Friedel Crafts reaction on [2,3]oxopolymethelene indoles

K J Rajendra Prasad*, R Balamurali & C Kavitha
Department of Chemistry, Bharathiar University,
Coimbatore 641 046, India

Received 10 January 2001; accepted (revised) 15 November 2001

1-Oxo-1,2,3,4-tetrahydrocarbazoles 1a-e and 1-oxo-1,2,3,4,5,10-hexahydrocyclohept[7]indoles 1F-j are treated with a mixture of glacial acetic acid and polyphosphoric acid in an expectation to yield 5,6-dihydro-2-methyl-1-oxopyrano[2,3-a]carbazoles 2a-e and 5,6,7,12-tetrahydro-2-methyl-4-oxopyranono[2',3':7,6]cyclohept[b]indoles 2F-j, respectively. Instead, acetyl derivatives of 1a-j are obtained. Their characterization and the effect of the substituents on the reactivity and orientation of the above reaction have been discussed.

In general pyrano, pyrazino, quinolinolo and simple benzocarbazole derivatives were reported to exhibit pharmacological properties like antihistaminic, antiinflammatory, antibiotic and antimicrobial activities. Cyclohept[b]indoles were reported to have antidepressant property. Pyridocarbazoles are well known as anticancer agents. Substitution of pyrido ring by other heterocyclic ring may lead to interesting variations in their pharmacological activities. Based on the above facts, it was aimed to derive an elegant synthetic route for 2-methyl-4-oxopyrano[2,3-a]carbazoles and 2-methyl-4-oxopyrano[2',3':7,6]cyclohept[b]indoles.

In order to achieve our objective, 1-oxo-1,2,3,4-tetrahydrocarbazole 1a was treated with a mixture of glacial acetic acid and polyphosphoric acid at 100°C in an expectation that the reaction would proceed as shown in Scheme I. This yielded a single product, which melted at 186°C. The IR spectrum of this compound showed strong absorptions at 3220 and 1660 cm⁻¹ which are accountable for NH and C=O stretching vibrations respectively. The ¹H NMR spectrum exhibited following resonances. A three proton singlet at δ 2.68, three two proton multiplets at δ 2.30, 2.75 and 3.06 respectively, two doublets at δ 7.45 (J = 8.76) and δ 8.02 (J = 8.76), a singlet at δ 8.32 and a broad singlet at δ 9.31. The absence of resonance in the olefinic region indicated that the expected product was not formed. This was also supported by the appearance of the molecular ion at m/z 227, whereas the expected product requires the molecular ion at m/z 251. The elemental analysis (C, 73.87, H, 05.62, N, 06.03%) was in agreement with the molecular formula C₁₅H₁₃NO₂. The three proton singlet at δ 2.68 was accountable for the acetyl group protons, two doublets in the aromatic region (δ 7.45 & 8.02) with J = 8.76 (ortho coupling) were assignable for the C₇ and C₈ protons and a singlet at δ 8.32 is accountable for the C₃ proton. Based on the above mentioned data the structure of the product was assigned to be 6-acetyl-1-oxo-1,2,3,4-tetrahydrocarbazole 1a which is a simple Friedel Crafts acylation product. A series of similar products 1b-o were obtained from 1b-e.

When the 6th position of 1a was blocked with either methyl (1e) or chloro (1e) group acylation occurred at 8th position (1m and 1o). When either 7th or 8th position (1d and 1b) was blocked by a methyl group the acetyl group entered the 6th position (1n and 1l). From the above observation it can be concluded that 6th position is more active towards an electrophile compared to other positions. This can be supported by the fact that the 6th position is para to the ring nitrogen atom. Further, when 6th position was substituted with chloro group poor yield was obtained. This may be due to the deactivating effect of the chloro group (Scheme II and Table I).

In order to study the generality of the above reaction it was extended to the system containing cycloheptanone ring fused with indole (1-oxo-1,2,3,4,5,10-hexahydrocyclohept[b]indoles 1F-j), a similar results were obtained as in the case of 1k-o.

