A Facile Synthesis of 1,2,3,4-Tetrahydroisoquinolines Through Cyclization of O,N-Acetals

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A mild and efficient method for the synthesis of 1,2,3,4-tetrahydroisoquinolines by a modified Pictet-Spengler reaction involving Lewis acid-mediated cyclization of O,N-acetals is described.

The majority of isoquinoline syntheses involve acid-catalysed ring closure to a benzene ring and benefit considerably from the presence of an electron-donating substituent.1 Although the
Pictet-Spengler reaction has proven to be an excellent method for the preparation of 1,2,3,4-tetrahydroisoquinolines, but the ring-closure reaction is sensitive to substituent effects. If an alkoxy or hydroxy group meta to the side chain of an imine is absent, cyclization fails to occur. During our synthetic studies in the field of isoquinolinequinone antibiotics such as mimoscin and safaramycin B, we intended the cyclization of 2-(3-methylphenyl)ethanamines having a highly oxygenated benzene ring to 1,2,3,4-tetrahydroisoquinoline derivatives. As a more electrophilic iminium salt equivalent we considered an O,N-acetal to be appropriate because it is a potential and masked iminium salt, and is readily prepared by conventional methods. The use of such O,N-acetals in the preparation of 1,2,3,4-tetrahydroisoquinolines has hitherto not been reported.

We report here a mild and efficient method for the synthesis of 1,2,3,4-tetrahydroisoquinolones through cyclization of O,N-acetals. The starting N-benzyl-2-(2,4,5-trimethoxy-3-methylphenyl)ethanamine (4a) was prepared by a slightly modified reported procedure. Condensation of 3a with benzaldehyde gave a Schiff base which was reduced with sodium borohydride to afford amine 4a (Table 1).

The reaction of 4a with paraformaldehyde in the presence of potassium carbonate in ethanol quantitatively afforded an O,N-acetal 5a (Table 2) which was treated with trifluoroacetic acid for 1 h to give the 1,2,3,4-tetrahydroisoquinoline 6a in 80% overall yield (Table 3).

### Table 1. N-Benzyl-2-phenylethylamines 4a-f Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yielda (%)</th>
<th>b.p. (°C/Torr)</th>
<th>Molecular Formula or Lit. b.p. (°C/Torr)</th>
<th>¹H-NMR (CDCl₃/TMS) δ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>OCH₃</td>
<td>34</td>
<td>195–197/2</td>
<td>C₁₂₂H₂₂NO₄ (315.4)</td>
<td>1.28 (s, 1H), 2.12 (s, 3H), 2.70 (br. s, 4H), 3.58 (s, 3H), 3.70 (s, 8H), 6.44 (m, 3H), 7.15 (m, 5H)</td>
</tr>
<tr>
<td>4b</td>
<td>OCH₃</td>
<td>H</td>
<td>H</td>
<td>47</td>
<td>155/1</td>
<td>C₁₂₂H₂₂NO₂ (274.4)</td>
<td>1.80 (s, 1H), 2.75 (br. s, 4H), 3.55 (s, 3H), 3.57 (s, 3H), 3.65 (s, 2H), 6.51 (m, 3H), 7.10 (m, 5H)</td>
</tr>
<tr>
<td>4c</td>
<td>H</td>
<td>OCH₃</td>
<td>H</td>
<td>62</td>
<td>180/2</td>
<td>C₁₂₂H₂₂NO₂ (274.4)</td>
<td>1.35 (s, 1H), 2.67 (m, 4H), 3.67 (s, 8H), 6.40 (s, 3H), 7.13 (s, 5H)</td>
</tr>
<tr>
<td>4d</td>
<td>OCH₃</td>
<td>H</td>
<td>OCH₃</td>
<td>14</td>
<td>160/2</td>
<td>C₁₂₂H₂₂NO₂ (285.4)</td>
<td>2.30 (br. s, 1H), 2.80 (br. s, 4H), 3.62 (s, 3H), 3.64 (s, 2H), 4.90 (s, 2H), 6.67 (m, 2H), 7.17–7.25 (m, 11H)</td>
</tr>
<tr>
<td>4e</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>OCH₃</td>
<td>27</td>
<td>190/2</td>
<td>C₁₂₂H₂₂NO₂ (285.4)</td>
<td>1.47 (s, 1H), 2.06 (s, 3H), 2.75 (s, 4H), 3.62 (s, 3H), 3.73 (s, 5H), 6.41 (d, 1H), 7.18 (d, 1H), 2.86 (m, 3H), 7.13 (m, 5H)</td>
</tr>
<tr>
<td>4f</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>H</td>
<td>17</td>
<td>195/2</td>
<td>m.p. 119–120°</td>
<td>2.20 (br. s, 1H), 2.76 (s, 4H), 3.70 (s, 5H), 3.74 (s, 3H), 6.60–6.80 (m, 3H), 7.13 (m, 5H)</td>
</tr>
</tbody>
</table>

