Synthesis of Some Novel Bisisoxazolidine Derivatives from Glyoxal-derived Bisnitrones via Simultaneous Double Cycloaddition Reactions in Water

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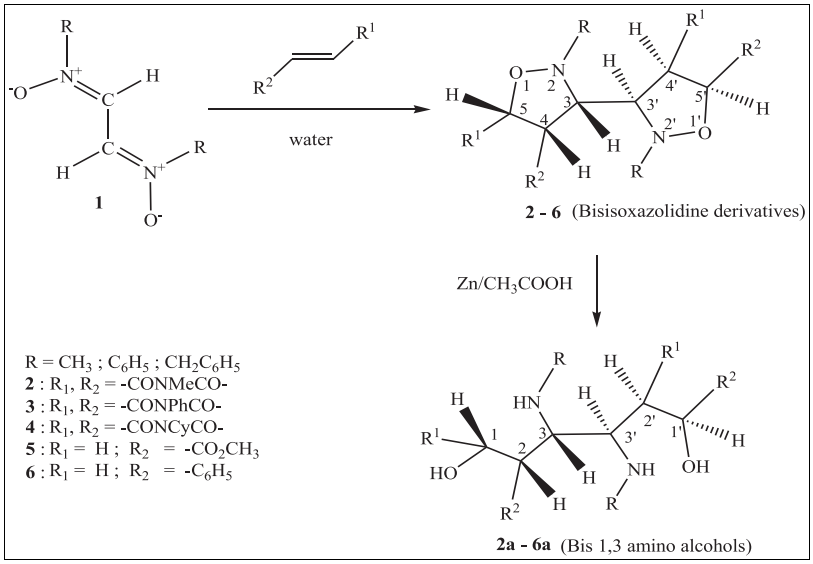
Additional supporting information may be found in the online version of this article at the publisher's website.
Received October 3, 2013
DOI 10.1002/jhet.2181
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



Simultaneous double 1,3-dipolar cycloaddition reactions of glyoxal-derived bisnitrones have been described in water. Significant rate acceleration and improved yields of exclusively diastereoselective and regioselective bisisoxazolidines in water have been observed at room temperature in a short reaction time compared with conventional solvents.

J. Heterocyclic Chem., **00,** 00 (2014).

INTRODUCTION

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 from their birth up to now, unequivocally witnesses to their leading chemistry. The so-called "conventional solvents" are organic solvents that have undoubtedly promoted their success. Yet, the toxicity aspect of these solvents impedes their use freely and with no fear. Not only is the operating chemist uncomfortable while experimenting, but also the environment is equally threatened. Working out the cycloaddition reactions and other organic ones in aqueous system would certainly bring some relief to the chemist and to the environment as well. Unusual outcomes in terms of yield, reactivity, and selectivity compared with those performed in organic solvents were commonly observed and have overwhelmed the chemists with surprise indeed [1,2]. The 1,3-dipolar cycloaddition methodology applied to aqueous media has brought forth a number of heterocyclic compounds, usually with a regio and stereoselectivity pecularity. These heterocycles include isoxazoles, isoxazolidines, and pyrrolidines. This rate of acceleration of organic reactions in aqueous media was ascribed to one or a combination of the following factors and phenomena [3], the high cohesive energy density of water, the high internal pressure within the medium, the hydrogen-bonding ability, the hydrophobic packing of diene and dienophile in cycloaddition reactions, the hydrophobic versus antihydrophobic effects, the micellar catalysis, the solvophobicity, and the solvent polarity. Today's status, the insolubility of organic reactants in water, once considered a drawback, turns out to be advantageously a leading factor for the success of organic reactions in pure water. In 2005, Sharpless coined these heterogeneous reactions as "on-water" reactions [4,5]. The "on water" method consists simply of stirring the reactant(s) with water to generate an aqueous suspension, and it has been observed that both kinetics and yields are extremely enhanced in most cases, compared with those in organic solvents.

