Synthesis of 2-Cinnamoyl-1,3-indandione Derivatives and their Reactions with Hydrazine, Hydroxylamine Hydrochloride, Thiourea, Secondary Amines and Diethyl Oxalate

El-Sayed Afsah, Fathy Abdel Kader Amer and Hassan Etman
Chemistry Department, Faculty of Science, Mansoura University, Mansoura, A. R. Egypt
Z. Naturforsch. 34b, 502–506 (1979); received October 25, 1978

2-Cinnamoyl-1,3-indandione Derivatives

A series of 2-cinnamoyl-1,3-indandiones (2a–e) were obtained by condensing 1 with aldehydes. Treatment of 2a with hydrazine or hydroxylamine hydrochloride gave 2-(5-phenyl-2-pyrazolinyl or -isoxazolinyl)-1,3-indandione (3 and 5) respectively, and when treated with thiourea gave 2-(6-phenyl-2-thioxo-4-pyrimidinyl)-1,3-indandione (6). The formation of 2-(β-piperidino-, -morpholino- and -arylmethylthiocinnamoyl)-1,3-indandiones (7a–b and 8a–b) from 2a was investigated. Compound 7b when treated with hydroxylamine gave 2-(5-phenyl-2-isoxazolinyl)-1,3-indandione (6). The formation of 2-(β-morpholinohydrocinnamoyl)-1,3-indandiones (7a–b and 8a–b) was obtained by the action of morpholine on the dibromo derivative (10). The Michael condensation of 2a with ethyl acetoacetate or acetyl acetone was investigated. Treatment of 1 with benzaldehyde in (3:1) molar ratio gave 14, which reacted with diethyl oxalate to give 15. Cyclization of 15 with polyphosphoric acid lead to the formation of 16.

In view of the reported biological activity of 2-aryl-1,3-indandiones in treatment of thrombosis [1–3], as antiinflammatory agents [4], and miticides [5]. 2-Cinnamoyl-1,3-indandiones [6] (2) represent an adaptable starting material for the introduction of heterocyclic moieties in the 2-position of 1,3-indandione, and for the synthesis of some new heterocyclic binary systems, which have demonstrated biological activity in different areas of chemistry.

Therefore, Claisen-Schmidt condensation of 2-acetyl-1,3-indandione (1) with the appropriate aromatic aldehyde gave the corresponding 2-cinnamoyl-1,3-indandiones (2a–e).

Since 1 was reported to react with hydrazine to give 3-methylindeno[1,2-c][pyrazol-4(1H)]-one [7], while α,β-unsaturated ketones react to give pyrazolines [8]. Therefore, in the present study, our first interest was focused on the reaction of 2a with hydrazine to investigate whether this compound react as 1,3-diketone or as α,β-unsaturated ketone.

The condensation of 2a with hydrazine was carried out in a 1:1 molar ratio with elimination of one molecule of water to give 2-(5-phenyl-2-pyrazolin-3-yl)-1,3-indandione (3a).

Confirmatory evidence for structure 3a is provided by elemental analyses and spectral data. The alternative structure 4 was ruled out, because the IR spectrum of 3a show absorptions at 3065 (elevated CO) and 1670 cm⁻¹ (β-diketone), and lack the absorption band of the indene ring carbonyl. Treatment of 3a with acetic anhydride-acetic acid mixture, or benzene sulphonyl chloride in pyridine afforded the N-acetyl and N-benzene sulphonyl derivatives (3b and e).

Similarly, the reaction of 2a with hydroxylamine hydrochloride in pyridine gave 2-(5-phenyl-2-isoxazolin-3-yl)-1,3-indandione (5). On the other hand, condensation between 2a and thiourea in a 1:1 molar ratio afforded 2-(1,2,5,6-tetrahydro-6-phenyl-2-thioxo-4-pyrimidinyl)-1,3-indandione (6). The IR
spectrum of 6 showed bands assigned to NH (3448 cm\(^{-1}\)), enolized CO (3070 cm\(^{-1}\)), \(\beta\)-diketone (1670 cm\(^{-1}\)), C=N (1615 cm\(^{-1}\)), C=S (1340 cm\(^{-1}\)) and N–C=S (1535 cm\(^{-1}\)).

