Novel Synthesis of 4-Aroyl-6-phenylpyridazin-3(2H)-ones

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4-Aroyl-6-phenylpyridazin-3(2H)-ones, ¹H NMR Spectra

4-Aroyl-6-phenylpyridazin-3(2H)-ones (4a–c) were synthesized by the oxidation of the corresponding 4-arylmethyl-6-phenylpyridazin-3(2H)-ones (3a–c) using sodium dichromate in glacial acetic acid. The reactions of 4a–c with hydrazine hydrate and hydroxylamine hydrochloride proceeded smoothly to give the corresponding hydrazones (5) and oxime (6). 4a–c reacted with dimethyl sulphate to give 4-aroyl-2-methyl-6-phenylpyridazin-3(2H)-ones (7a–c), respectively while their reaction with phosphorus oxychloride gave 4-aroyl-3-chloro-6-phenylpyridazines (9a–c), respectively.

In the course of our study on the synthesis of fused pyridazine derivatives [1], the need arose for a new method for the synthesis of 4-aroylpyridazin-3(2H)-ones. 4-Pyridazinyl ketones were previously prepared by the reaction of monohydrazone of dicarbonyl compounds with compounds having active methylene groups [2].

A new general and convenient method for the synthesis of 4-aroylpyridazin-3(2H)-ones (4a–c) involves the oxidation of 4-arylmethylpyridazin-3(2H)-ones (3a–c) with sodium dichromate in acetic acid. The latter compounds can be easily prepared by the base-catalysed condensation of aromatic aldehydes with 4,5-dihydro-6-phenylpyridazin-3(2H)-ones (1) [3].

The product of the reaction of 1 with p-chlorobenzaldehyde was previously [4] given the 4-arylmethylen-4,5-dihydropyridazin-3(2H)-one structure (2). However, the similarity of its chemical and spectral properties to those of 3a, b, which differ sharply from that expected to structure of the type 2, confirms the 4-arylmethyl structure (3c) for that product. It is stable towards acids and bases and its IR spectrum shows a typical pyridazine absorption (νC=O = 1640 cm⁻¹, νNH,OH = 2800–3100 cm⁻¹).

The IR spectra of 4 are similar to those of other 6-arylpzridazin-3(2H)-ones [5]. They show strong carbonyl stretching frequencies of cyclic amides and aryl ketones. This fact proves the existence of 4 in the lactam form. In some cases, the carbonyl absorption was found as a broad band. This may be accounted for by the presence of the hydrogen bonding in the tautomeric lactim form (4) (cf. Table I).

The structure was further confirmed by the fact that the ¹H NMR spectrum of 4a, lacks the signal characteristic for a –CH₂– group. Thus, whereas the ¹H NMR of 3a shows a sharp signal at δ 3.9 (s, 2H) characteristic of –CH₂– protons in addition to signal characteristic of –CH = C– and aromatic protons at δ 7.2–7.9 (m, 11H), that of 4a shows the latter absorptions at δ 7.4–8.4 (m). The presence of the aryl ketonic group was further confirmed by the fact that 4a, c react readily with hydrazine hydrate to give the corresponding hydrazone (5a, b). 4b reacted also with hydroxylamine hydrochloride to give the corresponding oxime (6) (cf. Table I). Compounds 4 undergo typical pyridazine reactions with dimethyl sulphate in alkaline medium where 4-aroyl-2-methyl-6-phenylpyridazin-3(2H)-ones (7a–c) are formed in good yields (cf. Table I). 7b, c were independently synthesized via oxidation of the corresponding 4-arylmethyl-2-methyl-6-phenylpyridazin-3(2H)-ones (8a, b), prepared by the action of dimethyl sulphate on 3b, c.

When 4-aroyl-6-phenylpyridazin-3(2H)-ones (4a–c) were reacted with phosphorus oxychloride 4-aroyl-3-chloro-6-phenylpyridazines (9a–c) were formed in good yields (cf. Table I).

