Synthesis of Venlafaxine from Azadiene via a Hetero-Diels–Alder Approach: New Microwave-Assisted Transketalization and Hydroxymethylation Reactions

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Abstract: Hetero-Diels–Alder (HDA) methodology has been applied to the synthesis of Venlafaxine taking advantage of a novel MW-assisted transketalization and hydroxymethylation reaction.

Key words: 1,3-aminol, hetero-Diels–Alder reaction, MAOS, Venlafaxine, transketalization

2-Azadienes¹ have been demonstrated to be versatile intermediates in hetero-Diels–Alder (HDA) reactions² with aldehydes to furnish perhydroxazin-4-ones. The latter have been utilized for the production of the 1,3-hydroxyamino moiety, or skeleton, of different biologically active compounds and of important chiral auxiliaries/ligands in asymmetric organic synthesis.³ In the course of our studies on these interesting intermediates, we have reported on the preparation of biologically active CNS-drugs, Prozac and Duloxetine, in racemic and optically pure form as well, presenting a scaffold of an 1,3-aminol unsubstituted in the 2-position and a secondary hydroxy functionality.⁴ In this paper we report our attempts to apply this strategy to the synthesis of (±)-Venlafaxine (I)⁵ characterized by the presence of a substituent (4-methoxyphenyl group) in the 2-position of the 1,3-aminol skeleton (Figure 1) and a tertiary hydroxy functionality. The importance of 1 resides in the fact that, among a large number of chemical structures found to exhibit antidepressant activity with diminished cardiovascular and anti-cholinergic liability, this compound has been proven to be the most potent antidepressant agent and has been approved by the drug agencies of many countries for the treatment of depression thanks to its faster onset of action and increased efficiency. From synthetic point of view, the choice of this particular target was dictated by our attempts of rendering the HDA protocol, developed in our laboratories, suitable for the preparation of a library of variably functionalized compounds presenting the 1-hydroxy-3-amino functionalities with or without further substitutions in the backbone chain identified by 1,3-aminol moiety and using as carbonyl-dienophile a ketone. Previous results showed that perhydroxazin-2-ones may be prepared from an 2-aza-1,3-diene variably substituted in the position 1 but unsubstituted in position 4, and a ketone as dienophile, including hindered ones such as menthone.⁶ These results were very interesting since the poor reactivity of ketones compared to aldehydes in hetero-Diels–Alder reactions is well known, owing to both steric and electronic reasons. As a matter of fact, until recently, only a very few examples of HDA reactions of ketones have been reported.⁷ Having in hand this information, we started our studies by preparing the intermediate azadiene 4 from (4-methoxyphenyl)acetyl chloride (2) and the trimethylsilylbenzaldimine 3 according to an existing protocol¹⁺²⁺⁸ (Scheme 1).

The necessary [4+2] HDA reaction was next attempted taking advantage of our recent procedure for the preparation of 1,3-perhydrooxazin-4-ones by EuFod [europium(III) tris(1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanodionate]-catalyzed microwave-assisted organic synthesis (MAOS).⁹ Accordingly, reaction of the azadiene 4 with dienophile cyclohexanone (5) was performed, using EuFod (0.05%) as catalyst and chlorobenzene as solvent under microwave irradiation (Scheme 2). Workup of the reaction mixture showed the formation of traces of the desired 1,3-perhydrooxazin-4-one 6 (Table 1, entry 1)
whereas the major product was constituted by the trans-β-lactam ring 7, arising from a [2+2] electrocyclization (for the sake of easy reading only one enantiomer of the racemic mixtures has been depicted in Scheme 2) irrespective of the presence or not of the Lewis acid (Table 1, entry 2). Use of chloroform as solvent, which is known to promote HDA via hydrogen bonding was unsuccessful, even in the presence of BF$_3$ as Lewis acid (Table 1, entries 11 and 12).

Further experiments, changing different reaction parameters including the very nature of the Lewis acids (Table 1), showed that the preference for a [2+2] electrocyclization versus a [4+2] HDA is strictly dependent on the reaction temperature used. The best results in the formation of the HDA adduct are obtained at very low temperature (–78 °C, 8 h) in the presence of BF$_3$ as Lewis acid and dichloromethane as solvent (Table 1, entry 7). Once obtained, the intermediate perhydroxazin-4-one 6 was used in the synthesis of racemic 1 in a straightforward manner (Scheme 3) by taking advantage of a new MW-mediated transketalization and hydroxymethylation methodologies. In detail, treatment of perhydroxazin-4-one 6 with a mixture of formic acid and formaldehyde under microwave irradiation furnished the $\text{N}$-hydroxymethyl derivative 8 in 70% yield. Further treatment of this product in the same reaction conditions gave the transketalized derivative 9 in 58% yield. Alternatively, exhaustive treatment of 6 reported as above (formic acid and formaldehyde, under microwave irradiation) furnished directly a stable intermediate 9 in 58% yield from 6. Finally, reduction of 9 with LiAlH$_4$ in THF afforded the target racemic 1 in 66% yield.

