Chapter – IV

Synthesis of 1-(2-Aryl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one and 1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one
Introduction

The family of azepan-2-ones are particularly interesting core structure due to its growing use in compounds of therapeutic importance.\textsuperscript{1-7} In previous two chapters we have discussed the importance of 4-amino-1,2,3,4-tetrahydroquinolines and synthetic utility of N-vinyl pyrrolidin-2-one as dienophile in imino Diels-Alder reaction. The interesting results obtained has stimulated our interest in the use of N-vinyl caprolactam as dienophile, which is similar in structure to that of N-vinyl pyrrolidin-2-one in the synthesis 1-(2-substituted-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-ones. Hence, in the present work we have demonstrated the facile synthesis of 1-(methyl/aryl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-ones via imino Diels-Alder reaction catalyzed by antimony trichloride in acetonitrile at room temperature. The effect of concentration of catalyst and effect of solvents on the reaction was also systematically investigated.

\begin{center}
\begin{tikzpicture}
  \node[anchor=west] (1) at (0,0) {\textbf{Scheme 1}};
  \node[anchor=west] (2) at (0,-1.5) {\textbf{Scheme 2}};
  \node[anchor=west] (3) at (0,0) {\textbf{Scheme 1}};
  \node[anchor=west] (4) at (0,-1.5) {\textbf{Scheme 2}};
\end{tikzpicture}
\end{center}
Present work

To begin our studies, first we employed 10 mol% SbCl₃ in the imino Diels-Alder reaction between N-benzylideneaniline (1a) with N-vinyl caprolactum (2) in anhydrous acetonitrile solvent. This afforded the corresponding tetrahydroquinoline (3a) at room temperature. Further we examined the catalytic activity of SbCl₃ in different anhydrous reaction media to investigate the solvent effect on reaction in the model reaction of N-benzylideneaniline with N-vinyl caprolactum. The results are summarized in the Table 1 and show that acetonitrile was better solvent compared to other solvents to this reaction.

Table 1. Effect of solvent and amount of catalyst in the synthesis of tetrahydroquinoline 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>SbCl₃ / mol%</th>
<th>Time / h</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>10</td>
<td>0.55</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>5</td>
<td>1.30</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>15</td>
<td>0.45</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>10</td>
<td>3.00</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>15</td>
<td>2.30</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>10</td>
<td>1.30</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>15</td>
<td>1.20</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>CHCl₃</td>
<td>10</td>
<td>3.00</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>Toluene</td>
<td>10</td>
<td>3.00</td>
<td>35</td>
</tr>
</tbody>
</table>

*isolated yields

Having established reaction conditions, various N-benzylideneanilines (1) were made to react with N-vinyl caprolactum (2) to investigate the scope of the reaction (Scheme 1) and several representative results are summarized in the Table 2.
Table 2. Synthesis of tetrahydroquinolines 3 at room temperature using 10 mol% of antimony trichloride as catalyst in anhydrous acetonitrile

<table>
<thead>
<tr>
<th>Entries</th>
<th>Product</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Time / h</th>
<th>Yields² / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>0.55</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>1.20</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>OCH₃</td>
<td>H</td>
<td>H</td>
<td>0.55</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>0.55</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>0.50</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>1.40</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>H</td>
<td>H</td>
<td>NO₂</td>
<td>0.50</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>1.30</td>
<td>85</td>
</tr>
</tbody>
</table>

Further we examined the possibility of employing SbCl₃ in the domino reaction of aryl amines and N-vinyl caprolactum for the synthesis of 1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-ones. Various aryl amines (4) were made to react with (2) in presence of 15 mol% SbCl₃ (Scheme 2) and the reaction proceeded smoothly to afford the expected tetrahydroquinolines (5) in good yields (Table 3). Through this reaction it was noticed that the SbCl₃ facilitates the Schiff’s base formation in the initial stage (monitored by TLC) followed by cycloaddition with (2) to afford tetrahydroquinolines. These cycloaddition reactions were performed under room temperature in the presence of 15 mol% SbCl₃ in anhydrous acetonitrile (Scheme 2).
Table 3. Synthesis of 2-methyl tetrahydroquinolines 5.