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a Yields based on 1.

b Satisfactory microanalyses obtained: C ± 0.30, H ± 0.15, N ± 0.12.

c Amine hydrochloride.
Table 3. 2-Benzyl-1,2,3,4-tetrahydroisosquinolines 6a-f and 7a,b Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yielda (%)</th>
<th>m.p. (°C) (solvent)</th>
<th>Molecular Formula</th>
<th>IR (CHCl₃)ν (cm⁻¹)</th>
<th>¹H-NMR (CDCl₃/TMS)mδ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>80</td>
<td>b.p. 128–132/1</td>
<td>C₂₀H₂₂N₂O₄</td>
<td>2.12 (s, 3H); 2.65 (m, 4H); 3.50 (s, 2H); 3.59 (s, 5H); 3.68 (s, 3H); 3.72 (t, 3H); 7.23 (m, 5H)</td>
<td></td>
</tr>
<tr>
<td>6b</td>
<td>69</td>
<td>m.p. 77–78.5 (other)</td>
<td>C₁₅H₁₈N₂O₄</td>
<td>2.66 (t, 2H, J = 7.5 Hz); 2.75 (t, 2H, J = 5.7 Hz); 3.60 (s, 2H)</td>
<td></td>
</tr>
<tr>
<td>6c</td>
<td>62</td>
<td>m.p. 86–88 (other)</td>
<td>C₁₅H₁₈N₂O₄</td>
<td>2.73 (m, 4H); 3.50 (br, s, 2H); 3.63 (s, 2H); 3.78 (3H)</td>
<td></td>
</tr>
<tr>
<td>6d</td>
<td>44</td>
<td>m.p. 68–70 (other)</td>
<td>C₁₄H₁₆N₂O₄</td>
<td>2.73 (m, 4H); 3.55 (br, s, 2H); 3.63 (s, 5H); 4.90 (2H)</td>
<td></td>
</tr>
<tr>
<td>6e</td>
<td>57c</td>
<td></td>
<td>C₁₃H₁₈N₂O₄</td>
<td>2.08 (s, 3H); 2.72 (m, 4H); 3.10 (s, 2H); 3.61 (s, 2H); 3.65 (s, 3H); 3.73 (s, 3H); 6.17 (s, 1H); 7.27 (m, 7H)</td>
<td></td>
</tr>
<tr>
<td>6f</td>
<td>60c</td>
<td></td>
<td>C₁₃H₁₆N₂O₄</td>
<td>2.65 (m, 4H); 3.42 (s, 2H); 3.53 (s, 2H); 3.66 (s, 3H); 3.71 (s, 3H); 6.50 (s, 2H); 7.20 (m, 5H)</td>
<td></td>
</tr>
<tr>
<td>7a</td>
<td>74c</td>
<td></td>
<td>C₁₃H₁₂N₂O₅</td>
<td>1725 (C=O)</td>
<td></td>
</tr>
<tr>
<td>7b</td>
<td>84c</td>
<td></td>
<td>C₁₃H₁₂N₂O₅</td>
<td>1725 (C=O)</td>
<td>4.48 (s, 1H); 7.60–7.50 (m, 5H)</td>
</tr>
</tbody>
</table>

a. Yields based on 4.  
b. Satisfactory microanalyses obtained: C ± 0.10, H ± 0.14, N ± 0.05. Mass and UV spectra in accord with structures.

c. Purified by column chromatography on silica gel, eluent: hexane.

d. Lit. 34 m.p. 88–90 C.