Experimental Section

Thin layer chromatography was used to access the purity of the products. Melting points were determined using mettler FP 5 apparatus and Boetius microheating table and are uncorrected. IR spectra in KBr disc were recorded on a Shimadzu FTIR 8021 (PC) spectrometer and ¹H NMR spectra on a Varian 400 MHz spectrometer as solutions in CDCl₃. The resonance are quoted in parts per million downfield to the internal standard TMS. Jeol JMS-D 300 mass spectrometer was used to record mass spectra. Satisfactory microanalyses were obtained from Perkin Elmer model 240 CHN analyzer.
Synthesis of acetyl derivatives of 1-oxo-1,2,3,4-tetrahydrocarbazoles 1k-o. Respective 1-oxo-1,2,3,4-tetrahydrocarbazoles la-e (0.001 mole) was heated with a mixture of acetic acid (0.002 mole) and polyphosphoric acid (10 g P₂O₅ in 4 mL H₃PO₄) at 100°C for 8 hr. The reaction mixture was cooled, poured into ice water, the precipitated product was filtered and dried. The crude residue was purified by passing through a column of silica gel and eluting with petroleum ether-ethyl acetate mixture (75:25).

Synthesis of acetyl derivatives of 1-oxo-1,2,3,4,5,10-hexahydrocyclohept[b]indoles If-j (0.001 mole) was heated with a mixture of acetic acid (0.002 mole) and polyphosphoric acid (10 g P₂O₅ in 4 mL H₃PO₄) at 100°C for 8 hr. The reaction mixture was cooled, poured into ice water, the precipitated product was filtered and dried. The crude residue was purified by passing through a column of silica gel and eluting with petroleum ether-ethyl acetate mixture (92:8).

Acknowledgement

Authors thank the SIF, IISc, Bangalore for providing the spectral and analytical data and one of the authors (CK) is grateful to the CSIR, New Delhi for the award of Senior Research Fellowship.
**Scheme II**

Table 1 — Physical and spectral data of 1k-1t.