<table>
<thead>
<tr>
<th>Entries</th>
<th>Product</th>
<th>R_4</th>
<th>R_5</th>
<th>Time / h</th>
<th>Yields* / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>Cl</td>
<td>H</td>
<td>3.0</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>H</td>
<td>H</td>
<td>4.0</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>OCH₃</td>
<td>H</td>
<td>2.0</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>CH₃</td>
<td>H</td>
<td>2.0</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>F</td>
<td>H</td>
<td>3.5</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>Br</td>
<td>H</td>
<td>3.0</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>H</td>
<td>CH₃</td>
<td>3.5</td>
<td>90</td>
</tr>
</tbody>
</table>

*isolated yields

In conclusion, the synthesis of 1-(2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-ones and 1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-ones via imino Diels-Alder reaction was successfully carried out in presence of a catalytic amount of antimony(III)trichloride at room temperature. Antimony(III)trichloride can be used as an efficient catalyst in the imino Diels-Alder reaction of N-benylideneanilines with N-vinyl caprolactum and also in the Domino reaction of anilines with N-vinyl caprolactum. This method offers several significant advantages, such as high conversions, easy handling, cheaper catalyst, cleaner reaction profiles, and short reaction time.
Experimental

Anhydrous acetonitrile was used for the reaction.

Synthesis of 1-(2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-ones using SbCl$_3$ as catalyst: 3

To a mixture of 1.0 mmol $N$-benzylideneanilines (1) and 1.1 mmol $N$-vinyl caprolactum (2) in 10 cm$^3$ acetonitrile, 0.10 mmol of SbCl$_3$ was added. The reaction mixture was stirred at room temperature for the appropriate time. The reaction was monitored by TLC (petroleum ether:ethyl acetate). After completion of reaction, the reaction mixture was poured into 50 cm$^3$ water and extracted with 3 x 10 cm$^3$ ethyl acetate. The combined organic layer washed with 10 cm$^3$ brine, followed by 10 cm$^3$ water and dried over anhydrous Na$_2$SO$_4$, then concentrated under reduced pressure. The residue, thus obtained was purified by column chromatography using silica gel (60-120 mesh) and eluted with petroleum ether:ethyl acetate to afford tetrahydroquinolines (3).

$\text{cis-1-(2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 3a}$

Colorless needles, M. P.: 124-126 °C; IR (KBr): $\tilde{\nu} = 3315$ (NH) cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta =$ 7.26-7.42 (m, 5H), 7.04 (t, $J =$ 7.6 Hz, 1H), 6.85 (d, $J =$ 7.7 Hz, 1H), 6.70 (t, $J =$ 7.7 Hz, 1H), 6.54 (d, $J =$ 7.6 Hz, 1H), 5.83 (dd, $J =$ 11.3, 6.4 Hz, 1H), 4.64 (dd, $J =$ 9.9, 3.2 Hz, 1H), 3.96 (brs, 1H), 3.13-3.25 (m, 1H), 3.03-3.13 (m, 1H), 2.53-2.75 (m, 2H), 2.13-2.23 (m, 1H), 1.88-2.09 (m, 4H), 1.69-1.79 (m, 2H), 1.36-1.54 (m, 1H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta =$ 176.1, 144.7, 142.8, 129.0, 128.5, 128.3, 126.7, 126.5, 123.0, 120.7, 116.3, 57.4, 47.9, 44.4, 43.8, 35.2, 31.3, 25.4, 22.3 ppm; MS: $m/z =$ 320 (M+).
cis-1-(6-chloro-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 3b

