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 the 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 has 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 synthesis and 1,3-Dipolar cycloaddition reactions of* α*-amino nitrones and studies of biological activities of the cycloadducts"* reports synthesis and cycloaddition reactions of α*-amino nitrones* following *green chemistry* methodologies and their further applications. Evidence of stereoselectivity and regioselectivity was observed in the 1,3-dipolar cycloaddition reactions of α*-amino nitrones* with olefins and alkynes. Majority of these reactions have been carried out in aqueous phase (in water) and under microwave irradiation. High yield and short reaction time was the major advantage in these protocols of synthesis of *cycloadducts* (both isoxazolidine & isoxazoline derivatives) compared with the reactions performed in conventional solvents[2]. *Isoxazolidine derivatives* have been also successfully converted into synthetically more important *peptides*[4]. This may be considered as one of most important applications in this chemistry. In addition, isoxazoline derivatives have been successfully converted into 1,3-amino alcohols while α*-amino nitrones* have been 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[5].

General nature of cycloaddition reaction and review of earlier work

1,3-dipolar cycloaddition reactions of *nitrones* are not only regioselective but also stereoselective in nature. The relative configurations of C_3, C_4, C_5 (asymmetric centres) protons of the isoxazolidines are *syn* in most of the cases since most of the nitrones exist

exclusively in the *Z* configuration. Therefore, the isoxazolidines are formed from *Z* nitrone through an *exo*-transition state geometry. The stereochemistry of the isoxazoline derivatives are usually difficult to assign due to the absence of hydrogen atoms at C_4, C_5 positions. The C-C bond of the isoxazolidine ring is more developed in the transition state then C-O bond. In 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 yields of the cycloadducts are also extremely high.

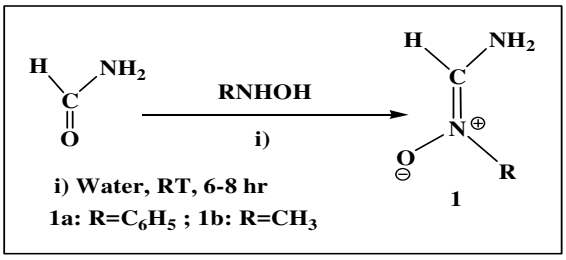
In this dissertation, for the synthesis and 1,3-dipolar cycloaddition reaction of nitones, we have employed the following methodologies of "*Green Chemistry Techniques*".

- *Aqueous phase synthesis and 1,3-dipolar cycloaddition reactions of* α*-amino nitrones*
- *Microwave assisted (solid phase) synthesis and 1,3-dipolar cycloaddition reactions of* α*-amino nitrones*
- *To utilize* α*-amino nitrones* as potential oxidizing reagents
- *To utilize products (cycloadducts) in further reactions (atom efficiency)*

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

Laboratory experimental work with results

Synthesis of* α*-amino nitrones in water

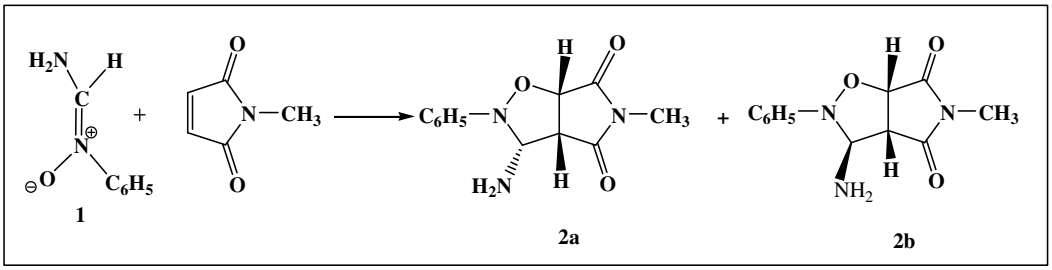


***Spectral data of N-Phenyl-α-amino nitrone*:**

Pale yellow crystalline solid. Yield: 92%; R_f = 0.36, m.p: 42^{0}C (uncorrected); $UV_{\lambda max}$: 238 nm; IR (KBr): 3310 (br), 3020 (m), 1610 (s), 1180 (s), 785 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.49-7.13 (m, 5H, C_6H_5), 6.84 (s, 1H, CH=N$^+$), 1.62 (s, 2H, -NH_2);

Majority of α-*amino nitrones* (R=CH_3; C_6H_5; $CH_2C_6H_5$; R_1=R_2=H; R_1=R_2=CH_3) decomposes on keeping at room temperature, therefore *in situ* reactions were performed with various activated alkene and alkynes.

