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Synthesis Of Novel Isoxazolidine Derivatives From Methional-Derived Nitrone: A Greener Approach

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Abstract: *The 1,3-dipolar cycloaddition reactions of methional-derived nitrones with various dipolarophiles have been extensively investigated to develop an efficient method for synthesizing structurally diverse isoxazolidines. These reactions demonstrated remarkable efficiency when conducted in green solvents, exhibiting significantly increased reaction rates and higher yields compared to those obtained with traditional organic solvents. The use of eco-friendly solvents not only improved the reaction outcomes but also had a profound impact on the stereoselectivity and regioselectivity of the reaction. This observation underscores the critical role of sustainable solvents in optimizing the synthesis of target compounds, in alignment with the principles of green chemistry. The synthesized isoxazolidines were subjected to rigorous structural characterization using a combination of spectroscopic and analytical techniques to determine their structures. This comprehensive analysis unequivocally confirmed the molecular structures of all newly synthesized compounds. Additionally, the potential practical applications of these novel isoxazolidines were explored through antibacterial activity assays. The evaluation revealed promising bioactivity profiles, suggesting that these compounds could serve as valuable leads for further development in medicinal chemistry applications. This finding opens new avenues for research into the therapeutic potential of isoxazolidines, particularly in the context of addressing bacterial infections and potentially contributing to ongoing efforts to combat antimicrobial resistance.*

Key Words: *Methional derived nitrone, DCR, alcohol – water medium, isoxazolidine, stereoselectivity, regioselectivity*

INTRODUCTION:

The 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is widely acknowledged as a potent and versatile method for synthesizing isoxazolidine ring systems in the pharmaceutical industry. These cycloadducts are of significant synthetic importance as stable heterocycles and as valuable intermediates. Notably, the reductive cleavage of the N–O bond offers direct access to γ-amino alcohols, which are crucial structural motifs in natural products, pharmaceuticals, and other bioactive compounds. In addition to their synthetic versatility, several nitrone-derived cycloadducts exhibit antimicrobial activity, further enhancing their relevance in medicinal chemistry. In recent decades, efforts to enhance the stereoselectivity and regioselectivity of nitrone–olefin cycloadditions have included strategies for incorporating chiral elements in either the dipole or dipolarophile. Recently, the adoption of green solvents has gained traction as a sustainable approach to improve reactivity, while simultaneously addressing environmental concerns. Alcohol–water mixtures have emerged as appealing media because of their low cost, abundance, and eco-friendliness. In addition to being environmentally acceptable, these solvent systems exhibit unique reactivity and selectivity profiles that are often unattainable in conventional organic solvents. Despite their synthetic utility, the inherent instability of nitrones often precludes their isolation, necessitating their in situ generation and trapping with various dipolarophiles during 1,3-dipolar cycloaddition processes. In this context, the development of efficient catalyst-free synthetic methodologies in alcohol–water media is highly valuable. Encouragingly, reactions conducted in these solvent mixtures often proceed with a significant rate acceleration. For instance, cycloadditions involving maleimides were completed within 4–5 h, whereas reactions with ethyl acrylate and methyl vinyl ketone required only 7–8 h. In contrast, the same transformations carried out in traditional organic media have been reported to take 26–48 hours, underscoring the remarkable rate enhancement achieved in aqueous-alcoholic conditions. This acceleration may be attributed to hydrogen bonding effects, wherein the alcohol–water medium interacts with the carbonyl oxygen of the α,β-unsaturated dipolarophile, thereby enhancing the electrophilic character of the β-carbon atom. This activation facilitates a favorable nucleophilic attack by the nitrone oxygen, leading to rapid cycloaddition. In this study, we synthesized a series of novel isoxazolidine derivatives using methional-derived nitrone and a set of electron-rich and electron-poor dipolarophiles, namely, three different maleimides, ethyl acrylate, and methyl vinyl ketone. The scope and efficiency of these transformations were examined using varying proportions of alcohol–

water mixtures. This study revealed high yields, rapid reaction rates, and remarkable changes in stereoselectivity, establishing alcohol–water as a green, efficient, and selective reaction medium for nitrone cycloadditions.

