RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.3, No.3 (2010), 454-460
ISSN: 0974-1496
CODEN: RJCABP

GREEN SYNTHESIS OF NITRONE AND ISOXAZOLIDINES: ONE POT CONVENIENT CYCLOADDITION REACTIONS IN WATER

Bhaskar Chakraborty* **and Prawin K. Sharma**
Organic Chemistry Laboratory, Sikkim Government College, Gangtok, Sikkim 737 102, India,
E-mail:bhaskargtk@yahoo.com

ABSTRACT

Novel *N*-methyl-α-chloral nitrone has been synthesized from chloral in water and one pot cycloaddition reactions are reported in the diastereo and regioselective synthesis of some novel isoxazolidine derivatives with high yield at room temperature in a very short reaction time.

Keywords : *N*-methyl-α-chloral nitrone, novel isoxazolidine derivatives, stereo & regioselectivity, aqueous phase.

INTRODUCTION

Organic reactions in water have received increased attention primarily because of their environmental acceptability, abundance and low cost.[1-3] However, water also exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents.[4-6] Thus, the development of efficient procedures for useful chemical transformations in water without any catalyst are highly appreciated. Keeping in touch with green chemistry methodologies our group has already reported 1,3-Dipolar cycloaddition reactions with *N*-phenyl-α-chloro nitrone[7,8] and *N*-cyclohexyl-α-amino nitrone[9,10] in water, solvent free conditions. Among a plethora of functional groups, the nitrone functionality has etched a place of distinction in organic synthesis. Remarkable regio, stereo, face and chemoselectivity along with efficient incorporation of multiple stereocenters have made nitrone cycloaddition reactions an attractive and efficient key step in the synthesis of great many natural products of biological interest.[11] In recent years, focus has been shifted towards asymmetric nitrone cycloaddition reactions, enantioselective, catalytic enantioselective and diastereoselective synthetic methodologies in aqueous phase.[12,13]

Herein, we would like to report diastereo and regioselective synthesis of some novel isoxazolidine derivatives with high yield in water using 1,3-Dipolar cycloaddition reaction with novel *N*-methyl-α-chloral nitrone (**1**) in a short reaction time (Scheme-1).

EXPERIMENTAL

General remarks: Melting points were determined in open capillary tubes and are uncorrected.

^{1}H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q–Tof micro instrument (YA–105). Elemental analyses (CHN) were performed with a Perkin-Elmer 2400 series CHN analyzer. TLC's were run on Fluka silica gel precoated TLC plates. Pure chloral was prepared following standard methods available in literature. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-methylhydroxylamine was purchased from Aldrich Chemical Company and has been used already along with *N*-phenylhydroxylamine in the aldehyde[14-16], ketone[17] and spiro cycloadducts[18]synthesis.

General procedure for synthesis of nitrone (1) in water

N-methylhydroxylamine (250 mg, 5.3191 mmole) was added to freshly prepared dry distilled chloral (778 mg, 5.3222 mmole) in water (15 mL) under N_2 atmosphere and the reaction mixture was kept at 5-10^{0}C with constant stirring with a magnetic stirrer for 8 hr. The formation of nitrone was monitored by TLC (R_f = 0.37). After completion of reaction, the nitrone was 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 nitrone was isolated under reduced pressure vaccum pump as white needdle shape crystals (**86%**; m.p:48^{0}C). As the nitrone decomposes at room temperature therefore trapped *in-situ* by the dipolarophiles for cycloaddition reactions.

Spectroscopic data for nitrone 1

Yield 86%; white needdle shape crystals; R_f = 0.37, m.p: 48^{0}C (uncorrected); UV (υ_{max}): 238 nm; IR (KBr): 1610 (s), 1185 (s), 805 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.65 (s, 1H, CH=N$^+$), 3.35 (s, 3H, N$^+$- CH_3); ^{13}C NMR ($CDCl_3$): δ 142.24 (CH=N$^+$), 35.66 (N$^+$-CH_3), 26.20 (CCl_3); HRMS–EI: Calcd. for $C_3H_4ONCl_3$, (M), 175.0320, Found: M$^+$, 175.0308.

