An Improved Synthesis of \( N \)-Substituted 1-Aryl-3-oxo-1,2,3,4-tetrahydroisoquinolines

A. P. Venkov, N. M. Molloy

Department of Chemistry, University of Plovdiv, BG-4000 Plovdiv, Bulgaria

3-Oxo-1,2,3,4-tetrahydroisoquinolines are of interest as potential drugs\(^1\)\(^-\)\(^5\) and as starting materials for the synthesis of tetrahydroisoquinolines or alkaloids of this type\(^6\)\(^-\)\(^7\). They are usually prepared:

(a) from nitriles or amides of arylacetic acids and aldehydes in acidic medium\(^1\)\(^-\)\(^10\);

(b) from arylacetyl chlorides and Schiff bases in the presence of aluminum chloride as catalyst\(^15\)\(^-\)\(^17\).

A wide variety of 3-oxo-1,2,3,4-tetrahydroisoquinolines may be obtained by these two methods. Method (b) is preferred for the synthesis of \( N \)-substituted 3-oxo-1,2,3,4-tetrahydroisoquinolines; a variant of this method represents an improvement\(^18\) of the Pictet-Spengler reaction. However, in some cases the applicability of the method is limited by the difficult preparation and purification of the arylacetyl chlorides 1. The reaction proceeds as an intramolecular \( \alpha \)-amidoalkylation; thus, arylacetic acids cannot be used as starting materials because the low electrophilicity of the carboxy group as well as salt formation with the imine 2 will lower the yield of the \( N \)-substituted carboxamides required for the cyclization. We therefore tried to modify Method (b) in such a manner that the synthesis of the arylacetyl chlorides 1 from the corresponding acids and their reaction with the imines 2 is performed as a one-pot procedure so that the arylacetic acids themselves can be used as starting materials. We report here the results of these experiments which were carried out in 1,2-dichloroethane as solvent using thionyl chloride for conversion of the acids into the chlorides 1 and aluminium chloride as catalyst for cyclization of the intermediate carboxamides 3.

\[
\begin{align*}
&\text{X}^1\text{C}_\text{H}_2\text{COOH} \\
&\text{X}^2\text{C}_\text{H}_2\text{COOH} \\
&\text{X}^3\text{C}_\text{H}_2\text{COOH} \\
&\text{SOCI}_2/ \\
&\text{1,2-dichloroethane}
\end{align*}
\]

\[
\begin{align*}
&\text{X}^1\text{C}_\text{H}_2\text{CO} \quad + \quad \text{X}^4\text{CH}=\text{N} \quad \rightarrow \\
&\text{X}^2\text{C}_\text{H}_2\text{CO} \\
&\text{X}^3\text{C}_\text{H}_2\text{CO} \\
&\text{X}^4\text{CH}=\text{N} \quad \rightarrow
\end{align*}
\]

It should be noted that our new procedure also works well with arylacetic acids having hydroxy groups on the benzene ring; in these cases, Method (b) gives unsatisfactory results. The hydroxy derivatives 4k and 4f were converted into compounds 4e and 4f, respectively, by treatment with diazome-
Table 3-Oxo-1-phenyl-1,2,3,4-tetrahydroisoquinolines (4)

