A Metal-Free Approach for the Synthesis of 2-Tetralones via Carbanion-Induced Ring Transformation of 2H-Pyran-2-ones

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Abstract A metal-free, ultrasound-assisted approach for the synthesis of highly functionalized 2-tetralones in high yields is described. The process involves ring transformation of 2H-pyran-2-ones with the spirocyclic ketone 1,4-cyclohexanedione monoethylene ketal to yield spirocyclic ketals and subsequent acid-mediated hydrolysis. This protocol is free from any organometallic reagents, is economical and tolerates a wide range of functional groups.

Key words 2-tetralones, 2H-pyran-2-ones, ring transformation reactions, 1,4-cyclohexanedione monoethylene ketal, spirocyclic ketals

Tetralone-cored systems have been identified as important synthetic intermediates in organic and medicinal chemistry. Among all aromatic bicyclic ketones, 2-tetralones constitute a significant class of building blocks due to their versatile reactivity. They are important starting materials for the synthesis of various biologically active synthetic and naturally occurring compounds. Moreover, these scaffolds are potential precursors for the synthesis of different drug molecules such as nepilalone, treprostinil, idarubicin, (±)-daunomycinone and rotigotine. In addition, 2-tetralones have been used as key substrates for the construction of merocyanine dyes and some fluorescent polycyclic compounds.

Over the years, numerous synthetic methodologies have been employed for the preparation of 2-tetralones. In 2009, Hon and Devulapally developed the titanium(IV)-mediated synthesis of 2-tetralones by intramolecular cyclization of 4-methoxy-5-arylethyl-1,3-dioxolan-2-ones. Subsequently, the same group reported a new synthetic route to obtain a variety of substituted 2-tetralone derivatives via cyclization of 4-aryl-2-hydroxybutanal diethyl acetal using TiCl4 as the promoter. In 2013, Flowers and co-workers developed a Ce(IV)-mediated approach for the intramolecular cyclization of β-dicarbonyl compounds to functionalized β-tetralones. In 2015, the intramolecular hydroarylation/isomerization of propargyl alcohols leading to a diverse array of 2-tetralones was reported using Bi(OTf)3 as the catalyst. Furthermore, Lei and co-workers synthesized similar systems by the oxidation of β-alkyl styrenes using a combination of Fukuzumi’s catalyst with cobaloxime. Recently, the Au-catalyzed oxidation of terminal alkynes in the presence of 2,6-dichloropyridine 1-oxide was used to achieve the synthesis of similar compounds.

However, most of the available methods are associated with limitations such as the use of toxic metals, prolonged reaction times, poor yields and harsh reaction conditions. Thus, this prompted us to develop an efficient, simple and economical synthetic protocol to produce 2-tetralones that would overcome the drawbacks of existing approaches.

2H-Pyran-2-ones are of great interest as they are versatile synths for the construction of functionally crowded benzenes, polarylbenzenes and nitrogen-containing heterocyclic compounds, all of which find wide-scale application in biological and materials chemistry. 2-oxo-2H-Pyran-3-carbonitriles possess three electrophilic centers: C-2, C-4, C-6, and the latter is highly prone to nucleophilic attack because of the extended conjugation and presence of a cyano group at position 3 of the pyran ring.

The synthesis of substrates was achieved by the reaction of ketene dithioacetal with various substituted aryl ketones in DMSO using KOH as the base. The methylsulfonyl group of 2-pyranones is a good leaving group which can be easily replaced by several cyclic secondary amines under refluxing conditions in methanol for 6–8 hours to yield compounds (Scheme 1). The parent precursor ketene dithioacetal was synthesized by the re-
action of ethyl cyanoacetate, carbon disulfide and dimethyl sulfate in the presence of sodium methoxide as the base in absolute methanol.$^{23c,26}$

Herein, we report a new synthetic route for the preparation of highly functionalized spirocyclic ketal $7a$–$n$ via carbanion-induced ring transformation of 2$H$-pyran-2-ones $5a$–$n$ with 1,4-cyclohexanedione monoethylene ketal $6$ at room temperature in an ultrasonic bath. Subsequent acid-mediated hydrolysis of kets $7a$–$n$ yields 2-tetralones $11a$–$f$ in high yields. This protocol is free from any organometallic reagents and transition-metal catalysts and tolerates a wide range of functional groups.