General procedure for cycloaddition (for diastereomers)

To a stirred solution of *N*-methylhydroxylamine (250 mg, 5.3191 mmoles) and freshly prepared dry distilled chloral (1 equivalent) in 15 mL water under N_2 atmosphere at 5-10^{0}C, dipolarophiles were added (1 equivalent) *insitu* at the time of formation of nitrone. Stirring continued at RT with a magnetic stirrer under N_2 atmosphere for 3-4 hr. The progress of the reaction was monitored by TLC. 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 **2-4** (Scheme 1, Table 1). This procedure was followed for the substrates **1–3** listed in Table 1.

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

Yield 66%; white crystals; R_f = 0.46; IR (KBr): 2920 (m), 2830 (m), 1762 (s), 1660 (s), 1474 (m), 1190 (m), 814 (s), 778 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.31 (d, 1H, *J* = 6.60 Hz, C_5H), 2.99 (s, 2X3H, 2-CH_3 protons), 2.85 (d, 1H, *J* = 6.42 Hz, C_3H), 2.50 (dd, 1H, *J* = 6.06, 6.20 Hz, C_4H); ^{13}C NMR ($CDCl_3$): δ 178.12, 176.80 (carbonyl carbons), 87.15 (C_5), 76.00 (C_3), 53.54 (C_4), 38.00, 37.14 (CH_3 carbons), 22.32 (CCl_3); FAB-MS: *m/z* 288 (M$^+$+2), 286 (M$^+$), 271, 256, 241, 169, 154 (B.P), 117; HRMS – EI: Calcd for $C_8H_9O_3N_2Cl_3$ (M) *m/z* 286.0690. Found: M$^+$ 286.0678. Anal. Found: C, 33.48; H, 3.08; N, 9.62. $C_8H_9O_3N_2Cl_3$ requires C, 33.56; H, 3.16; N, 9.79%.

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

Yield 31%; white crystals; R_f = 0.52; IR (KBr): 2926 (m), 2820 (m), 1760 (s), 1664 (s), 1470 (m), 1185 (m), 810 (s), 776 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.36 (d, 1H, *J* = 3.24 Hz, C_5H), 2.83 (s, 2X3H, 2-CH_3 protons), 2.74 (d, 1H, *J* = 2.70 Hz, C_3H), 2.58 (dd, 1H, *J* = 2.46, 2.36 Hz, C_4H); ^{13}C NMR ($CDCl_3$): δ 176.45, 175.00 (carbonyl carbons), 85.64 (C_5), 74.82 (C_3), 55.23 (C_4), 34.64, 33.26 (CH_3 carbons), 24.17 (CCl_3); FAB-MS: *m/z* 288 (M$^+$ +2), 286 (M$^+$), 271, 256, 169, 154 (B.P), 117; HRMS – EI: Calcd for $C_8H_9O_3N_2Cl_3$ (M) *m/z* 286.0690. Found: M$^+$ 286.0673. Anal. Found: C, 33.45; H, 3.09; N, 9.68. $C_8H_9O_3N_2Cl_3$ requires C, 33.56; H, 3.16; N, 9.79%.

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

Yield 63%; white solid; R_f = 0.40; IR(KBr): 3050 (m), 2960 (m), 2840 (m), 1760 (s), 1660 (s), 1345 (m), 815 (s), 770 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.46 – 7.26 (m, 5H, C_6H_5), 4.37 (d, 1H, *J* = 6.74 Hz, C_5H), 3.18 (d, 1H, *J* = 6.22 Hz, C_3H), 2.89 (dd, 1H, *J* = 6.04, 6.16 Hz, C_4H), 2.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.50, 173.00 (carbonyl carbons), 135.10, 134.34, 132.00, 131.20 (aromatic carbons), 85.00 (C_5), 77.86 (C_3), 57.40 (C_4), 34.67 (CH_3), 25.00 (CCl_3); FAB-MS: *m/z* 350 (M$^+$ +2), 348 (M$^+$), 333, 271, 256, 231, 216 (B.P), 117, 77; HRMS – EI: Calcd for $C_{13}H_{11}O_3N_2Cl_3$ (M) *m/z* 348.0880. Found: M$^+$

