Condensation of 2-Acetyl-1,3-indandione with Amines and Diazonium Salts

Fathy Abdel Kader Amer, El-Sayed Afsah*, and Hassan Etman
Chemistry Department, Faculty of Science, Mansoura University, Mansoura, A. R. Egypt
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2-Acetyl-1,3-indandione Derivatives, Amines, Diazonium Salts

2-Acetyl-1,3-indandione (1) undergoes the Mannich reaction with piperidine or diethylamine hydrochloride to give compounds 2 and 3, respectively. On treatment 1 with ethylenediamine hydrochloride and formaldehyde, 2,2'-[ethylene bis[iminol(1-oxotrimethylene)]di-1,3-indandione (4) was obtained.

With primary aromatic amines it yielded 2-[N-(substituted phenyl)acetimidoyl]-1,3-indandione (5a-4). The condensation of 1 with o-aminophenol yielded a mixture of 5e and the oxazepinone (6), while condensation with 2,3-diaminopropidine gave the diazepinone (7). Mannich reaction of 5a and 6 with piperidine hydrochloride and formaldehyde gave 8a, b.

The coupling of 1 with diazonium salts was investigated.

Recently, it was reported that 2-aryl-aminomethyl-1,3-indandiones, with anticoagulant and psychopharmacological properties, were prepared by treating 2-alkyl, aryl and aralkyl-1,3-indandiones with formaldehyde and arylamines [1]. Also, it was reported that certain 2-acyl-1,3-indandiones have high anticoagulant activity and were effective rodenticides [2]. For continuing our investigation of the biological activity of 1,3-indandione derivatives [3], we report here the synthesis of some new 2-substituted derivatives by the action of amines on 2-acetyl-1,3-indandione (1).

Thus, upon treatment of 1 with piperidine or diethylamine hydrochloride and paraformaldehyde gave 2-[3-(piperidinopropionyl)-1,3-indandione hydrochloride (2a) and 2-(N,N-diethyl-β-alanyl)-1,3-indandione hydrochloride (3a) respectively. Compounds 2b and 3b were obtained by the action of piperidine or diethylamine hydrochloride and paraformaldehyde (CH2CHO), on 1. On the other hand, reaction of 1 with ethylene diamine hydrochloride and paraformaldehyde in ethanol lead to the formation of 2,2'-[ethylene bis[iminol(1-oxotrimethylene)]di-1,3-indandione hydrochloride (4).

Supporting evidence for the structures of compounds 2 and 3 is provided by elemental analyses and spectral data. The IR spectra show absorptions at (3300 cm-1) enolized CO, (2700–2725 cm-1) tert-NH+, (1725 and 1700 cm-1) cyclic CO and (1590 cm-1) –CH2–CO– [5]. In addition, compound 4 shows absorption at (2800 cm-1) sec. NH2.

To explore the synthetic potentialities of 1 as intermediate for the synthesis of 2-Substituted-1,3-indandiones, the condensation of 1 with aromatic amines was performed. Thus, upon treatment of 1 with aromatic amines in acetic acid, 2-[N-(substituted phenyl)acetimidoyl]-1,3-indandiones (5a–i) were obtained.

The assignment of the [N-(aryl)acetimidoyl] group on the side chain, is based on the IR spectra of these compounds, which shows absorption bands at (1700 cm-1) cyclic CO and (1590 cm-1) C=N, and also by analogy with the previously prepared 2-[N-(o-aminophenyl)acetimidoyl]-1,3-indandione[6]. Condensation of 1 with o-aminophenol, yielded a mixture of two compounds, which were separated by their different solubilities in methanol. The insoluble compound was found to be 11-methyl-12H-benz[b]indeno[2,1-f][1,4]oxazepin-12-one (6), while...
the methanol soluble one, was identified by elemental analysis, IR spectrum and the formation of red colouration with ferric chloride to be 5c. Further, the identity of 6 is established by converting 5c to 6, by treatment with boiling acetic acid.

Based on the evidence that 1 reacts with o-phenylenediamine to give 11-methyl-benz[b]indeno[1,2-e][1,4]diazepin-12(5H)-one [6], 1 was treated with 2,3-diaminopyridine to give 11-methyl-pyrido[b]indeno[1,2-e][1,4]diazepin-10(5H)-one (7). That the condensation has involved the amino group at the 2 position of the pyridine moiety, and the acetyl group, is based on the work of Gurg [7]. The IR spectrum of 7 shows absorption peaks at (3300 cm\(^{-1}\)) NH, (1680 cm\(^{-1}\)) CO and (1590 cm\(^{-1}\)) C=N.

The reactivity of structure 5, which contains a methyl group activated by a \((C=N)\) moiety, towards Mannich reaction with secondary amines, has now been investigated. Thus, when 5a and g were treated with piperidine and formaldehyde, 2-[N-(m-chloro- and m-nitrophenyl)-3-piperidinopropionimido]-1,3-indandione hydrochloride (8a, b) were obtained. Structure 8 was confirmed by elemental analysis and IR spectra, which showed bands at (3200 cm\(^{-1}\)) enolized carboxyl and (2840 and 1470 cm\(^{-1}\)) \(-CH_2-N\) tert. amine [5], in addition to the regular bands of CO and C=N. Furthermore, in the NMR spectrum of 8 the CH_2-N protons appear at (2.8 ppm, s) and the \(-N=C-CH_2-\) protons at (3.2 ppm, s).

