High Yield One-Pot Synthesis of Some Novel *N*-Methyl Isoxazolidine Derivatives Using *N*-Methyl-α-chloro Nitrone in Water

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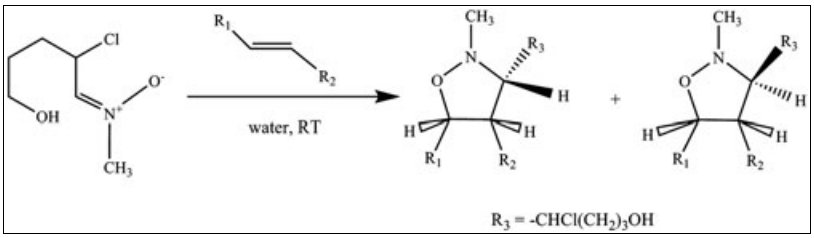

A simple one pot and high yield efficient method is described in water for the diastereo and regioselective synthesis of some novel isoxazolidine derivatives at room temperature in a short reaction time.

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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 is highly appreciated. Keeping in touch with green chemical pathway of synthesis 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. 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 a variety of natural products of biological interest [11]. In recent years, focus has been shifted toward asymmetric nitrone cycloaddition reactions, enantioselective, catalytic enantioselective, and diastereoselective synthetic methodologies in aqueous phase [12,13].

RESULTS AND DISCUSSION

Herein, we would like to report high yield diastereo and regioselective synthesis of some novel isoxazolidine derivatives in water using 1,3-dipolar cycloaddition reaction with *N*-methyl-α-chloro nitrone (**1**) in a short reaction time (Scheme 1). The synthetic potentiality of nitrone **1** has been already reported in aldehyde and ketone synthesis [14–17]. This is quite a new approach of nitrone synthesis from hemiacetal. The efficacy of a diastereoselective approach using a chiral nitrone very much depends on the ability of the chiral auxiliary to effectively transfer chirality to the newly created stereocenters. This study 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 (CH_2Cl_2). Although reactions are found to be diastereo and regioselective but reaction rate and yields are not impressive (Table 1).

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. Almost all the reactions in water are very fast (3–4 h in case of maleimides,ethyl acrylate and 5 h for styrene) compared with the normal cycloaddition reactions in organic solvents which were reported to take longer periods (26–48 h) [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. 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 the 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

Scheme 1

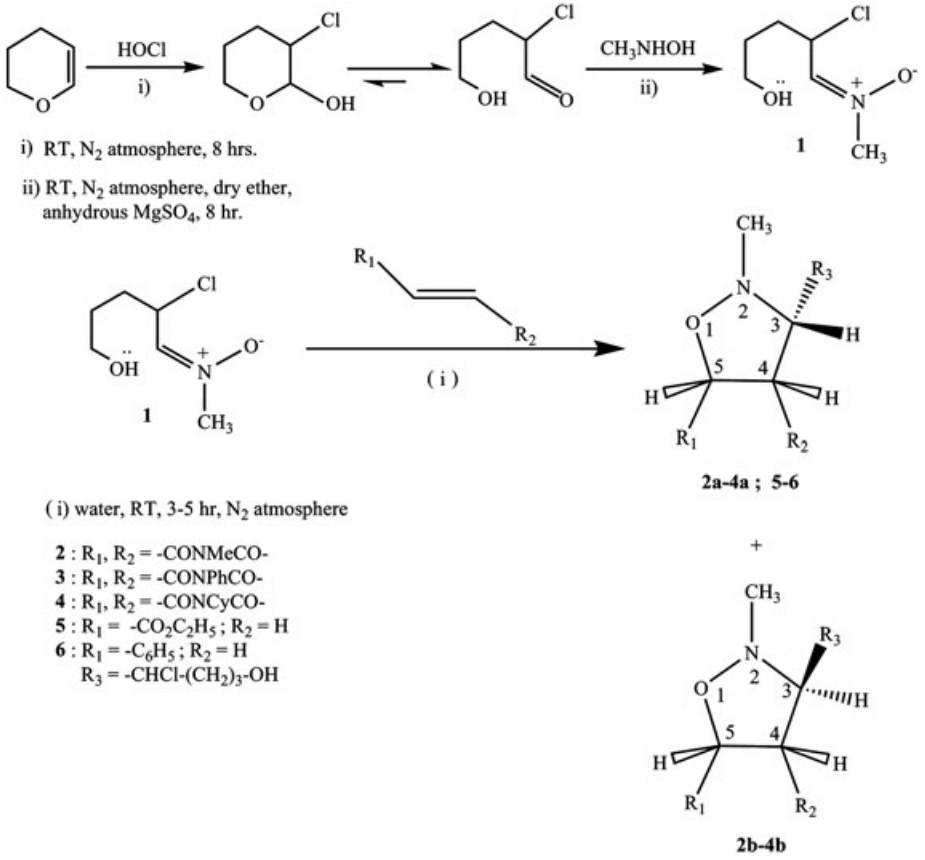

Table 1

Physicochemical data of synthesized compounds (**2–6**).