RESULTS AND DISCUSSION:

Significant diastereofacial selectivity was observed in the addition of nitrone to alcohol-water media. The reaction of nitrone 1 with maleimides yielded a mixture of diastereomers 2a-4a and 2b-4b, with an approximate ratio of 70:30 in all instances, resulting in the formation of three to four chiral centers in a single step. Studies of organic reactions in alcohol-water media indicate a higher likelihood of diastereomeric mixture formation when water is employed as the solvent compared to conventional organic solvents7. These findings can be explained by an exo approach to nitrone 1, which possesses a Z configuration for the formation of major cycloadducts 2a-4a (transition state I). Minor cycloadducts 2b-4b were formed via the endo approach of Z nitrone (transition state II). The diastereomeric mixture was identified by analyzing the multiplicity of the proton signals at 3-H and 4-H, along with their corresponding coupling constants. The most notable difference in the 1H NMR spectra of the diastereomers was the position and multiplicity of the 3-H signal. In minor adducts 2b-4b, 3-H resonates upfield at approximately δH = 4.10 ppm, whereas in major adducts 2a-4a, it resonates at approximately δH = 4.55 ppm, with J3,4 approximately 9.16 Hz. For the minor adducts, J3,4 is approximately 2.26 Hz. These differences can be attributed to the conformation of the isoxazolidine ring system. Owing to the 4,5-fused pyrrolidindione, the isoxazolidine ring adopts an envelope conformation and allows for inversion; its nitrogen atom either extends out from the envelope, representing the minor conformation, or points inside the envelope, representing the major conformation. The minor conformer has an N-lone pair antiperiplanar, which can shield the 3-H proton; thus, this conformation was assigned to the minor conformer (Figure 1).

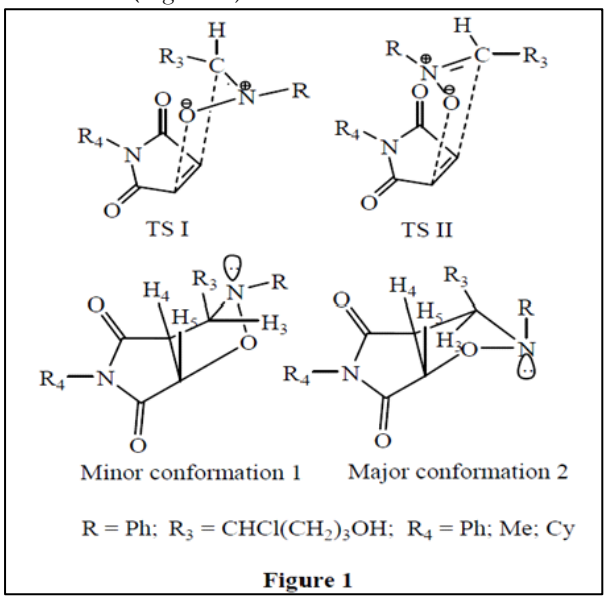
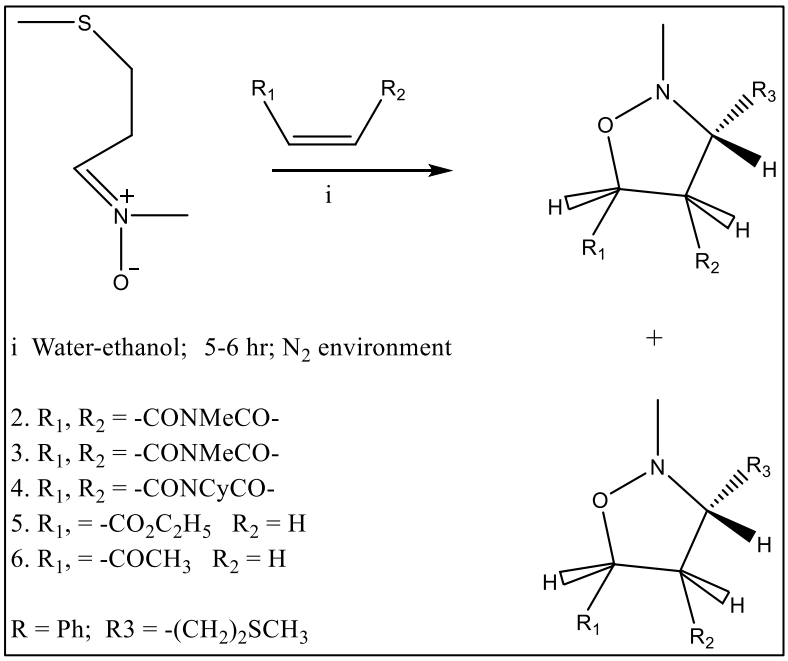