In continuation of our efforts to establish green methodologies in nitrone cycloaddition reactions [6–9], herein, we wish to report a new route to the synthesis and 1,3-dipolar cycloaddition reaction of glyoxal-derived bisnitrones (having vast synthetic potentials) with a variety of alkenes to produce

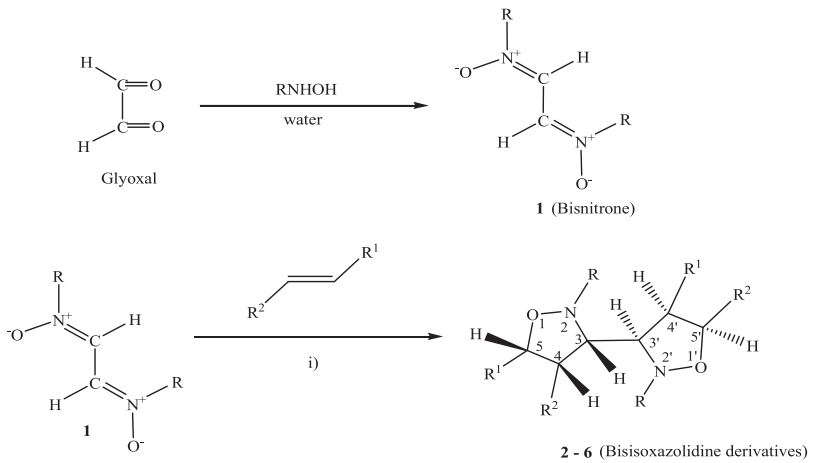
novel bisisoxazolidine derivatives (**2–6**) in water (Scheme 1) . This is quite a new approach of the synthesis of nitrone from glyoxal. The present study has been carried out with three different maleimides (*N*-methyl/phenyl/cyclohexyl) and ethyl acrylate, styrene respectively in water. Simultaneously, the reactions have been also studied in organic solvent (CH_2Cl_2) as well.

RESULTS AND DISCUSSION

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 are reported to take longer periods (26–48 h) [10,11].

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 and ethyl acrylate and thereby greatly facilitates the reaction. The 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 regioselectivity and to predict the yield, rate in 1,3-dipolar cycloadditions [12,13]. This theory states that the Gibbs energy of activation is related to the energy gap between the interacting highest occupied molecular orbital and lowest unoccupied molecular orbital. The dipolarophiles such as styrene are weak hydrogen bond acceptor, which means that their FMO's are only slightly affected by hydrogen bond interactions and leads to a reduction of the energy gap between the interacting FMO's (in this case, the highest occupied molecular orbital of the dipolarophile and lowest unoccupied molecular orbital 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. Bisnitrones (**1**) reacted with *N*-substituted maleimides giving bisisoxazolidines. Diastereoselective reactions of the dipole **1** furnished diastereoselective cycloadducts (**2–4**) and are classified as *trans* biscycloadducts as the 3-H and 4-H protons on each isoxazolidine ring are *trans* orientated as evidenced from ^{1}H-NMR spectroscopy [14,15]. On the other hand, bisnitrones **1** reacted with ethyl acrylate and styrene giving exclusively regioselective bisisoxazolidines (**5–6**). All the novel biscycloadducts (**2–6**) are obtained as diastereoselective and regioselective isomeric forms and stereochemical information portrayed in the drawing implies relative and not absolute relations [16]. The structures of the diastereoselective and regioselective

Scheme 1. Synthesis of bisnitrone and bisisoxazolidine derivatives from glyoxal.

