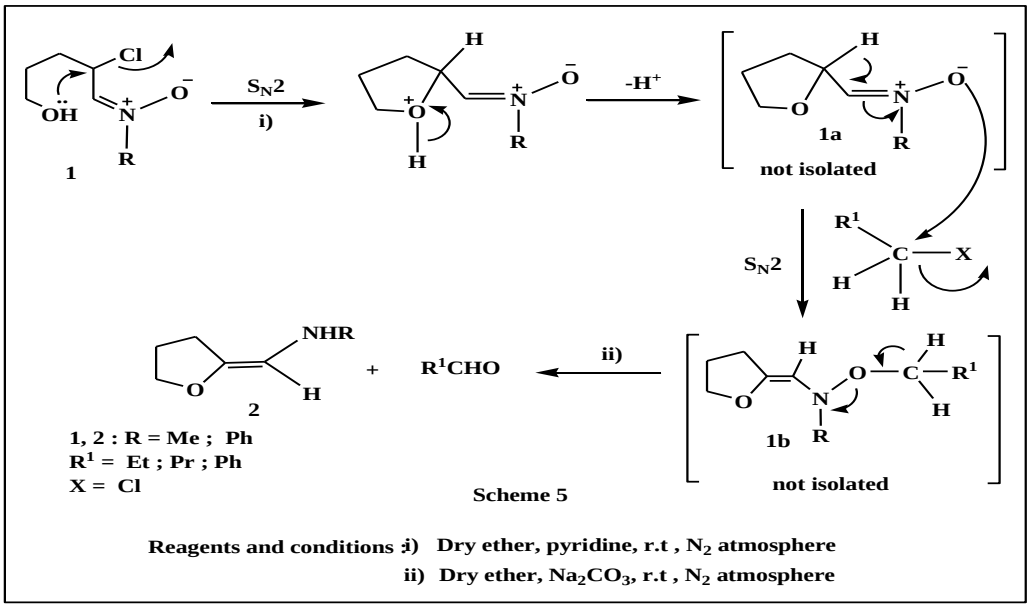
White crystal; Yield 66%; R_f = 0.4; IR (KBr): υ_{max} 3486 - 3430 (br), 2915 (m), 2832 (m), 1762 (s), 1660 (s), 1474 (m), 1190 (m), 814 (s), 778 (s) cm^{-1};

^{1}H NMR ($CDCl_3$): δ 4.83–4.72 (br, s, 1H, OH, exchanged in D_2O), 4.60 (dd, 1H, *J* = 6.0, 6.2 Hz, C_4H), 3.30 (s, 2x3H, 2-CH_3 protons), 3.00 (d, 1H, *J* = 6.6 Hz, C_5H), 2.70 (dd, 1H, *J* = 6.2, 6.2 Hz, C_3H), 2.34 (dt, 1H, *J* = 6.0, 6.0 Hz, CHCl), 1.82 - 1.50 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 178.1, 176.8 (carbonyl carbons), 87.1 (C_5), 76.0 (C_3), 67.1 (CH_2OH), 53.5 (C_4), 50.7 (CHCl), 38.0, 37.1 (2xCH_3), 22.3, 21.4 (2 CH_2 carbons); MS: *m/z* 278 (M^++2, 72%), 276 (M^+,100%), 261, 255, 226, 169, 154 (B.P), 107; HRMS–EI: Calcd for $C_{11}H_{17}O_4N_2Cl$ (M) *m/z* 276.1240. Found: M^+ 276.1228. Anal. Found: C, 47.69; H, 6.10; N, 10.07. $C_{11}H_{17}O_4N_2Cl$ requires C, 47.80; H, 6.19; N, 10.14%.