348.0869. Anal. Found: C, 44.74; H, 3.08; N, 7.86. $C_{13}H_{11}O_3N_2Cl_3$ requires C, 44.81; H, 3.18; N, 8.04%.

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

Yield: 32%; white solid; R_f = 0.44; IR(KBr): 3056 (m), 2954 (m), 2835 (m), 1760 (s), 1664 (s), 1340 (m), 810 (s), 775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35 – 7.20 (m, 5H, C_6H_5), 4.32 (d, 1H, *J* = 3.22 Hz, C_5H), 3.10 (d, 1H, *J* = 2.56 Hz, C_3H), 2.84 (dd, 1H, *J* = 2.30, 2.28 Hz, C_4H), 2.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 173.64, 172.17 (carbonyl carbons), 136.44, 135.86, 133.92, 132.41 (aromatic carbons), 84.75 (C_5), 74.32 (C_3), 55.18 (C_4), 34.00 (CH_3), 23.64 (CCl_3); FAB-MS: *m/z* 350 (M^++2), 348 (M^+), 333, 303, 256, 231, 216 (B.P), 117, 77; HRMS – EI: Calcd for $C_{13}H_{11}O_3N_2Cl_3$ (M) *m/z* 348.0880. Found: M^+ 348.0863. Anal. Found: C, 44.70; H, 3.09; N, 7.89. $C_{13}H_{11}O_3N_2Cl_3$ requires C, 44.81; H, 3.18; N, 8.04%.

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

Yield 68%; yellow crystals; R_f = 0.48; IR (KBr): 2870 (s), 1770 (s), 1683 (s), 1446 (m), 1380 (m), 1265 (m), 815 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.94 (d, 1H, *J* = 6.64 Hz, C_5H), 4.32 (d, 1H, *J* = 7.18 Hz, C_3H), 3.86 (dd, 1H, *J* = 6.26, 6.08 Hz, C_4H), 2.34 (s, 3H, CH_3), 1.43 – 1.14 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 177.58, 176.00 (carbonyl carbons), 86.80 (C_5), 77.08 (C_3), 55.00 (C_4), 38.80 (CH_3), 31.10 (CCl_3), 29.52, 27.70, 26.30, 25.00, 23.28, 18.27 (cyclohexyl carbons); FAB-MS: *m/z* 356 (M^++2), 354 (M^+), 339, 309, 271, 256, 236, 222 (B.P), 117, 83; HRMS – EI: Calcd for $C_{13}H_{17}O_3N_2Cl_3$ (M) *m/z* 354.1300. Found: M^+ 354.1289. Anal. Found: C, 43.93; H, 4.70; N, 7.84. $C_{13}H_{17}O_3N_2Cl_3$ requires C, 44.05; H, 4.83; N, 7.90%.

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

Yield 26%; yellow crystals; R_f = 0.56; IR (KBr): 2880 (s), 1776 (s), 1680 (s), 1442 (m), 1373 (m), 1260 (m), 810 (s), 784 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.87 (d, 1H, *J* = 4.10 Hz, C_5H), 4.46 (d, 1H, *J* = 2.34 Hz, C_3H), 3.68 (dd, 1H, *J* = 3.74, 3.60 Hz, C_4H), 2.30 (s, 3H, CH_3), 1.50 – 1.26 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 175.70, 174.13 (carbonyl carbons), 85.00 (C_5), 76.43 (C_3), 55.64 (C_4), 36.92 (CH_3), 33.22 (CCl_3), 27.32, 26.24, 24.85, 23.00, 21.54, 20.12 (cyclohexyl carbons); FAB-MS: *m/z* 354 (M^+), 339, 309, 271, 256, 237, 236, 222 (B.P), 117, 83; HRMS – EI: Calcd for $C_{13}H_{17}O_3N_2Cl_3$ (M) *m/z* 354.1300. Found: M^+ 354.1292. Anal. Found: C, 43.91; H, 4.73; N, 7.81. $C_{13}H_{17}O_3N_2Cl_3$ requires C, 44.05; H, 4.83; N, 7.90%.