Entry	Nitrone	Dipolarophile[a]	Time (h)	Cycloadduct[b] and mp (°C): **2a**–**4a**, *cis*; **2b**–**4b**, *trans*	*Cis/trans* ratio(%)	Yield[c] (%)
1	*N*-Methyl-α-chloro nitrone	*N*-Methyl maleimide	3 (27)	**2a**: White crystals, 137 **2b**: White crystals, 106	**2a**: 66 **2b**: 31	97 (78)
2	*N*-Methyl-α-chloro nitrone	*N*-Phenyl maleimide	3 (29)	**3a**: White solid, 145 **3b**: White solid, 122	**3a**: 63 **3b**: 32	95 (76)
3	*N*-Methyl-α-chloro nitrone	*N*-Cyclohexyl maleimide	4 (32)	**4a**: Yellow crystals, 140 **4b**: Yellow crystals, 113	**4a**: 68 **4b**: 26	94 (76)
4	*N*-Methyl-α-chloro nitrone	Ethyl acrylate	4 (34)	**5**: Colorless gummy liquid		92 (69)
5	*N*-Methyl-α-chloro nitrone	Styrene	5 (38)	**6**: Colorless viscous liquid		91 (67)

Figures in parentheses indicate reactions performed in CH_2Cl_2.
[a]Reaction condition: α-chloro 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.

regioselectivity and to predict the yield, rate in 1,3-dipolar cycloadditions [18,19]. 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 of 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 is observed in nitrone additions in water. The addition of nitrone **1** to maleimides results in a mixture of diastereomer **2a–4a** and **2b–4b** (almost 65:35 ratio in all cases) and generation of as many as three to four chiral

centres in a single step. Studies 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. 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** is formed by the *endo* approach of *Z* nitrone (transition state **2**). The mixture of diastereomers are 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 differences in the ^{1}H NMR data for the diastereomers are the position and multiplicity of the 3-H signal. In the major adducts **2a–4a**, coupling constant between 3-H and 4-H has been measured as $J_{3,4}$ ~6.26 Hz, whilst for minor adducts **2b–4b**, $J_{3,4}$ is ~2.26 Hz. These differences can be explained by considering the available isoxazolidine ring conformations. Because of 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 is assigned to the minor conformer (Fig. 1). The diastereomeric isoxazolidines **2a–4a** and **2b–4b** were separated by column chromatography and obtained in analytically pure form. The endo/exo stereochemistry aforementioned is based on extensive NMR investigations. Most relevant are the coupling constants ($J_{H3,\,H4}$) of the diastereomers. For **2a-4a**, this coupling constant is almost 6.26 Hz, implying a *cis* relationship between H-3 and H-4, whereas for **2b–4b**, the coupling constant is almost 2.26 Hz, which implies a *trans* relationship between H-3 and H-4 [20,21].

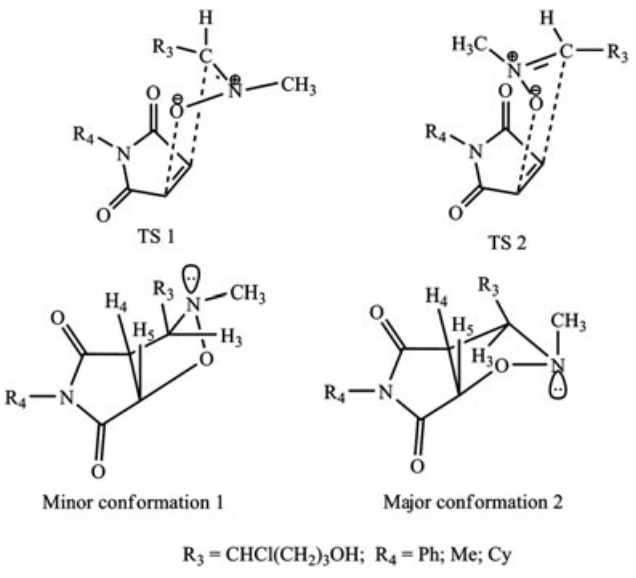

Figure 1. Transition states the development of isoxazolidines and their conformations.