Colorless needles, M. P.: 156-158 °C; IR (KBr): ν = 3315 (NH) cm⁻¹; ¹H NMR (CDCl₃): δ = 7.28-7.42 (m, 5H), 6.99 (dd, 1H,  J = 8.1, 2.2 Hz, H-7), 6.77 (d, 1H,  J = 2.3 Hz, H-5), 6.51 (d, 1H,  J = 8.6 Hz, H-8), 5.21 (dd, 1H,  J = 11.1, 6.1 Hz, H-4), 4.52 (dd,  J = 10.1, 3.6 Hz, 1H), 4.01 (br, NH, 1H), 3.33-3.45 (m, 1H), 3.23-3.29 (m, 1H), 2.78-2.84 (m, 2H), 2.33-2.42 (m, 1H), 2.01-2.29 (m, 4H), 1.89-1.97 (m, 2H), 1.48-1.56 (m, 1H) ppm; ¹³C NMR (CDCl₃): δ = 176.1, 144.7, 142.8, 129.0, 128.5, 128.3, 126.7, 126.5, 123.0, 120.7, 116.3, 56.9, 47.4, 44.9, 43.7, 32.6, 32.1, 30.8, 24.1, 21.4 ppm; MS: m/z = 355 (M⁺).

cis-1-(6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 3c

Colorless needles, M. P.: 145-148 °C; IR (KBr): ν = 3315 (NH) cm⁻¹; ¹H NMR (CDCl₃): δ = 7.44-7.27 (m, 5H), 7.01 (dd,  J = 8.8, 2.4 Hz, 1H), 6.57 (d,  J = 2.8 Hz, 1H), 6.45 (d,  J = 8.8 Hz, 1H), 5.70 (dd,  J = 10.5, 6.8 Hz, 1H), 4.51 (dd,  J = 9.6, 3.2 Hz, 1H), 3.98 (brs, 1H), 3.71 (s, 3H), 3.24-3.39 (m, 1H), 3.17-3.25 (m, 1H), 2.71-2.78 (m, 2H), 2.26-2.34 (m, 1H), 1.95-2.14 (m, 4H), 1.82-1.94 (m, 2H), 1.36-1.45 (m, 1H) ppm; ¹³C NMR (CDCl₃): δ = 175.7, 152.6, 143.1, 140.1, 128.6, 127.8, 126.4, 120.1, 116.1, 114.4, 112.1, 56.6, 54.4, 52.1, 48.6, 42.3, 35.2, 34.8, 31.3, 24.7, 22.3 ppm; MS: m/z = 350 (M⁺).
cis-1-(6-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 3d

Colorless crystalline solid, M.p.: 164-166 °C; IR (KBr): ν\(^{\text{max}}\) = 3356 (NH) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): δ = 7.33-7.51 (m, 5H), 7.25 (d, J = 6.6 Hz, 1H), 6.99 (dd, J = 8.1, 2.8 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 5.22 (dd, J = 10.8, 6.4 Hz, 1H), 4.55 (dd, J = 9.0, 3.9 Hz, 1H), 4.02 (bri s, NH), 3.23-3.45 (m, 2H), 2.81-2.89 (m, 2H), 2.37-2.46 (m, 1H), 2.04-2.32 (m, 7H), 1.91-1.99 (m, 2H), 1.51-1.58 (m, 1H) ppm; \(^{13}\)C NMR (CDCl\(_3\)): δ = 175.6, 143.1, 142.5, 129.5, 129.4, 128.7, 127.9, 127.7, 126.6, 122.2, 121.8, 118.4, 55.3, 48.9, 43.1, 41.4, 33.6, 32.1, 30.8, 24.1, 22.4, 21.2 ppm; MS: m/z = 334 (M+).

