Synthesis of new scaffolds of isoxazolidine derivatives from dihydrofuran via 1,3-dipolar cycloaddition reactions under solvent free conditions

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Synthesis of a new class of isoxazolidine derivatives have been reported from dihydrofuran under solvent free conditions via 1,3-dipolar cycloaddition reactions. The new cycloadducts have been found to have good synthetic potentiality as they could be easily functionalized into 1,3-amino alcohols. High selectivity, good to excellent yields, greener approach and good synthetic potentiality are the important features in these syntheses.

Keywords: Isoxazolidines, cycloaddition reaction, solvent free reaction, stereoselectivity, green chemistry

The importance of microwave irradiation in organic synthesis has increased considerably in recent years. This nonconventional energy source is able to reduce chemical reaction times without involvement of solvents and to increase yields, and in some cases can lead to outcomes different from those obtained with conventional heating. Microwave reactions are quite often cleaner, faster, and higher-yielding than conventional ones. This methodology can be regarded as environmentally friendly, mainly because solvent-free reactions are especially suited to microwave conditions. Microwave technology has been successfully used to perform difficult cycloaddition reactions and to obtain temperature sensitive compounds. Particularly interesting 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 aminoalcohols. In fact, 1,3-dipolar cycloaddition was one of the first microwave-assisted organic reactions to be explored.

In continuation of our efforts to synthesize new organic molecules using green methodologies via nitrone cycloaddition reactions, we report herein microwave assisted synthesis of new scaffolds of isoxazolidine derivatives from dihydrofuran derived nitrone (Scheme I, Table I) with good to excellent yields and their further functionalization into a new class of 1,3-amino alcohols (Scheme II, Table II).

Results and Discussion

In the present study the formation of nitrone 1 has been achieved by treating 2,3-dihydrofuran with N-phenylhydroxylamine under microwave irradiation and has been trapped in situ by different maleimides, acenaphthylene, styrene and methyl acrylate respectively in 1,3-dipolar cycloaddition reactions with high selectivity resulting new isoxazolidines 2-7 (Scheme I, Table I). Dimerization of nitrone could also be controlled under this condition. Induction of three asymmetric centres at C5, C4 and C3 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–5a (transition state 1). The minor cycloadducts 2b–5b 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. 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–5a, coupling constant between 3-H and 4-H has been measured as $J_{3,4} \approx 6.26$ Hz whilst for minor adducts 2b–5b, $J_{3,4}$ is $\approx 2.54$ 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
Scheme I — Synthesis of new isoxazolidine derivatives from dihydrofuran derived nitrone

Scheme II — Synthesis of new 1,3-amino alcohols
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–5a and 2b–5b were separated by column chromatography and obtained in analytically pure form by recrystallization from heptane-ethyl acetate19.

In all the diastereomers, the configurations of H-5 and H-4 are cis as evidenced from their coupling constant values. For methyl acrylate and styrene the regioselectivity was rationalized by using frontier orbital theory20 (FMO approach) and ¹H NMR experiments. Cycloadditions to α,β-unsaturated carboxylic acid derivatives, e.g. methyl acrylate are particularly useful because high regioselectivity is often observed in solvent less conditions. The reactions were found to be highly regioselective to form solely 5-substituted isoxazolidines. This is due to the fact that, nitrone (LUMO)-dipolarophile (HOMO) interactions completely dominate the reaction and lead to the formation of only 5-substituted adducts21,22.

From the ¹H NMR spectrum of cycloadducts 6 and 7, it was found that clear double doublet signal for H-4 protons and triplet signals for H-5 protons were