In summary, the synthesis of 1 through a hetero-Diels–Alder approach has been achieved. This study has pointed out the high competition between a [2+2] and a [4+2] reactions probably due to stereoelectronic reasons. Notwithstanding, we have been able to address the formation of the sole [4+2] product arising from a HDA pathway by the right choice of the temperature and Lewis acid. Theoretical calculations and studies are currently in progress to fully clarify this important aspect. The results will be reported in due course.

**Table 1** Reaction of Azadiene 4 with Cyclohexanone (5) under Different Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene 4 (equiv)</th>
<th>Cyclohexanone 5 (equiv)</th>
<th>Lewis acid (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)/Time</th>
<th>Yield of 6 (%)</th>
<th>Yield of 7 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>EuFOD (0.05)</td>
<td>PhCl$^a$</td>
<td>135 (40 min) DH 300 W</td>
<td>trace</td>
<td>55.0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td>PhCl</td>
<td>135 (2 h) DH 300 W</td>
<td>0</td>
<td>40.0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.5</td>
<td>EuFOD (0.05)</td>
<td>PhCl</td>
<td>135 (10 h) CH$^b$</td>
<td>trace</td>
<td>33.0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.5</td>
<td>EuFOD (0.05)</td>
<td>toluene</td>
<td>110 (3 h) DH 300 W</td>
<td>0</td>
<td>32.0</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0.5</td>
<td>EuFOD (0.05)</td>
<td>toluene</td>
<td>110 (20 h) CH</td>
<td>0</td>
<td>30.0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>BF$_3$·OEt$_2$ (1)</td>
<td>CH$_2$Cl$_2$</td>
<td>–78 to r.t (12 h)</td>
<td>48.0</td>
<td>8.0</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>BF$_3$·OEt$_2$ (1)</td>
<td>CH$_2$Cl$_2$</td>
<td>–78 (8 h)</td>
<td>62.0</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1</td>
<td>BF$_3$·OEt$_2$ (1)</td>
<td>CH$_2$Cl$_2$</td>
<td>0 (8 h)</td>
<td>0</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>BF$_3$·OEt$_2$ (1)</td>
<td>CH$_2$Cl$_2$</td>
<td>25 (72 h)</td>
<td>0</td>
<td>12.0</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1</td>
<td>EuFOD (0.05)</td>
<td>CH$_2$Cl$_2$</td>
<td>–78 (8 h)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>1</td>
<td>CHCl$_3$</td>
<td>–78 (8 h)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>1</td>
<td>BF$_3$·OEt$_2$ (1)</td>
<td>CHCl$_3$</td>
<td>25 (12 h)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>0.5</td>
<td>ZnCl$_2$ (0.05)</td>
<td>toluene</td>
<td>110 (1 h) DH 300 W</td>
<td>0</td>
<td>9.0</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>0.5</td>
<td>ZnCl$_2$ (0.05)</td>
<td>PhCl</td>
<td>135 (40 min) DH 300 W</td>
<td>0</td>
<td>14.0</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>0.5</td>
<td>TiCl$_3$ (0.05)</td>
<td>PhCl</td>
<td>135 (40 min) DH 300 W</td>
<td>0</td>
<td>11.0</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>0.5</td>
<td>AlCl$_3$ (0.05)</td>
<td>PhCl</td>
<td>135 (40 min) DH 300 W</td>
<td>0</td>
<td>17.0</td>
</tr>
</tbody>
</table>

$^a$ PhCl = chlorobenzene.

$^b$ DH = dielectric heating.

$^c$ CH = convective heating.
Scheme 3 Synthesis of 1 from perhydroxazine 6

All starting compounds, unless otherwise stated, were purchased. Reactions were run under an atmosphere of dry N₂ or argon. FT-IR spectra were recorded on a PerkinElmer IR spectrometer, mass spectra on a Finnigan MAT instrument, and NMR spectra on a Varian Mercury spectrometer using the residual signal of the solvent as an internal standard. Chemical shifts are reported on the δ scale and coupling constants (J) in Hertz. Microwave reactions were performed on a Prolabo Synthewave 402 microwave oven. Solvents were distilled and dried according to standard procedures.

[(1Z,3E)-1-(4-Methoxyphenyl)-4-phenylbuta-1,3-dien-2-yloxy]trimethylsilyl (4)

An oven dried 100 mL three-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, a spirit thermometer, and a needle for nitrogen inlet was charged with anhyd hexane (15 mL) and LiN(SiMe₃)₂ (1 M soln in THF; 1 mL, 1 mmol) and placed in an ice bath. At 0 °C, benzaldehyde (0.101 mL, 1 mmol) was added. The mixture was stirred at this temperature for 1 h. A solution of Me₂SiCl (0.126 mL, 1 mmol) in hexane (1 mL) was added at 0 °C and the stirring was maintained for 1 h at rt. A white precipitate was observed. At 0 °C were added Et₃N (0.278 mL, 2 mmol) in hexane (1 mL) and (4-methoxyphenyl)acetyl chloride (184 mg, 1 mmol) in anhyd Et₂O (1 mL) and the mixture was stirred for 2 h at rt. The mixture was filtered through a Celite pad and the solvent was evaporated, furnishing the azadiene, which was identified by 1H and 13C NMR spectra.