<table>
<thead>
<tr>
<th>4</th>
<th>X^1</th>
<th>X^2</th>
<th>X^3</th>
<th>X^4</th>
<th>X^5</th>
<th>R</th>
<th>Yields [%]</th>
<th>m.p. [°C]</th>
<th>m.p. [°C] reported or Molecular formula^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>40</td>
<td>65</td>
<td>137-139°</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>62</td>
<td>62</td>
<td>94-95°</td>
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<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>NO\textsubscript{2}</td>
<td>H</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>68</td>
<td>61</td>
<td>55-57°</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OCH\textsubscript{3}</td>
<td>OCH\textsubscript{3}</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>30</td>
<td>36</td>
<td>61-62°</td>
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<tr>
<td>e</td>
<td>OCH\textsubscript{3}</td>
<td>OCH\textsubscript{3}</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>80</td>
<td>70</td>
<td>164-165°</td>
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<tr>
<td>f</td>
<td>OCH\textsubscript{3}</td>
<td>OCH\textsubscript{3}</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>60</td>
<td>75</td>
<td>141-142°</td>
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<tr>
<td>g</td>
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<td>OCH\textsubscript{3}</td>
<td>H</td>
<td>NO\textsubscript{2}</td>
<td>H</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>76</td>
<td>65</td>
<td>183-184°</td>
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<tr>
<td>h</td>
<td>OCH\textsubscript{3}</td>
<td>OCH\textsubscript{3}</td>
<td>H</td>
<td>NO\textsubscript{2}</td>
<td>H</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>68</td>
<td>63</td>
<td>140-141°</td>
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<tr>
<td>i</td>
<td>OCH\textsubscript{3}</td>
<td>OCH\textsubscript{3}</td>
<td>H</td>
<td>NO\textsubscript{2}</td>
<td>H</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>54</td>
<td>65</td>
<td>184-185°</td>
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<tr>
<td>j</td>
<td>OCH\textsubscript{3}</td>
<td>OCH\textsubscript{3}</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
<td>--</td>
<td>55</td>
<td>oil</td>
<td>C\textsubscript{6}H\textsubscript{3}NO\textsubscript{2} (327.4)</td>
</tr>
<tr>
<td>k^4</td>
<td>OCH\textsubscript{3}</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
<td>--</td>
<td>65</td>
<td>250-252°</td>
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<tr>
<td>l^4</td>
<td>OCH\textsubscript{3}</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
<td>--</td>
<td>70</td>
<td>203-204°</td>
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</table>

^a Yields from literature.

^b The microanalyses were in satisfactory agreement with the calculated values: C, ±0.32; H, ±0.18; N, ±0.16.

^c I.R. (nujol): ν = 1670 cm\(^{-1}\) (C=O).

^d H-N.M.R. (CDCl\(_3\)/TMS\(_{\text{eq}}\)): δ = 3.93, 3.95, 3.85 (3 s, 9 H, 6, 7, 8-OCH\textsubscript{3}); 2.90 (s, 3 H, N–CH\textsubscript{3}); 6.25 (s, 1 H, 1-H); 5.15 (s, 2 H, 4,4′-H); 7.0-7.3 ppm (m, H\(_{\text{mono}}\)).

thane in ether at room temperature overnight. Compound 4k is also obtained in 55% yield from the reaction of 3,4-dimethoxyphenylacetamide according to the general procedure with the modification that 3 mol equiv of aluminium chloride are used: under these conditions, the 7-methoxy group in 4e is cleaved selectively.

The known products 4a-i were identified by comparison of their physical data with the corresponding data from the literature and by T.L.C. purity control. The structures of the new compounds 4j, k, l were established by microanalyses, I.R. and H-N.M.R. spectra, and by G.L.C. purity control.

Melting points were determined on a Boetius apparatus and are uncorrected. The I.R. spectra were recorded on a Perkin-Elmer 337 spectrophotometer and H-N.M.R. spectra on a Perkin-Elmer R-24B 60 MHz spectrophotometer.

1-Aryl-3-oxo-1,2,3,4-tetrahydroisoquinolines (4); General Procedure: Thionyl chloride (0.357 g, 3 mmol) is added to a solution of the arylacetic acid (2 mmol) in dry 1,2-dichloroethane (10 ml) and the mixture is heated at 80°C for 3 h. To the solution of the arylacetyl chloride (1) thus obtained, the imine (2 mmol) is added and the mixture is stirred for 15 min at room temperature. Then, anhydrous aluminum chloride (0.266 g, 2 mmol) is added, the mixture stirred at 50°C for 1 h, cooled to 20°C, hydrolyzed with 10% hydrochloric acid (10 ml), and extracted with chloroform (3 × 10 ml). The organic extract is washed with water (20 ml), dried with sodium sulfate, and evaporated in vacuo. The residual product is purified by recrystallization from ether/hexane or by column chromatography on silica gel 40 (Merck) using ether or ether/methanol as eluents.

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^4 Address for correspondence.