The additive property of the conjugated (C=C) in 2a; prompted us to investigate its behaviour towards the action of secondary amines. Thus, treatment of 2a with piperidine and/or morpholine, afforded 2-(\(\beta\)-piperidino-or-\(\beta\)-morpholinohydrocinnamoyl)-1,3-indandione (7a–b), respectively. The IR spectra of 7 showed absorptions at 3060 and 1675 cm\(^{-1}\) enolized CO and \(\beta\)-diketone and at 1570 cm\(^{-1}\) (\(\beta\)-nitrogen). Similarly, condensation of 2a with thiophenol or p-thiocresol gave the corresponding 2-(\(\beta\)-arylmercaptohydrocinnamoyl)-1,3-indandione (8a–b).

Treatment of 7b with hydrazine in boiling methanol, afforded 3-(\(\beta\)-morpholinophenethyl)-indenol[1,2-c]pyrazol-4(1H)-one (9). The structure of 9 was assigned from its correct analytical data and the exhibition of CO stretching at 1695 cm\(^{-1}\) and NH stretching at 3400 cm\(^{-1}\).

Addition of bromine in carbon tetrachloride to 2a yields 2-(\(\alpha,\beta\)-dibromohydrocinnamoyl)-1,3-indandione (10). Its IR spectrum showed bands at 3065 cm\(^{-1}\) (enolized CO), 1665 cm\(^{-1}\) (\(\beta\)-diketone) and 695 cm\(^{-1}\) (C–Br).

In view of the reported reaction of dibromoalchones with morpholine to give \(\alpha,\beta\)-dimorpholinohydrocinnamoyl-1,3-indandione derivatives [9, 10]. The dibromo-derivative 10 was treated with morpholine to give 2-(\(\alpha,\beta\)-dimorpholinohydrocinnamoyl)-1,3-indandione (11).

In order to explore the synthetic potentialities of compounds 2 as intermediates for the preparation of 2-substituted-1,3-indandiones, the Michael condensation of 2a was performed. Thus, ethyl acetoacetate or acetyl acetone was condensed with 2a in boiling butanol using piperidine as catalyst to give 2-(4-ethoxycarbonyl- or 4-acetyl-3-oxo-5-phenyl-1-cyclohexen-1-yl)-1,3-indandione (12a–b), respectively. The structures of compounds 12 are based on elemental analyses and IR spectra. Furthermore, hydrolysis and decarboxylation of 12a gave 2-(3-oxo-5-phenyl-1-cyclohexen-1-yl)-1,3-indandione (13). Structure of 13 was confirmed through independent synthesis, by condensation of benzylideneacetone with 1.

On the other hand, condensation of 1 with benzaldehyde in 3:1 molar ratio, lead to the formation of 2,2’-(3-phenylglutaryl)di-1,3-indandione (14). The IR spectrum of 14 indicated bands characteristic of the enolized CO at (3050 cm\(^{-1}\)), (1675 cm\(^{-1}\)) \(\beta\)-diketone and (1430 cm\(^{-1}\)) -CH\(_2\)-CO-. [11]. In particular, the formation of 14 is confirmed through independent synthesis, by condensation of 2a with 1.
In view of the reported formation of 3,5-diethoxy-carbonyl-4-phenylcyclopentane-1,2-dione, by Dieckmann condensation of diethyl oxalate and diethyl β-phenylglutarate [12], compound 14 was condensed with diethyl oxalate in presence of sodium ethoxide to give 2,2'-(4,5-dioxo-2-phenyl-1,3-cyclopentylene)dicarbonyl[di-1,3-indandione (15). Structure 15 was inferred from the correct analytical data, and its IR spectrum which shows absorption bands at (1730 cm⁻¹) 1,2-diketone (five-ring), 1670 cm⁻¹ β-diketone and the disappearance of the -CH₂-CO- band. Compound 15 underwent cyclization on treatment with polyphosphoric acid to give 13-phenylnH-diindeno[2,1-e:2',1'-e']cyclopenta[2,1-b:3,4-b']dipyran-11,12,14,15(13H)tetrone (16). Structure 16 was assigned from its correct analytical data and the exhibition of indene CO at 1705 cm⁻¹ and the pyrone CO at 1660 cm⁻¹.