cis-1-(8-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 3e

Colorless crystalline solid, M.p.: 174-176 °C; IR (KBr): ν\(^{\text{max}}\) = 3348 (NH) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): δ = 7.26-7.45 (m, 6H), 7.16 (d, J = 7.8 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 5.12 (dd, J = 11.2, 2.8 Hz, 1H), 4.45 (dd, J = 8.6, 3.8 Hz, 1H), 3.97 (bri s, NH), 3.18-3.35 (m, 1H), 3.01-3.18 (m, 1H), 2.61-2.80 (m, 2H), 2.15-2.26 (m, 4H), 1.97-2.11 (m, 4H), 1.60-1.690 (m, 2H), 1.23-1.36 (m, 1H) ppm; \(^{13}\)C NMR (CDCl\(_3\)): δ = 175.4, 141.9, 141.0, 129.3, 129.2, 128.8, 128.1, 127.8, 121.9, 118.1, 117.0, 57.5, 47.2, 44.2, 43.2, 34.5, 23.3, 31.8, 26.6, 22.9, 15.5 ppm; MS: m/z = 334 (M+).
cis-1-[6-chloro-2-(4-chlorophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]azepan-2-one: 3f

Colorless needles, M. P.: 208-210 °C; IR (KBr): γ = 3427 (NH) cm⁻¹; ¹H NMR (CDCl₃): δ = 7.48-7.26 (m, 4H), 6.99 (d, J = 2.8 Hz, 1H), 6.87 (s, 1H) 6.51 (d, J = 8.0 Hz, 1H), 6.15 (dd, J = 10.8, 5.9 Hz, 1H), 4.53 (dd, J = 10.3, 2.6 Hz, 1H), 3.99 (brs, 1H), 3.15-3.30 (m, 1H), 3.00-3.15 (m, 1H), 2.55-2.75 (m, 2H), 2.13-2.23 (m, 1H), 1.89-2.14 (m, 4H), 1.64-1.75 (m, 2H), 1.31-1.51 (m, 1H) ppm; ¹³C NMR (CDCl₃): δ = 172.9, 141.4, 136.9, 131.1, 129.7, 129.5, 128.8, 127.6, 126.5, 124.1, 122.3, 113.8, 56.8, 46.5, 44.6, 43.9, 33.0, 32.6, 25.7, 22.1 ppm; MS: m/z = 389 (M⁺).

cis-1-(6-nitro-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl]azepan-2-one: 3g

Yellow needles, M. P.: 186-188 °C; IR (KBr): γ = 3335 (NH) cm⁻¹; ¹H NMR (CDCl₃): δ = 8.20 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.09 (dd, J = 7.6, 7.2 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.56 (dd, J = 7.6, 7.2 Hz, 1H), 6.65 (d, J = 7.6 Hz, H-8), 5.65 (dd, J = 11.4, 6.3 Hz, 1H), 4.98 (dd, J = 10.3, 3.1 Hz, 1H), 4.12 (brs, NH, 1H) 3.22-3.38 (m, 1H), 3.04-3.19 (m, 1H), 2.59-2.80 (m, 2H), 2.15-2.24 (m, 1H), 1.91-2.12 (m, 4H), 1.68-1.78 (m, 2H), 1.34-1.55 (m, 1H) ppm; ¹³C NMR (CDCl₃): δ = 176.2, 150.7, 147.8, 145.5, 128.7, 127.6, 127.0, 124.3, 119.1, 119.0, 115.6, 57.6, 47.3, 43.8, 41.8, 34.5, 33.5, 25.6, 23.1 ppm; MS: m/z = 365 (M⁺).
cis-1-(6-bromo-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 3h