Treatment of 1 with diazotised p-nitroaniline and bis(diazotised)benzidine, in basic medium, gave the expected result of a Japp–Klingemann reaction [8]. The acetyl group was cleaved with the formation of indan-1,2,3-trione-2-p-nitrophenylhydrazone (9), and \(2,2'(4,4''-\text{biphenylenedihydrazone})\)bis(indan-1,2,3-trione) (10) respectively. The melting point of 9 and 10 was depressed when mixed with an authentic samples [9, 10]. Similar behaviour has been reported for the reaction of 1-acetyl-2-oxo-4-chloro-5-methoxycumarin with benzene diazonium chloride [11].

Experimental

All melting points are uncorrected. IR spectra were recorded in KBr on a Unicam SP 2000 Infrared Spectrophotometer. NMR spectra were recorded on a Varian Model T-60 NMR spectrometer, in CD_3COOD solution, using TMS as internal standard.

Condensation of 1 with piperidine or diethylamine hydrochloride and paraformaldehyde

2-Acetyl-1,3-indandione (1) (0.01 mole), piperidine or diethylamine hydrochloride (0.01 mole) and paraformaldehyde (1.5 g) in ethanol (50 ml) were refluxed for 30 min, then left to stand overnight. The product obtained on concentration and cooling was crystallized from ethanol, to give 2a and 3a respectively. Compounds 2b and 3b were obtained according to the same procedure, but using paraaldehyde (CH_2-CHO)\(_n\) instead of paraformaldehyde. The results are given in Table I.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M.p. [°C]</th>
<th>Yield [%]</th>
<th>Formula</th>
<th>Carbon [%] found</th>
<th>Carbon [%] calcd</th>
<th>Hydrogen [%] found</th>
<th>Hydrogen [%] calcd</th>
<th>Nitrogen [%] found</th>
<th>Nitrogen [%] calcd</th>
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<tr>
<td>2a</td>
<td>165</td>
<td>58</td>
<td>C_{17}H_{20}NO_3Cl</td>
<td>63.24</td>
<td>63.44</td>
<td>6.20</td>
<td>6.26</td>
<td>4.01</td>
<td>4.35</td>
</tr>
<tr>
<td>3a</td>
<td>88</td>
<td>46</td>
<td>C_{18}H_{20}NO_3Cl</td>
<td>61.92</td>
<td>62.02</td>
<td>6.39</td>
<td>6.50</td>
<td>4.28</td>
<td>4.51</td>
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<tr>
<td>2b</td>
<td>93</td>
<td>42</td>
<td>C_{18}H_{22}NO_3Cl</td>
<td>64.11</td>
<td>64.36</td>
<td>6.48</td>
<td>6.60</td>
<td>4.02</td>
<td>4.16</td>
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<tr>
<td>3b</td>
<td>100</td>
<td>44</td>
<td>C_{18}H_{22}NO_3Cl</td>
<td>62.86</td>
<td>63.04</td>
<td>6.71</td>
<td>6.84</td>
<td>4.11</td>
<td>4.32</td>
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</tbody>
</table>
Table II. 2-N-(substituted phenyl)acetimidoyl-1,3-indandiones (5a-i).

<table>
<thead>
<tr>
<th>Compound</th>
<th>M. p. [°C]</th>
<th>Yield [%]</th>
<th>Formula</th>
<th>Carbon [%] found</th>
<th>Carbon [%] calcd</th>
<th>Hydrogen [%] found</th>
<th>Hydrogen [%] calcd</th>
<th>Nitrogen [%] found</th>
<th>Nitrogen [%] calcd</th>
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<tr>
<td>5a</td>
<td>153</td>
<td>62</td>
<td>C_{17}H_{12}NO_2Cl</td>
<td>68.43</td>
<td>68.57</td>
<td>4.00</td>
<td>4.06</td>
<td>4.57</td>
<td>4.70</td>
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<tr>
<td>5b</td>
<td>196</td>
<td>60</td>
<td>C_{17}H_{12}NO_2Cl</td>
<td>68.48</td>
<td>68.57</td>
<td>5.92</td>
<td>4.06</td>
<td>4.69</td>
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<td>5c</td>
<td>140</td>
<td>44</td>
<td>C_{17}H_{13}NO_3</td>
<td>72.94</td>
<td>73.10</td>
<td>5.42</td>
<td>5.53</td>
<td>5.03</td>
<td>5.12</td>
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<tr>
<td>5d</td>
<td>175</td>
<td>47</td>
<td>C_{18}H_{15}NO_2</td>
<td>77.48</td>
<td>77.63</td>
<td>5.50</td>
<td>5.53</td>
<td>5.07</td>
<td>5.12</td>
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<td>5e</td>
<td>202</td>
<td>50</td>
<td>C_{18}H_{15}NO_2</td>
<td>77.56</td>
<td>77.63</td>
<td>5.50</td>
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<td>5f</td>
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<td>C_{18}H_{15}NO_2</td>
<td>73.15</td>
<td>73.33</td>
<td>5.12</td>
<td>5.22</td>
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<td>66</td>
<td>C_{18}H_{15}NO_2</td>
<td>66.13</td>
<td>66.22</td>
<td>3.88</td>
<td>3.92</td>
<td>9.00</td>
<td>9.08</td>
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<td>229</td>
<td>61</td>
<td>C_{18}H_{15}NO_2</td>
<td>66.17</td>
<td>66.22</td>
<td>3.84</td>
<td>3.92</td>
<td>8.97</td>
<td>9.08</td>
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<tr>
<td>5i</td>
<td>182</td>
<td>64</td>
<td>C_{18}H_{15}NO_3</td>
<td>52.66</td>
<td>52.73</td>
<td>3.57</td>
<td>3.64</td>
<td>3.50</td>
<td>3.61</td>
</tr>
</tbody>
</table>

