

Solvent-free one-pot 1,3-dipolar cycloaddition reactions of dihydropyran derived nitrone

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Abstract. Microwave-induced 1,3-dipolar cycloaddition reactions of dihydropyran derived nitrone with various activated alkenes have been studied *in situ* and found to afford new isoxazolidine derivatives with moderate selectivity.

Keywords. Solid phase; cycloaddition reaction; isoxazolidines and amino alcohols.

1. Introduction

The synthetic utility of microwave irradiation in organic synthesis has increased considerably in recent years.^{1–5} This non-conventional energy source is able to reduce chemical reaction time and to increase yield and in some cases leads to better result than those obtained with conventional heating methods. Microwave reactions are quite often cleaner, faster, and higher-yielding than conventional ones. This methodology can be regarded as environmental friendly, mainly because solvent-free reactions are especially suited to microwave conditions.^{6,7} Microwave technology has been successfully used to perform difficult cycloadditions and to obtain temperature sensitive compounds.^{8–13} Particularly interesting part is 1,3-dipolar cycloaddition, which represents one of the most versatile tools for the construction of five-membered heterocycles. Owing to the labile nature of the N–O bond under mild reducing conditions, isoxazolidines provide easy access to a variety of fascinating 1,3-difunctional amino alcohols.¹⁴ In continuation of our green methodological synthesis of spiro isoxazolidine, isoxazolidine, isoxazoline, aldehyde, ketone synthesis using α -chloro and α -amino nitrones in solid phase and in hydrated media,^{15–23} we report here microwave-assisted 1,3-dipolar cycloaddition reactions of dihydropyran derived nitrone leading to the green synthesis of new isoxazolidine derivatives with moderate selectivity and excellent yield (scheme 1, table 1).

Literature survey reveals that this is quite a new approach of synthesis of nitrone from dihydropyran using microwave irradiations.^{24–26}

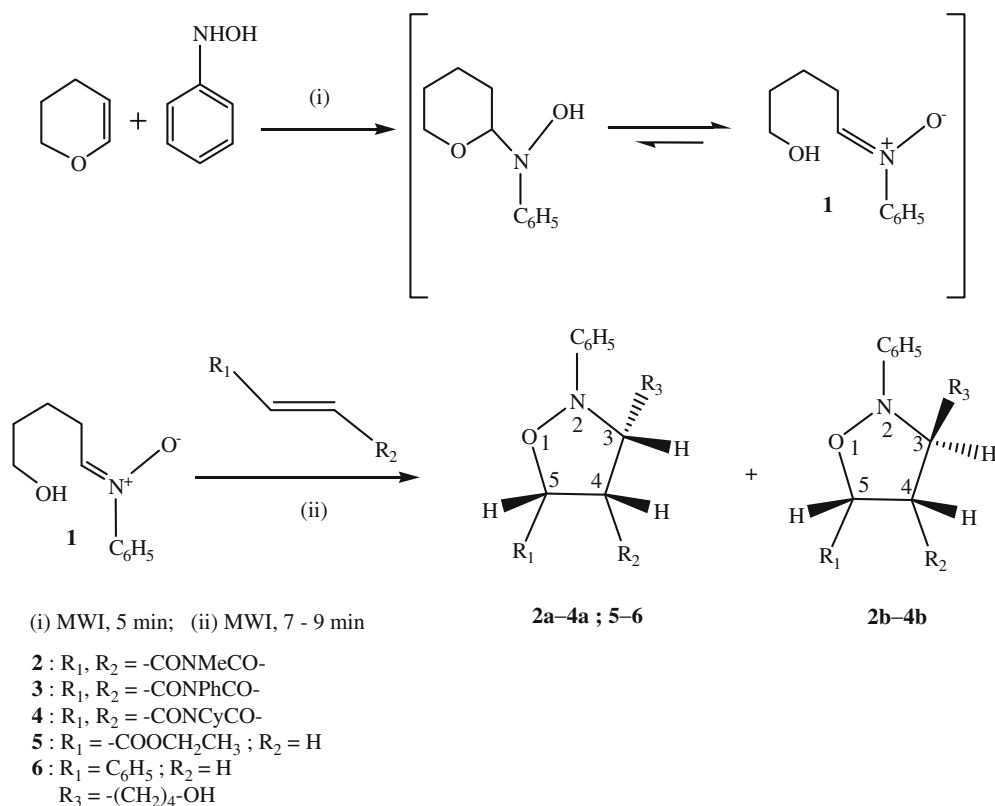
Synthetic potential of the new isoxazolidine derivatives (2–6) are tremendous as they could be converted into acyclic chiral 1,3 difunctional amino alcohols (scheme 2, table 2) by the reductive cleavage of the N–O bond by treatment with zinc powder in dil acetic acid under microwave irradiation.^{27–29}