General procedure for the synthesis of isoxazolidine derivatives using N-Phenyl-α-amino nitrone (1a)



To a stirred solution of *N*-phenylhydroxylamine and formamide (1 equivalent each) in 15 mL water *N*-methyl maleimide (1 equivalent) were added *insitu* at the time of formation of nitrone (monitored by TLC) and stirred at RT with a magnetic stirrer under N_2 atmosphere for 3 hr. The progress of the reaction was monitored by TLC (R_f = 0.44; 0.52). After completion of the reaction, the products were extracted with ether (2 X 25 mL), the organic layer was washed with saturated brine (2 X 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers were purified and separated by column chromatography using ethyl acetate - hexane to afford cycloadducts **2a & 2b**. Same methodology was adopted for the synthesis of other new isoxazolidine derivatives.

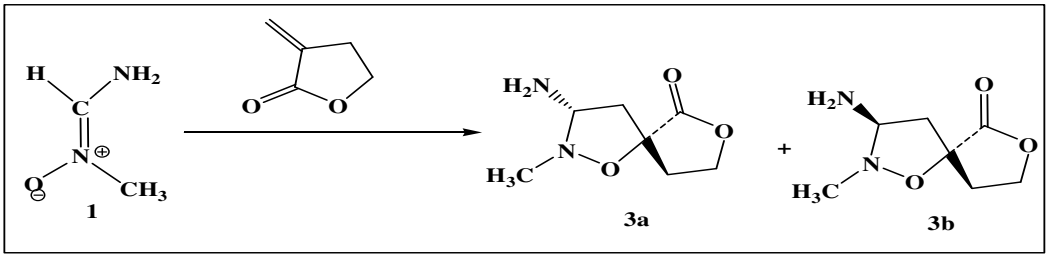
(*3S*)–3-(amino)-5-methyl-2-phenyldihydro-2H pyrrolo[3,4-d]isoxazole-4,6 (5H,6 a-H)-dione, 2a

2a: White crystals.Yield 68%; R_f = 0.44; M.P 146^{0}C; IR (KBr): 3408 (br), 3016 (s), 2937 (m), 1720 (s), 1448 (m), 1382 (m), 1217 (s), 758 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.86 – 6.75 (m, 5H, C_6H_5), 5.80 (br,s, 2H, NH_2, exchanged in D_2O), 5.24 (d, 1H, *J* = 6.06 Hz, C_5H), 4.93 (dd, 1H, *J* = 6.60, 6.52 Hz, C_4H), 3.23 (d, 1H, *J* = 6.20 Hz, C_3H), 2.14 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 170.85, 168.00 (carbonyl carbons), 136.40, 135.00, 134.22, 131.90 (aromatic carbons), 88.76 (C_5), 77.50 (C_3), 65.87 (C_4), 23.67 (CH_3); MS: *m/z* 247 (M$^+$), 232, 221, 207, 191, 154, 147, 107, 77; Anal. Found: C, 58.19; H, 5.22; N, 16.89. $C_{12}H_{13}O_3N_3$ requires C, 58.27; H, 5.30; N, 17.00%.

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

2b: White crystals. Yield 28%; R_f = 0.52; M.P: 123^{0}C; IR (KBr): 3410 (br), 3018 (s), 2935 (m), 1720 (s), 1440 (m), 1380 (m), 1215 (s), 760 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.86 – 6.75 (m, 5H, C_6H_5), 5.80 (br,s, 2H, NH_2, exchanged in D_2O), 5.24 (d, 1H, *J* = 6.06 Hz, C_5H), 4.93 (dd, 1H, *J* = 6.60, 6.52 Hz, C_4H), 3.23 (d, 1H, *J* = 6.20 Hz, C_3H), 2.14 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 170.60, 169.00 (carbonyl carbons), 135.40, 135.12, 134.50, 131.46 (aromatic carbons), 87.20 (C_5), 77.69 (C_3), 65.58 (C_4), 23.70 (CH_3); MS: *m/z* 247 (M^+), 232, 221, 207, 191, 154, 147, 107, 77; Anal. Found: C, 58.21; H, 5.24; N, 16.86. $C_{12}H_{13}O_3N_3$ requires C, 58.27; H, 5.30; N, 17.00%.

Synthesis of spiro isoxazolidine derivatives using α-amino nitrone



To a well stirred solution of nitrone **1** (R=Me; 1 mmole) in diethyl ether (20 mL) taken in a 50 mL conical flask, was added α-methylene-γ-butyrolactone (1 equivalent) and was stirred at RT with a magnetic stirrer under N_2 atmosphere for 4 hr. The progress of the reaction was monitored by TLC (R_f = 0.38; 0.44). After completion of the reaction, the crude spiro diastereomers 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 spiro cycloadducts **3a & 3b**. This procedure was followed for the reaction of nitrone **1** (R=Ph) with α-methylene-γ-butyrolactone.