In order to examine the scope of this procedure, the N-benzyl-2-phenylethylamines 4b-f (Table 1) were prepared and converted into the corresponding 2-benzyl-1,2,3,4-tetrahydroisosquinolines 6b-f (Table 3).

When butyl glyoxylate was used in the reaction with 4a and 4b, 1,2,3,4-tetrahydroisosquinoline-1-carboxylic acid esters 7a and 7b, respectively, were obtained (Table 3). Compound 7a is a versatile starting material for the synthesis of the isouquinolinequinone antibiotics renierone and 1-formyl-1,2-dihydrorenierone.11

The usefulness of our procedure was further demonstrated by the cyclization of compound 815 to the pentacyclic compound 9 in 81% yield.

These results show that the present method offers a facile entry to highly functionalized 1,2,3,4-tetrahydroisosquinolines. The application of the method to a synthesis of the dimeric isouquinolinequinone antibiotic saframycin B is under investigation.

N-Benzyl-2-(2,4,5-trimethoxy-3-methylphenyl)ethylamine (4a); Typical Procedure:

2.45 g (10.5 mmol) of 2,4,5-trimethoxy-3-methylbenzaldehyde (1a; 10.5 g, 50 mmol) in nitromethane (100 mL) at room temperature. The mixture is heated at reflux for 3 h, then poured into H₂O (200 mL) and extracted with benzene (3 × 200 mL). The combined extracts are dried (Na₂SO₄) and evaporated under reduced pressure and the remaining yellow solid is recrystallized from MeOH to afford 4a. The product 4a (2.4 g, 68%) by recrystallization from hexane. m.p. 121–123 °C (Lit. 34 m.p. 121–123 °C).

2-(2,4,5-Trimethoxy-3-methylphenyl)ethylamine (4a): 8.82 mmol, 8.07 mmol is added to a solution of amine 3a (1.8 g, 8 mmol in benzene (50 mL). The mixture is heated at reflux under a Dean-Stark separator. The organic layer is dried (Na₂SO₄) and the solvent is removed in vacuo to give the intermediate Schiff base as a colorless oil. This is dissolved in EtOH (50 mL) and NaBH₄ (300 mmol) is added in one portion with stirring. The mixture is stirred for 30 min, then diluted with H₂O (100 mL), and extracted with CHCl₃ (3 × 100 mL). The combined extracts are dried (Na₂SO₄) and evaporated in vacuo to give a pale yellow oil which is purified by distillation to afford 4a. 1H-NMR: 8.91 (70%), b. 192–197 °C, 2 Torr (Table 1).  

2-Benzyl-1,2,3,4-tetrahydroisosquinolines (6a-f); General Procedure: 
A solution of the N-benzyl-2-phenylethylamine 4 (1.5 mmol) and anhydrous K₂CO₃ (828 mg, 6 mmol) in EtOH (0.26 mL) is stirred for 10 min at room temperature. Paraformaldehyde (60 mg, 2 mmol) is then added in one portion, the mixture is stirred overnight at room temperature, then filtered. The filtrate is evaporated under reduced pressure to give
the O,N-acetal 5 (Table 2) which is used without purification. To the O,N-acetal 5 is added trifluoroacetic acid (3 mL), this mixture is stirred at room temperature for 1 h, then concentrated. The remaining mixture is washed with saturated NaHCO₃ solution (50 mL) and extracted with CHCl₃ (5 x 50 mL). The combined extracts are dried (Na₂SO₄) and evaporated to dryness. The residue is chromatographed on silica gel and the product 6 is purified by recrystallization or distillation. (Table 3).

Butyl 2-Benzyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (7a): Typical Procedure: A solution of N-benzyl-2-phenylethylamine 4a (315 mg, 1 mmol) in butanol (5 mL) is stirred with butyl glyoxalate¹⁰ (650 mg, 5 mmol) and anhydrous K₂CO₃ (690 mg, 5 mmol) for 30 min. Then, trifluoroacetic acid (2 mL) is added and stirring is continued for 60 min. The resultant yellow oil is chromatographed on silica gel using hexane/EtOAc (10:1) as eluent to afford 7a as a colorless oil; yield: 315 mg (74%). (Table 3).