2. Experimental

2.1 General procedures

Melting points were determined in open capillary tubes and are uncorrected. ¹H NMR spectra were recorded with a Bruker Avance DRX-300 spectrometer (300 MHz, FT NMR) using TMS as internal standard. ¹³C 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 KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. Elemental analyses (CHN) were performed with a Perkin–Elmer 2400 series CHN analyzer. TLC's were run on Fluka silica gel pre-coated TLC plates. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-phenylhydroxylamine was prepared following standard methods available in literature. Microwave irradiations were carried out using domestic microwave oven KENSTER (19LKH, 19SSLM, 800 W-2450 MHz).

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Scheme 1. Synthesis of novel isoxazolidine derivatives.

2.1a General procedure for cycloaddition reaction (conventional): *N*-phenylhydroxylamine (250 mg, 2.29 mmol) was added to a solution of 2,3-dihydro-4*H*-pyran (192 mg, 1 equivalent) in dry benzene (20 mL) under N_2 atmosphere and the reaction mixture was refluxed for 24 h while the progress of the reaction was monitored by TLC (hexane:ethyl acetate = 5:1; $R_f =$

0.38). Dipolarophiles were added (1 equivalent) at this stage and the reaction mixture was further refluxed for 13–15 h. The solvent was evaporated off and the cycloadducts (**2–6**; table 1) were isolated by column chromatography using benzene-pet ether as eluent. But this methodology was discarded because of lengthy reaction process, poor yield and use of benzene as solvent.

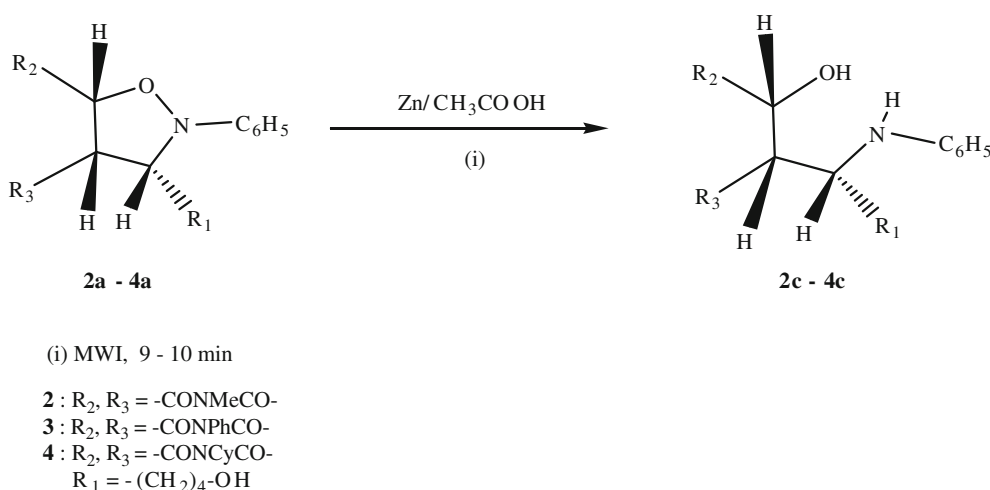
Table 1. Physicochemical data of synthesized compounds (**2a–4a**; **5–6** and **2b–4b**).

Entry	Nitrone	Dipolarophile ^a	Time (min)	Cycloadduct and m.p (°C) 2a–4a: cis ; 2b–4b: trans	<i>Cis/trans</i> ratio (%)	Yield ^b (%)
1	<i>N</i> -phenyl-5-hydroxy nitrone	<i>N</i> -methyl maleimide	7 (13 h)	2a : White crystal, 95 2b : White crystal, 82	2a : 64 2b : 32	96 (54)
2	<i>N</i> -phenyl-5-hydroxy nitrone	<i>N</i> -phenyl maleimide	9 (14 h)	3a : Pale yellow solid, 108 3b : White solid, 103	3a : 68 3b : 25	93 (52)
3	<i>N</i> -phenyl-5-hydroxy nitrone	<i>N</i> -cyclohexyl maleimide	9 (14 h)	4a : Yellow crystal, 80 4b : Yellow crystal, 88	4a : 62 4b : 31	93 (47)
4	<i>N</i> -phenyl-5-hydroxy nitrone	Ethyl acrylate	9 (15 h)	5 : Colourless thick liquid		92 (56)
5	<i>N</i> -phenyl-5-hydroxy nitrone	Styrene	9 (15 h)	6 : Colourless thick liquid		91 (50)

^aReaction condition: DHP (1 mmol), *N*-phenylhydroxylamine (1 equivalent), dipolarophile (1 equivalent), MWI.