Initially, our efforts were directed to find an appropriate base for the ring transformation of substrate $5a$ with spirocyclic ketone $6$ in DMF and the results are shown in Table 1. To begin with, potassium hydroxide was used as the base and the corresponding product $7a$ was isolated in 73% yield (Table 1, entry 1). The same ring transformation reaction was attempted with sodium hydroxide and the desired product $7a$ was obtained in 60% yield (Table 1, entry 2). Reaction product $7a$ was obtained in only 10% yield when Et$_3$N was used as the base (Table 1, entry 3), whereas no product formation was observed in the presence of potassium carbonate and starting materials were recovered (Table 1, entry 4). Finally, the reaction was also studied with KO$_2$Bu and NaH and the desired product $7a$ was isolated in 69% and 71% yields, respectively (Table 1, entries 5 and 6).

Table 1 Optimization of the Base for the Synthesis of Spirocyclic Ketal $7a$ by the Ring Transformation of 2$H$-Pyran-2-one $5a$ with Ketone $6$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time (H)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH</td>
<td>11</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>NaOH</td>
<td>14</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$CO$_3$</td>
<td>24</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>KO'Bu</td>
<td>8</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>NaH</td>
<td>9</td>
<td>71</td>
</tr>
</tbody>
</table>

The same ring transformation reaction was attempted with sodium hydroxide and the desired product $7a$ was obtained in 60% yield (Table 1, entry 2). Reaction product $7a$ was obtained in only 10% yield when Et$_3$N was used as the base (Table 1, entry 3), whereas no product formation was observed in the presence of potassium carbonate and starting materials were recovered (Table 1, entry 4). Finally, the reaction was also studied with KO$_2$Bu and NaH and the desired product $7a$ was isolated in 69% and 71% yields, respectively (Table 1, entries 5 and 6).

Next, our efforts were directed to examine the solvent effect on the ring transformation of lactone $5a$ with spirocyclic ketone $6$. The reaction was performed in a number of polar and non-polar solvents and the results are listed in Table 2. Initially, the reaction was carried out in DMF and the desired product $7a$ was isolated in 73% yield (Table 2, entry 1). An improved yield of 77% of the ring-transformed product $7a$ was obtained when the reaction was carried out in the dipolar aprotic solvent DMSO (Table 2, entry 2). The same reaction was performed in chloroform and the reaction product $7a$ was isolated in only 20% yield along with unreacted starting materials (Table 2, entry 3). Further, the reaction was carried out in the polar protic solvent ethanol, but the desired product $7a$ was not observed and starting materials were recovered (Table 2, entry 4). The reaction was also tested in THF and diethyl ether, with the reaction product $7a$ being isolated in 27% and 10% yields, respectively, along with unreacted starting materials (Table 2, entries 5 and 6).

Table 2 Optimization of the Solvent for the Synthesis of Spirocyclic Ketal $7a$ by the Ring Transformation of 2$H$-Pyran-2-one $5a$ with Ketone $6$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>11</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>CHCl$_3$</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>24</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>Et$_2$O</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>7*</td>
<td>DMSO</td>
<td>16 min</td>
<td>84</td>
</tr>
</tbody>
</table>

* The ring transformation reaction was performed in an ultrasonic bath.