Spectroscopic data for spiro isoxazolidine derivatives

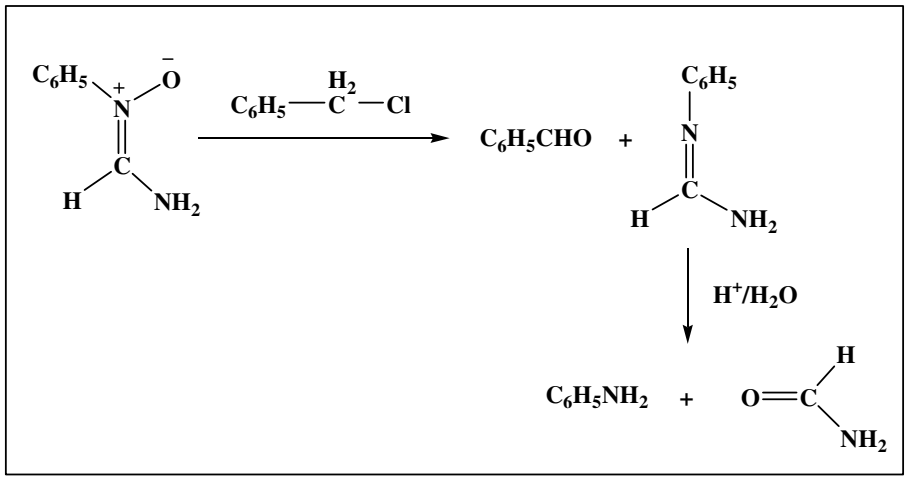
(3S,3'S)-spiro[tetrahydrofuran-2-one-3,5'-(2'-methyl,3'-amino)tetrahydroisoxazole] 3a

3a: Pale yellow liquid. Yield. 68%; R_f = 0.38; IR (KBr): 3390 (br), 3024 (m), 2910 (m), 1755 (s), 1650 (s), 1470 (m), 1290 (m), 1178 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.33 (br,s, 2H, NH_2, exchanged in D_2O), 4.50 (t, 1H, *J* = 6.80 Hz, C_3' H), 4.02 (dt, C_4' 2H, *J* = 6.08, 7.42 Hz), 3.33 (s, 3H, N-CH_3), 2.60 (t, 2H, *J* = 6.18 Hz, C_5 2H), 2.00 (ddd, C_4 2H, *J* = 6.56, 6.20 Hz); ^{13}C NMR ($CDCl_3$): δ 178.22 (carbonyl carbon), 88.43 (C_5'/C_3), 73.70 (C_3'), 65.20 (C_4'), 56.13 (C_4), 52.42 (C_5), 38.30 (N-CH_3); MS: *m/z* 172 (M^+), 157, 156, 141 (B.P); HRMS – EI: Calcd for $C_7H_{12}O_3N_2$ (M) *m/z* 172.1140. Found: M^+ 172.1112.

(3S,3'R)-spiro[tetrahydrofuran-2-one-3,5'-(2'-methyl,3'-amino)tetrahydroisoxazole] 3b

3b: Yellow liquid. Yield 24%; R_f = 0.44; IR(KBr): 3378 (br), 3012 (m), 2904 (m), 1762 (s), 1655 (s), 1478 (m), 1286 (m), 1182 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27 (br,s, 2H, NH_2, exchanged in D_2O), 4.40 (t, 1H, *J* = 3.42 Hz, C_3' H), 4.12 (dt, C_4' 2H, *J* = 2.24, 3.40 Hz), 3.26 (s, 3H, N-CH_3), 2.54 (t, 2H, *J* = 3.08 Hz, C_5 2H), 1.96 (ddd, C_4 2H, *J* = 4.24, 2.68 Hz); ^{13}C NMR ($CDCl_3$): δ 176.58 (carbonyl carbon), 86.90 (C_5'/C_3), 75.25 (C_3'), 64.32 (C_4'), 54.30 (C_4), 51.76 (C_5), 37.14 (N-CH_3); MS: *m/z* 172 (M^+), 156, 155, 141 (B.P); HRMS – EI: Calcd for $C_7H_{12}O_3N_2$ (M) *m/z* 172.1140. Found: M^+ 172.1117.

Synthesis of aldehyde using α-amino nitrone



One of the most important applications of α-amino nitrone is observed in the atom efficient synthesis of aldehydes. Various aldehydes have been synthesized with good yields following our proposed mechanism. For example, using *N*-phenyl-α-amino nitrone and benzyl chloride benzaldehyde may be synthesized following Kornblum type mechanistic procedure as shown above. Moreover, the side product of this reaction may be hydrolysed to obtain primary amine as well.

References

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