^bIsolated yields after purification.

Figures in parentheses indicate reactions performed in conventional method



Scheme 2. Synthesis of 1,3 amino alcohols.

2.1b General procedure for cycloaddition for diastereomers (MWI): A mixture of *N*-phenylhydroxylamine (250 mg, 2.29 mmol), 2,3-dihydro-4*H*-pyran (192 mg, 1 equivalent) was taken in a 25 mL Erlenmeyer flask, mixed well and subjected to microwave irradiation at 250 W for 5 min. The formation of nitron was monitored by TLC (hexane:ethyl acetate = 5:1; R_f = 0.38). *N*-methyl maleimide (254 mg, 1 equivalent) was added at this stage and the reaction mixture was further irradiated at 250 W for an appropriate time (table 1). After completion of the reaction, as indicated by TLC (hexane:ethyl acetate = 5:1; R_f = 0.44, 0.50), the reaction mixture was cooled to room temperature (RT) and washed with diethyl ether (3 × 10 mL). The combined ether extract was concentrated *in vacuo* and the resulting products were directly charged on silica gel column and eluted with a mixture of ethyl acetate:hexane to afford pure isoxazolidine derivatives **2a** and **2b** (entry 1, table 1). This procedure was followed for other substrates listed in table 1.

2.1c Dihydro-3-(4-hydroxybutyl)-5-methyl-2-phenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6*a*-*H*)-dione (2a): White crystal. Yield 64%; R_f = 0.44 (hexane-ethyl

acetate, 5:1); IR (KBr): ν_{\max} 3640–3530 (br), 2915 (m), 2832 (m), 1774 (s), 1680 (s), 1440 (m), 1380 (m), 772 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 6.88–6.73 (m, 5H, C_6H_5), 4.83 (br, s, 1H, OH, exchanged in D_2O), 4.64 (d, 1H, J = 6.30 Hz, C_5H), 4.23 (dd, 1H, J = 6.06, 6.04 Hz, C_4H), 3.30 (s, 3H, CH_3 protons), 2.78 (dt, 1H, J = 6.40, 6.54 Hz, C_3H), 2.36 (dt~m, 2H, CH_2 protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.80–1.43 (m, 6H, CH_2 protons); ^{13}C NMR (CDCl_3): δ 176.22, 176.10 (carbonyl carbons), 130.62, 130.16, 128.88, 128.15 (aromatic carbons), 87.15 (C_5), 76.42 (C_3), 66.23 (CH_2OH), 55.50 (C_4), 38.00 (CH_3), 25.76, 22.31, 20.27 (3 CH_2 carbons); FAB-MS: m/z 304 (M^+), 289, 231, 227, 212, 154 (B.P), 77, 73; Anal. Found: C, 63.02; H, 6.35; N, 9.17. $\text{C}_{16}\text{H}_{20}\text{O}_4\text{N}_2$ requires C, 63.13; H, 6.61; N, 9.21%.

2.1d Dihydro-3-(4-hydroxybutyl)-5-methyl-2-phenyl-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6*a*-*H*)-dione (2b): White crystal. Yield 32%; R_f = 0.50 (hexane-ethyl acetate, 5:1); IR (KBr): ν_{\max} 3645–3550 (br), 2910 (m), 2830 (m), 1776 (s), 1676 (s), 1440 (m), 1385 (m), 775 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 6.76–6.63 (m, 5H, C_6H_5), 5.04 (br, s, 1H, OH, exchanged in

Table 2. Physicochemical data of synthesized 1,3 amino alcohols (2c–4c).

Entry	Isoxazolidine	Reagent ^a	Time (min)	1,3 amino alcohol (2c–4c)	Yield ^b (%)
1	2a	Zn and dil acetic acid	9	2c : Yellowish white thick liquid	84
2	3a	Zn and dil acetic acid	10	3c : White thick liquid	81
3	4a	Zn and dil acetic acid	10	4c : Dark gray thick liquid	80

^aReaction condition: Isoxazolidine (100 mg), Zn (5 mg), glacial acetic acid (3 mL), MWI.