Furthermore, our efforts were focused on reducing the reaction time for this ring transformation. Nowadays, ultrasound-assisted organic synthesis is a highly efficient and
attractive green technique, widely used as alternative energy source in many organic reactions.\textsuperscript{27–34} Hence we carried out the same reaction of 2H-pyran-2-one 5a with spirocyclic ketone 6 under ultrasound irradiation at room temperature. Surprisingly, the reaction was complete in just 16 minutes and the ring-transformation product 7a was obtained in 84\% yield (Table 2, entry 7). Thus, the optimized conditions for the synthesis of spirocyclic ketals 7 are: 2H-pyran-2-ones 5, spirocyclic ketone 6, powdered KOH (1.2 equiv), DMSO, ultrasound irradiation, room temperature.

Having optimized the conditions, we next examined the scope of different substrates in this ring transformation reaction (Table 3). Thus, lactones 5a–j were successfully converted into the corresponding spirocyclic ketals 7a–j in yields of 75–94\% (Table 3, entries 1–10). Interestingly, the reaction worked smoothly with bulky 6-naphthyl-2-pyran-2-ones 5k–n were successfully converted into fully functionalized spirocyclic ketals 7k–n in good yields under the optimized reaction conditions (Table 3, entries 11–14). Notably, various electron-donating and electron-withdrawing substituents on the phenyl ring in substrates 5 were successfully tolerated. Moreover, it was observed that ring-transformed products 7 were obtained in higher yields from substrates 5 having electron-withdrawing substituents on the phenyl ring (Table 3, entries 3 and 4). All the synthesized compounds were characterized by spectroscopic analysis.

On the basis of available literature,\textsuperscript{22,23} a proposed mechanism for the ring transformation of lactones 5 into the corresponding ketals 7 is depicted in Scheme 2. The reaction is initiated by nucleophilic attack of the carbamion generated from ketone 6 under basic conditions at C6 of 2H-pyran-2-one 5 to give intermediate 8, subsequent intramolecular cyclization of which yields the intermediate 9. Finally, intermediate 9 undergoes decarboxylation and dehydration to furnish the spirocyclic ketal product 7.

Furthermore, spirocyclic ketals 7a–f were hydrolyzed with 4\% ethanolic HCl under refluxing conditions to give highly substituted 2-tetralones 11a–f in 78–88\% yields (Table 4, entries 1–6).\textsuperscript{25} All the synthesized compounds were characterized by spectroscopic analysis.

In summary, we have achieved a metal-free approach for the ultrasound-assisted synthesis of highly functionalized spirocyclic ketals 7a–n through carbamion-induced ring transformation of 2-pyrroles 5a–n with 1,4-cyclohexanedione monoethylene ketal 6. Several examples of the spirocyclic ketal products 7 were converted into 2-tetralones 11a–f via ketal cleavage using 4\% ethanolic HCl. The present synthetic route is inexpensive, is free from organometallic reagents, involves an easy work-up procedure.

### Table 3  Synthesis of Spirocyclic Ketal 7a–n by the Ring Transformation of 2H-Pyr-2-ones 5a–n with Spiroyclic Ketone 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Amine</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H6</td>
<td>H</td>
<td>piperidine</td>
<td>7a</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>C6H6</td>
<td>H</td>
<td>N-phenyl/piperazine</td>
<td>7b</td>
<td>25</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>4-BrC6H4</td>
<td>H</td>
<td>piperidine</td>
<td>7c</td>
<td>18</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>4-BrC6H4</td>
<td>H</td>
<td>N-phenyl/piperazine</td>
<td>7d</td>
<td>27</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>4-MeOC6H4</td>
<td>H</td>
<td>piperidine</td>
<td>7e</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>4-MeOC6H4</td>
<td>H</td>
<td>N-phenyl/piperazine</td>
<td>7f</td>
<td>24</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>1-naphthyl</td>
<td>H</td>
<td>piperidine</td>
<td>7g</td>
<td>26</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>1-naphthyl</td>
<td>H</td>
<td>N-phenyl/piperazine</td>
<td>7h</td>
<td>38</td>
<td>79</td>
</tr>
<tr>
<td>9</td>
<td>2-naphthyl</td>
<td>H</td>
<td>piperidine</td>
<td>7i</td>
<td>32</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>2-naphthyl</td>
<td>H</td>
<td>N-phenyl/piperazine</td>
<td>7j</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>C6H6</td>
<td>Me</td>
<td>piperidine</td>
<td>7k</td>
<td>27</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>3-C6H4</td>
<td>Me</td>
<td>piperidine</td>
<td>7l</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>3-C6H4</td>
<td>Me</td>
<td>N-phenyl/piperazine</td>
<td>7m</td>
<td>35</td>
<td>82</td>
</tr>
<tr>
<td>14</td>
<td>4-MeOC6H4</td>
<td>Me</td>
<td>N-phenyl/piperazine</td>
<td>7n</td>
<td>37</td>
<td>75</td>
</tr>
</tbody>
</table>