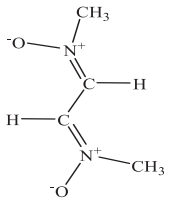
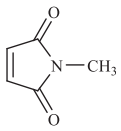
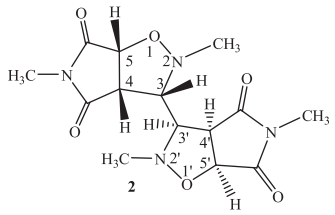
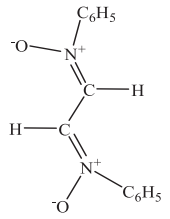
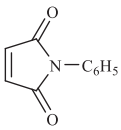
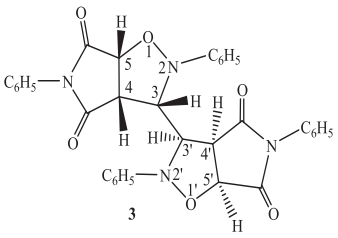
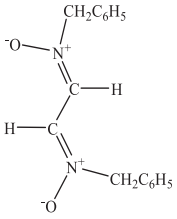
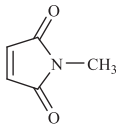
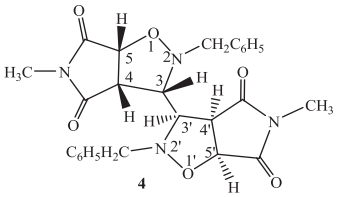
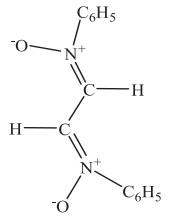
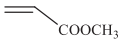
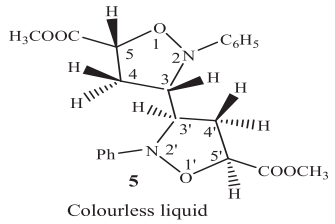
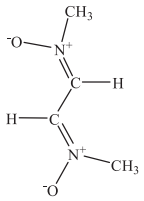
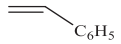
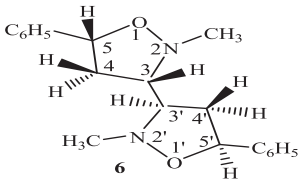


i) water, RT, 3-5 hr, N_2 atmosphere

R = CH_3 ; C_6H_5 ; $CH_2C_6H_5$
2 : R_1, R_2 = -CONMeCO-
3 : R_1, R_2 = -CONPhCO-
4 : R_1, R_2 = -CONCyCO-
5 : R_1 = H ; R_2 = $-CO_2CH_3$
6 : R_1 = H ; R_2 = $-C_6H_5$

Table 1

1,3-Dipolar cycloaddition reaction of glyoxal-derived bisnitrones with alkenes in water.

Entry	Bisnitrone[a] (**1**)	Alkene	Bisisoxazolidine[b] (**2–6**)	Time (h)	Yield[c] (%)
1			 **2** de = 88 ; Yellowish white crystals, m.p 142 ^{0}C	3 (26)	94 (62)
2			 **3** de = 96, Yellow solid, m.p 116^0 C	3 (27)	91 (59)
3			 **4** de = 92 ; White crystals, m.p 135^0 C	4 (28)	91 (60)
4			 **5** Colourless liquid	4 (30)	88 (60)
5			 **6** Greenish sticky liquid	5 (35)	83 (57)

[a]Reaction conditions: bisnitrone (1 mmol), alkenes (2 equivalent), water (15 mL), and N_2 atmosphere.
[b]All products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectral data.
[c]Isolated yield after purification. Figures in parentheses indicate reactions performed in conventional solvents (CH_2Cl_2).

(5-substituted) novel bisisoxazolidine derivatives are confirmed on the basis of ^{1}H-NMR spectroscopy [14,15]. It is also evident from the ^{1}H-NMR spectrum of the diastereoselective bisisoxazolidines (**2–4**) that the structures are expected to be symmetrical in nature and that 3-H and 4-H are *cis* orientated on both rings while vicinal coupling constant has been found to be $J_{3,4} \sim 6.80$ Hz [17]. Compared with conventional conditions, the cycloaddition reactions

performed in water are much faster and selective [18]. As an example, the reaction between nitrone **1** and alkenes, afforded bisisoxazolidine (**2**) at room temperature (RT) after 34 h in 57% yield in CH_2Cl_2 and after 3 h in 93% yield in water (entry 1), respectively. The reaction of nitrone **1** with various alkenes follow the general mechanistic pattern of 1,3-dipolar cycloaddition reactions as found in literature [10,11]. Initial study reports on the biological activity of the synthesized bisisoxazolidine derivatives are also very encouraging. All the novel bisisoxazolidine derivatives (**2–6**) have been found to be very effective against both gram-positive and gram-negative organisms, which gives an opportunity to develop new broad spectrum antimicrobial agents. Screening study (SEM and TEM) on these novel bisisoxazolidines are going on at present.