^bIsolated yields after purification

D₂O), 4.80 (d, 1H, $J = 3.76$ Hz, C₅H), 4.15 (dd, 1H, $J = 2.18, 2.64$ Hz, C₄H), 3.34 (s, 3H, CH₃ protons), 2.70 (dt, 1H, $J = 3.10, 2.80$ Hz, C₃H), 2.08 (dt~m, 2H, CH₂ protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.76–1.30 (m, 6H, CH₂ protons); ¹³C NMR (CDCl₃): δ 170.90, 170.17 (carbonyl carbons), 129.12, 128.75, 128.53, 127.33 (aromatic carbons), 85.56 (C₅), 73.21 (C₃), 63.08 (CH₂OH), 54.22 (C₄), 34.44 (CH₃), 23.63, 22.70, 22.12 (3 CH₂ carbons); FAB-MS: m/z 304 (M⁺), 289, 231, 230, 227, 212, 154 (B.P), 77, 73; Anal. Found: C, 62.98; H, 6.40; N, 9.09. C₁₆H₂₀O₄N₂ requires C, 63.13; H, 6.61; N, 9.21%.

2.1e Dihydro-3-(4-hydroxybutyl)-2,5-diphenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6a-H)-dione (3a): Pale yellow solid. Yield 68%; $R_f = 0.56$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{max} 3585–3453 (br), 2920 (m), 2835 (m), 1780 (s), 1684 (s), 1600 (s), 1480 (m), 1346 (m), 770 (s) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.49–7.26 (m, 2X5H, C₆H₅), 6.84 (br, s, 1H, OH, exchanged in D₂O), 4.95 (d, 1H, $J = 6.52$ Hz, C₅H), 3.91 (dt, 1H, $J = 6.04, 6.16$ Hz, C₃H), 3.55 (dd, 1H, $J = 6.18, 6.22$ Hz, C₄H), 1.90 (dt~m, 2H, CH₂ protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.63–1.18 (m, 6H, 3 CH₂ protons); ¹³C NMR (CDCl₃): δ 172.12, 171.86 (carbonyl carbons), 133.77, 133.14, 132.22, 131.78, 129.80, 129.61, 128.15, 127.72 (aromatic carbons), 87.80 (C₅), 75.18 (C₃), 65.27 (CH₂OH), 56.37 (C₄), 34.55, 26.40, 25.00 (3 CH₂ carbons); FAB-MS: m/z 366 (M⁺), 306, 293, 289, 216 (B.P), 77, 73, 59; Anal. Found: C, 68.67; H, 5.83; N, 7.52. C₂₁H₂₂O₄N₂ requires C, 68.82; H, 6.04; N, 7.65%.

2.1f Dihydro-3-(4-hydroxybutyl)-2,5-diphenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6a-H)-dione (3b): White solid. Yield 25%; $R_f = 0.48$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{max} 3590–3476 (br), 2934 (m), 2830 (m), 1780 (s), 1680 (s), 1610 (s), 1476 (m), 1340 (m), 776 (s) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.36–7.15 (m, 2X5H, C₆H₅), 6.25 (br, s, 1H, OH, exchanged in D₂O), 4.48 (d, 1H, $J = 2.70$ Hz, C₅H), 3.54 (dt, 1H, $J = 3.04, 2.86$ Hz, C₃H), 3.12 (dd, 1H, $J = 2.26, 2.18$ Hz, C₄H), 1.84 (dt~m, 2H, CH₂ protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.50–1.16 (m, 6H, 3 CH₂ protons); ¹³C NMR (CDCl₃): δ 170.63, 170.14 (carbonyl carbons), 131.62, 131.08, 130.27, 130.14, 129.19, 128.40, 128.05, 127.58 (aromatic carbons), 88.06 (C₅), 73.90 (C₃), 62.83 (CH₂OH), 53.45 (C₄), 31.72, 24.44, 23.19 (3 CH₂ carbons); FAB-MS: m/z 366 (M⁺), 306, 293, 289, 216 (B.P), 212, 77, 73, 59; Anal. Found: C, 68.63; H, 5.87; N, 7.60. C₂₁H₂₂O₄N₂ requires C, 68.82; H, 6.04; N, 7.65%.