**Experimental**

All melting points are uncorrected. IR spectra were recorded in KBr on a Unicam SP 2000 Infrared Spectrophotometer.

2-Cinnamoyl-1,3-indandiones (2)

Few drops of piperidine were added to a mixture of 1 (0.02 mol), and the appropriate aldehyde (0.02 mol), in 50 ml n-butanol. After refluxing for 6 h, product 2 that separated on cooling was crystallized from benzene-ethanol, in 50–60% yield. The results are given in Table I.

**2-(5-Phenyl-2-pyrazolin-3-yl)-1,3-indandione (3a)**

To a solution of 2a (0.005 mol) in 60 ml benzene-ethanol (1:1), hydrazine (98%) (0.005 mol) was added. The reaction mixture was refluxed for 6 h. The product obtained after concentration and cooling was filtered and reccrystallized from ethanol. Compound 3a formed yellow crystals; m.p. 215 °C; yield 82%.

**C₁₈H₁₄N₂O₂**  
Found C 74.22 H 4.80 N 9.43,  
Calcd C 74.46 H 4.86 N 9.65.

Compound 3b was obtained by heating 3a (0.5 g) in 30 ml acetic acid-acetic anhydride (1:1) for 1 h. The product obtained on dilution with water was crystallized from methanol. Compound 3b formed orange powder; m.p. 263 °C dec.; yield 76%.

**C₂₀H₁₆N₂O₃**  
Found C 84.27 H 5.50 N 9.66,  
Calcd C 84.47 H 5.67 N 9.85.

Compound 3c was obtained by adding benzene-sulphonyl chloride (0.5 ml) to a solution of 3a (0.4 ml) in pyridine (30 ml). After refluxing for 1 h, the reaction mixture was diluted with water. The product obtained was crystallized from methanol. Compound 3c formed orange powder; m.p. 280°C dec.; yield 68%.

**Table I. 2-Cinnamoyl-1,3-indandiones (2a–e).**

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Formula</th>
<th>Carbon [%] Found</th>
<th>Caled</th>
<th>Hydrogen [%] Found</th>
<th>Caled</th>
<th>Nitrogen [%] Found</th>
<th>Caled</th>
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<tbody>
<tr>
<td>2a</td>
<td>182</td>
<td>50</td>
<td>C₁₈H₁₂O₃</td>
<td>78.13</td>
<td>78.24</td>
<td>4.18</td>
<td>4.37</td>
<td>71.39</td>
<td>71.41</td>
</tr>
<tr>
<td>2b</td>
<td>180</td>
<td>55</td>
<td>C₁₉H₁₄O₄</td>
<td>74.23</td>
<td>74.49</td>
<td>4.46</td>
<td>4.60</td>
<td>75.11</td>
<td>75.21</td>
</tr>
<tr>
<td>2c</td>
<td>142</td>
<td>57</td>
<td>C₂₀H₁₆O₅</td>
<td>71.39</td>
<td>71.41</td>
<td>4.66</td>
<td>4.79</td>
<td>75.11</td>
<td>75.21</td>
</tr>
<tr>
<td>2d</td>
<td>186</td>
<td>51</td>
<td>C₂₀H₁₇NO₃</td>
<td>75.11</td>
<td>75.21</td>
<td>5.13</td>
<td>5.36</td>
<td>4.16</td>
<td>4.38</td>
</tr>
<tr>
<td>2e</td>
<td>246</td>
<td>62</td>
<td>C₁₈H₁₁NO₅</td>
<td>67.20</td>
<td>67.28</td>
<td>3.31</td>
<td>3.45</td>
<td>4.08</td>
<td>4.35</td>
</tr>
</tbody>
</table>
C_{24}H_{18}N_{2}O_{4}S  
Found C 66.78 H 4.08 N 6.30 S 7.27,  
Caled C 66.96 H 4.21 N 6.50 S 7.44.