### Table I — Physicochemical data of synthesized compounds 2a–5a, 2b–5b and 6, 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrone</th>
<th>Dipolarophile</th>
<th>Time (min)</th>
<th>Cycloadduct, m.p. (°C)</th>
<th>Cis/trans ratio</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-Phenyl-4-hydroxy nitrone</td>
<td>N-methyl maleimide</td>
<td>5 (12h)</td>
<td>2a-6a: cis ; 2b–6b: trans</td>
<td>2a: 64</td>
<td>96 (68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2a: Yellow crystals, 130</td>
<td>2b: 32</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>N-Phenyl-4-hydroxy nitrone</td>
<td>N-phenyl maleimide</td>
<td>6 (13h)</td>
<td>3a: Brown crystals, 106</td>
<td>3a: 70</td>
<td>94 (66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3b: Yellow crystals, 85</td>
<td>3b: 24</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>N-Phenyl-4-hydroxy nitrone</td>
<td>N-cyclohexyl Maleimide</td>
<td>6 (13h)</td>
<td>4a: White crystals, 147</td>
<td>4a: 63</td>
<td>94 (66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4b: White crystals, 104</td>
<td>4b: 31</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>N-Phenyl-4-hydroxy nitrone</td>
<td>Acenaphthylene</td>
<td>6 (12h)</td>
<td>5a: White solid, 112</td>
<td>5a: 68</td>
<td>94 (62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5b: White solid, 97</td>
<td>5b: 26</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>N-Phenyl-4-hydroxy nitrone</td>
<td>Styrene</td>
<td>7 (12 h)</td>
<td>6: Colourless thick liquid</td>
<td></td>
<td>91 (65)</td>
</tr>
<tr>
<td>6</td>
<td>N-Phenyl-4-hydroxy nitrone</td>
<td>Methyl acrylate</td>
<td>8 (12h)</td>
<td>7: Colourless thick liquid</td>
<td></td>
<td>86 (66)</td>
</tr>
</tbody>
</table>

### Table II — Physicochemical data of synthesized 1,3 amino alcohols (2c–5c; 8 & 9)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isoxazolidine</th>
<th>Reagent</th>
<th>Time (min)</th>
<th>1,3 amino alcohol (2c–5c; 8, 9)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>Zn &amp; dil acetic acid</td>
<td>5</td>
<td>2c: Yellowish white gummy liquid</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>Zn &amp; dil acetic acid</td>
<td>6</td>
<td>3c: White gummy liquid</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>Zn &amp; dil acetic acid</td>
<td>8</td>
<td>4c: Dark gray gummy liquid</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>Zn &amp; dil acetic acid</td>
<td>8</td>
<td>5c: Pale yellow liquid</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Zn &amp; dil acetic acid</td>
<td>10</td>
<td>8: Yellow liquid</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>Zn &amp; dil acetic acid</td>
<td>10</td>
<td>9: White liquid</td>
<td>70</td>
</tr>
</tbody>
</table>

**a** Reaction conditions: nitrone (1 mmol), dipolarophile (1 equivalent), water, N₂ atmosphere, RT.

**b** All products were characterized by IR,¹H NMR, ¹³C NMR and MS spectral data.

**c** Isolated yield after purification. Figures in parentheses indicate reactions performed in conventional methods.

### Table III — Synthesis of 1,3 amino alcohols (2c–5c; 8 & 9)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isoxazolidine</th>
<th>Reagent</th>
<th>Time (min)</th>
<th>1,3 amino alcohol (2c–5c; 8, 9)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>Zn &amp; dil acetic acid</td>
<td>5</td>
<td>2c: Yellowish white gummy liquid</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>Zn &amp; dil acetic acid</td>
<td>6</td>
<td>3c: White gummy liquid</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>Zn &amp; dil acetic acid</td>
<td>8</td>
<td>4c: Dark gray gummy liquid</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>Zn &amp; dil acetic acid</td>
<td>8</td>
<td>5c: Pale yellow liquid</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Zn &amp; dil acetic acid</td>
<td>10</td>
<td>8: Yellow liquid</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>Zn &amp; dil acetic acid</td>
<td>10</td>
<td>9: White liquid</td>
<td>70</td>
</tr>
</tbody>
</table>
obtained in these cycloadducts and hence confirms in favour 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 6 and 7, it is also confirmed that no diastereomers are formed. The relative configurations of H-3, H-4 and H-5 protons in these cycloadducts are $^{syn}$ and the cycloadducts are in favour of $^{exo}$ transition state geometry as evidenced from their coupling constant values ($J_{H4,H5} \approx 6.06-7.40$ Hz; $J_{H4,H3} \approx 6.20-6.80$ Hz).

In general, the reactions are very clean and high yielding compared to usual cycloaddition reactions of nitrones. The products have been characterized from their spectroscopic (IR, $^1$H NMR, $^{13}$C NMR, MS) data. No catalyst or co-organic solvent is required. Furthermore, good synthetic potentiality of the new isoxazolidine derivatives (2a-5a, 6 and 7) was also observed as they could be easily converted into acyclic chiral new 1,3 bifunctional amino alcohols (2c-5c) are $^{syn}$ as evidenced from their coupling constant values ($J_{H1,H2} \approx 6.70$ Hz; $J_{H2,H3} \approx 6.10$ Hz). Expected broad signals for N-H proton around $\delta$ 3.40 and alcoholic OH groups around $\delta$ 5.20 are also obtained. Synthesis of 1,3-amino alcohols using other diastereomeric isoxazolidine derivatives 2b-5b are in progress at present.