2.1g 5-cyclohexyl-dihydro-3-(4-hydroxybutyl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (4a): Yellow crystal. Yield 62%, $R_f = 0.50$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{max} 3638–3515 (br), 2865 (s), 1785 (s), 1680 (s), 1446 (m), 1380 (m), 1265 (m), 780 (s) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.40–7.17 (m, 5H, C₆H₅), 5.94 (d, 1H, $J = 6.64$ Hz, C₅H), 4.40 (br, s, 1H, OH, exchanged in D₂O), 3.44 (dd, 1H, $J = 6.26, 6.08$ Hz, C₄H), 2.23 (dt, 1H, $J = 6.60, 6.14$ Hz, C₃H), 1.69 (dt~m, 2H, CH₂ protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.45–1.17 (m, 17H, cyclohexyl and CH₂ protons); ¹³C NMR (CDCl₃): δ 173.16, 171.37 (carbonyl carbons), 136.04, 135.52, 134.07, 133.93 (aromatic carbons), 86.80 (C₅), 77.08 (C₃), 62.50 (CH₂OH), 55.62 (C₄), 38.51, 36.07, 34.40, 31.10, 29.52, 27.70, 26.30, 25.00, 23.28 (cyclohexyl and CH₂ carbons); FAB-MS: m/z 372 (M⁺), 313, 299, 222 (B.P), 216, 83, 77, 73, 59; Anal. Found: C, 67.62; H, 7.43; N, 7.35. C₂₁H₂₈O₄N₂ requires C, 67.71; H, 7.56; N, 7.52%.

2.1h 5-cyclohexyl-dihydro-3-(4-hydroxybutyl)-2-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (4b): Yellow crystal. Yield 31%, $R_f = 0.44$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{max} 3623–3534 (br), 2880 (s), 1782 (s), 1680 (s), 1440 (m), 1385 (m), 1260 (m), 774 (s) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.26–7.08 (m, 5H, C₆H₅), 4.90 (d, 1H, $J = 2.66$ Hz, C₅H), 4.56 (br, s, 1H, OH, exchanged in D₂O), 3.54 (dd, 1H, $J = 2.22, 2.50$ Hz, C₄H), 2.40 (dt, 1H, $J = 3.08, 3.04$ Hz, C₃H), 1.60 (dt~m, 2H, CH₂ protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.52–1.20 (m, 17H, cyclohexyl and CH₂ protons); ¹³C NMR (CDCl₃): δ 170.22, 170.04 (carbonyl carbons), 132.68, 132.30, 131.54, 131.38 (aromatic carbons), 85.10 (C₅), 76.20 (C₃), 63.44 (CH₂OH), 56.70 (C₄), 37.32, 36.40, 33.69, 31.28, 30.55, 28.12, 26.90, 25.43, 24.20 (cyclohexyl and CH₂ carbons); FAB-MS: m/z 372 (M⁺), 313, 299, 289, 222 (B.P), 216, 83, 77, 73, 59; Anal. Found: C, 67.57; H, 7.45; N, 7.30. C₂₁H₂₈O₄N₂ requires C, 67.71; H, 7.56; N, 7.52%.

2.1i General procedure for cycloaddition for regioisomers (MWI): A mixture of *N*-phenylhydroxylamine (250 mg, 2.29 mmol), 2,3-dihydro-4*H*-pyran (192 mg, 1 equivalent) was taken in a 25 mL Erlenmeyer flask, mixed well and subjected to microwave irradiation at 250 W for 5 min. The formation of nitrone was monitored by TLC (hexane:ethyl acetate = 5:1; $R_f = 0.38$). Ethyl acrylate (229 mg, 1 equivalent) was added at this stage and the reaction mixture was further irradiated at 250 W for appropriate time (table 1). After completion of the reaction, as indicated by TLC (hexane:ethyl acetate = 5:1; $R_f = 0.52$), the reaction mixture was

cooled to RT and washed with diethyl ether (3×10 mL). The combined ether extract was concentrated *in vacuo* and the resulting product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:hexane to afford pure isoxazolidine derivative **5** (entry 4, table 1). This procedure was followed for other substrate listed in table 1.