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 by using frontier orbital theory [18] and ^{1}HNMR 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 were 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 chlorine. Therefore, nitrone (LUMO)-dipolarophile (HOMO) interactions completely dominate the reaction and lead to the formation of only 5-substituted adducts [18,22]. From the ^{1}H NMR spectrum of cycloadducts **5–6**, it has been found that clear double doublet signal for H-4 protons and doublet of triplet signal for H-3 protons are obtained in both the cases due to further coupling from vicinal hydrogens and hence confirms in favor of 5-substituted adducts. From the detailed investigations on the nature of these cycloaddition reactions using TLC and ^{1}H NMR spectrum studies for the cycloadducts **5–6**, it is also confirmed that no diastereomers are formed. The relative configurations of H-3, H-4 and H-5 protons in these adducts are *syn* and the cycloadducts are in favor of *exo* transition state geometry as evidenced from their coupling constant values ($J_{H4,H5}$ ~ 6.06–7.40 Hz; $J_{H4,H3}$ ~ 6.20–6.80 Hz). In general, the reactions are very clean and high yielding compared with usual cycloaddition reactions of nitrones. The products have been characterized from their spectroscopic (IR, ^{1}HNMR, HRMS, ^{13}CNMR) data. No catalyst or coorganic solvent are required. The structures of **2–6** have been confirmed by ^{1}H and ^{13}CNMR spectroscopy in $CDCl_3$ solution along with MS and IR spectra. Thus, the ^{1}H NMR spectra of **2–4** indicate that these isoxazolidine derivatives are formed as a mixture of diastereomers in almost 65:35 ratio with *cis* and *trans* configurations relative to the spatial orientation of the R_3 group at C_3 with respect to the H atom at C_4 position. These diastereomers have been separated by column chromatography and recrystallized from heptane-ethyl acetate [23]. The ^{1}HNMR spectrum of **2a–4a** and **2b–4b** displayed different spectrum (position of signals) for the diastereomers. In contrast, the ^{1}HNMR spectrum of **5–6** displayed only one set of signals indicating that they are formed as unique cycloadducts. The exact stereochemistry at the asymmetric CHCl carbon atom of almost all the cycloadducts could not be determined due to multiplet signals (doublet of triplet appears almost as multiplet) obtained in the NMR spectrum, and also, because of freely rotating carbon centre at CHCl. In the ^{13}CNMR spectrum, four signals were obtained in case of phenyl ring carbon atoms due to the equivalent nature of C-2 and C-6 and C-3 and C-5

carbons. In the mass spectrum, significant M^++2 ion peak signals of characteristic height are obtained in most of the diastereomers and regioselective cycloadducts due to presence of isotopic abundance of Cl^{37} atom in these compounds. In addition, mass fragmentation peaks of different value are also obtained for diastereomers of a particular cycloadduct. Studies of HRMS spectra show almost exact masses in majority of the compounds.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance DRX-300 spectrometer (300 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75 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 DART-HRMS, JMS–T100LC, Accu-TOF instrument. Elemental analyses (CHN) were performed with a Perkin-Elmer 2400 series CHN Analyzer. TLC's were run on Fluka silica gel precoated TLC plates. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-Methylhydroxylamine was purchased from Aldrich Chemical Company and was used as received.

General procedure for the synthesis of nitrone 1. *N*-Methylhydroxylamine (250 mg, 5.3127 mmole) was added to chlorohydrin (720 mg,1 equivalent) in dry ether (25 mL) and the reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 10 h. The formation of nitrone was monitored by TLC (R_f = 0.34). The nitrone was isolated under reduced pressure vacuum pump as white needle shape crystals (94%; m.p: 52°C).

Nitrone 1. Yield: 94%; white needle shape crystals; R_f = 0.34, m.p: 52°C (uncorrected); IR (KBr): 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* = 6.16, 6.08 Hz, CHCl), 3.31 (s, 3H, N^+– CH_3), 1.88–1.15 (m, 6H, CH_2 protons); ^{13}C NMR($CDCl_3$): δ 141.55 (CH═N^+), 55.76 (CHCl), 34.84 (N^+- CH_3), 28.50, 27.22, 26.00 (3 CH_2 carbons); HRMS–EI: Calcd. for $C_6H_{12}O_2NCl$, (M), 165.0870, Found: M^+, 165.0861.