2b. Spectral data of (3*R*)-3-((*S*)-1-chloro-4-hydroxybutyl)-dihydro-2,5-dimethyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a-*H*)-dione

White crystal; Yield 31%; R_f = 0.5; IR (KBr): υ_{max} 3510 - 3454 (br), 2920 (m), 2826 (m), 1750 (s), 1664 (s), 1470 (m), 1205 (m), 810 (s), 780 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.03–4.90 (br, s, 1H, OH, exchanged in D_2O), 4.54 (dd, 1H, *J* = 2.5, 2.5 Hz, C_4H), 3.14 (s, 2x3H, 2-CH_3 protons), 3.04 (d, 1H, *J* = 4.5 Hz, C_5H), 2.62 (dd, 1H, *J* = 3.6, 3.6 Hz, C_3H), 2.27 (dt, 1H, *J* = 1.8, 1.8 Hz, CHCl), 1.90 - 1.54 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 179.0, 178.3 (carbonyl carbons), 86.9 (C_5), 75.4 (C_3), 64.7 (CH_2OH), 54.3 (C_4), 51.2 (CHCl), 41.1, 39.0 (2xCH_3), 24.0, 23.2 (2 CH_2 carbons); MS: *m/z* 278 (M^++2, 68%), 276 (M^+,100%), 261, 255, 246, 226, 169, 154 (B.P), 107; HRMS–EI: Calcd for $C_{11}H_{17}O_4N_2Cl$ (M) *m/z* 276.1240. Found: M^+ 276.1231. Anal. Found: C, 47.72; H, 6.11; N, 10.10. $C_{11}H_{17}O_4N_2Cl$ requires C, 47.80; H, 6.19; N, 10.14%.

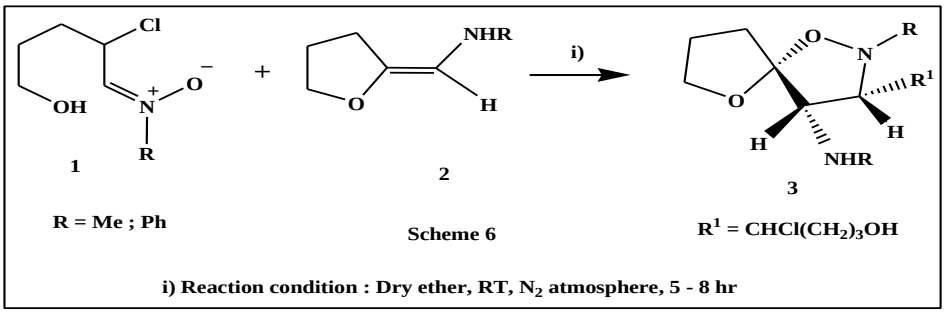
Atom efficient aldehyde synthesis[6,7,8]



Scheme 5

Reagents and conditions : i) Dry ether, pyridine, r.t , N_2 atmosphere
ii) Dry ether, Na_2CO_3, r.t , N_2 atmosphere

***General procedure for the synthesis of regioselective spiro cycloadducts)*[6]**



Scheme 6

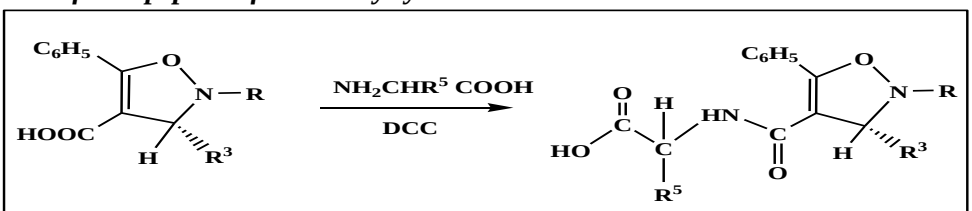
i) Reaction condition : Dry ether, RT, N_2 atmosphere, 5 - 8 hr

Salient features found in cycloaddition reactions

Excellent diastereofacial selectivity has been observed in nitrone additions in water. The addition of nitrone **1** to maleimides results in a mixture of *diastereomers* (almost 65: 35 ratio in all cases) and generation of as many as *three to four chiral centres* in a single step.

Future scopes from our reported work

Synthesis of new peptides from newly synthesized isoxazoline derivatives



R = CH_3 ; C_6H_5; $C_6H_5CH_2$
R^3 = $ClCH(CH_2)_3OH$

Scheme 7- Synthesis of peptides using isoxazoline derivatives

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