Figure 1

diastereomeric isoxazolidines **2a-4a** and **2b-4b** were separated by column chromatography and obtained in analytically pure form[9]. The *endo/exo* stereochemistry mentioned above is based on extensive NMR investigations. The most relevant parameters were the coupling constants ($J_{H3,\ H4}$) of the diastereomers. For **2a-4a**, this coupling constant is almost 9.2-9.4 Hz, implying a *cis* relationship between H-3 and H-4, whereas for **2b-4b**, the coupling constant is almost 2.5-4.2 Hz which implies a trans relationship between H-3 and H-4 (Ref 10). In all the diastereomers, the configurations of H-5 and H-4 were *cis*, as evidenced by their coupling constant values. For ethyl acrylate and methyl vinyl ketone, the regioselectivity was rationalized using frontier orbital theory[11] and ^{1}H NMR experiments. Cycloaddition to α, β-unsaturated carboxylic acid derivatives, *such as* ethyl acrylate, is particularly useful because high regioselectivity is often observed in water[6]. The reactions were highly regioselective, forming only 5-substituted isoxazolidines. Nitrone **1** has a considerably higher ionization potential than normal nitrones owing to the electron-withdrawing effect of chlorine. Therefore, nitrone (LUMO)–dipolarophile (HOMO) interactions completely dominate the reaction, leading to the formation of only 5-substituted adducts[11,12]. The ^{1}H NMR spectrum of cycloadducts **5,6**, it has been found that clear double doublet signals for the H-4

protons and double triplet signals for the H-3 protons in all cases due to further coupling from vicinal hydrogens, confirming the formation of 5-substituted adducts. Detailed investigations of the nature of these cycloaddition reactions using TLC and ^{1}H NMR spectroscopy for the cycloadducts **5,6** also confirmed that no diastereomers were formed. The relative configurations of the H-3, H-4, and H-5 protons in these adducts are *syn*, and the cycloadducts favor *exo* transition state geometry, as evidenced by their coupling constant values ($J_{H4,H5}$ = 6-8.4 Hz; $J_{H4,\ H3}$ = 6.2–7.6 Hz) (Ref 10). Similar cycloaddition reactions of nitrones with these dipolarophiles usually give both 5- and 4-substituted adducts in conventional solvents, with some exceptions of either 5- or 4-substituted adducts[13,14].

Scheme 1



i Water-ethanol; 5-6 hr; N_2 environment

2. R_1, R_2 = -CONMeCO-
3. R_1, R_2 = -CONMeCO-
4. R_1, R_2 = -CONCyCO-
5. R_1, = $-CO_2C_2H_5$ R_2 = H
6. R_1, = $-COCH_3$ R_2 = H

R = Ph; R3 = $-(CH_2)_2SCH_3$

Table I — Physicochemical data of synthesized compounds

Entry	Nitrone	Dipolarophile	Time (hr)	Cycloadduct[a] & m.p. (°C) *Cis/trans* ratio (%) **2a-4a** : *cis*; **2b-4b**: *trans*	Yield[b] (%)
1	*N*-phenyl-α-chloro nitrone	*N*-methyl maleimide	4	**2a**: White solid, 108 **2a**: 74 **2b**: White solid, 125 **2b**: 20	94
2	*N*-phenyl-α-chloro nitrone	*N*-phenyl maleimide	5	**3a**: Yellow solid, 116 **3a**: 71 **3b**: Yellowish white solid, 131 **3b**: 24	95
3	*N*-phenyl-α-chloro nitrone	*N*-cyclohexyl maleimide	5	**4a**: Dark yellow crystals, 88 **4a**: 68 **4b**: Yellow crystals, 96 **4b**: 27	95
4	*N*-phenyl-α-chloro nitrone	Ethyl acrylate	5	**5**: White gummy liquid	92
5	*N*-phenyl-α-chloro nitrone	Methyl vinyl ketone	5	**6**: Pale yellow oil	91

In general, these reactions are very clean and yield higher than the usual cycloaddition reactions of nitrones. The products were characterized using spectroscopic data (IR, 1H NMR, HRMS, and 13C NMR). No catalyst or co-organic solvents were required. The structures of 2-6 were confirmed by 1H and 13C NMR spectroscopy in $CDCl_3$, along with MS and IR spectra. Thus, the 1H NMR spectra of 2-4 indicate that these isoxazolidine derivatives are formed as a mixture of diastereomers in an almost 70:30 ratio with cis and trans configurations relative to the spatial orientation of the R3 group at C3 with respect to the H atom at the C4 position. The diastereomers were separated by column chromatography and recrystallized from heptane-ethyl acetate 9,15. The 1H NMR spectrum of 2a-4a and 2b-4b displayed different spectra (positions of signals) for the diastereomers. In contrast, the 1H NMR spectrum of 5,6

displayed only one set of signals, indicating the formation of unique cycloadducts. The exact stereochemistry at the asymmetric CHCl carbon atom of all the cycloadducts could not be determined because of the multiplets (doublet of triplet appears almost as a multiplet) obtained in the NMR spectrum and the freely rotating carbon center at CHCl. In the ^{13}C NMR spectrum, four signals were obtained for the phenyl ring carbon atoms owing to the equivalent nature of C-2 and C-6 and C-3 and C-5. In the mass spectrum, significant M^++2 ion peak signals were obtained for most of the diastereomers and regioselective cycloadducts as the peak of highest intensity, owing to the isotopic abundance of the Cl^{37} atom in these compounds. In addition, mass fragmentation peaks of different values were obtained for the diastereomers of a particular cycloadduct. HRMS spectra showed almost exact masses for most compounds.