**Experimental Section**

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. Elemental analyses (CHN) were performed with a Perkin-Elmer 2400 series CHN Analyzer. TLC was carried out on Fluka silica gel TLC cards while column chromatography was performed with silica gel (E. Merck India) 60–200 mesh. 2,3-Dihydrofuran, N-methyl maleimide, N-phenyl maleimide and N-cyclohexyl maleimide were purchased from Sigma-Aldrich Chemical Company and were used as

![TS 1 and 2 – Addition of nitrone to maleimides; Conformations of new isoxazolidines](image)
received. All other reagents and solvents were purified after receiving from commercial suppliers. N-Phenylhydroxylamine was prepared following standard methods available in literature and has been used in various reported synthesis9-16. Microwave studies were carried out in Discover Bench Mate system (Make: CEM-USA) producing continuous irradiation at 2445 MHz and infrared control system. Microwave experiments were carried out in open vessels with an effective magnetic stirring and reflux (which avoids all problems of non homogeneity in temperature).

**General procedure for cycloaddition for diastereomers 2a-5a using MWI**

A mixture of N-phenylhydroxylamine (250 mg, 2.29 mmol), 2,3-dihydrofuran (160 mg, 1 equivalent) was taken in a 25 mL Erlenmeyer flask and a paste was made. The reaction mixture was irradiated for 5 min at 30°C. The formation of nitrone was monitored by TLC (Rf = 0.42). N-Methyl maleimide (254mg, 1 equivalent) was added in situ at this stage and the reaction mixture was further irradiated for 5 min at 30°C. The completion of the reaction was monitored by TLC (Rf = 0.64, 70). The reaction mixture was cooled to RT and extracted with diethyl ether. The products were concentrated in a rotary evaporator and finally the mixture of diastereomers were purified and separated by column chromatography using ethyl acetate-hexane to afford pure isoxazolidine derivatives 2a and 2b (entry 1, Table I). This procedure was followed for other substrates listed in Table I.

**3R,3aS,6aR**–Dihydro-3-(3-hydroxypropyl)-5-methyl-2-phenyl-2H-furrolo[3,4-d]isoxazole-4, 6(5H,6 a-H)-dione, 2a: Yellow crystals. Yield 64%. Rf = 0.64; IR (KBr): 3625 - 3510 (br), 2915 (m), 2830 (m), 1770 (s), 1680 (s), 1440 (m), 1375 (m), 780 (s) cm−1; 1H NMR (CDCl3): δ 6.80 – 6.72 (m, 5H, C6H5), 5.06 (br, s, 1H, OH, exchanged in D2O), 4.34 (dd, 1H, J = 6.00, 6.00 Hz, C6H), 3.40 (dd, 1H, J = 6.00, 6.00 Hz, C6H), 3.28 (s, 3H, CH3 protons), 2.80 (dt, 1H, δ 6.24, 6.30 Hz, C3H), 2.18 (dt–m, 2H, CH2 protons of –CH2(CH2)2OH), 1.74 – 1.36 (m, 4H, CH2 protons); 13C NMR (CDCl3): δ 172.43, 172.25 (carbonyl carbons), 136.47, 136.34, 136.25, 135.95 (aromatic carbons), 85.48 (C3), 75.24 (C3), 66.28 (CH3OH), 58.20 (C4), 36.18 (CH3), 22.36, 21.87 (2 CH2 carbons); MS: m/z 290 (M+), 231, 230, 213, 212, 198, 154 (B.P.), 77, 59. Anal. Found: C, 61.88; H, 6.15; N, 9.30. C15H18O4N2 requires C, 62.04; H, 6.24; N, 9.65%.