2,2'-[Ethylene bis(imino(1-oxotrimethylene))] di-1,3-indandione hydrochloride (4)

Compound 4 was synthesised from I (0.02 mole), ethylenediamine hydrochloride (0.01 mole) and paraformaldehyde (2 g) using the experimental procedure described above for the synthesis of 2a.

Compound 4 is orange needles, m. p. 120 °C, yield 41%.

Analysis: C_{26}H_{36}N_{2}O_{4}Cl_{2} (533.40)
Calcd C 58.54 H 4.91 N 5.25,
Found C 58.33 H 4.77 N 5.07.

2-[N-(Substituted phenyl)acetimidoyl]-1,3-indandiones (5a-i)

A mixture of 1 (0.01 mole) and the appropriate primary aromatic amine (0.01 mole) in 30 ml acetic acid, was heated at 80 °C for 30 min. The solid that obtained after cooling or dilution with water, was crystallized from ethanol to give 5a-i in 50-60% yield. The results are given in Table II.

11-Methyl-12H-benz[b]indeno[2,1-j][1,4]oxazepin-12-one (6)

A mixture of 1 (0.01 mole) and o-aminophenol (0.01 mole) in 30 ml acetic acid, was heated at 80 °C for one hour. The reaction mixture gave on cooling dark green solid, which on treatment with methanol gave 6 as insoluble dark green solid. Recrystallization from acetic acid afforded 6; m. p. 238 °C, yield 40%.

Analysis: C_{17}H_{11}NO_2 (261.26)
Calcd C 78.14 H 4.24 N 5.35,
Found C 77.98 H 4.11 N 5.20.

Concentration of the methanol filterate after separation of 6 gave 5c; m. p. 140 °C. Compound 5c was converted into 6 by treatment with boiling acetic acid.

Condensation of 1 with 2,3-diaminopyridine

A solution of 1 (0.01 mole) and 2,3-diaminopyridine (0.01 mole) in 60 ml ethanol containing (2 ml) of formic acid, was refluxed for 6 h. The product obtained on cooling and dilution with water was crystallized from methanol-ammonium hydroxide (5:1).

Compound 7 is a brown powder, m. p. 218 °C, yield 46%.

Analysis: C_{16}H_{12}N_{2}O_{3} (261.27)
Calcd C 73.54 H 4.24 N 16.08,
Found C 73.37 H 4.08 N 16.12.

2-[N-(m-Chloro, and m-nitrophenyl)-3-piperidinopropionimidoyl] -1,3-indandione hydrochloride (8a, b)

Compounds 8a, b were obtained from 5a and g, piperidine hydrochloride and paraformaldehyde, according to the same procedure used above for the synthesis of 2a.

Compound 8a is a white crystals, m. p. 183 °C, yield 42%.

Analysis: C_{23}H_{24}N_{2}O_{2}Cl_2 (431.35)
Calcd C 64.03 H 5.60 N 6.49,
Found C 64.18 H 5.66 N 6.26.

Compound 8b is a yellow crystals, m. p. 203 °C, yield 33%.
Analysis: C\textsubscript{23}H\textsubscript{24}N\textsubscript{3}O\textsubscript{4}Cl (441.94)
Calcd  C 62.50  H 5.47  N 9.50,

**Coupling of 1 with diazonium salts**

Diazotised p-nitroaniline (0.005 mole) or bis-
diazotised benzidine (0.0025 mole), was added with
stirring to a cold solution of 1 (0.005 mole), in
50 ml. 2.5\% aq. NaOH. Sodium acetate (2 g) was
added, and the reaction mixture was left to stand
under cooling overnight. The brown solid obtained
was crystallized from acetic acid to give 9 and 10
respectively in a 70\% yield. The two compounds
were identical in every respect with the correspond-
ing authentic samples prepared from 1,3-indand-
ione [9].

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