Water excellent solvent for the synthesis of bifunctionalized cyclopentenones

M. Nardi,*a,b P. Costanzo,c A. De Nino,a M. L. Di Gioia,d F. Olivito,c G. Sindona a and A. Procopioc

d Dipartimento di Chimica, Università della Calabria, Cubo 12C, 87036-Arcavacata di Rende (CS), Italy, Tel.: +39 0984 492850. Fax: +39 0984493307. E-mail: monica.nardi@unical.it
b Dipartimento di Agraria, Università Telematica San Raffaele, Roma, Via di Val Cannuta, 247, 00166, Italia.
c Dipartimento di Scienze della Salute, Università Magna Graecia, Viale Europa, 88100-Germaneto (CZ), Italia.
d Dipartimento di Farmacia e Scienze della Salute e della Nutrizione, Edificio Polifunzionale, Università della Calabria, 87030 Arcavacata di Rende, Cosenza.
<table>
<thead>
<tr>
<th>INDICE</th>
<th>Pag.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental Section</td>
<td>3</td>
</tr>
<tr>
<td>General MW-assisted protocol for synthesis of trans- 4,5 diaminocyclopent-2-enones (1a-10a).</td>
<td>3</td>
</tr>
<tr>
<td>Spectroscopic data (1a-10a).</td>
<td>3</td>
</tr>
<tr>
<td>General protocol for the synthesis of 2,4 diaminocyclopent-2-enones (1b-3b) and (1c-1j).</td>
<td>4</td>
</tr>
<tr>
<td>Spectroscopic data (1b-3b) and (1c-1j).</td>
<td>4</td>
</tr>
<tr>
<td>$^1$H NMR  spectrum (1b)</td>
<td>6</td>
</tr>
<tr>
<td>$^{13}$C NMR  spectrum (1b)</td>
<td>7</td>
</tr>
<tr>
<td>$^1$H NMR  spectrum (1j)</td>
<td>8</td>
</tr>
<tr>
<td>$^{13}$C NMR  spectrum (1j)</td>
<td>9</td>
</tr>
<tr>
<td>HRMS (ESI) spectrum (3a, 4a, 6a)</td>
<td>10</td>
</tr>
<tr>
<td>HRMS (ESI) spectrum (1c, 1e, 1f, 1g, 1j)</td>
<td>11</td>
</tr>
</tbody>
</table>
Experimental section

All chemicals and solvents were purchased from common commercial sources and were used as received without any further purification. All reactions were monitored by TLC on silica Merck 60 F\textsubscript{254} pre-coated aluminum plates Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Brüker spectrometer at 300 MHz. Chemical shifts are reported in δ units (ppm) with TMS as reference (δ 0.00). All coupling constants (J) are reported in Hertz. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Brüker at 75 MHz. Chemical shifts are reported in δ units (ppm) relative to CDCl\textsubscript{3} (δ 77.0). MW-assisted reactions were performed on a Synthos 3000 instrument from Anton Paar, equipped with a 4×24MG5 Rotor and an IR probe used for external temperature control.

LC-MS analysis were carried using an Agilent 6540 UHD Accurate Mass Q-TOF LC–MS (Agilent, Santa Clara, CA) fitted with a electrospray ionisation source (Dual AJS ESI) operating in positive ion mode. Chromatographic separation was achieved using a C18 RP analytical column (Poroshell 120, SB-C18, 50 × 2.1 mm, 2.7 μm) at 30°C with a elution gradient from 5% to 95% of B over 13 min, A being H\textsubscript{2}O (0.1% FA) and B CH\textsubscript{3}CN (0.1% FA). Flow rate was 0.4 ml/min.

General MW-assisted protocol for synthesis of trans- 4,5 diaminocyclopent-2-enones (1a-10a).