Colorless crystalline solid, M.p.: 160-162 °C; IR (KBr): $\nu = 3315$ (NH) cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta = 7.48$ (s, 1H), 7.32-7.44 (m, 5H), 7.21 (dd, $J = 7.6$, 2.6 Hz, 1H), 6.50 (d, $J = 7.8$ Hz, 1H), 5.38 (dd, $J = 11.6$, 5.9 Hz, 1H), 4.38 (dd, $J = 10.6$, 2.8 Hz, 1H), 4.12 (brs, 1H, NH), 3.26-3.44 (m, 1H), 3.07-3.23 (m, 1H), 2.45-2.68 (m, 2H), 2.11-2.20 (m, 1H), 1.92-2.11 (m, 4H), 1.69-1.78 (m, 2H), 1.38-1.57 (m, 1H) ppm; $^{13}$C NMR (CDCl$_3$): $\delta = 175.8$, 144.1, 140.7, 128.3, 127.9, 127.6, 127.2, 126.9, 123.1, 121.6, 116.6, 55.7, 48.8, 42.9, 41.5, 33.9, 33.1, 26.1, 22.7 ppm; MS: $m/z = 400$ (M+1).

General reaction protocol for the synthesis of 1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 5

A mixture 5 mmol of the aryl amines, 12 mmol N-vinyl caprolactum and 0.5 mmol of SbCl$_3$ in 5 cm$^3$ acetonitrile was stirred at 50 °C for the appropriate time (Table 2). After completion of reaction as indicated by TLC, the reaction mixture was quenched with 20 cm$^3$ water and extracted with 2 X 15 cm$^3$ ethyl acetate. The combined organic layer were dried over anhydrous sodium sulphate, concentrated and the crude product was purified by column chromatography on silica gel (60-120 mesh, ethyl acetate-petroleum ether, 3:7) to afford 2-methyl-1,2,3,4-tetrahydroquinolines (5).

cis-1-(6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 5a

Colorless crystalline solid, M.p.: 145-147 °C; IR (KBr): $\nu = 3365$ cm$^{-1}$; $^1$H NMR (400 MHz, DMSO): $\delta = 6.91$ (dd, $J = 8.4$, 2.6 Hz, 1H), 6.64 (s, 1H), 6.49 (d, $J = 8.5$ Hz, 1H),
Chapter IV

5.9 (burs, 1H), 5.71 (dd, J = 11.4, 5.8 Hz, 1H), 3.40-3.48 (m, 1H), 3.12-3.23 (m, 1H), 2.83-2.91 (m, 1H), 2.71-2.76 (m, 1H), 2.35-2.45 (m, 1H), 1.66-1.86 (m, 4H), 1.37-1.58 (m, 3H), 1.21-1.33(m, 1H), 1.13 (d, J = 6.2 Hz, 3H) ppm; 13C NMR (400 MHz, DMSO): δ = 175.9, 143.7, 128.7, 125.9, 122.7, 120.4, 116.2, 50.3, 45.9, 43.6, 36.8, 34.0, 29.1, 28.9, 23.1, 21.2 ppm; MS: m/z = 293 (M+)

cis-1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 5b

 Colourless crystalline solid, M.p.: 110-111 °C; IR (KBr): \( \tilde{\nu} = 3330 \text{ cm}^{-1} \); 1H NMR (400 MHz, CDCl3): δ = 6.99 (m, 2H), 6.8 (t, J = 7.5 Hz, 1H), 6.67 (td, J = 8.0, 1.1 Hz, 1H), 5.65 (dd, J = 11.5, 5.8 Hz, 1H), 4.34 (burs, 1H, NH), 3.33-3.41 (m, 1H), 3.08-3.18 (m, 1H), 2.80-2.88 (m, 1H), 2.67-2.74 (m, 1H), 2.31-2.39 (m, 1H), 1.51-1.69 (m, 4H), 1.21-1.36 (m, 3H), 1.18-1.27(m, 1H), 1.15 (d, J = 6.2 Hz, 3H) ppm; 13C NMR (400 MHz, CDCl3): δ = 175.8, 145.0, 128.5, 127.7, 122.9, 117.9, 114.3, 49.1, 43.8, 41.2, 34.4, 32.0, 27.9, 26.5, 21.3, 18.9 ppm; MS: m/z = 258 (M+).