General procedure for cycloaddition (for diastereomers). In a 50 mL conical flask, nitrone **1** (1 mmole), dipolarophile (1 mmole) and water (15 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 3–4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the products were extracted with ether (2 × 25 mL); the organic layer was washed with saturated brine (2 × 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 (Scheme 1). This procedure was followed for the substrates **1**–**3** listed in Table 1.

(3S)-3-((R)-1-Chloro-4-hydroxybutyl)-dihydro-2,5-dimethyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione, 2a. White crystals. Yield 66%; R_f = 0.46; 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* = 6.06, 6.20 Hz, C_4H), 3.30 (s, 2 × 3H, 2-CH_3 protons), 3.00 (d, 1H, *J* = 6.60 Hz, C_5H), 2.70 (dd, 1H, *J* = 6.42, 6.20 Hz, C_3H), 2.34 (dt, 1H, *J* = 6.04, 6.00 Hz, CHCl), 1.82–1.50 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 178.12, 176.80 (carbonyl carbons), 87.15 (C_5), 76.00 (C_3), 67.10 (CH_2OH), 53.54 (C_4), 50.70 (CHCl), 38.00, 37.14 (2 × CH_3), 22.32, 21.45 (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%.

(3R)-3-((S)-1-Chloro-4-hydroxybutyl)-dihydro-2,5-dimethyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6a-H)-dione, 2b. White crystals. Yield 31%; R_f = 0.52; 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* = 2.52, 2.36 Hz, C_4H), 3.14 (s, 2 × 3H, 2-CH_3 protons), 3.04 (d, 1H, *J* = 4.54 Hz, C_5H), 2.62 (dd, 1H, *J* = 3.60, 3.12 Hz, C_3H), 2.27 (dt, 1H, *J* = 1.80, 1.64 Hz, CHCl), 1.90–1.54 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 179.00, 178.30 (carbonyl carbons), 86.92 (C_5), 75.46 (C_3), 64.77 (CH_2OH), 54.32 (C_4), 51.20 (CHCl), 41.10, 39.00 (2xCH_3), 24.00, 23.22 (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%.

(3S)-3-((R)-1-Chloro-4 hydroxy butyl)-dihydro-2-methyl-5-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione, 3a. White solid. Yield 63%; R_f = 0.38; IR (KBr): υ_{max} 3585–3453 (br), 2920 (m), 2835 (m), 1758 (s), 1660 (s), 1480 (m), 1346 (m), 805 (s), 770 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.10 – 6.95 (m, 5H, C_6H_5), 5.80 (d, 1H, *J* = 6.74 Hz, C_5H), 5.04–4.93 (br, s, 1H, OH, exchanged in D_2O), 3.44 (dd, 1H, *J* = 6.04, 6.16 Hz, C_4H), 3.26 (s, 3H, CH_3), 2.70 (dt∼m, 1H, CHCl), 1.84 (dd, 1H, *J* = 6.22, 6.28 Hz, C_3H), 1.55–1.14 (m, 6H, CH_2 protons); ^{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), 62.73 (CH_2OH), 57.40 (C_4), 54.00 (CHCl), 39.55 (CH_3), 26.40, 25.00 (2 CH_2 carbons); FAB-MS: *m/z* 340 (M^++2, 87%), 338 (M^+,100%), 323, 307, 261, 247, 231, 216 (B.P), 107, 77; HRMS–EI: Calcd for $C_{16}H_{19}O_4N_2Cl$ (M) *m/z* 338.1360. Found: M^+ 338.1347. Anal. Found: C, 56.77; H, 5.53; N, 8.22. $C_{16}H_{19}O_4N_2Cl$ requires C, 56.82; H, 5.65; N, 8.28%.