tetramethylsilane (Me4Si) as an internal standard. Mass spectra (EI, CI, MI) of the compound were recorded on a VarioMICRO Select 15162036 Analyzer. 1H NMR and 13C NMR spectra were recorded under electron impact (EI), electrospray (ES) or chemical ionization (CI). CHN analysis was performed using an Elementar Vario MICRO Select 15162036 Analyzer.

**Table 4** Synthesis of Functionalized 2-Tetralones 11a–f by Acidic Hydrolysis of Ketals 7a–f

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>Amines</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5</td>
<td>H</td>
<td>piperidine</td>
<td>11a</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>4-BrC6H4</td>
<td>H</td>
<td>piperidine</td>
<td>11b</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>4-BrC6H4</td>
<td>H</td>
<td>N-phenylpiperazine</td>
<td>11c</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>4-MeOC6H4</td>
<td>H</td>
<td>N-phenylpiperazine</td>
<td>11d</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>C6H5</td>
<td>Me</td>
<td>piperidine</td>
<td>11e</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>3-ClC6H4</td>
<td>Me</td>
<td>N-phenylpiperazine</td>
<td>11f</td>
<td>84</td>
</tr>
</tbody>
</table>

and does not require harsh reaction conditions. Studies on the further application of this approach are currently in progress.

All experiments were performed without using an inert atmosphere. Dimethyl sulfoxide and other solvents were purchased from Avra Synthesis Pvt. Ltd. All other purchased chemicals were used without further purification. All reactions were monitored by thin-layer chromatography (TLC) performed on Merck KGA pre-coated sheets of silica gel 60. Column chromatography was performed with silica gel or neutral alumina (Avra synthesis, 100–125 mesh). Eluting solvents are indicated in the text. Melting points were measured with a REMI DDDS 2545 melting point apparatus. IR spectra were recorded on a Thermo Scientific Nicolet Nexus 470 FT/IR spectrophotometer and band positions are reported in reciprocal centimeters. Samples were prepared as KBr pellets. 1H NMR and 13C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on an AV-400 Bruker spectrometer. Deuterated chloroform (CDCl3) was used as the solvent and tetramethylsilane (Me4Si) as an internal standard. Mass spectra (m/z) were recorded under electron impact (EI), electrospray (ES) or chemical ionization (CI). CHN analysis was performed using an Elementar Vario MICRO Select 15162036 Analyzer.

Ethyl cyano acetate (11.3 mL, 100.0 mmol) was added dropwise over a period of 15 min to an ice-cold solution of sodium methoxide, freshly prepared in situ by dissolving sodium metal (3.44 g, 150.0 mmol) in absolute MeOH (40 mL) at 0 °C. The resulting white-colored precipitate was stirred vigorously for another 15 min followed by the dropwise addition of carbon disulfide (6.4 mL, 100.0 mmol) at 20 °C to give a yellow-colored liquid. Next, dimethyl sulfate (23.6 mL, 248 mmol) was added slowly over a period of 30 min. The resulting yellow semi-solid material was stirred for another 15 min and excess MeOH was removed under high vacuum. Finally, the reaction mixture was poured onto crushed ice with constant stirring and the precipitate thus obtained was filtered, washed with cold H2O, dried and recrystallized from EtOAc/hexane (1:4) to give yellow, crystalline compound 1.23e