2-(5-Phenyl-2-isoxazolin-3-yl)-1,3-indandione (5)  
To a solution of 2a (0.005 mol) in 50 ml pyridine,  
hydroxylamine hydrochloride (0.005 mol) was  
added. After refluxing for 6 h, the reaction mixture  
was diluted with water. The product obtained was  
crystallized from ethanol.  
Compound 5 formed orange crystals; m.p. 184 °C  
dec.; yield 78%.

C_{18}H_{13}NO_{3}  
Found C 74.06 H 4.33 N 4.67,  
Caled C 74.21 H 4.49 N 4.80.

2-(1,2,5,6-Tetrahydro-6-phenyl-2-thioxo-4-pyrimidinyl)-1,3-indandione (6)  
A mixture of 2a (0.005 mol), thiourea (0.005 mol);  
potassium hydroxide (0.5 g), ethanol (100 ml) and  
water (2 ml) was refluxed for 3 h. The product  
formed on concentration and cooling was filtered,  
washed with water, dried and crystallized from  
ethanol.  
Compound 6 formed yellow crystals; m.p. >300 °C; yield 41%.

C_{19}H_{14}N_{2}O_{2}S  
Found C 68.07 H 4.13 N 8.11 S 9.34,  
Caled C 68.24 H 4.21 N 8.37 S 9.58.

2-(ß-Piperidino- or ß-morpholino-hydrocinnamoyl)-1,3-indandione (7)  
A solution of 2a (0.005 mol) and piperidine or  
morpholine (0.005 mol) in 50 ml dry benzene stirred  
and heated at 60 °C for 30 min. The reaction  
mixture was allowed to stand overnight at room  
temperature. Light petrol (b.p. 40-60 °C) was  
added, and the precipitated solid was filtered and  
crystallized from benzene-ethanol.  
Compound 7a formed yellow needles; m.p. 185 °C; yield 47%.

C_{23}H_{23}NO_{3}  
Found C 76.22 H 6.27 N 3.67,  
Caled C 76.43 H 6.41 N 3.87.

Compound 7b formed yellow powder; m.p. 190 °C; yield 53%.

C_{22}H_{19}NO_{3}  
Found C 72.48 H 5.67 N 3.70,  
Caled C 72.70 H 5.82 N 3.85.

2-(ß-Arylmercaptohydrocinnamoyl)-1,3-indandione (8)  
To a solution of 2a (0.005 mol) in 50 ml dry  
benzene was added (0.005 mol) of thiophenol or  
p-thiocresol, followed by 2 drops of piperidine. The  
reaction mixture was heated at 60 °C for 30 min,  
and allowed to stand overnight at room temperature.  
Light petrol (b.p. 40-60 °C) was added, and  
the solid that separated was filtered and crystallized  
from methanol.  
Compound 8a formed pale yellow crystals; m.p.  
195 °C.

C_{24}H_{18}O_{3}S  
Found C 74.33 H 4.58 S 8.02,  
Caled C 74.58 H 4.69 S 8.29.

Compound 8b formed yellow crystals; m.p. 110 °C.

C_{25}H_{20}O_{3}S  
Found C 74.90 H 4.88 S 7.83,  
Caled C 74.97 H 4.93 S 8.00.

3-(ß-Morpholinophenethyl)indenol[1,2-c]-pyrazol-4(1H)-one (9)  
The experimental procedure described for the  
synthesis of 3a was adopted. Compound 9 was  
formed in 67% yield.  
Compound 9 formed yellow needles; m.p. 178 °C.