Furthermore, these novel biscycloadducts (**2–6**) are found to have vast synthetic potential as they could be converted into 1,3 difunctional amino alcohols (Scheme 2). Studies are in progress.

To explore the potentiality of this procedure, we are now extending the protocol, to *N*-substituted bisnitrones (with hydroxyl derivatives in phenyl ring also) for the synthesis of novel bisisoxazolidine derivatives. Synthesis of various bisisoxazolidine derivatives from terepthaldehyde-derived bisnitrones are also in progress at present. All the biscycloadducts are found to be stable and have prominent molecular ion peak and base peaks in the mass spectrum as expected. It has been observed that the *N*-methyl dipole reacts less selectively but furnishes higher yields than its electron poor *N*-phenyl analog. A plausible stereochemistry of the bisisoxazolidines obtained from maleimides (**2–4**) has been assigned on the basis of 3-H and 4-H proton signals of both the isoxazolidine rings appeared as double doublet and doublets, respectively [19,20].

In addition, these bisisoxazolidine derivatives could be easily recovered on work-up. Because the products are fairly soluble in water, they could be easily extracted with ether. Important signals of C_3H, C_4H, and C_5H protons of both the isoxazolidine rings (*cis*, *cis*) of the novel bisisoxazolidine derivatives have been found to be merged and obtained as a single signal. Double doublet signal of C_4H protons appeared as broad signal in majority of the novel biscycloadducts and coupling constant values could not be calculated. High selectivity is observed in these simultaneous double cycloaddition reactions and best selectivity (diastereomeric excess) was observed in the cycloaddition reactions of *N*-phenylbisnitrone with *N*-phenyl maleimide (de% 96, entry **2**, Table 1). Enhanced reaction rates, excellent yields, and high selectivity are the features observed in these double cycloaddition reactions. All the products are characterized by ^{1}H-NMR, ^{13}C-NMR, IR and mass spectrometry (MS) spectroscopic data.

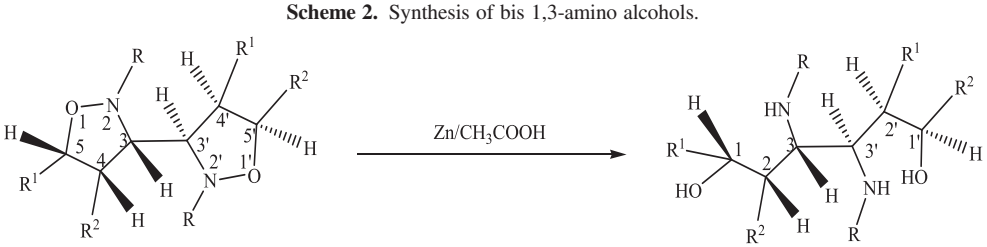
CONCLUSION

In conclusion, we have reported a new methodology of the synthesis of bisisoxazolidines from one pot double cycloaddition reactions on bifunctional nitrones with maleimides and other activated alkenes. *N*-methyl dipoles are more reactive, but less selective than their *N*-phenyl analogs. Biscycloadducts with *N*-methyl/*N*-phenyl substituents on the isoxazolidine ring are *cis* disposed with respect to 3-H and 4-H protons. Finally, we have also shown that these cycloaddition reactions may be conveniently carried out in water with the obtainment of corresponding novel bisisoxazolidines in good conversions and yields with high synthetic potentials, selectivities.