6-Aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitriles 3a–n; General Procedure23e,26

A mixture of ethyl 2-cyano-3,3-dimethylsulfanylacrylate (1) (2.17 g, 10.0 mmol, 1.0 equiv), aryl ketone 2 (12 mmol, 1.2 equiv) and powdered KOH (0.84 g, 15 mmol, 1.5 equiv) in dry DMSO was stirred at room temperature for 14–18 h. On completion of the reaction, the mixture was poured into ice-cold H2O with constant stirring. The residue thus obtained was removed by filtration and purified by silica gel chromatography using CHCl3 as the eluant. The isolated products were characterized as 6-aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitriles 3a–n by spectroscopic analysis. The NMR data was found to correlate with those reported in the literature.23e,26

6-Aryl-4-amino-2-oxo-2H-pyran-3-carbonitrile 5a–n; General Procedure23e,26

A mixture of 6-aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitrile 3a–n (1.0 mmol, 1.0 equiv) and secondary amine 4 (1.2 mmol, 1.2 equiv) was refluxed in MeOH for 6–8 h. The course of the reaction was monitored by TLC. On completion, the reaction mixture was cooled, filtered and the remaining solid rinsed with MeOH (2 × 5 mL) to give products 5a–n.23e,26

Functionalized Spirocyclic Ketals 7a–n; General Procedure

A mixture of 6-arylsulfanyl-2-oxo-2H-pyran-3-carbonitrile 5a–n (1.0 mmol, 1.0 equiv), 1,4-cyclohexanediene monoethyleneketal 6 (1.2 mmol, 1.2 equiv) and powdered KOH (1.2 mmol) in dry DMSO (3.0 mL) was irradiated in an ultrasonic bath for 16–40 min at room temperature. The progress of the reaction was monitored by TLC. On completion, the reaction mixture was cooled, filtered and the remaining solid rinsed with MeOH (2 × 5 mL) to give products 7a–n.23e,26

8-Phenyl-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-1,3]dioxolane-5-carbonitrile (7a)

Yield: 0.315 g, 0.841 mmol (84%); white solid; mp 165–167 °C; Rf = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 3296, 3032, 2214 cm–1 (CN) cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.44–1.53 (m, 2 H, CH2), 1.62–1.74 (m, 4 H, 2 CH2), 1.91 (t, J = 6.8 Hz, 2 H, CH2), 2.63 (s, 2 H, CH2), 2.97–3.07 (m, 4 H, 2 NCH2), 3.14 (t, J = 6.8 Hz, 2 H, CH2), 3.78–3.92 (m, 4 H, 2 OCH2), 6.66 (s, 1 H, ArH), 7.13–7.20 (m, 2 H, ArH), 7.25–7.39 (m, 3 H, ArH).

13C NMR (100 MHz, CDCl3): δ = 24.1, 26.2, 27.9, 30.8, 37.6, 53.4, 64.5, 105.4, 107.9, 117.5, 118.4, 126.1, 127.6, 128.4, 128.6, 140.5, 140.7, 147.3, 155.7.

GC–MS: m/z = 375 [M + 1]+.

Anal. Calc for C24H21N2O2: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.62; H, 6.81; N, 7.34.


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8-Phenyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7b)

Yield: 0.477 g, 0.900 mmol (90%); yellow solid; mp 178–181 °C; IR (KBr): 2216 (CN) cm–1.

IR (KBr): 2216 (CN) cm–1.

8-(4-Methoxyphenyl)-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7b)

Yield: 0.393 g, 0.871 mmol (87%); yellow solid; mp 170–173 °C; IR (KBr): 2216 (CN) cm–1.

IR (KBr): 2216 (CN) cm–1.

8-(4-Bromophenyl)-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7b)

Yield: 0.376 g, 0.820 mmol (82%); white solid; mp 170–173 °C; \( R_f = 0.5 \) (EtOAc/hexane, 1:4).