cis-1-(6-methoxy-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 5c

 Colourless crystalline solid, M.p.: 120-122 °C; IR (KBr): \( \tilde{\nu} = 3415 \text{ cm}^{-1} \); 1H NMR (400 MHz, CDCl3): δ = 6.92 (d, J = 2.7 Hz, 1H) 6.65 (dd, J = 8.4, 2.5 Hz, 1H), 6.41 (d, J = 8.5 Hz, 1H), 5.24 (dd, J = 10.5, 5.6 Hz, 1H), 4.08 (burs, 1H, NH), 3.64 (s,3H), 3.33-3.39 (m, 1H), 3.10-3.18 (m, 1H), 2.65-2.73 (m, 1H), 2.44-2.51 (m, 1H), 2.26-2.34 (m, 1H), 1.41-1.53 (m, 4H), 1.30-1.39 (m, 3H), 1.23-1.28 (m, 1H), 1.21 (d, J = 6.2 Hz, 3H) ppm; 13C NMR (400 MHz, CDCl3): δ = 112.6, 115.2, 115.7, 124.3,
cis-1-(2,6-dimethyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 5d

Colorless crystalline solid, M.p.: 185-187 °C; IR (KBr): $\bar{\nu} = 3348$ cm$^{-1}$; $^1$H NMR (400 MHz, DMSO): $\delta = 6.71$ (d, $J = 8.0$ Hz, 1H), 6.51 (s, 1H), 6.41 (d, $J = 7.8$ Hz, 1H), 5.72 (dt, $J = 11.1$, 5.6 Hz, 1H), 5.43 (brs, 1H), 3.30-3.40 (m, 1H), 3.04-3.14 (m, 1H), 2.84-2.92 (m, 1H), 2.63-2.71 (m, 1H), 2.39-2.49 (m, 1H), 2.1 (m, 3H), 1.68-1.85 (m, 4H), 1.40-1.52 (m, 3H), 1.17-1.25 (m, 1H), 1.15 (d, $J = 5.8$ Hz, 3H) ppm; $^{13}$C NMR (400 MHz, DMSO): $\delta = 174, 144.1, 129.3, 128.1, 126.0, 124.2, 114.1, 49.1.3, 44.59, 42.1, 35.2, 32.3, 28.1, 27.2, 22.3, 21.5, 20.2 ppm; MS: $m/z = 273$ (M+1).

cis-1-(6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 5e

Colorless crystalline solid, M.p.: 128-129 °C; IR (KBr): $\bar{\nu} = 3358$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 6.76$ (td, $J = 8.4$, 2.4 Hz, 1H), 6.54 (m, 2H), 5.53 (dd, $J = 11.1$, 5.6 Hz, 1H), 4.01 (brs, 1H, NH), 3.34-3.42 (m, 1H), 3.08-3.17 (m, 1H), 2.63-2.70 (m, 1H), 2.48-2.56 (m, 1H), 2.24-2.33 (m, 1H), 1.43-1.51 (m, 4H), 1.34-1.41 (m, 3H), 1.18-1.28 (m, 1H), 1.17 (d, $J = 6.2$ Hz, 3H) ppm; $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta = 174.8, 142.2, 128.4, 125.8, 121.8, 120.18, 115.1, 48.3, 43.9, 40.2, 33.2, 29.8, 27.3, 23.9, 21.9, 19.3 ppm; MS: $m/z = 276$ (M+1).
cis-1-(6-bromo-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 5f

