Elaboration of 1-benzoyltetrahydroisoquinoline derivatives employing a Pictet–Spengler cyclization with α-chloro-α-phenylthioketones. Synthesis of O-methylvelucryptine

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Abstract—The reaction of N-tosyl-β-phenethylamines with α-chloro-α-phenylthioketones, leading to 1-benzoyl- and 1-pivaloyl-tetrahydroisoquinolines under modified Pictet–Spengler conditions, is described. The synthesis of O-methylvelucryptine employing this transformation as a key step is reported. © 2001 Elsevier Science Ltd. All rights reserved.

Being a very numerous class of natural products and covering a wide range of structural types, 1-benzylisoquinoline alkaloids and their derivatives are attractive targets for synthesis and drivers of the development of new synthetic methodologies.1

1-Benzylisoquinolines constitute a small group within the 1-benzylisoquinolines, with most of its members having been isolated during the past two decades. They are represented by natural products such as xanthaline (1) also known as papaveraldine, a degradation product and contaminant of the pharmaceutically useful papaverine,2 rugosinone (2),3 thalmicrinone (3)4 and the unnamed base 4.5

It has been proposed that fully aromatic members result from biochemical dehydrogenation of their corresponding tetrahydroisoquinoline precursors, being the 3,4-dihydroroisoquinolines like velucryptine (5),6 dihydrorugosinone (6), canellilinoxine (7),7 longifolinone8 (8) and o xo-3,4-dihydroryafranine (9)5 produced as intermediates during this process.

Interestingly, the in vitro air oxidation of certain tetrahydroisoquinolines to produce 1-benzoyl-3,4-dihydror isoquinolines has been observed.9 In addition, 1-benzylisoquinolines are also structurally related to other oxidized alkaloids, such as oxocularines10,11 and oxaaporphines.

Few and scattered syntheses of these compounds are known. 1-Benzylisoquinolines have been elaborated by oxidation of 1-benzyl-3,4-dihydroisoquinolines obtained by the Bischler–Napieralski cyclization,6,12

Keywords: 1-benzoyltetrahydroisoquinolines; Pictet–Spengler; α-chloro-α-phenylthioketones; O-methylvelucryptine.

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and in a one-pot reaction of phenethylamines with vicinal diketones under modified Pictet–Spengler conditions, involving hydrolysis and decarboxylation of a 1,1-disubstituted tetrahydroisoquinoline carboxylate intermediate. Non-natural 1-benzoylisoquinolines have also been obtained by photolysis of berberinium salts and as intermediates during the synthesis of phthalide derivatives by Pictet–Spengler condensation of substituted 1-phenethylamines with the natural product 

Table 1. Synthesis of 1-benzoyl- and 1-pivaloyl-tetrahydroisoquinoline derivatives by reaction of \( \alpha \)-chloro-\( \alpha \)-methylthiocarbonyl ketones with \( N \)-tosyl-\( \beta \)-phenethylamines under Lewis-acid promotion

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R )</th>
<th>( R_1 )</th>
<th>( R_2 )</th>
<th>( R_3 )</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>( r )-Butyl</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>64</td>
</tr>
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<td>2</td>
<td>Ph</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>( r )-Butyl</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>( r )-Butyl</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>( r )-Butyl</td>
<td>OCH(_3)</td>
<td>OCH(_3)</td>
<td>H</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>OCH(_3)</td>
<td>OCH(_3)</td>
<td>H</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>( r )-Butyl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>( \text{ZnBr}_2, \text{CICH}_2\text{CH}_2\text{Cl}, \text{reflux} \ 8 \text{ h} )</td>
<td>77</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>( \text{ZnBr}_2, \text{CICH}_2\text{CH}_2\text{Cl}, \text{reflux} \ 8 \text{ h} )</td>
<td>82</td>
</tr>
<tr>
<td>11</td>
<td>( r )-Butyl</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>( \text{ZnBr}_2, \text{CICH}_2\text{CH}_2\text{Cl}, \text{reflux} \ 8 \text{ h} )</td>
<td>61</td>
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<td>Cl</td>
<td>H</td>
<td>H</td>
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<td>54</td>
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<tr>
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<td>H</td>
<td>Me</td>
<td>H</td>
<td>( \text{ZnBr}_2, \text{CICH}_2\text{CH}_2\text{Cl}, \text{reflux} \ 8 \text{ h} )</td>
<td>60</td>
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<tr>
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<td>H</td>
<td>Me</td>
<td>H</td>
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<td>60</td>
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<tr>
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<td>OMe</td>
<td>H</td>
<td>( \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow \text{rt} \ 5 \text{ h} )</td>
<td>51</td>
</tr>
</tbody>
</table>