**3S,3aS,6aR**–Dihydro-3-(3-hydroxypropyl)-5-methyl-2-phenyl-2H-furrolo[3,4-d]isoxazole-4, 6(5H,6 a-H)-dione, 2b: Yellow crystals. Yield 32%. Rf = 0.70; IR (KBr): 3610 - 3535 (br), 2930 (m), 2825 (m), 1765 (s), 1680 (s), 1440 (m), 1375 (m), 780 (s) cm−1; 1H NMR (CDCl3): δ 6.73-6.62 (m, 5H, C6H5), 5.00 (br, s, 1H, OH, exchanged in D2O), 4.75 (d, 1H, J = 5.30 Hz, C6H), 4.30 (dd, 1H, J = 3.00, 3.00 Hz, C6H), 3.22 (s, 3H, CH3 protons), 2.47 (dt, 1H, J = 2.20, 2.16 Hz, C3H), 2.10 (dt–m, 2H, CH2 protons of –CH2(CH2)2OH), 1.70 – 1.28 (m, 4H, CH2 protons); 13C NMR (CDCl3): δ 171.25, 171.10 (carbonyl carbons), 135.50, 135.12, 134.80, 134.64 (aromatic carbons), 87.24 (C4), 76.63 (C3), 65.90 (CH3OH), 58.46 (C4), 35.05 (CH3), 23.13, 22.68 (2 CH2 carbons); MS: m/z 290 (M+), 231, 230, 213, 212, 198, 154 (B.P.), 77, 59. Anal. Found: C, 61.78; H, 6.20; N, 9.37. C15H18O4N2 requires C, 62.04; H, 6.24; N, 9.65%.

**3R,3aS,6aR**–Dihydro-3-(3-hydroxypropyl)-2,5-diphenyl-2H-furrolo[3,4-d]isoxazole-4,6(5H,6a-H)-dione, 3a: Brown crystals. Yield 70%. Rf = 0.56; IR (KBr): 3615 - 3560 (br), 2930 (m), 2840 (m), 1780 (s), 1682 (s), 1610 (s), 1480 (m), 790 (s) cm−1; 1H NMR (CDCl3): δ 7.46 – 7.22 (m, 2X5H, C6H5), 5.36 (br, s, 1H, OH, exchanged in D2O), 4.86 (d, 1H, J = 6.16 Hz, C6H), 3.74 (dd, 1H, J = 6.00, 6.00 Hz, C6H, C3H), 3.40 (dd, 1H, J = 6.16, 6.16 Hz, C6H), 1.76 (dt–m, 2H, CH2 protons of –CH2(CH2)2OH), 1.34 (m, 4H, 2 CH2 protons); 13C NMR (CDCl3): δ 173.15, 172.80 (carbonyl carbons), 134.54, 134.30, 133.92, 132.78, 132.50, 132.23, 131.44, 130.92 (aromatic carbons), 84.48 (C3), 75.30 (C3), 64.28 (CH3OH), 55.57 (C4), 33.67, 32.4 (2 CH2 carbons); MS: m/z 352 (M+), 293, 292, 275, 216 (B.P.), 198, 77, 59. Anal. Found: C, 68.04; H, 5.62; N, 7.82. C20H20O4N2 requires C, 68.15; H, 5.71; N, 7.95%.

**3S,3aS,6aR**–Dihydro-3-(3-hydroxypropyl)-2,5-diphenyl-2H-furrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione, 3b: Yellow crystals. Yield 24%. Rf = 0.50; IR (KBr): 3620 - 3556 (br), 2925 (m), 2832 (m), 1785 (s), 1675 (s), 1590 (s), 1470 (m), 1340 (m), 784 (s) cm−1; 1H NMR (CDCl3): δ 7.20 – 7.05 (m, 2X5H, C6H5), 5.08 (br, s, 1H, OH, exchanged in D2O), 4.58 (d, 1H, J = 2.10 Hz, C6H), 3.80 (dt, 1H, J = 2.30, 2.16 Hz, C3H), 3.54 (dd, 1H, J = 2.44, 2.44 Hz, C3H), 1.60 (dt–m, 2H, CH2 protons of –CH2(CH2)3OH),
1.40 (m, 4H, 2 CH2 protons); 13C NMR (CDCl3): δ 171.30, 171.15 (carbonyl carbons), 132.30, 132.15, 132.00, 131.87, 130.27, 130.13, 129.44, 129.06 (aromatic carbons), 87.54 (C3), 76.58 (C5), 66.20 (CH2OH), 54.25 (C4), 30.45, 30.16 (2 CH2 carbons); MS: m/z 352 (M+), 293, 292, 275, 216 (B.P.), 198, 77, 59. Anal. Found: C, 67.30; H, 7.30; N, 7.82%.