Colorless crystalline solid, M.p.: 170-172 °C; IR (KBr): \( \tilde{\nu} = 3407 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, DMSO): \( \delta = 7.03 \) (d, \( J = 7.8 \) Hz, 1H), 7.02 (s, 1H), 6.46 (d, \( J = 8.3 \) Hz, 1H), 5.9 (s, 1H), 5.72 (dd, \( J = 10.8, 5.8 \) Hz, 1H), 3.38-3.48 (m, 1H), 3.12-3.23 (m, 1H), 2.83-2.92 (m, 1H), 2.73 (m, 1H), 2.35-2.46 (m, 1H), 1.70-1.88 (m, 4H), 1.59-1.40 (m, 3H), 1.36-1.28 (m, 1H), 1.15 (d, \( J = 6.1 \) Hz, 3H) ppm; \(^1^3\)C NMR (400 MHz, DMSO): \( \delta = 175.9, 146.6, 130.4, 128.6, 121.7, 116.6, 106.7, 50.6, 46.6, 44.0, 37.1, 34.2, 29.6, 29.4, 23.6, 22.0 \) ppm; MS: \( m/z = 337 \) (M+).

cis-1-(2,8-dimethyl-1,2,3,4-tetrahydroquinolin-4-yl)azepan-2-one: 5g

Colourless crystalline solid, M.p.: 150-151 °C; IR (KBr): \( \tilde{\nu} = 3415 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.23 \) (dd, \( J = 7.8, 1.2 \) Hz, 1H), 6.89 (dd, \( J = 8.0, 1.6 \) Hz, 1H), 6.38-6.45 (m, 1H), 5.08 (dd, \( J = 11.4, 5.6 \) Hz, 1H), 4.00 (brs, 1H, NH), 3.37-3.46 (m, 1H), 3.15-3.24 (m, 1H), 2.94-2.99 (m, 1H), 2.73-2.81 (m, 1H), 2.51-2.58 (m, 1H), 2.16 (m, 3H), 1.76-1.93 (m, 4H), 1.51-1.59 (m, 3H), 1.29-1.38 (m, 1H), 1.23 (d, \( J = 6.3 \) Hz, 3H) ppm; \(^1^3\)C NMR (400 MHz, CDCl\(_3\)): \( \delta = 174.9, 144.0, 131.4, 126.2, 123.5, 123.1, 117.6, 50.4, 48.4, 42.3, 35.5, 33.1, 24.8, 23.4, 21.5, 20.5, 19.8 \) ppm; MS: \( m/z = 273 \) (M+1).
References


Sample Report:

Mass spectrum of 3f

<table>
<thead>
<tr>
<th>Peak Number</th>
<th>Time</th>
<th>AreaAbs</th>
<th>Area %Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.29</td>
<td>1e+003</td>
<td>1.17</td>
</tr>
<tr>
<td>2</td>
<td>1.35</td>
<td>8e+004</td>
<td>97.54</td>
</tr>
<tr>
<td>3</td>
<td>1.48</td>
<td>7e+002</td>
<td>0.77</td>
</tr>
<tr>
<td>4</td>
<td>1.56</td>
<td>5e+002</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Peak ID Time | Peak ID Time
-------------|-------------
1: 114.2     | 2: 114.1
2: 120.1     | 2: 276.2
2: 142.1     | 2: 389.3
2: 155.2     | 2: 393.4
2: 280.2     | 2: 393.3
2: 393.3     | 2: 679.6

Peak ID Time | Peak ID Time
-------------|-------------
3: 142.1     | 3: 115.2
3: 155.2     | 3: 280.2
3: 280.2     | 3: 389.3
3: 392.3     | 3: 399.6
3: 400.0     | 3: 500.0

Peak ID Time | Peak ID Time
-------------|-------------
4: 115.2     | 4: 276.2
4: 152.1     | 4: 389.3
4: 217.3     | 4: 393.3
4: 3452.4    | 4: 399.6
4: 400.0     | 4: 500.0

Mobile A: 0.1% HCOOH (aq)
Mobile B: 0.1% HCOOH in ACN
%B: 0.0-0.2 min = 20% 1.25 min = 95% 2.0 min = 20%
Column: BEH C18 (2.1x50) mm; 1.7 µm
Flow Rate: 0.8 ml/min
Inj Date: 14-May-2008
Sample Report:

3: UV Detector: 254

Peak Number | Time  | AreaAbs | Area %Total
---|---|---|---
1 | 1.14 | 6e+004 | 100.00

Peak ID | Time | m/z
---|---|---
1 | 1.14 | 182.2 293.3 179.8 295.3 183.2 296.3

Peak ID | Time | m/z
---|---|---
1: MS ES+ | 7.9e+007 | 607.5
2: MS ES- | 1.4e+005 | 482.3673.6710.1
$^1$H-NMR spectrum of 5e

Current Data Parameters
NAME GF809781-8138419
EXPMO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20080707
Time 13:23
INSTRUM spect
PROBND 5 mm DUL 13C-1
PULPROG zg30
TD 33852
SOLVENT DMSO
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.236702 Hz
AQ 2.1124148 sec
RG 322.5
DW 62.400 usec
DE 6.00 usec
TE 295.8 K
DI 2.0000000 sec
DD0 1

====== CHANNEL 1 ======
NUC1 1H
P1 13.70 usec
PL1 0.00 dB
SF01 400.2324714 MHz

F2 - Processing parameters
SI 32768
SF 400.2300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

SC/AD/01-002
Sample Report:

**Mass spectrum of 5e**

![Mass spectrum of 5e](image)

<table>
<thead>
<tr>
<th>Peak Number</th>
<th>Time</th>
<th>AreaAbs</th>
<th>Area %Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.92</td>
<td>6e+004</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Peak ID**

<table>
<thead>
<tr>
<th>Peak ID</th>
<th>Time</th>
<th>AreaAbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.92</td>
<td>8.6e+007</td>
</tr>
<tr>
<td>1:MS ES+</td>
<td>0.92</td>
<td>1.9e+005</td>
</tr>
<tr>
<td>2:MS ES-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IR spectrum of 5f

![IR Spectrum Diagram]

- % Transmittance
- Wavenumbers (cm⁻¹)

Key Wavenumbers:
- 3407.7
- 2940.4
- 1670.2
- 1512.2
- 1354.3
- 1281.9
- 1038.4
- 2881.2
$^{13}$C-NMR spectrum of 5f

![Chemical Structure Image]
Sample Report:

Mass spectrum of 5f

Peak Number | Time | AreaAbs | Area%Total |
---|---|---|---|
1 | 1.07 | 7e+004 | 98.80 |
2 | 1.38 | 8e+002 | 1.20 |

Peak ID | Time | Peak ID | Time |
---|---|---|---|
1:(Time: 1.07) | 1.07 | 2:(Time: 1.38) | 1.38 |

Peak ID | Time | Peak ID | Time |
---|---|---|---|
1:(Time: 1.07) | 1.07 | 2:(Time: 1.38) | 1.38 |
Sample Name: GF809711
Data File: 8138423
Acq. Method: PTC_NONPOLAR.olp
Instrument Code: SC/AD/17-001

UPLC Report
Mobile A: 0.1% HCOOH (Aq)
Mobile B: 0.1% HCOOH in ACN
% B: 0.0-0.2 min = 20% 1.25 min = 95% 2.0 min = 20%
Column: HSS T3 (2.1 x 50 mm; 1.8 μm)

Sample Report:

3: UV Detector: 254

Mass spectrum of 5g

Range: 6.964e-1

Peak Number | Time | AreaAbs | Area %Total
--- | --- | --- | ---
1 | 1.03 | 2e+004 | 97.28
2 | 1.22 | 3e+002 | 1.56
3 | 1.55 | 2e+002 | 1.16

Peak ID | Time | Value
--- | --- | ---
1: MS ES+ | 1.03 | 8.3e+007
2: MS ES- | 1.22 | 2.7e+007
3: MS ES+ | 1.55 | 6.4e+007

Peak ID | Time | Value
--- | --- | ---
1: MS ES- | 1.03 | 2.9e+005
2: MS ES+ | 1.15 | 172.2