General procedure for cycloaddition (for regioselective cycloadducts)

To a stirred solution of *N*-methylhydroxylamine (250 mg, 5.3191 mmoles) and freshly prepared dry distilled chloral (1 equivalent) in water (15 mL) under N_2 atmosphere at 5-10^{0}C, dipolarophiles were added (1 equivalent) *insitu* at the time of formation of nitrone. Stirring continued at RT with a magnetic stirrer under N_2 atmosphere for 4-5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was 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 crude product was purified by column chromatography using ethyl acetate - hexane to afford pure cycloadduct **5-6** (Scheme 1, Table 1).This procedure was followed for the substrates **4** and **5** listed in Table 1.

(3*S*)-ethyl-3-(trichloromethyl)-2-methyl isoxazolidine-5-carboxylate, 5

Yield 92%; colourless gummy liquid; R_f = 0.42; IR (KBr): 2874 (m), 1750 (s), 1425 (s), 875 (s), 790 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.89 (t, 1H, *J* = 7.46 Hz, C_5H), 4.11 (q, 2H, *J* = 4.64, 4.34 Hz, -OCH_2CH_3), 3.51 (dd, 2H, *J* = 7.12, 7.44 Hz, C_4 2H), 2.79 (t, 1H, *J* = 7.46 Hz, C_3H), 2.29 (s, 3H, CH_3), 1.23 (t, 3H, *J* = 5.40 Hz, -OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 169.32 (carbonyl carbon), 84.70 (C_5), 79.12 (C_3), 61.00 (CH_2 carbon of -OCH_2CH_3), 56.90 (C_4), 37.20 (CH_3), 20.73 (CCl_3), 15.45 (CH_3 carbon of OCH_2CH_3); FAB-MS: *m/z* 277 (M^++2), 275 (M^+), 260, 230, 202, 201, 158, 157, 143 (B.P), 117, 73; HRMS - EI: Calcd for $C_8H_{12}O_3NCl_3$ (M) *m/z* 275.0850. Found: M^+ 275.0841. Anal. Found: C, 34.82; H, 4.30; N, 4.98. $C_8H_{12}O_3NCl_3$ requires C, 34.90; H, 4.39; N, 5.10%.

(3*S*)-3-(trichloromethyl)-2-methyl-5-phenyl isoxazolidine, 6

Yield 91%; colourless viscous liquid; R_f = 0.50; IR (KBr): 3050 (m), 2844 (m), 1710 (s), 1440 (m), 1324 (s), 804 (m), 776 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 - 7.26 (m, 5H, C_6H_5), 4.39 (t, 1H, *J* = 6.08 Hz, C_5H), 3.24 (t, 1H, *J* = 6.52 Hz, C_3H), 2.89 (dd, 2H, *J* = 6.48, 6.12 Hz, C_4 2H), 2.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 136.75, 135.22, 133.00, 132.14 (aromatic carbons), 85.95 (C_5), 77.32 (C_3), 56.40 (C_4), 38.66 (CH_3), 19.20 (CCl_3); FAB-MS: *m/z* 281 (M^++2), 279 (M^+), 234, 202, 201, 162, 161, 147 (B.P), 117, 77; HRMS-EI: Calcd for $C_{11}H_{12}ONCl_3$ (M) *m/z* 279.0960. Found: M^+ 279.0948. Anal. Found: C, 47.22; H, 4.24; N, 4.85. $C_{11}H_{12}ONCl_3$ requires C, 47.29; H, 4.32; N, 5.01%.