(3R,3aS,6aR)-5-Cyclohexyl-dihydro-3-(3-hydroxypropyl)-2-phenyl-2H-furrolo[3,4-d] isoxazole-4,6(5H,6 a-H)-dione, 4a: White crystals. Yield 31%, Rf = 0.46; IR (KBr): 3620 – 3555 (br), 2860 (s), 1784 (s), 1680 (s), 1442 (m), 1380 (m), 1260 (m), 785 (s) cm⁻¹; 1H NMR (CDCl3): δ 7.28 – 7.15 (m, 11H, acenapthylene and C6H5 protons), 5.10 (br, s, 1H, OH, exchanged in D2O), 3.47 (dd, 1H, J = 6.20, 6.20 Hz, C3H), 2.48 (dt, 1H, J = 6.40, 6.36 Hz, C3H), 1.73 (dt – m, 2H, CH2 protons of –CH2-(CH2)3OH), 1.43 (m, 4H, 2 CH2 protons); 13C NMR (CDCl3): δ 170.44, 170.16 (carbonyl carbons), 135.48, 135.27, 135.18, 134.90 (aromatic carbons), 86.80 (C3), 77.08 (C5), 62.37 (CH2OH), 55.70 (C4), 38.34, 34.30, 33.22, 32.14, 30.37, 28.26, 26.17, 25.38, 23.04 (cyclohexyl and CH2 carbons); MS: m/z 358 (M⁺), 299, 281, 275, 222 (B.P.), 216, 83, 77, 59. Anal. Found: C, 66.80; H, 7.15; N, 7.44. C20H20O2N2 requires: C, 67.05; H, 7.30; N, 7.82%.

(3S,3aS,6aR)-5-Cyclohexyl-dihydro-3-(3-hydroxypropyl)-2-phenyl-2H-furrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione, 4b: White crystals. Yield 31%, Rf = 0.46; IR (KBr): 3620 – 3555 (br), 2860 (s), 1784 (s), 1680 (s), 1442 (m), 1380 (m), 1260 (m), 785 (s) cm⁻¹; 1H NMR (CDCl3): δ 7.28 – 7.15 (m, 5H, C6H5 protons), 5.15 (br, s, 1H, OH, exchanged in D2O), 3.47 (dd, 1H, J = 6.20, 6.20 Hz, C3H), 2.48 (dt, 1H, J = 6.40, 6.36 Hz, C3H), 1.73 (dt – m, 2H, CH2 protons of –CH2-(CH2)3OH), 1.43 (m, 4H, 2 CH2 protons); 13C NMR (CDCl3): δ 170.44, 170.16 (carbonyl carbons), 135.48, 135.27, 135.18, 134.90 (aromatic carbons), 86.80 (C3), 77.08 (C5), 62.37 (CH2OH), 55.70 (C4), 38.34, 34.30, 33.22, 32.14, 30.37, 28.26, 26.17, 25.38, 23.04 (cyclohexyl and CH2 carbons); MS: m/z 358 (M⁺), 299, 281, 275, 222 (B.P.), 216, 83, 77, 59. Anal. Found: C, 66.80; H, 7.15; N, 7.44. C20H20O2N2 requires: C, 67.05; H, 7.30; N, 7.82%.

(3S,3aS,6aR)-5-(Cyclohexa-1,3-dienyl)-2,4-diphenyl-2H-furrolo[3,4-d]isoxazolidin-3--(3-hydroxypropyl) 5b: White solid. Yield 26%, Rf = 0.56; M.P: 97°C; IR (KBr): 3495-3438 (br), 3085 (s), 2360 (m), 1600 (m), 1390 (m), 1140 (s), 835 (s), 770 (s) cm⁻¹; 1H NMR (CDCl3): δ 7.30 - 7.15 (m, 11H, acenapthylene and C6H5 protons), 5.10 (br, s, 1H, OH, exchanged in D2O), 4.30 (d, 1H, J = 3.04 Hz, C3H), 3.52 (dt, 1H, J = 2.80 Hz, C3H), 2.68 (dd, 1H, J = 2.50, 2.50 Hz, C3H), 1.70 (dt – m, 2H, CH2 protons of –CH2-(CH2)3OH), 1.43 (m, 4H, 2 CH2 protons); 13C NMR (CDCl3): δ 136.30, 136.22, 136.10, 135.90, 135.80, 135.62, 134.27, 134.10, 133.25, 133.05 (acenapthylene carbons), 130.46, 130.25, 129.76, 129.48, 127.16, 126.59 (aromatic carbons), 84.38 (C3), 76.80 (C4), 66.40 (C3), 60.14 (CH2OH), 31.27, 30.03 (2 CH2 carbons); MS: m/z 331 (M⁺), 272, 254, 195, 77, 59. Anal. Found: C, 79.36; H, 6.27; N, 4.12. C22H20O2N2 requires: C, 79.72; H, 6.38; N, 4.22%.