Experimental Section

The melting points were determined using open capillary tubes and remained uncorrected. Proton nuclear magnetic resonance (1H NMR) spectra were recorded on a Bruker Avance DPX 400 spectrometer operating at 400 MHz spectrometer, with tetramethylsilane (TMS) serving as the internal standard. Carbon-13 nuclear magnetic resonance (13C NMR) spectra were obtained using the same instrument at a frequency of 100 MHz. The coupling constants (J) are expressed in hertz. Infrared (IR) spectra were acquired using a Perkin-Elmer RX 1-881 instrument, either as a film or in potassium bromide (KBr) pellets, for all products. Mass spectrometry (MS) spectra were recorded using a JEOL SX-102 (FAB) instrument. High-resolution mass spectrometry (HRMS) spectra were obtained using a Q-Tof micro instrument (YA-105). Elemental analyses of carbon, hydrogen, and nitrogen (CHN) were conducted using a PerkinElmer 2400 series CHN analyzer. Thin-layer chromatography (TLC) was performed on silica gel-precoated TLC plates (Fluka). All other reagents and solvents were purchased from commercial suppliers. N-Phenylhydroxylamine was synthesized following established methods in the literature and has been previously utilized for the synthesis of aldehydes and cycloaddition reactions involving α-amino nitrones in organic solvents4,5.

General Procedure for Cycloaddition (for Diastereomers)

Nitrone 1 (1 mmol), dipolarophile (1 mmol), and water (15 mL) were introduced into a 50 mL conical flask and stirred at room temperature with a magnetic stirrer under a nitrogen atmosphere for 15 min under sonication .The progress of the reaction was monitored by TLC. Upon completion, the products were extracted with diethyl ether (2 × 25 mL), and the organic layer was washed with saturated brine (2 × 15 mL), dried over anhydrous sodium sulfate (Na2SO4), and then concentrated. The resulting mixture of diastereomers was purified and separated by column chromatography using an ethyl acetate/hexane solvent system to obtain the cycloadducts (Scheme I). This procedure was applied to substrates 1-3 as listed in Table I.

The synthesis of (3R,3aS,6aR)-5-methyl-3-(2-(methylthio)ethyl)-2-phenyltetrahydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione was conducted as follows:

A solution of nitrone 1 (1 mmol) in 15 mL of water was prepared, to which N-methylmaleimide (1 mmol) was added at room temperature under a nitrogen atmosphere for 20-25 min under sonication. The reaction mixture was stirred for four hours, and its progress was monitored using thin-layer chromatography (TLC) with Rf values of 0.42 and 0.37. The reaction products were extracted with ether (2 × 25 mL), and the organic layers were subsequently washed with saturated brine (2 × 15 mL), dried over anhydrous Na2SO4, and concentrated. The resulting diastereomeric mixture was purified and separated by column chromatography using an ethyl acetate-hexane solvent system, ultimately yielding a white solid upon solvent removal under reduced pressure.

(3R,3aS,6aR)-5-methyl-3-(2-(methylthio)ethyl)-2-phenyltetrahydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione,2a:

White solid. Yield 74%; R_f = 0.42; IR ($CHCl_3$): 3458 (s), 3083 (s), 2935 (m), 2865 (m), 1740 (s), 1678 (s), 1454 (m), 1328 (m), 809(s), 774(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.28 - 6.74 (m, 5H, C_6H_5), 5.22 (d, 1H, J = 6.8 Hz, C_5H),) ,4.78 (dd, 1H, J = 6.84, 9.2 Hz, C_3H), 3.26 (dd, 1H, J = 8.06, 9.20 Hz, C_4H), 3.30 (s, 3H, N-CH_3), 2.64-1.96 (m, 4H, CH_2 protons); 2.17 (s, 3H, S-CH_3 protons); ^{13}C NMR ($CDCl_3$): **δ 174.64, 173.42** (carbonyl carbons), 140.50, 133.26, 132.00, 130.64 (aromatic carbons), 84.6 (C_5), 72.8 (C_3), 59.00 (C_4), 34.3, 29 (2 CH_2 carbons); MS: ***m/z*** **308 (M^+ +2), 306 (M^+), 291, 231, 201,** 124, **107, 77**, 75; HRMS-EI: Calcd for $C_{15}H_{18}N_2O_3S$ (M) *m/z* 306.1473 Found: M^+ 306.1441; Anal. Found: C, 59.92%; H, 5.52%; N, 7.29%. $C_{15}H_{18}N_2O_3S$ requires C, 60.03%; H, 5.60%; N 7.35%