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. (°C)*</th>
<th>Yield (%)</th>
<th>Mol. formula (Mol. wt.)</th>
<th>Calcld (Found) %</th>
<th>1H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1k</td>
<td>186</td>
<td>70</td>
<td>C_{16}H_{17}NO_{2} (227.26)</td>
<td>74.00 (73.85) 05.72 (06.02) 06.16 (06.03)</td>
<td>2.30 (m, 2H, C_{7}-H), 2.68 (s, 3H, C_{6}-COCH_{3}), 2.75 (m, 2H, C_{7}-H), 3.06 (m, 2H, C_{7}-H), 7.45 (d, 1H, C_{7}-H, J=8.76 Hz), 8.02 (d, 1H, C_{7}-H, J=8.76 Hz), 8.32 (s, 1H, C_{7}-H), 9.31 (bs, 1H, NH).</td>
</tr>
<tr>
<td>II</td>
<td>200</td>
<td>72</td>
<td>C_{16}H_{17}NO_{2} (241.29)</td>
<td>74.68 (74.53) 06.22 (06.17) 05.80 (05.72)</td>
<td>2.29 (m, 2H, C_{7}-H), 2.53 (s, 3H, C_{6}-CH_{3}), 2.66 (s, 3H, C_{6}-COCH_{3}), 2.67 (m, 2H, C_{7}-H), 7.81 (1H, C_{7}-H), 8.19 (s, 1H, C_{7}-H), 8.34 (bs, 1H, NH).</td>
</tr>
<tr>
<td>Im</td>
<td>123</td>
<td>74</td>
<td>C_{16}H_{17}NO_{2} (241.29)</td>
<td>74.68 (74.58) 06.22 (06.14) 05.80 (05.75)</td>
<td>2.26 (m, 2H, C_{7}-H), 2.54 (s, 3H, C_{6}-CH_{3}), 2.64 (m, 2H, C_{7}-H), 2.67 (s, 3H, C_{6}-COCH_{3}), 2.97 (s, 1H, C_{7}-H), 7.74 (s, 1H, C_{7}-H), 10.48 (bs, 1H, NH).</td>
</tr>
<tr>
<td>In</td>
<td>174</td>
<td>67</td>
<td>C_{16}H_{17}NO_{2} (241.28)</td>
<td>74.68 (74.58) 06.22 (06.15) 05.80 (05.73)</td>
<td>2.29 (m, 2H, C_{7}-H), 2.66 (s, 3H, C_{6}-CH_{3}), 2.67 (s, 3H, C_{6}-COCH_{3}), 2.69 (m, 2H, C_{7}-H), 3.03 (m, 2H, C_{7}-H), 7.25 (1H, C_{7}-H), 8.10 (s, 1H, C_{7}-H), 9.23 (bs, 1H, NH).</td>
</tr>
<tr>
<td>Io</td>
<td>207</td>
<td>30</td>
<td>C_{16}H_{17}NO_{2}Cl (261.71)</td>
<td>64.36 (64.24) 04.59 (04.42) 05.36 (05.25)</td>
<td>2.28 (m, 2H, C_{7}-H), 2.62 (m, 2H, C_{7}-H), 2.69 (s, 3H, C_{6}-COCH_{3}), 3.01 (m, 2H, C_{7}-H), 7.65 (1H, C_{7}-H), 7.83 (s, 1H, C_{7}-H), 9.74 (bs, 1H, NH).</td>
</tr>
<tr>
<td>1p</td>
<td>219</td>
<td>75</td>
<td>C_{16}H_{17}NO_{2} (241.29)</td>
<td>74.67 (74.52) 06.27 (06.32) 05.80 (05.78)</td>
<td>1.92-1.99 (m, 2H, C_{7}-H), 2.03-2.09 (m, 2H, C_{7}-H), 2.60 (s, 3H, C_{6}-COCH_{3}), 2.79-2.82 (m, 2H, C_{7}-H), 3.12-3.15 (m, 2H, C_{7}-H), 7.32-7.34 (d, 1H, C_{7}-H, J=8.76 Hz), 7.91-7.94 (d, 1H, C_{7}-H, J=1.40 Hz), 8.28 (s, 1H, C_{7}-H), 9.14 (bs, 1H, NH).</td>
</tr>
<tr>
<td>Ig</td>
<td>230</td>
<td>70</td>
<td>C_{16}H_{17}NO_{2} (255.31)</td>
<td>75.27 (75.26) 06.71 (06.81) 05.49 (05.32)</td>
<td>1.99-2.04 (m, 2H, C_{7}-H), 2.10-2.15 (m, 2H, C_{7}-H), 2.52 (s, 3H, C_{6}-CH_{3}), 2.66 (s, 3H, C_{6}-COCH_{3}), 2.86-2.87 (m, 2H, C_{7}-H), 3.19-3.22 (m, 2H, C_{7}-H), 7.79 (1H, C_{7}-H), 8.20 (s, 1H, C_{7}-H), 8.98 (bs, 1H, NH).</td>
</tr>
<tr>
<td>1r</td>
<td>145</td>
<td>72</td>
<td>C_{16}H_{17}NO_{2} (255.31)</td>
<td>75.27 (75.40) 06.71 (06.66) 05.49 (05.30)</td>
<td>1.91-1.97 (m, 2H, C_{7}-H), 2.03-2.08 (m, 2H, C_{7}-H), 2.45 (s, 3H, C_{6}-CH_{3}), 2.59 (s, 3H, C_{6}-COCH_{3}), 2.78-2.81 (m, 2H, C_{7}-H), 3.11-3.14 (m, 2H, C_{7}-H), 7.72 (1H, C_{7}-H), 8.99 (s, 1H, C_{7}-H), 9.11 (bs, 1H, NH).</td>
</tr>
</tbody>
</table>

**NOTES**
Table 1 — Physical and spectral data of Il-I.—Contd

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p.</th>
<th>Yield</th>
<th>Mol. formula</th>
<th>Calcd (Found) %</th>
<th>$^1$H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(°C)*</td>
<td>(%)</td>
<td>(Mol.wt)</td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>Ir</td>
<td>145</td>
<td>72</td>
<td>C$_{10}$H$_7$NO$_2$</td>
<td>75.27</td>
<td>6.71</td>
</tr>
<tr>
<td>Is</td>
<td>195</td>
<td>78</td>
<td>C$_{10}$H$_7$NO$_2$</td>
<td>75.27</td>
<td>6.71</td>
</tr>
<tr>
<td>It</td>
<td>110</td>
<td>39</td>
<td>C$_{10}$H$_7$NOCl</td>
<td>65.34</td>
<td>5.12</td>
</tr>
</tbody>
</table>

* Recrystallised from suitable mixtures of petroleum ether - ethyl acetate

References
   (c) Sanisbary M, Synthesis, 1977, 438.
   (g) Sowmithran D & Rajendra Prasad K J, Heterocycles, 24, 1986, 2197.