Experimental

All melting points are uncorrected. Elemental analyses were carried out at the microanalytical
Table I. Physical data of compounds 4–9.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M. p. (°C)</th>
<th>Solvent of crystn.</th>
<th>Yield (%)</th>
<th>Molecular formula</th>
<th>Analysis Found/Calcd (%)</th>
<th>IR (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>4a</td>
<td>225–226</td>
<td>B/E</td>
<td>50</td>
<td>C₁₅H₁₂N₄O₂</td>
<td>74.30</td>
<td>4.70</td>
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<tr>
<td>4b</td>
<td>217–219</td>
<td>B/E</td>
<td>53</td>
<td>C₁₅H₁₄N₃O₃</td>
<td>70.20</td>
<td>4.20</td>
</tr>
<tr>
<td>4c</td>
<td>254–255</td>
<td>B</td>
<td>58</td>
<td>C₁₃H₁₁N₂O₂Cl</td>
<td>66.00</td>
<td>3.70</td>
</tr>
<tr>
<td>4d</td>
<td>242–243</td>
<td>E</td>
<td>54</td>
<td>C₁₅H₁₄N₄O</td>
<td>70.60</td>
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<tr>
<td>4e</td>
<td>263–265</td>
<td>n-Bu</td>
<td>58</td>
<td>C₁₅H₁₃N₂OCl</td>
<td>63.00</td>
<td>3.60</td>
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<tr>
<td>4f</td>
<td>260–261</td>
<td>E</td>
<td>60</td>
<td>C₁₈H₁₅N₃O₃</td>
<td>67.10</td>
<td>5.00</td>
</tr>
<tr>
<td>4g</td>
<td>145–147</td>
<td>E</td>
<td>60</td>
<td>C₁₅H₁₄N₂O₂</td>
<td>74.40</td>
<td>4.70</td>
</tr>
<tr>
<td>4h</td>
<td>147–148</td>
<td>P</td>
<td>70</td>
<td>C₁₅H₁₆N₂O₃</td>
<td>70.80</td>
<td>5.40</td>
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<td>4i</td>
<td>203–204</td>
<td>H</td>
<td>75</td>
<td>C₁₅H₁₃N₂O₂Cl</td>
<td>66.10</td>
<td>4.60</td>
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<tr>
<td>4j</td>
<td>109–110</td>
<td>P</td>
<td>57</td>
<td>C₁₅H₁₈N₂O₂</td>
<td>73.90</td>
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<td>4k</td>
<td>95–96</td>
<td>L.P</td>
<td>60</td>
<td>C₁₅H₁₃N₂OCl</td>
<td>69.80</td>
<td>4.90</td>
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<tr>
<td>4l</td>
<td>122–124</td>
<td>B/P</td>
<td>56</td>
<td>C₁₅H₁₁N₂OCl</td>
<td>69.80</td>
<td>3.50</td>
</tr>
<tr>
<td>4m</td>
<td>124–125</td>
<td>B/P</td>
<td>58</td>
<td>C₁₅H₁₃N₂O₂Cl</td>
<td>66.60</td>
<td>4.50</td>
</tr>
<tr>
<td>4n</td>
<td>150–152</td>
<td>B/P</td>
<td>61</td>
<td>C₁₅H₁₀N₂OCl₂</td>
<td>62.20</td>
<td>3.00</td>
</tr>
</tbody>
</table>

B = benzene; E = ethanol; n-Bu = n-butanol; H = n-hexane; P = light petroleum (b.p. 90–100 °C); L.P = light petroleum (b.p. 60–80 °C).

unit, Cairo University. IR spectra in KBr were recorded on a Pye Unicam SP 1200 spectrophotometer. ¹H NMR spectra were carried out on Varian EM-360L using DMSO as a solvent.

Synthesis of 4-aryloyl-6-phenylpyridazin-3(2H)-ones (4a–c)

A solution of 4-arylmethyl-6-phenylpyridazin-3(2H)-ones (3a–c) (0.01 mole) in glacial acetic acid (40 ml) was treated with sodium dichromate (0.015 mole). The reaction mixture was heated under reflux for 8–9 h, cooled and poured over ice-cold water. The solid formed was filtered off, washed with cold water and crystallized from a
suitable solvent to give 4a-c, as colourless crystals (cf. Table I).

Reaction of (4a-c) with hydrazine hydrate
A solution of (1a, c; 0.01 mole) in ethanol (20 ml) was treated with hydrazine hydrate (1 ml). The reaction mixture was heated under reflux for 4 h, and left to cool. The solid formed was filtered off and crystallized from a suitable solvent to give the hydrazone derivatives (5a, b), respectively, as yellow crystals (cf. Table I).

Reaction of 4b with hydroxylamine hydrochloride
Hydroxylamine hydrochloride (0.12 g) dissolved in the least amount of water was added to a solution of 4b (0.5 g) in pyridine (10 ml). The reaction mixture was heated under reflux for 8 h, cooled and poured over a mixture of water and conc. hydrochloric acid. The solid formed was filtered off and crystallized from ethanol to give the oxime (6), as colourless crystals (cf. Table I).

Reaction of 4a-c with dimethyl sulphate
Dimethyl sulphate (0.015 mole) was added to a solution of 4b (0.5 g) in pyridine (10 ml). The reaction mixture was heated under reflux for 8 h, cooled and poured over a mixture of water and conc. hydrochloric acid. The solid formed was filtered off and crystallized from ethanol to give the oxime (6), as colourless crystals (cf. Table I).

Synthesis of authentic samples of 7b, c
(i) Reaction of 3b, c with dimethyl sulphate; synthesis of 4-arylmethyl-2-methyl-6-phenylpyridazin-3(2H)-ones (8a, b):
The reaction was carried out as described in the previous experiment to give 8a, b as colourless crystals (cf. Table I).
(ii) Oxidation of 8a, b to 7b, c:

Synthesis of 4-aroyl-3-chloro-6-phenylpyridazines (9a-c)
A mixture of 4a-c (1 g) and phosphorus oxychloride (5 ml) was heated on a boiling water-bath for 1 h. The reaction mixture was treated with crushed ice (50 g), and made just alkaline by the addition of aqueous sodium hydroxide solution (10%). The resulting solid was filtered off and crystallized from a suitable solvent to give 9a-c as colourless crystals (cf. Table I).

\[ \begin{align*}
3 & \quad | \quad (\text{CH}_3)_2\text{SO}\quad N\text{H}_2\text{NH}_2 \\
\text{Ar} = \text{C}_6\text{H}_5 & \quad \text{O} \\
4 & \quad | \quad (\text{CH}_3)_2\text{SO}\quad N\text{H}_2\text{NH}_2
\end{align*} \]