2.2 Ethyl 3-(4-hydroxy butyl)-2-phenyl isoxazolidine-5-carboxylate (**5**)

Colourless thick liquid. Yield 92%, $R_f = 0.52$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{\max} 3610–3525 (br), 2930 (s), 2842 (m), 1760 (s), 1444 (s), 790 (s) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 7.24–7.08 (m, 5H, C_6H_5), 4.92–4.80 (br, s, 1H, $-\text{OH}$, exchanged in D_2O), 4.20 (q, 2H, $J = 6.10, 6.06$ Hz, $-\text{OCH}_2\text{CH}_3$), 4.06 (t, 1H, $J = 6.68$ Hz, C_5H), 3.40 (ddd, 1H, $J = 6.54, 6.58$ Hz, C_3H), 3.18 (dd, 2H, $J = 6.12, 6.14$ Hz, C_4 2H), 1.68 (dt~m, 2H, CH_2 protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.26 (t, 3H, $J = 5.40$ Hz, $-\text{OCH}_2\text{CH}_3$), 1.18–0.82 (m, 6H, CH_2 protons); $^{13}\text{C NMR}$ (CDCl_3): δ 169.77 (carbonyl carbon), 130.72, 130.54, 130.27, 129.88 (aromatic carbons), 84.16 (C_5), 79.62 (C_3), 66.40 (CH_2OH), 61.52 (CH_2 carbon of $-\text{OCH}_2\text{CH}_3$), 56.86 (C_4), 22.28, 21.68, 20.94 (3 CH_2 carbons), 16.40 (CH_3 carbon of OCH_2CH_3); FAB-MS: m/z 293 (M^+), 220, 219, 143 (B.P), 111, 77, 73; Anal. Found: C, 65.22; H, 7.48; N, 4.54. $\text{C}_{16}\text{H}_{23}\text{O}_4\text{N}$ requires C, 65.49; H, 7.89; N, 4.77%.

2.2a 4-(2,5-diphenyl-isoxazolidin-3-yl)butan-1-ol (6**):** Colourless thick liquid. Yield 91%, $R_f = 0.50$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{\max} 3620–3565 (br), 2925 (s), 2844 (m), 1710 (s), 1440 (m), 1324 (s), 804 (m), 776 (s) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 6.93–6.56 (m, 2X5H, C_6H_5 protons), 5.02 (t, 1H, $J = 6.08$ Hz, C_5H), 4.85–4.76 (br, s, 1H, exchanged in D_2O), 4.28 (ddd, 1H, $J = 6.52, 6.50$ Hz, C_3H), 3.87 (dd, 2H, $J = 6.22, 6.20$ Hz, C_4 2H), 1.96 (dt~m, 2H, CH_2 protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.50–1.24 (m, 6H, CH_2 protons); $^{13}\text{C NMR}$ (CDCl_3): δ 136.75, 136.52, 136.17, 135.94, 131.88, 131.54, 131.12, 130.82 (aromatic carbons), 85.95 (C_5), 77.32 (C_3), 60.64 (CH_2OH), 56.40 (C_4), 21.48, 20.10, 19.63 (3 CH_2 carbons); FAB-MS: m/z 297 (M^+), 265, 224, 219, 147 (B.P), 77, 73; Anal. Found: C, 76.60; H, 7.47; N, 4.63. $\text{C}_{19}\text{H}_{23}\text{O}_2\text{N}$ requires C, 76.73; H, 7.78; N, 4.71%.

2.2b General procedure for synthesis of 1,3 amino alcohols (MWI): A mixture of isoxazolidine **2a** (100 mg) and Zn dust (5 mg) in dil acetic acid (3 mL)

was taken in a 25 mL Erlenmeyer flask, mixed well and subjected to microwave irradiation at 250 W for appropriate time (entry 1, table 2). The completion of reaction was monitored by TLC ((hexane:ethyl acetate, 5:1; $R_f = 0.66$). The reaction mixture was cooled to RT, extracted with diethyl ether and filtered. Excess acetic acid in the filtrate was removed through basic work up and finally charged on silica gel column and eluted with a mixture of ethyl acetate:hexane to afford pure 1,3 amino alcohol in 84% yield (entry 1; scheme 2; table 2). This procedure was followed for other substrates listed in table 2.

2.2c 3-hydroxy-4-(5-hydroxy-1-(phenylamino)pentyl)-1-methylpyrrolidine-2,5-dione (2c**):** Yellowish white thick liquid. Yield 84%, $R_f = 0.66$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{\max} 3650–3585 (br), 3510–3435 (br), 2845 (m), 1782 (s), 1685 (m), 1490 (m), 783 (s) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 7.05–6.88 (m, 5H, C_6H_5), 5.24 (br, 2H, 2XOH, exchanged in D_2O), 4.52 (d, 1H, $J = 6.50$ Hz, C_1H), 3.80 (dd, 1H, $J = 6.54, 6.30$ Hz, C_2H), 3.50 (br, 1H, $-\text{NHC}_6\text{H}_5$), 3.36 (s, 3H, CH_3 proton), 2.90 (dt, 1H, $J = 6.36, 6.28$ Hz, C_3H), 2.64 (dt~m, 2H, CH_2 protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 2.12–1.65 (m, 6H, CH_2 protons); $^{13}\text{C NMR}$ (CDCl_3): δ 173.70, 172.66 (carbonyl carbons), 129.94, 129.66, 129.14, 128.85 (aromatic carbons), 86.54 (C_1), 74.62 (C_3), 66.30 (CH_2OH), 55.08 (C_2), 33.12 (CH_3), 26.50, 24.22, 22.77 (3 CH_2 carbons); FAB-MS: m/z 306 (M^+), 233, 229, 156, 77, 73; Anal. Found: C, 62.36; H, 7.06; N, 9.01. $\text{C}_{16}\text{H}_{22}\text{O}_4\text{N}_2$ requires C, 62.74; H, 7.23; N, 9.15%.