(3R)-3-((S)-1-Chloro-4-hydroxybutyl)-5-phenyl-2-methyldihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6a-H)-dione, 3b. White solid. Yield: 32%, R_f = 0.44; IR (KBr): υ_{max} 3580–3448 (br), 2935 (m), 2830 (m), 1762 (s), 1664 (s), 1485 (m), 1280 (m), 800 (s), 776 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.98 – 6.93 (m, 5H, C_6H_5), 5.84 (d, 1H, *J* = 4.50 Hz, C_5H), 4.96–4.82 (br, s, 1H, OH, exchanged in D_2O), 3.51 (dd, 1H, *J* = 1.20, 1.35 Hz, C_4H), 3.30 (s, 3H, CH_3), 2.61 (dt∼m, 1H, CHCl), 1.90 (dd, 1H, *J* = 1.60, 1.54 Hz, C_3H), 1.50 – 1.10 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 176.00, 175.12 (carbonyl carbons), 136.25, 135.28, 133.60, 132.45 (aromatic carbons), 84.90 (C_5), 75.65 (C_3), 63.55 (CH_2OH), 56.60 (C_4), 55.20 (CHCl), 40.15 (CH_3), 21.87, 20.46 (2 CH_2 carbons); MS: *m/z* 340 (M^++2, 78%), 338 (M^+,100%), 323, 307, 288, 261, 255, 247, 231, 216 (B.P), 107, 77; HRMS – EI: Calcd for $C_{16}H_{19}O_4N_2Cl$ (M) *m/z* 338.1360. Found: M^+ 338.1344. Anal. Found: C, 56.75; H, 5.54; N, 8.17. $C_{16}H_{19}O_4N_2Cl$ requires C, 56.82; H, 5.65; N, 8.28%.

(3S)-3-((R)-1-Chloro-4-hydroxybutyl)-5-cyclohexyl–dihydro-2-methyl--2H-pyrrolo[3,4-d]isoxazole-4,6(5H, 6a-H)-dione, 4a. Yellow crystals. Yield 68%, R_f = 0.44; IR (KBr): υ_{max} 3530–3465 (br), 2870 (s), 1770 (s), 1683 (s), 1446 (m), 1380 (m), 1265 (m), 815 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.30 (d, 1H, *J* = 6.64 Hz, C_5H), 5.02–4.92 (br, s, 1H, OH, exchanged in D_2O), 4.70 (dd, 1H, *J* = 7.26, 7.18 Hz, C_3H), 4.20 (dd, 1H, *J* = 6.26, 6.08 Hz, C_4H), 2.92 (dt∼m, 1H, CHCl), 3.34 (s, 3H, CH_3), 1.43 – 1.14 (m, 17H, cyclohexyl and CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 177.58, 176.00 (carbonyl carbons), 86.80 (C_5), 77.08 (C_3), 63.50 (CH_2OH), 55.00 (C_4), 50.66 (CHCl), 38.80 (CH_3), 31.10, 29.52, 27.70, 26.30, 25.00, 23.28, 22.00, 18.27 (cyclohexyl and CH_2 carbons); FAB-MS: *m/z* 346 (M^+ +2, 77%), 344 (M^+,100%), 329, 294, 255, 237, 222 (B.P), 107, 83; HRMS – EI: Calcd for $C_{16}H_{25}O_4N_2Cl$ (M) *m/z* 344.1720. Found: M^+ 344.1707. Anal. Found: C, 55.69; H, 7.25; N, 8.05. $C_{16}H_{25}O_4N_2Cl$ requires C, 55.78; H, 7.31; N, 8.13%.

(3R)-3-((S)-1-Chloro-4-hydroxybutyl)-5-cyclohexyl–dihydro-2-methyl--2H-pyrrolo[3,4-d]isoxazole-4,6(5H, 6a-H)-dione, 4b. Yellow crystals. Yield 26%, R_f = 0.56; IR (KBr): υ_{max} 3523–3474 (br), 2880 (s), 1770 (s), 1680 (s), 1440 (m), 1385 (m), 1260 (m), 810 (s), 774 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.20 (d, 1H, *J* = 3.70 Hz, C_5H), 4.97–4.86 (br, s, 1H, OH, exchanged in D_2O), 4.66 (dd, 1H, *J* = 2.80, 2.04 Hz, C_3H), 4.30 (dd, 1H, *J* = 3.42, 3.60 Hz, C_4H), 2.90 (dt∼m, 1H, CHCl), 3.30 (s, 3H, CH_3), 1.48–1.08 (m, 17H, cyclohexyl and CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 179.00, 178.10 (carbonyl carbons), 86.00 (C_5), 76.40 (C_3), 64.25 (CH_2OH), 56.36 (C_4), 51.90 (CHCl), 37.23 (CH_3), 29.57, 28.00, 27.20, 25.34, 23.00, 20.54, 19.20, 18.28 (cyclohexyl and CH_2 carbons); MS: *m/z* 346 (M^++2, 70%), 344 (M^+, 100%), 329, 294, 261, 237, 236, 222 (B.P), 107, 83; HRMS–EI: Calcd for $C_{16}H_{25}O_4N_2Cl$ (M) *m/z* 344.1720. Found: M^+ 344.1704. Anal. Found: C, 55.64; H, 7.22; N, 8.06. $C_{16}H_{25}O_4N_2Cl$ requires C, 55.78; H, 7.31; N, 8.13%.

