Use of Substituted Acetamides for the Synthesis of 3-Substituted 2-Aminoquinolines

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A novel two-step conversion of 2-aminobenzaldehydes to 3-substituted 2-diethylaminoquinolines utilizes a modified Friedländer reaction in which a substituted acetamide is used, for the first time, as a source of the C₃ unit.

Heterocyclization of 2-aminobenzaldehydes is a subject of current interest and has been recently reviewed.¹,² The Friedländer synthesis and its modifications¹,² is a method of wide synthetic utility for the conversion of 2-aminobenzaldehydes to quinolines. The present two-step conversion of 2-aminobenzaldehydes to hitherto unknown 3-substituted 2-diethylaminoquinolines represents a new modification which involves, for the first time, the use of N,N-diethylacetamides as a source of two additional carbon atoms. The advantages of this method reside in the predetermined direction of ring closure, the direct and regioselective introduction of substituents into the newly formed heterocyclic ring, and the variety of substituents that can be incorporated into the starting compound. Another important feature of the present method is the production of a quinoline functionalized at the 2 position whereas the Friedländer method is more useful for the synthesis of quinolines functionalized at the 3 position.

Treatment of the aminodedehyde 1a with the preformed complex of phosphoryl chloride and N,N-diethylphenylacetamide (2a) resulted in a vigorous reaction. Since attempts to control this reaction were unsuccessful, the aminodehydes was acetylated to give the acetanilide 1b in 60% yield. The reaction of 1b with the above preformed complex in chloroform afforded a syrupy liquid after work-up (Table). The absence of carbonyl, hydroxy, and amino absorptions in the IR spectrum ruled out the initially expected structure 4. The ¹H-NMR signals assignable to -NEt₂ (0.98, t, 6 H; 3.2, q, 4 H), OCH₂O (6.0, s, 2 H), and aromatic protons (7.22–7.56, m, 5 H; 6.92, 7.18, 2 s, 1 H each, 8-H, 5-H; 7.60, 1 H, s, 4-H) coupled with the IR data and the mode of formation clearly required the compound to have structure 3ba. The product was obtained in 63% yield.

Similar reactions of the acetanilide 1b with other amides 2b–e afforded products identified as the quinolines 3bb–3be by their mode of formation in combination with their spectral and analytical data. These products were obtained in yields varying from 44 to 60%, while the reactions of acetanilide 1c with the amides 2a and 2b furnished 3ca and 3cb, respectively.

The reactions of unsubstituted 2-aminobenzaldehyde (1d) with amides 2 afforded different types of products. Their structures are under investigation.

Table: 3-Substituted 2-Diethylaminoquinolines 3 Prepared

| Product | Time (h) | Yield (%) | M.p. (°C) | Molecular Formula | ¹H-NMR (CDCl₃/TMS), δ¹⁵ | Other
<table>
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<td></td>
<td></td>
<td>N(CH₂--CH₃)₂ (t)</td>
<td>N(CH₂--CH₃)₂ (q)</td>
</tr>
<tr>
<td>3ba</td>
<td>24</td>
<td>63</td>
<td>syrupy liquid</td>
<td>70–72</td>
<td>C₁₂H₁₈N₂O₂ (320.4)</td>
<td>0.98</td>
</tr>
<tr>
<td>3bb</td>
<td>24</td>
<td>48</td>
<td>syrupy liquid</td>
<td>108</td>
<td>C₉H₁₄N₂O₂ (258.3)</td>
<td>1.19</td>
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<tr>
<td>3be</td>
<td>24</td>
<td>53</td>
<td>syrupy liquid</td>
<td>95–97</td>
<td>C₁₂H₁₈N₂O₂ (336.4)</td>
<td>1.94</td>
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<tr>
<td>3bd</td>
<td>18</td>
<td>60</td>
<td>syrupy liquid</td>
<td>95–97</td>
<td>C₁₂H₁₈N₂O₂ (336.4)</td>
<td>1.04</td>
</tr>
<tr>
<td>3be</td>
<td>16</td>
<td>48</td>
<td>syrupy liquid</td>
<td>108</td>
<td>C₁₂H₁₈N₂O₂ (336.4)</td>
<td>1.17</td>
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<tr>
<td>3ca</td>
<td>24</td>
<td>45</td>
<td>syrupy liquid</td>
<td>95–97</td>
<td>C₁₂H₁₈N₂O₂ (336.4)</td>
<td>1.10</td>
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<tr>
<td>3cb</td>
<td>24</td>
<td>45</td>
<td>syrupy liquid</td>
<td>95–97</td>
<td>C₁₂H₁₈N₂O₂ (336.4)</td>
<td>1.27</td>
</tr>
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¹ Yield of isolated pure product.
² Satisfactory microanalyses obtained: C ± 0.30, H ± 0.2.
³ Recorded on a Perkin Elmer R-32, 90 MHz instrument.
⁴ Additional 3H at δ = 2.34 (s) for Ar--Cl₂.
3-Substituted 2-Diethylaminoquinolines (3): General Procedure:
Phosphoryl chloride (0.154 g, 1 mmol) is added at 0°C to a stirred solution of the acetamide 2a-e (1 mmol) in dry CHCl₃ (10 mL). To this complex, the acetonilide 1b or 1e (1 mmol) is added. The mixture is heated to reflux for 18–24 h, then cooled. The CHCl₃ is removed and 10% Na₂CO₃ solution (10 mL) is added. This mixture is warmed on a water bath (60°C) for 10 min, then cooled, acidified with dilute HCl, and extracted with CHCl₃ (2 × 25 mL). The CHCl₃ extract is washed with water, dried (Na₂SO₄), concentrated, and passed through a short column of silica gel (10 g). Elution with hexane gives the pure product 3.

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