(3*R*)-3-(1-chloro-4-hydroxybutyl)-5-methyl-2-phe- nyldihydro-2*H*-pyrrolo[3,4-*d*] isoxazole - 4,6 (5*H*, 6a- *H*)-dione, 2b

White solid. Yield 20.4%, R_f = 0.40; IR ($CHCl_3$): 3580 - 3465 (br), 2895 (m), 1764 (s), 1660(s), 1482 (m), 1355 (m), 805 (s), 780 (s) $cm^{-1;}$ ^1H NMR ($CDCl_3$): δ 7.20 - 7.08 (m, 5H, C_6H_5), 5.26 (d, 1H, *J* = 6 Hz, C_5H), 5.10 - 4.94 (br, 1H, OH, exchanged in D_2O), 4.10 (dd, 1H, *J* = 2.50, 4.06 Hz, C_3H), 3.60 (dd, 1H, *J* = 2.52, 4.26 Hz, C_4H), 3.44 (s, 3H, CH_3), 3.22 - 3.05 (m, 1H, CHCl), 1.88 - 1.44 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.50, 171.00 (carbonyl carbons), 133.00, 132.00, 130.34, 128.60 (aromatic carbons), 88.62 (C_5), 74.00 (C_3), 61.44 (CH_2OH), 58.28 (C_4), 54.00 (CHCl), 37.00 (CH_3), 24.00, 21.00 (2 CH_2 carbons); MS: *m/z* 338 (M^+), 307, 261, 246, 231, 139, 111, 107, 77, 31; HRMS-EI: Calcd for $C_{16}H_{19}O_4N_2Cl$ (M) *m/z* 338.1338. Found: M^+ 338.1320. Anal. Found: C, 56.50; H, 5.52; N, 8.16. $C_{16}H_{19}O_4N_2Cl$ requires C, 56.63; H, 5.60; N, 8.25%.

(3S,3aS,6aR)-5-methyl-3-(2-(methylthio)ethyl)-2-phenyltetrahydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione, 2b

White solid. Yield 20%; R_f = 0.37; IR ($CHCl_3$): 3450 (s), 2931 (m), 2868 (m), 1740 (s), 1674 (s), 1452 (m), 1321 (m), 812(s), 776(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.23 - 6.70 (m, 5H, C_6H_5), 5.10 (d, 1H, *J* = 6.8 Hz, C_5H),), 4.84 (dd, 1H, *J* = 2.50, 4.06 Hz, C_3H), 3.35 (dd, 1H, *J* = 2.52, 4.26 Hz, C_4H), 3.38 (s, 3H, N-CH_3), 2.73-1.90 (m, 4H, CH_2 protons); 2.24 (s, 3H, S-CH_3 protons); ^{13}C NMR ($CDCl_3$): **δ 173.22, 172.24** (carbonyl carbons), 142.50, 135.24, 131.27, 130.64 (aromatic carbons), 84.6 (C_5), 72.8 (C_3), 59.00 (C_4), 34.3, 29 (2 CH_2 carbons); MS: ***m/z* 308 (M^+ +2), 306 (M^+), 231, 201,** 124, **107, 77**, 75; HRMS-EI: Calcd for $C_{15}H_{18}N_2O_3S$ (M) *m/z* 306.1473 Found: M^+ 306.1447; Anal. Found: C, 59.90%; H, 5.56%; N, 7.23%. $C_{15}H_{18}N_2O_3S$ requires C, 60.03%; H, 5.60%; N 7.35%

Synthesis of (3R,3aS,6aR)-3-(2-(methylthio)ethyl)-2,5-diphenyltetrahydro-4H-pyrrolo[3,4-d]isoxazole - 4,6(5H)-dione, 3a

N-Phenyl maleimide (1 mmol) was added to a stirred solution of nitrone **1** (1 mmole) in 15 mL water was added *N*-phenyl maleimide (1 mmole) at RT under nitrogen atmosphere and the reaction- mixture was stirred for 60 min under sonication . The progress of the reaction was monitored by TLC (R_f = 0.38, 0.44). The products were extracted with ether (2 × 25 mL), and the organic layers were washed with saturated brine (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers was purified and separated by column chromatography using ethyl acetate-hexane, and finally obtained by removal of the solvent under reduced pressure as yellow and yellowish-white solids.