C_{22}H_{21}N_{3}O  
Found C 76.71 H 5.97 N 12.06,  
Caled C 76.94 H 6.16 N 12.23.

2-(a,ß-Dibromohydrocinnamoyl)-1,3-indandione (10)  
Compound 10 was obtained by adding bromine  
(0.005 mol) to a solution of 2a (0.005 mol) in carbon  
tetrachloride 60 ml. The solid obtained on concentra- 
tion and cooling was filtered and crystallized from  
ethanol.  
Compound 10 formed pale yellow needles; m.p.  
160 °C; yield 85%.

C_{18}H_{12}O_{3}Br_{3}  
Found C 49.43 H 2.48 Br 36.55,  
Caled C 49.57 H 2.77 Br 36.64.

Condensation of 2a with ethylacetoacetate and acetyl  
acetone  
A solution of 2a (0.005 mol), ethylacetoacetate or  
acetyl acetone (0.005 mol), in 50 ml n-butanol,  
containing one ml piperidine, was refluxed for 8 h. The  
reaction mixture was added to dilute hydrochloric acid, the product so formed was filtered and  
crystallized from benzene ethanol.  
Compound 12a formed dark yellow crystals; m.p.  
80 °C dec.; yield 52%.
C_{24}H_{20}O_{5}

Found C 74.19 H 5.01,
Calcd C 74.21 H 5.19.

Compound 12b formed yellow crystals; m.p. 240 °C; yield 61%.

C_{23}H_{18}O_{4}

Found C 76.90 H 4.88,
Calcd C 77.07 H 5.06.

2-(3-Oxo-5-phenyl-1-cyclohexen-1-yl)-1,3-indandione (13)

Compound 13 was obtained from 12a in 46% yield, by hydrolysis with hot 5% aqueous sodium hydroxide, followed by decarboxylation with boiling dilute hydrochloric acid.

The same compound was also obtained by Michael condensation of an equimolar mixture of benzylideneacetone and 1. The experimental procedure described for the synthesis of 2 was adopted; yield 49%.

Compound 13 formed yellow crystals; m.p. 232 °C (benzene).

C_{21}H_{16}O_{3}

Found C 79.58 H 5.00,
Calcd C 79.72 H 5.09.

2,2'-(3-Phenylglutaryl)di-1,3-indandione (14)

To a solution of 1 (0.03 mol) and benzaldehyde (0.01 mol) in 80 ml n-butanol, piperidine one ml was added. The reaction mixture was refluxed for 20 h.

The product that obtained after concentration was crystallized from benzene-ethanol.

Compound 14 formed yellow powder; m.p. >300 °C; yield 73%.

C_{29}H_{20}O_{6}

Found C 74.78 H 4.11,
Calcd C 74.98 H 4.34.

The same compound was also obtained in a 46% yield, by the condensation of an equimolar mixture of 2a and 1, according to a procedure similar to the above one.

2,2'-(4,5-Dioxo-2-phenyl-1,3-cyclopentylene)-dicarbonyl/di-1,3-indandione (15)

To a sodium ethoxide solution (prepared from 0.2 g of sodium metal and 60 ml of ethanol) was added (0.0025 mol) of diethyl oxalate and (0.002 mol) of 14. The reaction mixture was stirred for 2 h, then refluxed for 6 h. The product that obtained after dilution with water and neutralization was filtered, and crystallized from benzene-ethanol.

Compound 15 formed yellow crystals; m.p. 210 °C; yield 55%.

C_{31}H_{18}O_{8}

Found C 71.65 H 3.33,
Calcd C 71.81 H 3.49.

Cyclization of 15 with polyphosphoric acid

A mixture of 15 (1 g) and polyphosphoric acid (10 g) was heated for 1 h at 110 °C. The reaction mixture was diluted with 100 ml water, and the solid obtained was filtered, and crystallized from benzene-ethanol.

Compound 16 formed orange powder; m.p. 170 °C; yield 68%.

C_{31}H_{14}O_{6}

Found C 77.02 H 2.81,
Calcd C 77.17 H 2.92.