EXPERIMENTAL

^{1}H-NMR spectra were recorded with a Bruker DRX 300 (SAIF-CDRI, Lucknow, Uttar Pradesh, India) spectrometer (300 MHz, FT-NMR) using tetramethylslane as internal standard. ^{13}C-NMR spectra were recorded on the same instrument at 75 MHz. The coupling constants (*J*) are given in hertz. IR spectra were obtained with a Perkin-Elmer RX 1-881 (SAIF-CDRI, Lucknow, Uttar Pradesh, India) machine as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) (SAIF-CDRI, Lucknow, Uttar Pradesh, India) instrument. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck 60 F_{254} UV indicator) while column chromatography was performed with silica gel (E. Merck India) 60–200 mesh. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-Benzylhydroxylamine, *N*-Phenyl maleimide, *N*-Methyl maleimide, starting materials, and reagents used in the reactions were obtained commercially from Aldrich, Lancaster, Fluka and were used without purification, unless otherwise indicated. Characterization of the novel biscycloadducts has been confirmed on the basis of spectral data.

Scheme 2. Synthesis of bis 1,3-amino alcohols.



2 (Bisisoxazolidine derivatives) **2a** (Bis 1,3-amino alcohols)

General procedure for the synthesis of nitrone 1. To a solution of glyoxal (309 mg, 5.3127 m*M*) in diethyl ether (20 mL), *N*-methylhydroxylamine (500 mg, 2 equivalent), and anhydrous $MgSO_4$ (2 g) was added. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 h. The formation of bisnitrone was monitored by TLC (R_f = 0.36). Usual workup followed by concentrated *in vacuo* furnished *N*-methyl bisnitrone as white crystals (86%; mp: 78°C). Same methodology was followed for the synthesis of other bisnitrones (R = C_6H_5; $CH_2C_6H_5$). All the bisnitrones were found to be stable and were reacted with various activated alkenes in 1,3-dipolar cycloaddition reaction in water at RT.

Spectroscopic data for nitrone **1** (R = CH_3): UV λ_{max} 233 nm. IR (KBr): υ_{max} 1635 (m), 1610 (s) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.45 (d, 1H, *J* = 3.22 Hz, –CH = N^+), 6.23 (d, *J* = 3.22 Hz, –CH=N^+), 3.84 (s, 6H, 2×CH_3, N^+–CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 141.60 (CH=N^+), 140.94 (CH=N^+), 24.74, 24.70 (N^+–CH_3).

General procedure of synthesis of diastereoselective bisisoxazolidine derivatives in water (Table 1; entry 1). *N*-methylmaleimide (2 equivalent) was added to a solution of bisnitrone (1 equivalent; R = CH_3) in water (15 mL), and the reaction mixture was stirred at RT for an appropriate time (Table 1). After completion of reaction, as indicated by TLC (R_f = 0.68, 0.62), the reaction mixture was extracted with diethyl ether (3 × 10 mL), the organic layer was washed with saturated brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude products were directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:6) to afford pure bisisoxazolidines **2** (Table 1, entry **1**, 94% and 6%, respectively) as yellowish white crystals. Same methodology was followed for other substrates depicted in Table 1.

Both the major and minor bis diastereomers gave satisfactory ^{1}H-NMR, ^{13}C-NMR, MS, IR, and elemental analyses data. Spectral data of the major bis diastereomers are represented as follows.

Spectral data of diastereomeric bisisoxazolidine derivatives (2–4)

(3R, 3aR, 6aS)-Dihydro-3-((3′S, 3′aS, 6aR)-hexahydro-2,5-dimethyl-4,6-dioxo-2H-pyrrolo[3,4-d]isoxazol-3-yl)-2′, 5′-dimethyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H, 6aH) dione 2. **2** (entry 1, Table 1): Yellowish white crystals, Yield 94%; R_f = 0.68; FTIR (KBr): υ_{max} 2820 (m), 1760 (s), 1675 (s), 1465 (m), 1230 (m), 1125 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.31 (d, 2H, *J* = 4.06 Hz, 2×C_5H), 3.10 (s, 6H, 2×$ONCH_3$), 2.99 (s, 6H, 2×(O=C)NCH_3), 2.85 (d, 2H, *J* = 4.22 Hz, 2×C_3H), 2.50 (dd, br, 2H, 2×C_4H). ^{13}C-NMR ($CDCl_3$): δ 174.78, 173.12 (carbonyl carbons), 75.80 (C_5, $C_{5'}$), 69.94 (C_3, $C_{3'}$), 56.77 (C_4, $C_{4'}$), 26.63, 26.58 (methyl carbons). FAB-MS (*m/z*): 338 (M^+), 169, 168, 154. Calcd for $C_{14}H_{18}O_6N_4$: C, 49.68; H, 5.36; N, 16.56%. Found: C, 49.53; H, 5.25; N, 16.44%.