To a water solution (3 mL) of furfural (1 mmol) in a 3 mL glass vial, the amine (2.2 mmol) was added. The mixture was reacted for 5 min in a Synthos 3000 microwave instrument, fixed on the temperature value of 60 °C (IR Limit). The reaction was monitored by TLC and GC/MS analysis. Diethyl ether was added after the completion of reaction and the products were isolated after evaporation of the solvent to yield compounds 1a-10a in 80-93 % yields.

trans-4,5-dimorpholinocyclopent-2-en-1-one (1a): Spectral data were in accordance with the literature.\textsuperscript{9a}

trans-4,5-bis(phenylamino)cyclopent-2-en-1-one (2a): Spectral data were in accordance with the literature.\textsuperscript{9a}
**trans-4,5-bis(methyl(phenyl)amino)cyclopent-2-en-1-one (3a):** Spectral data were in accordance with the literature.\(^9\text{a}\) HRMS (ESI) for ([C\(_{19}\)H\(_{20}\)N\(_2\)O] + H\(^+\)) \(293.1654\), found 293.1644 [M+H]*.

**trans-4,5-di(pyrrolidin-1-yl)cyclopent-2-en-1-one (4a):** Spectral data were in accordance with the literature.\(^8\text{f}\) HRMS (ESI) for ([C\(_{13}\)H\(_{20}\)N\(_2\)O] + H\(^+\)) 221.1654, found 221.1649 [M+H]*, 243.1452 [M+Na]*.

**trans-4,5-di(piperidin-1-yl)cyclopent-2-en-1-one (5a):** Spectral data were in accordance with the literature.\(^9\text{a}\)

**trans-4,5-bis(dibenzylamino)cyclopent-2-en-1-one (6a):** Spectral data were in accordance with the literature.\(^9\text{a}\) HRMS (ESI) for ([C\(_{33}\)H\(_{32}\)N\(_2\)O] + H\(^+\)) 473.2593, found 473.2583, [M+H]*, 495.2543, [M+Na]*.

**trans-4,5-di(isoindolin-2-yl)cyclopent-2-en-1-one (7a):** Spectral data were in accordance with the literature.\(^9\text{a}\)

**trans-4,5-bis(3,4-dihydroquinolin-1(2H)-yl)cyclopent-2-en-1-one (8a):** Spectral data were in accordance with the literature.\(^9\text{a}\)

**trans-4,5-bis(diisobutylamino)cyclopent-2-enone (9a):** Spectral data were in accordance with the literature.\(^1\text{1}\)

**trans-4,5-bis(diallylamino)cyclopent-2-enone (10a):** Spectral data were in accordance with the literature.\(^9\text{a}\)

**General protocol for the synthesis of 2,4 diaminocyclopent-2-enones (1b-3b) and (1c-1j).**

To a water solution (3 mL) of furfural (1 mmol) in a 3 mL glass vial, the amine (2.2 mmol) was added. The mixture was reacted for 5 min in a Synthos 3000 microwave instrument, fixed on the temperature value of 60 °C (IR Limit).

In order to obtain the 2,4 bisubstituted cyclopentenones 1b-3b the reaction mixture, after MW irradiation, was kept at room temperature for further 4 hour. After completion, diethyl ether was added (3 × 2 mL) and the organic phase was dried over Na\(_2\)SO\(_4\) and filtered. The products were isolated after evaporation of the diethyl ether to afford compounds 1b-3b in 85-91 % yields.
Instead, for the synthesis of compounds 1c-1j, after MW irradiation, the addition of various nucleophiles (1 mmol) was necessary. Also in this case the mixture was maintained at room temperature for further 4 hours. The reaction was monitored by TLC and GC/MS analysis. After completion, water was removed under reduced pressure and the resulting crude product was purified by flash chromatography (CH₂Cl₂/MeOH 9.5:0.5). The products 1c-1j were obtained in 79-89 % yields.