2.2d 3-hydroxy-4-(5-hydroxy-1-(phenylamino)pentyl)-1-phenyl pyrrolidine-2,5-dione (3c**):** White thick liquid. Yield 81%, $R_f = 0.68$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{\max} 3670–3590 (br), 3505–3420 (br), 2840 (m), 1780 (s), 1680 (m), 1486 (m), 775 (s) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 7.22–7.08 (m, 2X5H, C_6H_5), 5.18–5.00 (br, 2H, 2XOH, exchanged in D_2O), 4.80 (d, 1H, $J = 6.74$ Hz, C_1H), 3.76 (dd, 1H, $J = 6.30, 6.38$ Hz, C_2H), 3.43 (br, 1H, $-\text{NHC}_6\text{H}_5$), 2.78 (dt, 1H, $J = 6.44, 6.40$ Hz, C_3H), 2.55 (dt~m, 2H, CH_2 protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.95–1.40 (m, 6H, CH_2 protons); $^{13}\text{C NMR}$ (CDCl_3): δ 174.08, 172.55 (carbonyl carbons), 135.80, 135.47, 133.54, 133.11, 132.12, 130.80, 130.23, 129.90 (aromatic carbons), 85.66 (C_1), 75.20 (C_3), 63.90 (CH_2OH), 55.30 (C_2), 27.03, 24.80, 22.13 (3 CH_2 carbons); FAB-MS: m/z 368 (M^+), 295, 291, 218, 214, 77, 73; Anal. Found: C, 68.33; H, 6.25; N, 7.28. $\text{C}_{21}\text{H}_{24}\text{O}_4\text{N}_2$ requires C, 68.47; H, 6.52; N, 7.60%.

2.2e 1-cyclohexyl-3-hydroxy-4-(5-hydroxy-1-(phenylamino)pentyl)pyrrolidine-2,5-dione (4c): Dark gray thick liquid. Yield 80%, $R_f = 0.64$ (hexane-ethyl acetate, 5:1); IR (KBr): ν_{\max} 3665–3580 (br), 3500–3425 (br), 2845 (m), 1778 (s), 1684 (m), 1440 (m), 1210 (m), 770 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 6.83–6.66 (m, 5H, C_6H_5), 5.22–5.09 (br, 2H, 2XOH, exchanged in D_2O), 4.70 (d, 1H, $J = 6.50$ Hz, C_1H), 3.90 (dd, 1H, $J = 6.88, 6.76$ Hz, C_2H), 3.33 (br, 1H, $-\text{NHC}_6\text{H}_5$), 2.60 (dt, 1H, $J = 6.70, 6.26$ Hz, C_3H), 2.28 (dt~m, 2H, CH_2 protons of $-\text{CH}_2-(\text{CH}_2)_3\text{OH}$), 1.90–0.96 (m, 17H, CH_2 protons); ^{13}C NMR (CDCl_3): δ 170.20, 170.05 (carbonyl carbons), 128.90, 128.56, 128.05, 127.66 (aromatic carbons), 86.22 (C_1), 74.28 (C_3), 62.50 (CH_2OH), 56.80 (C_2), 29.00, 28.45, 28.19, 27.06, 25.60, 23.86, 22.32, 20.72, 20.16 (CH_2 carbons); FAB-MS: m/z 374 (M^+), 301, 291, 224, 214, 83, 77, 73; Anal. Found: C, 67.18; H, 7.88; N, 7.26. $\text{C}_{21}\text{H}_{30}\text{O}_4\text{N}_2$ requires C, 67.37; H, 8.02; N, 7.48%.

3. Results and discussion

In the present study, the formation of nitrone **1** has been achieved by treating 2,3-dihydro-4*H*-pyran with *N*-phenylhydroxylamine under microwave irradiation and has been trapped *in situ* by various activated alkenes in 1,3-dipolar cycloaddition reaction with moderate selectivity and high yield resulting new isoxazolidine derivatives (**2–6**) (scheme 1; table 1). Dimerization of nitrone could be controlled under this condition.