IR (KBr): 2216 (CN) cm–1.

\[ \text{Synthesis} \]

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**Synthesis**

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11C NMR (100 MHz, CDCl3): δ = 28.0, 30.9, 36.8, 49.6, 51.8, 64.5, 105.8, 107.7, 116.4, 117.3, 118.3, 120.1, 125.4, 125.5, 126.1, 126.2, 126.6, 128.3, 128.5, 128.6, 129.2, 131.1, 133.6, 137.9, 140.9, 146.1, 151.1, 154.2.

GC–MS: m/z = 502 [M + 1]+.


**8-(Naphthalene-2-yl)-6-(piperidin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7i)**

Yield: 0.376 g, 0.750 mmol (75%); yellow solid; mp 200–203 °C; Rf = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2210 (CN) cm–1.

GC–MS: m/z = 425 [M + 1]+.


**8-(Naphthalene-2-yl)-6-(4-methoxyphenyl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7n)**

Yield: 0.410 g, 0.820 mmol (82%); yellow solid; mp 163–166 °C; Rf = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2219 (CN) cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.81–1.95 (m, 5 H, CH3 + CH2), 2.39 (s, 3 H, CH3), 2.94–3.56 (m, 10 H, 4 NCH2 + CH2), 3.77–3.95 (m, 4 H, 2 OCH2), 6.68–6.95 (m, 3 H, ArH), 6.96–6.99 (s, 1 H, ArH), 7.15–7.25 (m, 2 H, ArH), 7.27–7.35 (m, 3 H, ArH).

GC–MS: m/z = 501 [M + 1]+.


**8-(3-Chlorophenyl)-7-methyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7m)**

Yield: 0.371 g, 0.750 mmol (75%); yellow solid; mp 207–210 °C; Rf = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 2218 (CN) cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.82–1.95 (m, 5 H, CH3 + CH2), 2.42 (s, 3 H, CH3), 3.04–3.60 (m, 10 H, 4 NCH2 + CH2), 3.78 (s, 3 H, OCH3), 3.80–3.91 (m, 4 H, 2 OCH2), 6.79 (t, J = 7.4 Hz, 1 H, ArH), 6.84–6.96 (m, 6 H, ArH), 7.15–7.25 (m, 2 H, ArH), 7.60–7.67 (m, 1 H, ArH), 7.73–7.86 (m, 3 H, ArH).

13C NMR (100 MHz, CDCl3): δ = 16.4, 27.4, 30.6, 38.5, 50.4, 50.5, 64.5, 107.6, 110.3, 116.6, 117.9, 128.8, 129.1, 130.3, 130.5, 133.4, 139.8, 141.4, 144.6, 151.6, 151.7.

GC–MS: m/z = 496 [M + 1]+.


**8-(3-Methoxyphenyl)-7-methyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7o)**

Yield: 0.371 g, 0.750 mmol (75%); yellow solid; mp 207–210 °C; Rf = 0.3 (EtOAc/hexane, 1:4).

IR (KBr): 2218 (CN) cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.82–1.95 (m, 5 H, CH3 + CH2), 2.42 (s, 3 H, CH3), 3.04–3.60 (m, 10 H, 4 NCH2 + CH2), 3.78 (s, 3 H, OCH3), 3.80–3.91 (m, 4 H, 2 OCH2), 6.79 (t, J = 7.4 Hz, 1 H, ArH), 6.84–6.96 (m, 6 H, ArH), 7.15–7.25 (m, 2 H, ArH), 7.60–7.67 (m, 1 H, ArH), 7.73–7.86 (m, 3 H, ArH).

13C NMR (100 MHz, CDCl3): δ = 16.4, 27.5, 30.7, 38.6, 50.5, 50.6, 55.3, 64.5, 107.8, 109.8, 114.4, 116.6, 117.7, 120.1, 129.1, 128.3, 131.2, 131.8, 133.9, 137.7, 147.9, 151.5, 151.6, 158.8.

GC–MS: m/z = 501 [M + 1]+.