2,4-dimorpholinocyclopent-2-enone (1b): ¹H NMR (300 MHz, CDCl₃) 6.24 (d, J = 2.9 Hz, 1H, COC=CH), 3.78 (t, J = 4.7 Hz, 4H, morpholine), 3.73 (t, J = 4.7 Hz, 4H, morpholine), 3.73-3.72 (m, 1H, COCH₂CHN), 3.15-3.14 (m, 4H, morpholine), 2.54-2.52 (m, 4H, morpholine), 2.49-2.48 (m, 1H, COCH₂), 2.46-2.45 (m, 1H, COCH₂); ¹³C NMR (75 MHz, CDCl₃) 38.1, 48.1, 50.0, 60.3, 66.6, 67.1, 129.5, 151.7, 202.0.

2,4-bis(phenylamino)cyclopent-2-enone (2b): Spectral data were in accordance with the literature.¹⁰a

2,4-bis(methyl(phenyl)amino)cyclopent-2-enone (3b): Spectral data were in accordance with the literature.¹⁰a

4-(ethylthio)-2-morpholinocyclopent-2-enone (1c): Spectral data were in accordance with the literature.¹⁰a HRMS (ESI) for ([C₁₁H₁₇NO₂S] + H)⁺ 228.1058, found 228.1048 [M+H]⁺.

4-(cyclohexylthio)-2-morpholinocyclopent-2-enone (1e): Spectral data were in accordance with the literature.¹⁰a HRMS (ESI) for ([C₁₅H₂₃NO₂S] + H)⁺ 282.1528, found 282.1523 [M+H]⁺.

4-(phenylthio)-2-morpholinocyclopent-2-enone (1f): Spectral data were in accordance with the literature.¹⁰a HRMS (ESI) for ([C₁₅H₁₇NO₂S] + H)⁺ 276.1058, found 276.1050 [M+H]⁺.

4-(benzylthio)-2-morpholinocyclopent-2-enone (1g): Spectral data were in accordance with the literature.¹⁰a HRMS (ESI) for ([C₁₆H₁₉NO₂S] + H)⁺ 290.1215, found 290.1212 [M+H]⁺.

4- (methyl-L-cysteinate)-2-morpholinocyclopent-2-enone (1j): ¹H NMR (300 MHz, CDCl₃) 6.23 (d, J = 3.0 Hz, 1H, COC=CH), 4.02 (dt, J = 9.3 Hz, J = 5.5 Hz, 1H, COCHNH₂), 3.75-3.64 (m, 4H, morpholine), 3.45-3.41 (m, 1H, SCh), 3.03 (s, 3H, CH₃), 2.79 (t, 2H, J = 9.3 Hz, COCH₂), 2.61-2.53 (m, 4H, morpholine), 2.49-2.46 (m, 1H, SCh₂), 2.45-2.39 (m, 1H, SCh₂); ¹³C NMR (75 MHz, CDCl₃) 37.9, 43.9, 44.2, 48.0, 49.0, 49.9, 66.9, 110.0, 152.9, 174.8, 201.8. HRMS (ESI) for ([C₁₆H₂₀N₂O₄S] + H)⁺ 301.1222, found 301.1214 [M+H]⁺.
$^1$H-NMR

Compound 1b

$^{13}$C-NMR

Compound 1b
1H-NMR

Compound 1j

H
O
N
O
MeO

N
S
O
$^{13}$C-NMR

Compound 1j
HRMS (ESI)
Compound 3a

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>RT</th>
<th>Mass</th>
<th>Abund</th>
<th>Formula</th>
<th>Tgt Mass</th>
<th>Diff (ppm)</th>
<th>MFG Formula</th>
<th>DB Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C19 H20 N2 O</td>
<td>5.959</td>
<td>292,1574</td>
<td>I01081</td>
<td>C19 H20 N2 O</td>
<td>292,1576</td>
<td>-0,64</td>
<td>C19 H20 N2 O</td>
<td>C19 H20 N2 O</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>m/z</th>
<th>RT</th>
<th>Algorithm</th>
<th>Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C19 H20 N2 O</td>
<td>293,1644</td>
<td>5.959</td>
<td>Find By Formula</td>
<td>292,1574</td>
</tr>
</tbody>
</table>