General procedure for cycloaddition for regioisomers (6 & 7) using MWI

A mixture of N-phenylhydroxylamine (250 mg, 2.29 mmol), 2,3-dihydrofuran (160 mg, 1 equivalent) was taken in a 25 mL Erlenmeyer flask and a paste was made. The reaction mixture was irradiated for 5 min at 30°C. The formation of nitrone was monitored by TLC (Rf = 0.42). Styrene (238mg, 1 equivalent) was added in situ at this stage and the reaction mixture was further irradiated for 7 min at 30°C. The completion of the reaction was monitored by TLC (Rf = 0.64). The reaction mixture was cooled to RT and extracted with diethyl ether. The single product
was concentrated in a rotary evaporator and finally purified by column chromatography using ethyl acetate-hexane to afford pure isoxazolidine derivative 6 (entry 5, Table I). This procedure was followed for the other substrate listed in Table I. 

(3R)-2,5-Diphenylisoxazolidin–(3-hydroxypropyl) 6: Colourless thick liquid. Yield 91%. R_f = 0.66; IR (KBr): 3485-3425 (br), 3015 (s), 2934 (s), 1690 (m), 1580 (s), 1507 (m), 1482 (m), 1475 (m), 1455 (m), 1443 (m), 1264 (m), 800 (s) cm⁻¹; ¹H NMR (CDCl₃): δ 7.77 - 7.04 (m, 2 x 5H, C₆H₅ protons), 5.26 (br.s, 1H, OH, exchanged in D₂O), 3.61 (dd, 2H, J = 3.20, 3.20 Hz, C₃H), 1.72 (m, 1H, C₄H), 1.53 (dt~m, 2H, CH₂ protons of –CH₂-(CH₂)₃OH), 1.27 (m, 4H, 2 CH₂ protons); ¹³C NMR (CDCl₃): δ 129.95, 129.80, 129.72, 128.33, 128.21, 128.10, 127.96 (phenyl carbons), 83.42 (C₅), 77.65 (C 3), 62.20 (CH₂OH), 58.35 (C 2), 30.28, 28.15 (2 CH₂ carbons); MS: m/z 283 (M⁺), 224, 223, 206, 147, 77, 59. Anal. Found: C, 76.10; H, 7.15; N, 4.66. C₁₈H₂₁NO₂ requires: C, 76.28; H, 7.46; N, 4.94%.

The completion of reaction was monitored by TLC (R_f = 0.60). The reaction mixture was subjected to microwave irradiation for 5 min at 30°C (entry 1; Table II). 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 column chromatographic purification resulted in the desired 1,3-amino alcohol in 84% yield (entry 1; Scheme II; Table II). This procedure was followed for other substrates listed in Table II.

(3R,4S)-3-Hydroxy-4-((R)-4-hydroxy-1-(phenylamino) penty1)-1-methylfurrolidine-2,5-dione 2c: Yellowish white gummy liquid, Yield 84%. R_f = 0.70; IR (KBr): 3610 - 3554 (br), 3530 - 3490 (br), 2845 (m), 1778 (s), 1680 (m), 1443 (m), 1264 (m), 800 (s) cm⁻¹; ¹H NMR (CDCl₃): δ 7.13-6.90 (m, 5H, C₆H₅), 5.06 (br, 2H, 2XOH, exchanged in D₂O), 4.60 (d, 1H, J = 6.34 Hz, C₁H), 3.66 (dd, 1H, J = 6.12, 6.12 Hz, C₃H), 3.50 (br, 1H, -NH₂CH₃), 3.30 (s, 3H, CH₃ proton), 2.76 (dt, 1H, J = 5.40, 5.20 Hz, C₂H), 2.30 (dt~m, 2H, CH₂ protons of –CH₂-(CH₂)₃OH), 1.80 - 1.55 (m, 4H, CH₂ protons); ¹³C NMR (CDCl₃): δ 172.30, 172.12 (carbonyl carbons), 130.77, 130.54, 130.16, 129.87 (aromatic carbons), 84.40 (C₁), 75.73 (C₃), 60.17 (CH₂OH), 57.18 (C₃), 30.80 (CH₃), 23.35, 24.58 (2 CH₂ carbons); MS: m/z 292 (M⁺), 275, 265, 232, 206, 198, 77, 59. Anal. Found: C, 61.45; H, 6.64; N, 9.37. C₁₈H₂₀O₄N₂ requires: C, 61.61; H, 6.89; N, 9.58%.