**8-(3-Chlorophenyl)-7-methyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7f)**

8-(3-Chlorophenyl)-7-methyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydro-1H-spiro[naphthalene-2,2′-[1,3]dioxolane]-5-carbonitrile (7f)
filtered and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography using EtOAc/hexane (1:4) as the eluent to give tetralones 11a–f.

6-Oxo-4-phenyl-2-(piperidin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11a)
Yield: 0.064 g, 0.195 mmol (78%); white solid; mp 165–167 °C; Rf = 0.5 (EtOAc/hexane, 1:4).

IR (KBr): 1719 (CO), 2221 (CN) cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 1.47–1.62 (m, 2 H, CH₂), 1.64–1.78 (m, 4 H, 2 CH₂), 2.49 (t, J = 6.8 Hz, 2 H, CH₂), 3.04–3.13 (m, 4 H, 2 NCH₂), 3.28 (t, J = 6.8 Hz, 2 H, CH₂), 3.36 (s, 2 H, CH₂), 6.76 (s, 1 H, ArH), 7.10–7.18 (m, 2 H, ArH), 7.28–7.40 (m, 3 H, ArH).
13C NMR (100 MHz, CDCl₃): δ = 24.0, 26.1, 27.5, 37.0, 42.4, 53.4, 104.8, 117.3, 118.8, 124.3, 128.0, 128.6, 128.7, 134.2, 142.2, 146.5, 155.8, 209.3.

GC–MS: m/z = 438 [M + 1]⁺.
Anal. Calcd for C₂₂H₂₁BrN₂O: C, 64.55; H, 5.17; N, 6.84. Found: C, 76.41; H, 5.89; N, 9.37.

3-Methyl-6-oxo-4-phenyl-2-(piperidin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11b)
Yield: 0.071 g, 0.206 mmol (80%); white solid; mp 122–125 °C; Rf = 0.4 (EtOAc/hexane, 1:4).

IR (KBr): 1717 (CO), 2219 (CN) cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 1.44–1.73 (m, 6 H, 3 CH₃), 1.89 (s, 3 H, CH₃), 2.49 (t, J = 6.8 Hz, 2 H, CH₂), 2.92–3.39 (m, 8 H, 2 CH₂ + 2 NCH₂), 6.89–7.00 (m, 2 H, ArH), 7.26–7.41 (m, 3 H, ArH).
13C NMR (100 MHz, CDCl₃): δ = 16.4, 24.2, 26.8, 27.0, 37.4, 43.0, 51.9, 108.4, 117.9, 127.7, 128.2 (3 C), 129.0, 134.3, 138.5, 138.9, 147.2, 153.6, 209.2.

GC–MS: m/z = 345 [M + 1]⁺.
Anal. Calcd for C₂₃H₂₄N₂O: C, 80.20; H, 7.02; N, 8.13. Found: C, 79.91; H, 6.88; N, 7.75.

4-(3-Chlorophenyl)-3-methyl-6-oxo-2-(4-phenylpiperazin-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (11f)
Yield: 0.077 g, 0.169 mmol (84%); white solid; mp 171–174 °C; Rf = 0.3 (EtOAc/hexane, 1:4).

IR (KBr): 1720 (CO), 2222 (CN) cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 1.96 (s, 3 H, CH₃), 2.47–2.56 (m, 2 H, CH₂), 3.04–3.64 (m, 12 H, 4 CH₂ + 2 CH₂), 6.82 (t, J = 7.2 Hz, 1 H, ArH), 6.84–6.89 (m, 1 H, ArH), 6.90–6.96 (m, 2 H, ArH), 6.97–7.01 (m, 1 H, ArH), 7.16–7.26 (m, 2 H, ArH), 7.28–7.37 (m, 3 H, ArH).

GC–MS: m/z = 456 [M + 1]⁺.
Anal. Calcd for C₂₃H₂₃ClNₓO: C, 73.75; H, 5.75; N, 9.22. Found: C, 73.34; H, 5.49; N, 9.09.

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References