(3R, 3aR, 6aS)-Dihydro-3-((3′S, 3′aS, 6aR)-hexahydro-4,6-dioxo-2,5-diphenyl-2H-pyrrolo[3,4-d]isoxazol-3-yl)-2′, 5′-diphenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H, 6aH)dione 3. **3** (entry 2, Table 1): White crystals, Yield 91%; R_f = 0.66; FTIR (KBr): υ_{max} 3025 (m), 2830 (m), 1764 (s), 1660 (s), 1485 (m), 1345 (m), 784 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.36–7.26 (m, 10H, 2×(O=C)NC_6H_5), 6.62–6.50 (m, 10H, 2×ONC_6H_5), 2.11 (dd, br, 2H, 2×C_4H), 1.85 (d, 2H, *J* = 6.00 Hz, 2×C_5H), 1.67 (d, 2H, *J* = 6.10 Hz, 2×C_3H). ^{13}C-NMR ($CDCl_3$): δ 172.40, 172.26 (carbonyl carbons), 138.83, 138.12, 137.94, 137.71, 129.74, 129.70, 129.33, 129.04 (aromatic carbons), 76.15 (C_5, $C_{5'}$), 66.47 (C_3, $C_{3'}$), 55.80 (C_4, $C_{4'}$). FAB-MS (*m/z*): 586 (M^+), 293, 292, 216, 77. Calcd for $C_{34}H_{26}O_6N_4$: C, 69.60; H, 4.46; N, 9.55%. Found: C, 69.50; H, 4.38; N, 9.49%.

(3R, 3aR, 6aS)-2-Benzyl-3-((3′S, 3′aS, 6aR)-2′-benzyl-hexahydro-5-methyl-4,6-dioxo-2H-pyrrolo[3,4-d]isoxazol-3-yl)-dihydro-5-methyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H, 6aH)dione 4. **4** (entry 3, Table 1): White crystals, Yield 91%; R_f = 0.62; FTIR (KBr): υ_{max} 3010 (m), 2900 (m), 1760 (s), 1660 (s), 1482 (m), 1340 (m), 780 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.46–7.26 (m, 10H, 2×$CH_2\underline{C_6H_5}$), 4.37 (d, 2H, *J* = 7.16 Hz, 2×C_5H), 3.24 (d, 2H, *J* = 7.14 Hz, 2×C_3H), 2.89 (dd, br, 2H, 2×C_4H), 2.60 (s, 6H, 2×N–CH_3 protons), 2.15 (s, 4H, 2×$\underline{CH_2}C_6H_5$). ^{13}C-NMR ($CDCl_3$): δ 177.18, 177.04 (carbonyl carbons), 133.22, 133.12, 132.90, 132.70 (aromatic carbons), 73.67 (C_5, $C_{5'}$), 64.80 (C_3, $C_{3'}$), 53.77 (C_4, $C_{4'}$), 32.05, 31.94 (benzyl carbons), 28.70, 28.58 (N–Me carbons). FAB-MS (*m/z*): 490 (M^+), 245, 244, 154, 77. Calcd for $C_{26}H_{26}O_6N_4$: C, 63.64; H, 5.34; N, 11.42%. Found: C, 63.57; H, 5.26; N, 11.35%.