(3R,4S)-3-Hydroxy-4-((R)-4-hydroxy-1-(phenylamino) penty1)-1-phenyl furrolidine-2,5-dione 3c: White gummy liquid, Yield 81%. R_f = 0.68; IR (KBr): 3630 - 3590 (br), 3520 (s), 2844 (m), 1778 (s), 1680 (m), 1482 (m), 785 (s) cm⁻¹; ¹H NMR (CDCl₃): δ 7.36-7.02 (m, 2X5H, C₆H₅), 5.06 (br, 2H, 2XOH, exchanged in D₂O), 4.76 (d, 1H, J = 5.80 Hz, C₁H), 3.92 (dd, 1H, J = 6.14, 6.14 Hz, C₂H), 3.40 (br, 1H, -NH₂CH₃), 2.73 (dt, 1H, J = 6.06, 6.06 Hz, C₃H), 2.50 (dt~m, 2H, CH₂ protons of –CH₂-(CH₂)₃OH), 1.90-1.40 (m, 4H, CH₂ protons); ¹³C NMR (CDCl₃): δ 172.55, 172.14 (carbonyl carbons), 135.68, 135.45, 133.54, 133.11, 132.40, 130.80, 130.23, 129.67 (aromatic carbons), 85.44 (C₁), 74.32 (C₃), 62.90 (CH₂OH), 53.42 (C₂), 24.16, 23.20 (2 CH₂ carbons); MS: m/z 354 (M⁺), 337, 294, 277, 260, 218, 77, 59. Anal. Found: C, 67.39; H, 6.23; N, 7.63. C₂₀H₂₂O₄N₂ requires: C, 67.76; H, 6.25; N, 7.90%.

(3R,4S)-1-Cyclohexyl-3-hydroxy-4-((R)-4-hydroxy-1-(phenylamino)pentyl)furrolidine-2,5-dione 4c: Dark gray gummy liquid, Yield 80%. R_f = 0.60; IR (KBr): 3660 - 3575 (br), 3530 - 3485 (br), 2845 (m), 1778 (s), 1680 (m), 1440 (m), 1210 (m), 790 (s) cm⁻¹; ¹H NMR (CDCl₃): δ 6.80-6.70 (m, 5H, C₆H₅), 5.06 - 5.05 (br, 2H, 2XOH, exchanged in D₂O), 4.64 (d, 1H, J = 6.20 Hz, C₁H), 3.80 (dd, 1H, J = 6.16, 6.16 Hz, C₂H), 3.44 (br, 1H, -NH₂CH₃), 2.53 (dt, 1H, J = 4.10,
4.26 Hz, C\text{H}), 2.37 (dt~m, 2H, CH\text{2} protons of –CH\text{2}- (CH\text{2})\text{3}OH), 1.85-0.90 (m, 15H, CH\text{2} protons); 1\text{3}C NMR (CDCl\text{3}): δ 171.34, 170.60 (carbonyl carbons), 129.70, 129.56, 128.77, 128.45 (aromatic carbons), 85.30 (C\text{1}), 72.26 (C\text{3}), 60.76 (CH\text{2}OH), 56.40 (C\text{2}), 29.34, 28.35, 28.12, 27.67, 25.60, 24.53, 22.47, 20.72 (CH\text{2} carbons); MS: m/z 360 (M\text{+}), 343, 300, 283, 277, 266, 224, 83, 77, 59. Anal. Found: C, 66.35; H, 7.71; N, 7.66. C\text{20}H\text{28}O\text{4}N\text{2} requires: C, 66.63; H, 7.82; N, 7.77%.

Conclusion

Finally, we have reported a new scaffold of isoxazolidine derivatives in solvent free conditions and these new molecules are further functionalized into synthetically more important new class of 1,3-amino alcohols. Atom efficient cycloaddition reactions, synthesis of new bifunctional amino alcohols, noninvolvement of catalysts, high yield of products and green chemistry methodologies are the salient features of the reported work which should attract chemists for further work in this area.

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