Yellow solid. Yield 71%; R_f = 0.38; IR ($CHCl_3$): 3465 (s), 2880 (m), 2345 (s), 1765 (s), 1650 (s), 1472 (m), 1365 (m), 795 (s), 775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55 - 7.40 (m, 2 × 5H, C_6H_5 protons), 5.42 (d, 1H, *J* = 8.24 Hz, C_5H), 4.46 (dd, 1H, *J* = 9.25, 7.28 Hz, C_3H), 3.76 (dd, 1H, *J* = 9.22, 6.08 Hz, C_4H), 2.45 - 1.65 (m, 4H, CH_2 protons), 2.24 (s, 3H, S-CH_3 protons); ^{13}C NMR ($CDCl_3$): δ 174.15, 172.35 (carbonyl carbons), 142.36, 138.00, 136.64, 135.42, 133.70, 132.00, 131.86, 131.20 (aromatic carbons), 87.70 (C_5), 75.00 (C_3), 58.42 (C_4), 32.20, 25.30 (2 CH_2 carbons); MS: *m/z* 369 (M^++1), 368 (M^+), 338, 265, 214, 180, 107, 100, 77; HRMS-EI: Calcd. for $C_{20}H_{20}N_2O_3Cl$, (M) *m/z* 368.4510. Found: M^+ 368.4498. Anal. Found: C, 65.65 H, 5.42; N, 7.24. $C_{20}H_{20}O_3N_2S$ requires C, 65.70; H, 5.48; N, 7.30%.

Synthesis of (3S,3aS,6aR)-3-(2-(methylthio)ethyl)-2,5-diphenyltetrahydro-4H-pyrrolo[3,4-d]isoxazole - 4,6(5H)-dione, 3b

Yellowish white solid. Yield: 24%, R_f = 0.44; IR ($CHCl_3$): 3480 (s), 2885 (m), 2340 (s), 1760 (s), 1684 (s), 1465 (m), 1370 (m), 810 (m), 772 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35 - 7.14 (m, 2 × 5H, C_6H_5 protons), 5.24 (d, 1H, *J* = 7.20 Hz, C_5H), 4.38 (dd, 1H, *J* = 3.25, 2.24 Hz, C_3H), 3.52 (dd, 1H, *J* = 4.42, 2.08 Hz, C_4H), 2.45 - 1345 (m, 4H, CH_2 protons), 2.20 (s, 3H, S-CH_3 protons); ^{13}C NMR ($CDCl_3$): δ 175.44, 172.86 (carbonyl carbons), 141.24, 136.48, 135.30, 134.26, 133.86, 132.84, 130.64, 129.10 (aromatic carbons), 85.60 (C_5), 72.20 (C_3), 57.40 (C_4), 31.20, 26.65 (2 CH_2 carbons); MS: *m/z* 369 (M^+ +1), 368 (M^+), 337, 265, 214, 180, 107, 100, 77; HRMS-EI: Calcd for $C_{20}H_{20}O_3N_2S$, (M) *m/z* 368.4510. Found: M^+ 368.4468. Anal. Found: C, 65.54; H, 5.36. N, 6.75. $C_{20}H_{20}O_3N_2S$, requires C, 65.54; H, 5.43; N, 7.27%.

Synthesis of (3R)-5-cyclohexyl-3-(2-(methylthio)ethyl)-2-phenyltetrahydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione, 4a

N-Cyclohexyl maleimide (1 mmol) was added to a stirred solution of **1** (1 mmol) in 15 mL of water was

added *N*-cyclohexyl maleimide (1 mmole) thend a mixture was stirred for 30 min under sonication. The progress of the reaction was monitored by TLC (R_f = 0.38, 0.42). The products were extracted with ether (2 × 25 mL), and the organic layers were washed with saturated brine (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated. The mixture of diastereomers was purified and separated by column chromatography using ethyl acetate-hexane, and finally obtained by removal of the solvent under reduced pressure as dark yellow and yellow crystals, respectively.