H NMR (400 MHz, CDCl₃): δ = 7.56 (m, 2 H), 7.46 (m, 3 H), 7.34 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 6.25 (br s, 1 H), 5.92 (s, 1 H), 3.78 (s, 3 H), 3.35 (s, 1 H), 2.27 (d, J = 9.2 Hz, 1 H), 1.62 (m, 5 H), 1.32 (m, 3 H), 1.13 (m, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 171.12, 158.84, 138.30, 130.47, 129.61, 129.03, 126.63, 113.80, 79.72, 76.92, 56.65, 55.21, 34.92, 33.28, 25.45, 22.08, 21.27.

MS: m/z = 352 (M + 1), 306, 253, 201, 159, 148, 120, 105, 91, 77.


(3S,4R*)-3-(4-Methoxyphenyl)-4-phenylazetidin-2-one (7)

Table 1: Entry 1: Compound 4 (325 mg, 1 mmol) was dissolved in anhyd chlorobenzene (5 mL). Cyclohexanone (5; 49 mg, 0.5 mmol) and EuFOD (50 mg, 0.05 mmol) were added. The resulting mixture was submitted to a microwave irradiation (40 min, 300 W). After the irradiation, the solvent was removed under vacuum. The crude mixture was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 7:3) to give the β-lactam 7; yield: 139 mg (55%).

Table 1, Entries 13, 14, 15, and 16: These experiments were performed following the same procedure and using the Lewis acid shown in the table.

Table 1, Entry 5: Compound 4 (325 mg, 1 mmol) was dissolved in anhyd toluene (10 mL), cyclohexanone (5; 49 mg, 0.5 mmol) and EuFOD (50 mg, 0.05 mmol) were added and the mixture was refluxed for 20 h. The solvent was removed under vacuum and the mixture was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 7:3) to give the β-lactam 7; yield: 76 mg (30%); white solid; mp 135–138 °C.

IR (CHCl₃): 1761 cm⁻¹.

Table 1; Entry 1:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Pubchem CID</th>
<th>Yield</th>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>12055799</td>
<td>62%</td>
<td>4+3+EuFOD</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>12055799</td>
<td>75%</td>
<td>4+EuFOD</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>12055799</td>
<td>55%</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

(3S*,4R*)-5-(4-Methoxyphenyl)-2-phenyl-1-oxa-3-azaspiro[5.5]undecan-4-one (8)

Compound 6 (120 mg, 0.34 mmol) was dissolved in toluene (2 mL), and formic acid (0.1 mL) and formaldehyde (37% in H₂O, 1 mL) were added. The mixture was irradiated in a microwave oven (6 min, 150 W). The formic acid was removed under vacuum and the mixture poured into sat. aq NaHCO₃ (5 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The organic layers were dried (Na₂SO₄) and the solvent was removed under vacuum. The mixture was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 4:6) to give 6; yield: 217 mg (62%); white solid; mp 186–188 °C.

IR (CHCl₃): 1665 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.56 (m, 2 H), 7.46 (m, 3 H), 7.34 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 6.25 (br s, 1 H), 5.92 (s, 1 H), 3.78 (s, 3 H), 3.35 (s, 1 H), 2.27 (d, J = 9.2 Hz, 1 H), 1.62 (m, 5 H), 1.32 (m, 3 H), 1.13 (m, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 169.77, 159.10, 139.50, 129.99, 128.51, 128.47, 126.75, 125.48, 114.31, 65.58, 60.48, 55.23.

MS: m/z = 254 (M + 1), 210, 194, 179, 165, 148, 120, 105, 91, 77.

Anal. Calcd for C₁₆H₁₅NO₂: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.60; H, 5.02; N, 5.48.

(2R*,5R*)-3-Hydroxymethyl-5-(4-methoxyphenyl)-2-phenyl-1-oxa-3-azaspiro[5.5]undecan-4-one (8)

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basified (pH 10) with NH₄OH and extracted with CH₂Cl₂ (3 mL) and formaldehyde (37% in H₂O, 1 mL). The mixture was irradiated in a microwave oven (1 min, 75 W). The formic acid was removed under vacuum and the mixture poured into sat. aq NaHCO₃ (5 mL) and then extracted with EtOAc (3 mL). The mixture was irradiated in a microwave oven (5 min, 150 W). The formic acid was removed under vacuum and the mixture poured into sat. aq NaHCO₃ and then extracted with EtOAc (3 mL). The organic layers were dried (Na₂SO₄) and the solvent removed under vacuum. The crude mixture was purified by flash chromatography on silica gel to give 9; yield: 80 mg (58%); colorless oil.

IR (CHCl₃): 3388, 1644 cm⁻¹.

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