![HRMS Spectrum for Compound 3a](image)
### Compound 4a

#### Compound Table

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>m/z</th>
<th>RT</th>
<th>Algorithm</th>
<th>Mass</th>
<th>Compound</th>
<th>Target Mass</th>
<th>Diff (ppm)</th>
<th>MFG Formula</th>
<th>DB Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C13 H20 N2 O</td>
<td>221,1649</td>
<td>1,928</td>
<td>Find By Formula</td>
<td>220,1576</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### MS Spectrum Peak List

<table>
<thead>
<tr>
<th>m/z</th>
<th>z</th>
<th>Abund</th>
<th>Formula</th>
<th>Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>221,1649</td>
<td>1</td>
<td>699293.06</td>
<td>C13H20N2O</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>222,1679</td>
<td>1</td>
<td>92918.73</td>
<td>C13H20N2O</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>223,1702</td>
<td>1</td>
<td>7771.66</td>
<td>C13H20N2O</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>224,1697</td>
<td>1</td>
<td>568.99</td>
<td>C13H20N2O</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>243,1452</td>
<td>1</td>
<td>1133.93</td>
<td>C13H20N2O</td>
<td>(M+Na)+</td>
</tr>
<tr>
<td>244,1474</td>
<td>1</td>
<td>230.81</td>
<td>C13H20N2O</td>
<td>(M+Na)+</td>
</tr>
</tbody>
</table>

### Compound 6a

#### Compound Table

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>m/z</th>
<th>RT</th>
<th>Algorithm</th>
<th>Mass</th>
<th>Compound</th>
<th>Target Mass</th>
<th>Diff (ppm)</th>
<th>MFG Formula</th>
<th>DB Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C33 H32 N2 O</td>
<td>473,2583</td>
<td>8.975</td>
<td>Find By Formula</td>
<td>472,2554</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### MS Spectrum Peak List

<table>
<thead>
<tr>
<th>m/z</th>
<th>z</th>
<th>Abund</th>
<th>Formula</th>
<th>Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>473,2583</td>
<td>1</td>
<td>2059</td>
<td>C33H32N2O</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>495,2543</td>
<td>1</td>
<td>83</td>
<td>C33H32N2O</td>
<td>(M+Na)+</td>
</tr>
</tbody>
</table>
**MS Spectrum Peak List**

<table>
<thead>
<tr>
<th>m/z</th>
<th>z</th>
<th>Abund</th>
<th>Formula</th>
<th>Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>473.2583</td>
<td>1</td>
<td>20558.72</td>
<td>C33H32N2O</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>474.253</td>
<td>1</td>
<td>7872.94</td>
<td>C33H32N2O</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>495.2543</td>
<td>1</td>
<td>9128.57</td>
<td>C33H32N2O</td>
<td>(M+Na)+</td>
</tr>
<tr>
<td>496.2627</td>
<td>1</td>
<td>1655.41</td>
<td>C33H32N2O</td>
<td>(M+Na)+</td>
</tr>
</tbody>
</table>

**Compound 1c**

**Compound Table**

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>m/z</th>
<th>RT</th>
<th>Mass</th>
<th>Abund</th>
<th>Formula</th>
<th>Tgt Mass</th>
<th>Diff (ppm)</th>
<th>MFG Formula</th>
<th>DB Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C11 H17NO25</td>
<td>228.1048</td>
<td>4.938</td>
<td></td>
<td></td>
<td>669183.06 C11 H17NO25</td>
<td>227.0978</td>
<td>-1.21</td>
<td>C11 H17NO25</td>
<td>C11 H17NO25</td>
</tr>
</tbody>
</table>