General procedure for cycloaddition (for regioselective cycloadducts). In a 50 mL conical flask, nitrone **1** (1 mmole), dipolarophile (1 mmole) and water (15 mL) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 4–5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with ether (2 × 25 mL), the organic layer was washed with saturated brine (2 × 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 (Scheme 1). This procedure was followed for the substrates **4** and **5** listed in Table 1.

(3S)-Ethyl-3-(1-chloro-4 hydroxy butyl)-2-methyl isoxazolidine-5-carboxylate, 5. Colorless gummy liquid. Yield 92%, R_f = 0.40; IR (KBr): υ_{max} 3514–3440 (br), 2925 (s), 2842 (m), 1755 (s), 1444 (s), 790 (s) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 4.90–4.78 (br, s, 1H, —OH, exchanged in D_2O), 4.18 (q, 2H, *J* = 4.64, 4.34 Hz, —OCH_2CH_3), 4.02 (t, 1H, *J* = 7.46 Hz, C_5H), 3.40 (dt, 1H, *J* = 6.54, 6.70 Hz, C_3H), 3.18 (dd, 2H, *J* = 7.12, 7.44 Hz, C_4 2H), 2.84 (dt∼m, 1H, CHCl), 3.15 (s, 3H, CH_3), 1.26 (t, 3H, *J* = 5.40 Hz, —OCH_2CH_3), 1.18 – 0.86 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169.32 (carbonyl carbon), 84.70 (C_5), 79.12 (C_3), 67.42 (CH_2OH), 61.00 (CH_2 carbon of —OCH_2CH_3), 56.90 (C_4), 53.64 (CHCl), 37.20 (CH_3), 22.40, 21.35 (2 CH_2 carbons), 15.45 (CH_3 carbon of OCH_2CH_3); MS: *m/z* 267 (M^++2, 64%), 265 (M^+,100%), 220, 192, 191, 158, 143 (B.P), 108, 107, 73, 45; HRMS-EI: Calcd for $C_{11}H_{20}O_4NCl$ (M) *m/z* 265.1320. Found: M^+ 265.1303. Anal. Found: C, 49.69; H, 7.48; N, 5.24. $C_{11}H_{20}O_4NCl$ requires C, 49.78; H, 7.59; N, 5.28%.

4-Chloro-4-((3S)-2-methyl-5-phenyl-isoxazolidin-3-yl)butan-1-ol, 6. Colorless viscous liquid. Yield 91%, R_f = 0.50; IR (KBr): υ_{max} 3520–3380 (br), 2925 (s), 2844 (m), 1710 (s), 1440 (m), 1324 (s), 804 (m), 776 (s) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 6.80–6.73 (m, 5H, C_6H_5), 4.94 (t,1H, *J* = 6.08 Hz, C_5H), 4.85–4.77 (br, s, 1H, exchanged in D_2O), 4.28 (dt, 1H, *J* = 6.52 Hz, C_3H), 3.90 (dd, 2H, *J* = 6.48, 6.12 Hz, C_4 2H), 3.66 (dt∼m, 1H, CHCl), 3.18 (s, 3H, CH_3), 1.47–1.08 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 136.75, 135.22, 133.00, 132.14 (aromatic carbons), 85.95 (C_5), 77.32 (C_3), 60.64 (CH_2OH), 56.40 (C_4), 52.38 (CHCl), 38.66 (CH_3), 20.27, 19.20 (2 CH_2 carbons); FAB-MS: *m/z* 271 (M^++2, 62%), 269 (M^+,100%), 192, 191, 162, 147 (B.P), 107, 77; HRMS-EI: Calcd for $C_{14}H_{20}O_2NCl$ (M) *m/z* 269.1370. Found: M^+ 269.1357. Anal. Found: C, 62.32; H, 7.40; N, 5.13. $C_{14}H_{20}O_2NCl$ requires C, 62.42; H, 7.48; N, 5.20%.

CONCLUSIONS

In summary, the present procedure provides an example of green chemistry methodology for the synthesis of regio and stereoselective novel isoxazolidines in aqueous phase with high yield in a short reaction time. The notable factors 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 isoxazolidine derivatives and thereby offering greater scope for aqueous phase cycloaddition reactions.

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