Dark yellow crystals. Yield 68%, R_f = 0.38; IR ($CHCl_3$): 3620 (s), 2877 (s), 1772 (s), 1690 (s), 1446 (m), 1385 (m), 1260 (m), 805 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.02 - 6.92 (m, 5H, C_6H_5), 5.32 (d, 1H, *J* = 6.12 Hz, C_5H), 4.52 (dd, 1H, *J* = 9.26, 6.08 Hz, C_3H), 4.26 (dd, 1H, *J* = 9.24, 7.06 Hz, C_4H), 1.64 - 1.24 (m, 17 H, cyclohexyl and CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.34, 170.26 (carbonyl carbons), 131.30, 130.55 128.63, 127.42 (aromatic carbons), 86.00 (C_5), 78.00 (C_3), 55.00(C_4), 30.00, 28.00, 26.74, 25.42, 24.36, 23.58, 21.30, 22.24, 19.00 (cyclohexyl, CH_2 carbons and S-CH_3 carbon); MS: *m/z* 376 (M^+ +2), 374 (M^+), 347, 328, 300, 297, 328, 267, 193, 107, 83, 77; HRMS-EI: Calcd for $C_{20}H_{26}N_2O_3S$ (M) *m/z* 374.4992. Found: M^+ 374.4962.

Synthesis of (3S)-5-cyclohexyl-3-(2-(methylthio)ethyl)-2-phenyltetrahydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione, 4b

Yellow crystals. Yield 27%, R_f = 0.42; IR ($CHCl_3$): 3630 (s), 2868 (s), 1765 (s), 1675 (s), 1440 (m), 1375(m), 1265 (m), 810 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36 - 7.24 (m, 5H, C_6H_5), 5.24 (d, 1H, *J* = 7.22 Hz, C_5H), 4.54 (dd, 1H, *J* = 4.32, 3.26 Hz, C_3H), 4.23 (dd, 1H, *J* = 3.22, 2.08 Hz, C_4H), 2.42 - 1.34 (m, 15 H, cyclohexyl and CH_2 protons) 2.08 (s, 3H, -SCH_3) ; ^{13}C NMR ($CDCl_3$): δ 172.74, 170.86 (carbonyl carbons), 135.36, 134.50, 133.82, 132.58 (aromatic carbons), 84.34 (C_5), 75.00 (C_3), 53.50 (C_4), 27.00, 26.52, 25.46, 24.00, 23.00, 21.54, 21.25 20.55, 19.00 (cyclohexyl, CH_2 carbons and S-CH_3 carbon); MS: *m/z* 376 (M^+ +2), 374 (M^+), 327, 301, 297, 267, 192, 107, 83, 77; HRMS-EI: Calcd for $C_{20}H_{26}N_2O_3S$ (M) *m/z* 374.4992. Found: M^+ 374.4975.

White gummy liquid. Yield 93%, R_f = 0.48; IR ($CHCl_3$): 3610 - 3525 (br), 2930 (s), 2856 (m), 1750 (s), 1445 (s), 795 (s), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.22 - 7.14 (m, 5H, C_6H_5), 5.15 - 5.03 (br, 1H, -OH, exchanged in D_2O), 4.84 (t, 1H, *J* = 8.2 Hz, C_5H), 4.48 - 4.33 (dt, 1H, *J* = 7.22 Hz, C_3H), 4.22 (q, 2H, *J* = 6, 6.02 Hz, -OCH_2CH_3), 3.88 (dd, 2H, *J* = 9.24, 8.18 Hz, C_4 2H), 3.60 - 3.46 (m, 1H, CHCl), 1.84 - 1.46 (m, 6H, CH_2 protons), 1.24 (t, 3H, *J* = 7.52 Hz, - OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 167.40 (carbonyl carbon), 136.40, 134.50, 133.25, 132.60 (aromatic carbons), 88.00 (C_5), 76.00 (C_3), 63.00 (CH_2OH), 60.00 (CH_2 carbon of -OCH_2CH_3), 58.00 (C_4), 55.00(CHCl), 32.00, 24.00 (2 CH_2 carbons), 16.00 (CH_3 carbon of OCH_2CH_3); MS: *m/z* 329 (M^+ +2), 327(M^+), 296, 250, 219, 207, 177, 142, 108, 107, 77, 73, 31; HRMS-EI: Calcd for $C_{16}H_{22}O_4NCl$ (M) *m/z* 327.1542. Found: M^+ 327.1533.

General procedure for cycloaddition (for regioselective cycloadducts)

Nitrone **1** (1 mmol), dipolarophile (1 mmol), and water (15 mL) were added to a 50 mL conical flask and stirred at RT with a magnetic stirrer under a N_2 atmosphere for 45 min under sonication. The reaction progress was monitored using TLC. After completion of the reaction, the product was extracted with ether (2×25 mL), and 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 a pure cycloadduct (**Scheme I**). This procedure was followed for substrates **4** and **5, as** listed in **Table I**.

Synthesis of ethyl 3-(2-(methylthio)ethyl)-2-phenylisoxazolidine-5-carboxylate, 5

Ethyl acrylate (1 mmol) was added to a stirred solution of nitrone **1** (1 mmol) in 15 mL of water, and the reaction mixture was stirred for another 180 min under sonication. The progress of the reaction was monitored by TLC (R_f = 0.52). The product was extracted with ether (2 × 25 mL), and the organic layer was washed with saturated brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified and separated by column chromatography using ethyl acetate-hexane and finally obtained by removing the solvent under reduced pressure as a white gummy liquid.