Induction of three asymmetric centres at C_5 , C_4 and C_3 positions of the newly developed isoxazolidine derivatives have made this one-pot synthesis highly attractive. The development of diastereomers 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 are identified by considering the multiplicity of the proton signals at 3-H and 4-H along with their coupling constant values.^{30,31} The most significant differences in the ^1H 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 $J_{3,4} \sim 6.26$ Hz whilst for minor adducts **2b–4b**, $J_{3,4}$ is ~ 2.54 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 is assigned to the minor conformer (figure 1). The diastereomeric isoxazolidines **2a–4a** and **2b–4b** were separated by column chromatography and obtained in analytically pure form by recrystallization from heptane-ethyl acetate.

In all the diastereomers, the configurations of H-5 and H-4 are *cis* as evidenced from their coupling constant values. The cycloaddition reactions of *N*-phenyl-5-hydroxy nitrone with ethyl acrylate and styrene are found to be regioselective and results 5-substituted isoxazolidine derivatives exclusively. This was rationalized by using frontier molecular orbital theory and ^1H NMR experiments. The results remind us the pioneering works on the study of regioselectivity in cycloaddition reactions by Houk *et al.* and Huisgen which state that exclusively regioselective cycloadducts are possible only when LUMO (nitrone)-HOMO (dipolarophile) interactions completely dominate the reaction and lead to the formation of only 5-substituted adducts.^{32–34} From the ^1H NMR spectrum of cycloadducts **5–6**, it has been found that clear double-doublet signal for H-4 protons and double triplet (ddd) signal for H-3 protons are obtained in all the cases due to further coupling from vicinal hydrogens and hence confirms in favour of 5-substituted adducts. From the detailed investigations on the nature of these cycloaddition reactions using TLC and ^1H 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

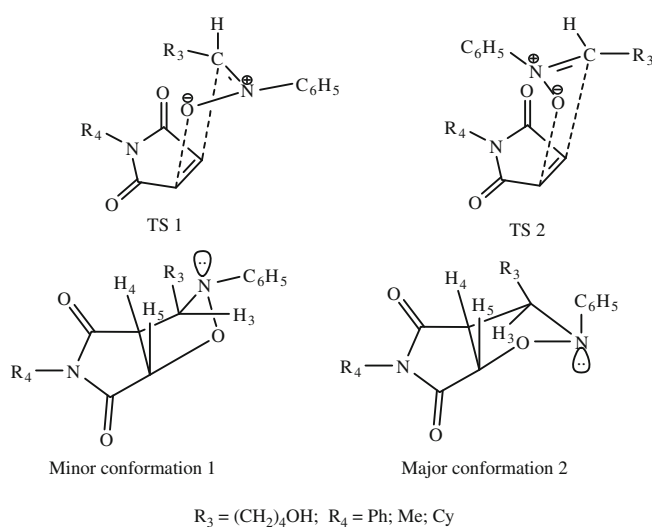


Figure 1. TS for the development of cycloadducts and their conformations.

are in favour of *exo* transition state geometry as evidenced from their coupling constant values ($J_{\text{H4}, \text{H5}} = 6.08\text{--}6.52\text{ Hz}$; $J_{\text{H4}, \text{H3}} = 6.10\text{--}6.68\text{ Hz}$).

The newly developed *N*-phenyl isoxazolidine derivatives (**2a–4a**) can be easily converted into acyclic chiral 1,3 difunctional amino alcohols (**2c–4c**) (scheme 2, table 2) by the reductive cleavage of the N–O bond. These conversions have been achieved by simply treating the substrates with zinc powder in dil acetic acid under microwave irradiation.^{27–29}

The relative configurations of H-1, H-2 and H-3 protons of the newly developed 1,3 amino alcohols (**2c–4c**) are *syn* as evidenced from their coupling constant values ($J_{\text{H1}, \text{H2}} \sim 6.70\text{ Hz}$; $J_{\text{H2}, \text{H3}} \sim 6.10\text{ Hz}$). Expected broad signals for N–H proton around δ 3.40 and alcoholic OH groups around δ 5.20 ppm are also obtained. Synthesis of 1,3 amino alcohols using other isoxazolidine derivatives (**2b–4b**; **5,6**) are in progress. In general, all the reactions are very clean and high yielding compared to conventional cycloaddition reactions of nitrones.^{24–26} The products have been characterized from their spectroscopic (IR, ¹H NMR, ¹³C NMR, MS) data. No catalyst or co-organic solvent is required.

4. Conclusion

This paper represents an extension of our studies dealing with the synthesis of heterocyclic compounds having isoxazolidine and isoxazoline cores in their structure. Further studies will be carried out in the near future to test their potential biological activities.

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