1.2,4,10,11,13-Hexamethoxy-3,12,16-trimethyl-6,15-imino-5H-isoquinoline[3,2-b][1]benzazocine (9): A mixture of 2-(2,6-dimethyl-3-phenylphenylimethyI)-7,9,10-trimethoxy-8,11-dimethyl-(1x,2a,5a)-1,2,3,4,5,6-hexahydro-1H-imino-3-benzazocine (8b); 48.6 mg, 0.1 mmol) in EtOH (0.5 mL) and anhydrous K₂CO₃ (221 mg, 1.6 mmol) is stirred for 10 min at room temperature. Paraformaldehyde (24 mg, 0.8 mmol) is then added in one portion and the mixture is stirred for 24 h, then filtered, and the filtrate evaporated in vacuo. The residue (72.4 mg) is stirred with trifluoroacetic acid (2 mL) for 1 h at room temperature. The mixture is diluted with H₂O (20 mL) and extracted with CHCl₃ (3 x 20 mL). The combined extracts are washed with 5% NaHCO₃ solution (40 mL), dried (Na₂SO₄), and evaporated. Recrystallization of the residue from EtOAc/ether gives product 9 as colorless prisms; yield: 40.2 mg (81%); m.p. 158.5-160°C.

C₁₇H₁₉N₂O₆ calc. C 67.44 H 7.68 N 5.62
(498.6) found 67.14 7.86 5.54
MS: m/z = 498 (M⁺, 18%); 248 (100); 234 (10); 218 (11)
IR (KBr): v = 2930; 1465; 1405; 1115; 1070 cm⁻¹.
UV (MeOH): λmax = 224 (log e = 4.33); 272 (2.83); 278 (2.90) nm.
¹H-NMR (CDCl₃/TMS): δ = 2.12 (s, 3 H, Ar-CH₃); 2.16 (s, 3 H, Ar-CH₃); 2.24 (dd, 1 H, J = 11.2 Hz, 11.5 Hz, 14β-H); 2.32 (s, 3 H, N-CH₃); 2.61 (d, 1 H, J = 8.3 Hz, 5β-H); 2.72 (dd, 1 H, J = 12.2 Hz, 3.4 Hz, 2.0 Hz, 14α-H); 3.01 (dd, 1 H, J = 12.2 Hz, 3.4 Hz, 14β-H); 3.05 (d, 2 H, J = 2.0 Hz, 14β-H); 3.06 (dd, 1 H, J = 18.3 Hz, 7.7 Hz, 9α-H); 3.12 (d, 1 H, J = 15.6 Hz, 9β-H); 3.25 (m, 1 H, 6-H); 3.58 (s, 3 H, OCH₃); 3.70 (s, 3 H, OCH₃); 3.73 (s, 3 H, OCH₃); 3.76 (s, 3 H, OCH₃); 3.77 (s, 3 H, OCH₃); 3.85 (s, 3 H, OCH₃); 3.95 (d, 1 H, J = 15.6 Hz, 15α-H); 4.08 (dd, 1 H, J = 2.2 Hz, 0.5 Hz, 15-H).
¹³C-NMR (CDCl₃/TMS): δ = 9.1 (q, Ar-CH₃); 9.3 (q, Ar-CH₃); 22.5 (t, C-5); 26.8 (t, C-14); 41.3 (q, N-CH₃); 52.5 (d, C-6); 53.3 (t, C-9); 53.7 (d, C-5); 59.4 (q, OCH₃); 59.4 (q, OCH₃); 59.5 (q, OCH₃); 59.8 (q, OCH₃); 60.0 (q, OCH₃); 60.1 (q, OCH₃); 60.6 (t, C-14α); 63.4 (t, C-7); 122.6 (s); 123.4 (s); 123.5 (s); 124.3 (s); 124.4 (s); 125.5 (s); 145.1 (s); 147.9 (s); 149.1 (s); 149.1 (s); 151.5 (s); 152.0 (s).

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