RESULTS AND DISCUSSION

The present study of cycloaddition reaction has been carried out with three different maleimides (*N*-methyl/phenyl/cyclohexyl) and ethyl acrylate, styrene respectively in water. Simultaneously the reactions have been also studied in organic solvent. Remarkably reactions are found to be highly regioselective in CH_2Cl_2 and reaction rate, yields are also not impressive (Table 1). Almost all the reactions in water are very fast (3 - 4 hrs in case of maleimides and ethyl acrylate & 5 hrs for styrene) compared to the normal cycloaddition reactions in organic solvents which are reported to take longer periods (26-48 hrs)[11]. It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β-unsaturated carbonyl compounds and thereby increasing the eletrophilic character at the β-carbon which is attacked by nucleophilic oxygen atom of the nitrone. Thus water activates maleimide, ethyl acrylate and thereby greately facilitates the reaction. We classified dipolarophiles into water-super and water-normal on the basis of the magnitude of their rate response to water. A ketone (C=O) conjugated to an alkene or alkyne is a water-super dipolarophile. Esters, ethers and aryl rings conjugated to an alkene are water-normal dipolarophiles. Reaction rate is comparatively slower in styrene because of very lesser possibility of the formation of hydrogen bonding between water and alkenes but still the rate of the reaction and yield is higher than the cycloaddition reactions performed in solvents like THF, CH_2Cl_2 (Table 1). We suggest an explanation for these results in terms of the frontier molecular orbital (FMO) theory which has been used extensively to explain regioselectivity, yield and rate in 1,3-Dipolar cycloadditions[19]. This theory states that the Gibbs energy of activation is related to the energy gap between the interacting HOMO and LUMO. The dipolarophiles like styrene, cyclohexene etc. are weak hydrogen bond acceptors, which means that their FMO's are only slightly affected by hydrogen bond interactions and lead to a reduction in the energy gap between the interacting FMO's (in this case, the HOMO of the dipolarophile and LUMO of the 1,3 dipole). Consequently, the Gibbs energy of activation of the reaction is reduced and the reaction is accelerated in water with good yield.

Excellent diastereofacial selectivity has been observed in the reported nitrone cycloaddition reactions in water. The addition of nitrone **1** to maleimides result in a mixture of diastereomer **2a–4a** and **2b–4b** (almost 65 : 35 ratio in all cases) and generation of three asymmetric centers in a single step. Study of organic reactions in aqueous media shows that there is a higher probability of the formation of mixture of diastereomers when water is used as solvent rather than conventional organic solvents[5]. These results can be rationalized by an *exo* approach of nitrone **1** which has *Z* configuration for the formation of major cycloadducts **2a–4a** (transition state 1). The minor cycloadducts **2b–4b** are formed by the *endo* approach of *Z* nitrone (transition state 2). The mixture of diastereomers have been identified by considering the multiplicity of the proton signals at 3-H and 4-H along with their coupling constant values.[20,21] The most significant difference in the ^1H NMR data of the diastereomers are the position and multiplicity of the 3-H signal. In the minor adducts **2b–4b**, 3-H resonates around δ_H 2.74 - 4.10 while for the same proton in major adducts **2a–4a** around δ_H 2.85 - 4.32 and $J_{3,4}$ ~ 6.26 Hz for major adducts whilst for minor adducts $J_{3,4}$ is ~ 2.26 Hz. These differences can be explained by considering the available isoxazolidine ring conformations. Due to the 4,5-fused pyrrolidindione, the isoxazolidine ring adopts an envelope conformation and allowing for inversion its nitrogen atom will either extend out from the envelope, *i.e.*, minor conformation, or point inside the envelope, *i.e.*, major conformation. The minor conformer has the N-lone pair antiperiplanar and therefore capable of shielding 3-H proton, so this conformation has been assigned as minor conformer (Figure 1). The diastereomeric isoxazolidines **2a–4a** and **2b–4b** were

separated by column chromatography and obtained in analytically pure form. The *endo/exo* stereochemistry of the novel isoxazolidines are based upon extensive NMR investigations. Most relevant are the coupling constants ($J_{H3, H4}$) of the diastereomers. For **2a-4a**, this coupling constant is 6.06–7.18 Hz, implying a *cis* relationship between H-3 and H-4, whereas for **2b–4b**, the coupling constant is 2.28–3.74 Hz implying a trans relationship between H-3 and H-4.[20,21] In all the diastereomers, the configurations of H-5 and H-4 are *cis* as evidenced from their coupling constant values.