**MS Spectrum Peak List**

<table>
<thead>
<tr>
<th>m/z</th>
<th>z</th>
<th>Abund</th>
<th>Formula</th>
<th>Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>228.1048</td>
<td>1</td>
<td>669183.06</td>
<td>C15 H23NO2S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>229.1148</td>
<td>1</td>
<td>90819.63</td>
<td>C15 H23NO2S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>230.109</td>
<td>1</td>
<td>7817.65</td>
<td>C15 H23NO2S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>231.11</td>
<td>1</td>
<td>684.93</td>
<td>C15 H23NO2S</td>
<td>(M+H)+</td>
</tr>
</tbody>
</table>

**Compound 1e**

**Compound Table**

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>m/z</th>
<th>RT</th>
<th>Mass</th>
<th>Abund</th>
<th>Formula</th>
<th>Tgt Mass</th>
<th>Diff (ppm)</th>
<th>MFG Formula</th>
<th>DB Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C15 H23NO25</td>
<td>282.1523</td>
<td>4.938</td>
<td></td>
<td></td>
<td>381.1449 C15 H23NO25</td>
<td>281.1449</td>
<td>-1.04</td>
<td>C15 H23NO25</td>
<td>C15 H23NO25</td>
</tr>
</tbody>
</table>
### Compound 1f

**Compound Table**

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>m/z</th>
<th>RT</th>
<th>Algorithm</th>
<th>Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C15 H17NO2S</td>
<td>276,105</td>
<td>6,558</td>
<td>Find By Formula</td>
<td>275,0977</td>
</tr>
</tbody>
</table>

### Compound 1g

**Compound Table**

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>m/z</th>
<th>RT</th>
<th>Algorithm</th>
<th>Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C16H19NO2S</td>
<td>290,1212</td>
<td>6,706</td>
<td>Find By Formula</td>
<td>289,1131</td>
</tr>
</tbody>
</table>
MS Spectrum Peak List

<table>
<thead>
<tr>
<th>m/z</th>
<th>z</th>
<th>Abund</th>
<th>Formula</th>
<th>Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>290,1212</td>
<td>1</td>
<td>98910,05</td>
<td>C16H19NO2S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>291,1218</td>
<td>1</td>
<td>17825,25</td>
<td>C16H19NO2S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>292,1209</td>
<td>1</td>
<td>6943,81</td>
<td>C16H19NO2S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>293,1183</td>
<td>1</td>
<td>988,98</td>
<td>C16H19NO2S</td>
<td>(M+H)+</td>
</tr>
</tbody>
</table>

Compound 1j

Compound Table

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>m/z</th>
<th>RT</th>
<th>Mass</th>
<th>Abund</th>
<th>Formula</th>
<th>Tgt Mass</th>
<th>Diff (ppm)</th>
<th>MFG Formula</th>
<th>DB Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C13 H20 N2 O4 S</td>
<td>301,1214</td>
<td>2,403</td>
<td>300,1141</td>
<td>10311</td>
<td>C13 H20 N2 O4 S</td>
<td>300,1144</td>
<td>-1,04</td>
<td>C13 H20 N2 O4 S</td>
<td>C13 H20 N2 O4 S</td>
</tr>
</tbody>
</table>

MS Spectrum Peak List

<table>
<thead>
<tr>
<th>m/z</th>
<th>z</th>
<th>Abund</th>
<th>Formula</th>
<th>Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>301,1214</td>
<td>1</td>
<td>10310,61</td>
<td>C13H2ON2O4S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>302,1242</td>
<td>1</td>
<td>1674,74</td>
<td>C13H2ON2O4S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>303,1194</td>
<td>1</td>
<td>733,96</td>
<td>C13H2ON2O4S</td>
<td>(M+H)+</td>
</tr>
<tr>
<td>304,1182</td>
<td>1</td>
<td>149,4</td>
<td>C13H2ON2O4S</td>
<td>(M+H)+</td>
</tr>
</tbody>
</table>