\( ^a \) A 5.0:1.0:1.3 relationship between Lewis acid, \( \beta \)-phenethylamine and haloketone, respectively, was used.

\( ^b \) Isolated yield after column chromatography purification.

\( ^c \) Reaction of 10 with the \( N \)-carbamoyl-\( \beta \)-phenethylamine.
obtained by O-methylation of longifolinone. To this end, α-halo-α-phenylthioketone 14 was prepared from the commercially available 4-methoxy acetophenone following the strategy outlined in Scheme 1 and reacted with N-tosyl-β-phenethyamine 15 at −78°C under SnCl₄ catalysis, to afford tetrahydroisoquinoline 13 in 66% yield.

In turn (Scheme 2), this was submitted to a microwave-assisted eliminative detosylation with potassium fluoride supported on alumina, cleanly furnishing the final product 12 in 77% yield.

Analogously, submission of the tetrahydroisoquinoline product prepared by the reaction of the corresponding 3,4-methylenedioxy phenethylamine with 14 (SnCl₄, CH₂Cl₂, −78°C to rt, 5 h, 54% yield) to reaction with KF/Al₂O₃ under microwave irradiation (490 W, 60 s), provided the unnamed base 4 in 49% yield.

This and all new products were fully characterized by spectral means, including IR, ¹H and ¹³C NMR spectroscopy, and mass spectrometry.

In conclusion, this work demonstrated the usefulness of α-halo-α-phenylthioketones as convenient building blocks for the elaboration of 1-benzylisoquinoline derivatives by Pictet-Spengler condensation with activated β-phenethyamines under Lewis-acid catalysis. This transformation, in conjunction with a microwave-assisted oxidative removal of the sulfonyl moiety, was employed for the synthesis of O-methylvelucryptine and the unnamed natural product 4.

It is noteworthy that the latter constitutes an interesting and unprecedented use of the KF/Al₂O₃ reagent, the scope and limitations of which are currently under study. The synthetic strategy may be useful for the elaboration of other 1-benzylisoquinolines.

Acknowledgements

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References

23. Compound 4: mp 152–154°C (lit. 5 152–153°C); 1H NMR (200 MHz, CDCl3): δ 3.87 (s, 3H), 6.09 (s, 2H), 6.94 (d, 2H, J = 8 Hz), 7.14 (s, 1H), 7.84 (s, 1H), 7.60 (d, 1H, J = 5.4 Hz), 7.93 (d, 2H, J = 8 Hz), 8.43 (d, 1H, J = 5.4 Hz); 13C NMR (50 MHz, CDCl3): δ 25.40, 47.13, 55.49, 55.98, 56.07, 109.77, 110.52, 113.83 (2C), 121.80, 123.87, 129.66, 133.18 (2C), 135.52, 140.44, 149.27, 151.10, 154.81, 164.01, 193.61.
O-Methylvelucryptine (12): mp 91–92°C; 1H NMR (200 MHz, CDCl3): δ 3.87 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 3.87–3.95 (m, 2H), 6.74 (s, 1H), 6.92 (s, 1H), 6.94 (d, 2H, J = 8 Hz), 8.02 (d, 2H, J = 8 Hz); 13C NMR (50 MHz, CDCl3): δ 25.40, 47.13, 55.49, 55.98, 56.07, 109.77, 110.52, 113.83 (2C), 119.43, 128.48, 131.10, 132.82 (2C), 147.66, 151.71, 164.24, 164.70, 192.56.