For ethyl acrylate and styrene, the regioselectivity was rationalized using frontier orbital theory[22] and ^{1}H NMR experiments. Cycloadditions to α,β-unsaturated carboxylic acid derivatives, *e.g.* ethyl acrylate are particularly useful because high regioselectivity is often observed in water[5]. The reactions have been found to be highly regioselective to form solely 5-substituted isoxazolidines. Nitrone **1** has considerably higher ionization potential than normal nitrones due to the electron withdrawing effect of three chlorine atoms. Therefore, nitrone (LUMO)-dipolarophile (HOMO) interactions completely dominate the reaction and leads to the formation of only 5-substituted adducts[22,23]. From the ^{1}H NMR spectrum of cycloadducts **5** and **6**, it has been found that clear double doublet signal for H-4 proton and triplet signal for H-3 proton has been obtained in both the cases due to further coupling from vicinal hydrogens and hence confirms in favour of 5-substituted adducts. From the detailed investigation on the nature of these cycloaddition reactions using TLC and ^{1}H NMR spectrum studies for the cycloadducts **5** and **6,** it has been also confirmed that no diastereomers have been formed. The relative configurations of H-3, H-4 and H-5 protons of **5** and **6** are *syn* and the cycloadducts are in favour of *exo* transition state geometry as evidenced from their coupling constant values ($J_{H4,H5}$ ~ 6.08–7.46 Hz ; $J_{H3,H4}$ ~ 6.12–7.44 Hz). In the mass spectrum, significant M^++2 ion peak signals of characteristic height are obtained in most of the diastereomers and regioselective cycloadducts as the peak of highest intensity due to isotopic abundance of Cl^{37} atom in these compounds.