General procedure of synthesis of regioselective bisisoxazolidine derivatives in water (Table 1; entry 4). Methyl acrylate (2 equivalent) was added to a solution of bisnitrone (1 equivalent; R = C_6H_5) in water (15 mL), and the reaction mixture was stirred at RT for an appropriate time (Table 1). After completion of reaction, as indicated by TLC (R_f = 0.76), the reaction mixture was extracted with diethyl ether (3 × 10 mL), the organic layer was washed with saturated brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:6) to afford pure bisisoxazolidine **5** (Table 1, entry **4**, 88%) as colorless liquid. Same methodology was followed for other substrate depicted in Table 1.

Spectral data of regioselective bisisoxazolidine derivatives (5–6)

(3S,5S)-Methyl-3-(((5′R)-5-(methoxycarbonyl)-2-phenylisoxazolidine-3-yl)methyl)-2′-phenyl isoxazolidine-5′-carboxylate 5. **5** (entry 4, Table 1): Colorless gummy liquid, Yield 88%; R_f = 0.58; FTIR (KBr): υ_{max} 3026 (m), 2890 (m), 1760 (s), 1664 (s), 1485 (m), 783 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.07–8.02 (m, 5H, C_6H_5), 7.52–7.45 (m, 5H, C_6H_5), 3.72 (dd, 2×1H, *J* = 5.44, 5.40 Hz, C_4H, *endo*), 3.43 (s, 2×3H, –$COOCH_3$), 2.96 (d, 2H, *J* = 6.32 Hz, 2×C_5H), 2.59 (d, 2H, *J* = 6.30 Hz, 2×C_3H), 1.24 (dd, 2×1H, *J* = 2.80, 2.82 Hz, C_4H). ^{13}C-NMR ($CDCl_3$): δ 170.24, 170.15 (carbonyl carbons), 129.47, 129.38, 129.25, 129.17 (aromatic carbons), 70.46(C_5, $C_{5'}$), 60.54 (C_3, $C_{3'}$), 52.49 (C_4, $C_{4'}$), 17.22, 17.07 (ester methyl carbons). FAB-MS (*m/z*): 412 (M^+), 206, 205, 147, 129, 77, 59. Calcd for $C_{22}H_{24}O_6N_2$: C, 64.05; H, 5.86; N, 6.79%. Found: C, 63.97; H, 5.74; N, 6.70%.

(3S, 5S)-2-Methyl-3-(((5′R)-2′-methyl-5-phenylisoxazolidin-3-yl)methyl)-5′-phenylisoxazolidine 6. **6** (entry 5, Table 1): Greenish thick liquid, Yield 83%; R_f = 0.52; FTIR (KBr): υ_{max} 3215 (m), 2905 (m), 2245 (s), 1484 (m), 780 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.88–7.73 (m, 5H, C_6H_5), 7.50–7.44 (m, 5H, C_6H_5), 3.60 (dd, 2×1H, *J* = 6.24, 6.22 Hz, C_4H, *endo*), 2.76 (d, 2H, *J* = 6.06 Hz, 2×C_5H), 2.62 (d, 2H, *J* = 6.28 Hz, 2×C_3H), 2.30 (s, 2×3H, N–Me protons), 1.70 (dd, 2×1H, *J* = 3.66, 3.62 Hz, C_4H). ^{13}C-NMR ($CDCl_3$): δ 136.67, 136.58, 136.52, 136.38, 131.80, 131.72, 131.55, 131.23 (aromatic carbons), 73.60 (C_5, $C_{5'}$), 58.45 (C_3, $C_{3'}$), 55.37 (C_4, $C_{4'}$), 36.64, 35.21 (N–Me carbons). FAB-MS (*m/z*): 324 (M^+), 246, 161, 147, 77. Calcd for $C_{20}H_{24}O_2N_2$: C, 74.03; H, 7.45; N, 8.64%. Found: C, 73.95; H, 7.33; N, 8.59%.

Acknowledgments. We are pleased to acknowledge the financial support from the Department of Science & Technology, Government of India, New Delhi (grant no:SR/S1/OC-34/2011). We are equally grateful to SAIF (Sophisticated Analytical Instrumentation Facility), CDRI (Central Drug Research Institute), Lucknow, India for providing spectral data.

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