White gummy liquid. Yield 92%, R_f = 0.52 e; IR ($CHCl_3$): 3610 (s), 2930 (s), 2856 (m), 1750, (s), 1445 (s), 795 (s), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36 - 7.20 (m, 5H, C_6H_5), 4.84 (t, 1H, *J* = 8.2 Hz, C_5H), 4.48 - 4.33 (dt, 1H, *J* = 7.22 Hz, C_3H), 4.22 (q, 2H, *J* = 6, 6.02 Hz, -OCH_2CH_3), 3.88 (dd, 2H, *J* = 9.24, 8.18 Hz, C_4 2H), 2.67 - 1.42 (m, 4H, CH_2 protons), 2.18 (s, 3H, -SCH_3) 1.28 (t, 3H, *J* = 7.52 Hz, - OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 171.40 (carbonyl carbon), 136.45, 133.40, 132.25, 130.85 (aromatic carbons), 89.50 (C_5), 74.40 (C_3), 62.00 (CH_2 carbon of -OCH_2CH_3), 58.00 (C_4), 32.00, 24.00 (2 CH_2 carbons), 21.25 (S-

CH_3) 16.00 (CH_3 carbon of OCH_2CH_3); MS: m/z 298 (M^+ +2), 296 (M^+), 267, 248, 222, 218, 147, 77; HRMS-EI: Calcd for $C_{15}H_{21}NO_3S$ (M) *m/z* 295.3742. Found: M^+ 295.3733.

Synthesis of 1-(3-(2-(methylthio)ethyl)-2-phenylisoxazolidin-5-yl)ethan-1-one, 6

Methyl vinyl ketone (1 mmol) was added to a stirred solution of nitrone **1** (1 mmol) in 15 mL of water, and the reaction mixture was stirred for another 15 min under sonication. The progress of the reaction was monitored by TLC (R_f = 0.48). The product was extracted with ether (2 × 25 mL), and the organic layer was washed with saturated brine (2 ×15 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified and separated by column chromatography using ethyl acetate-hexane and finally obtained by removing the solvent under reduced pressure as a pale yellow oil.

Pale yellow oil. Yield 91%, R_f = 0.48; IR ($CHCl_3$): 3520 - 3380 (br), 2925 (s), 2844 (m), 1710 (s), 1440 (m), 1324 (s), 804 (m), 776 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.16 - 7.04 (m, 5H, C_6H_5), 5.32 (t,1H, *J* = 7.82 Hz, C_5H), 4.54 - 4.43 (dt, 1H, *J* = 8.30 Hz, C_3H), 4.28 (dd, 2H, *J* = 9.48, 7.10Hz, C_4 2H), 2.12 (s, 3H, $COCH_3$), 2.46 - 1.54 (m, 4H), 2.18 (s, 3H, -SCH_3); ^{13}C NMR ($CDCl_3$): δ 174.42 (carbonyl carbon), 133.25, 131.95, 130.50, 127.30 (aromatic carbons), 88.00 (C_5), 78.00 (C_3), 58.00 (C_4), 25.70 ($COCH_3$), 25.00, 23.00 (2 CH_2 carbons), 20.45 (S-CH_3); MS: *m/z* 266 (M^+), 251, 218, 188, 222, 107, 77, 43; HRMS-EI: Calcd for $C_{14}H_{19}NO_2S$ (M) *m/z* 297.3485. Found: M^+ 297.3462.

CONCLUSION:

The current procedure demonstrates a significant advancement in green chemistry, specifically in the synthesis of novel isoxazolidines. By employing an alcohol-water medium, this method achieves both regio- and stereoselectivity while maintaining high yields and efficiency. The use of environmentally friendly solvents is in accordance with the principles of green chemistry, reducing the environmental impact typically associated with conventional organic synthesis. The rapid reaction time further enhances the appeal of this method, as it minimizes energy consumption and increases overall process efficiency. The key strengths of this methodology lie in its combination of high yields, short reaction times, mild conditions, and eco-friendly approach. These attributes make it particularly attractive for industrial applications and the large-scale synthesis of isoxazolidine derivatives. The absence of conventional organic solvents not only reduces the environmental footprint, but also simplifies purification processes and waste management. As the field of chemistry continues to prioritize sustainability, this procedure serves as a model for developing greener alternatives for cycloaddition reactions and beyond, potentially inspiring similar approaches in other areas of organic synthesis.

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