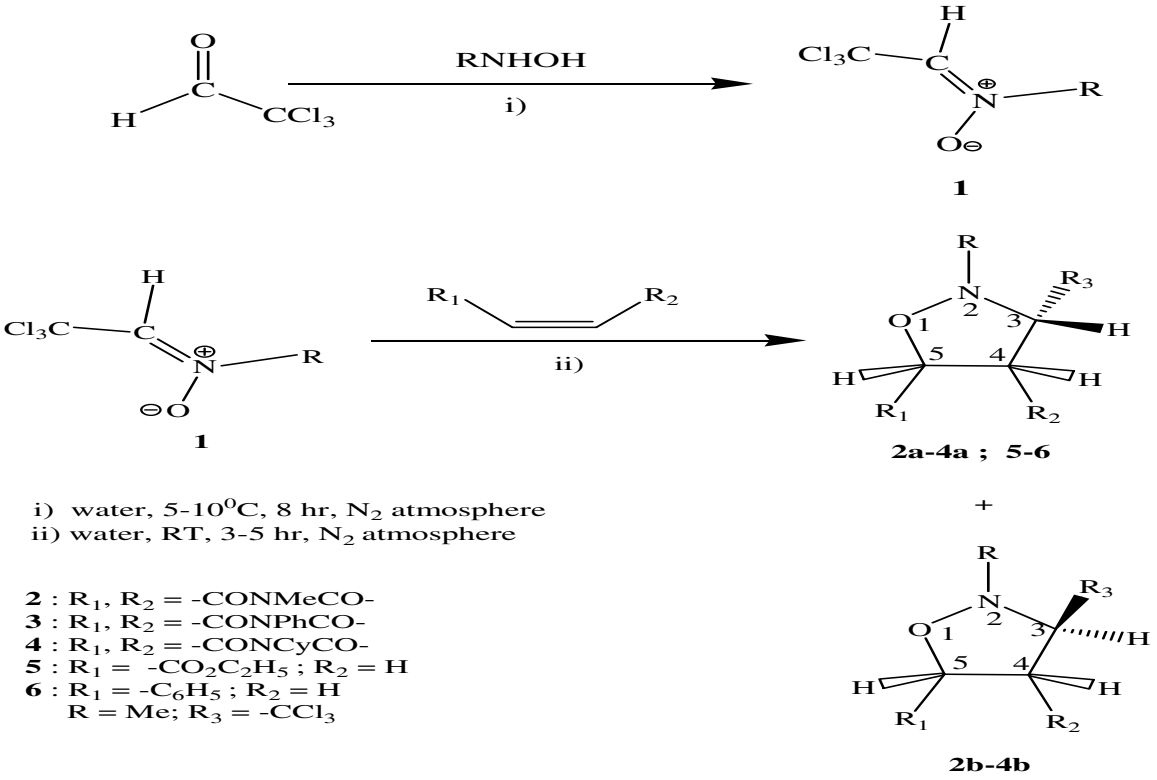
CONCLUSION

In summary, the present procedure provides an example of green chemistry methodology for the synthesis of nitrone and stereo & regioselective novel isoxazolidines in aqueous phase with high yield in a very short reaction time. The notable advantages of this methodology are: (a) high yields (b) faster reaction (c) mild reaction conditions and (d) green synthesis avoiding use of organic solvents. Therefore, it is believed that procedure described here will find important applications in the synthesis of nitrone and isoxazolidine derivatives and thereby offering greater scope for aqueous phase cycloaddition reactions.

Table-1: Physicochemical data of synthesized compounds

Entry	Nitrone	Dipolarophile[a]	Time (hr)	Cycloadduct[b] & m.p (°c) **2a-4a** : ***cis*** ; **2b–4b**: ***trans***	*Cis/trans ratio*(%)	Yield[c] (%)
1	*N*-methyl-α-chloral nitrone	*N*-methyl maleimide	3 (27)	**2a**: White crystals, 142 **2b**: White crystals, 129	**2a**: 66 **2b**: 31	97 (78)
2	*N*-methyl-α-chloral nitrone	*N*-phenyl maleimide	3 (29)	**3a**: White solid, 138 **3b**: White solid, 147	**3a**: 63 **3b**: 32	95 (76)
3	*N*-methyl-α-chloral nitrone	*N*-cyclohexyl maleimide	4 (32)	**4a**: Yellow crystals, 154 **4b**: Yellow crystals, 130	**4a**: 68 **4b**: 26	94 (76)
4	*N*-methyl-α-chloral nitrone	Ethyl acrylate	4 (34)	**5**: Colourless gummy liquid		92 (69)
5	*N*-methyl-α-chloral nitrone	Styrene	5 (38)	**6**: Colourless viscous liquid		91 (67)

[a] Reaction condition: α-chloral nitrone (1 mmol), dipolarophile (1 equivalent), water, N_2 atmosphere, RT
[b]All the reactions were carried out at RT
[c]Isolated yields after purification, Figures in parentheses indicate reactions performed in CH_2Cl_2 .



Scheme 1

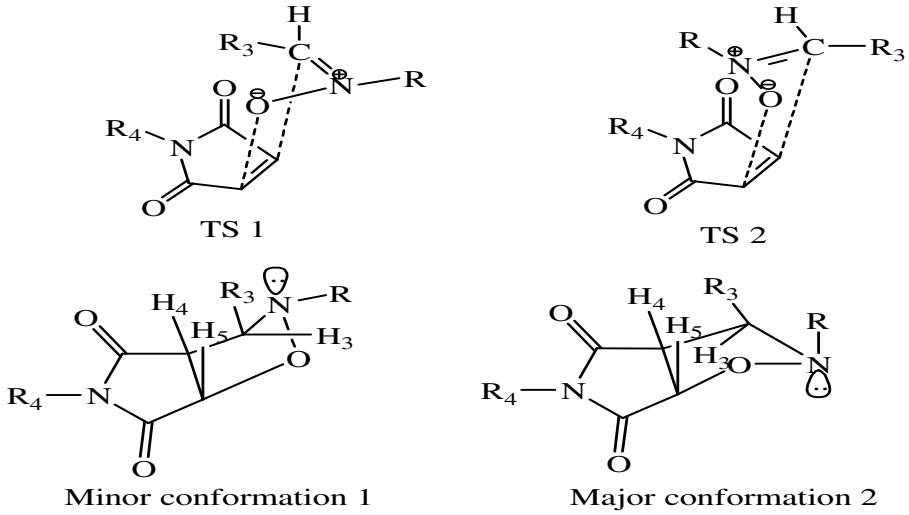


Figure 1

ACKNOWLEDGEMENTS

The authors are pleased to acknowledge the financial support from UGC, New Delhi (Grant no.34-304/2008-SR). The authors are equally grateful to SAIF-CDRI, Lucknow and Prof. A.K. Nanda, University of North Bengal, Darjeeling for providing spectral data.

REFERENCES

1. C.J. Li and T.H. Chang, *Organic reactions in aqueous media*, Wiley, New York., (2007, 1997).
2. Y. Hayashi, *Angew Chem Int Ed (Engl).*, **45**, 8103-8106 (2006).
3. A.P. Brogan, T.J. Dickerson and K.D. Janda, *Angew Chem Int Ed (Engl).*, **45**, 8100(2006).
4. P.A. Grieco, *Organic synthesis in water,* Blackie Academic and Professional, London., (1998).
5. U.M. Lindstrom, *Organic reactions in water,* Blackwell Publishing, Oxford., (2007)
6. B.C. Ranu and S. Banerjee, *Tetrahedron lett.*, **48**, 141(2007)
7. B.Chakraborty, M.S. Chettri, S. Kafley and A. Samanta, *Indian J. Chem.*, **49B**, 209(2010)
8. B.Chakraborty, S. Kafley and M.S. Chhetri, *Indian J. Heterocycl Chem.*, **18**, 203(2008).
9. B.Chakraborty and M.S. Chhetri, *Indian J. Heterocycl Chem.*, **18**, 201(2008).
10. B.Chakraborty and M.S. Chhetri, *Indian J. Chem.*, **49B**, 102 and 394 (2010).
11. A. Padwa and W.H. Pearson, Synthetic application of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products, Wiley, New Jersy., (2003).
12. S.A. Ali and M.Z.N. Iman, *Tetrahedron.*, **63**, 9134(2007)
13. R.N. Butler, W.J. Cunningham, A.G. Coyne and L.A. Burke, *J. Am. Chem. Soc.*, **126**,11923(2004).
14. B. Chakraborty, P. Sharma, S. Kafley, M.S. Chhetri and A.R. Ghosh, *Rasayan J. Chem.*, **2 (4),** 946(2009)
15. B. Chakraborty and M.S. Chhetri, *Indian J. Chem.*, **47B**, 485(2008)
16. B. Chakraborty, P. Sharma, N. Rai, S. Kafley and M.S.Chhetri, *J. Ind. Chem. Soc.,* in press (2010).
17. B. Chakraborty, P. Sharma, S. Kafley and M.S. Chhetri, *Synthesis.,*under revision (2010).
18. B. Chakraborty, P. Sharma, N. Rai, S. Kafley and M.S. Chhetri, *J. Chem. Res* (*RSC*)*.,* **3**, 147 (2010).
19. D. Mersbergen, W.J. Wijnen and B.F.N. Engberts, *J. Org. Chem.,* **63**, 8801(1998).
20. P. Deshong, W. Li, J.W. Kennington and H.L. Ammon, *J. Org. Chem.,* **56**, 1364(1991).
21. R. Gandolfi and P. Grunanger, *The chemistry of heterocyclic compounds,* Wiley Interscience, **49 (2)**774(1999).
22. K.N. Houk, J. Sims and C.R. Luskus, *J. Am. Chem. Soc.,* **95**, 7302(1973).
23. K. Kranjc and M. Kocevar, *Tetrahedron.*, **64**, 45 (2008).

(Received: 1 July 2010 Accepted: 31 July 2010 RJC-594)