Study of the Reactivity of 2-Cinnamoylbenzimidazole towards Thiourea, Urea, Hydrazines and Hydroxylamine Hydrochloride

H. H. Zoorob, H. A. Hammouda, and E. Ismail
Faculty of Science, Mansoura University; Faculty of Science, Cairo University; National Research Centre, Cairo, Egypt
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Pyrimidone, Pyrimidinethione, Pyrazoline, Isoxazoline, Pyrrolo[1,2-a]benzimidazole

The reactivity of heterocyclic a,β-unsaturated ketones towards the title compounds has been studied. A pyrimidine, pyrazoline, isoxazoline and a fused pyrrolidine rings have been built up. Mannich reaction was tried with the pyrazoline derivative (4d). Bromination of the 2-cinnamoyl compounds (1a-e), and cyclization of the products were also undertaken.

Considerable attention has been devoted to 2-benzimidazole derivatives as chemotherapeutic compound 1-7 and in connection with their possible pharmaceutical activity 3-4. Accordingly, it was of interest to synthesize new series of heterocyclic compounds, structurally including the benzimidazole moiety as well as another heterocycle like pyrimidine (and its thione analogue), pyrazoline, isoxazoline or pyrrolidine.

a,β-Unsaturated ketones provide a valuable mediate for building up various heterocycles. A series of 2-cinnamoylbenzimidazoles (1a-f) are used here for this purpose 5-6.

\[ \text{CO}-\text{CH}==\text{CH}-\text{Ar} \]

\( \text{a) } \text{Ar} = \text{C}_6\text{H}_5, \\
\text{b) } \text{Ar} = \text{C}_6\text{H}_4\text{OCH}_3-p, \\
\text{c) } \text{Ar} = \text{C}_6\text{H}_4\text{N(CH}_3)_2-p, \\
\text{d) } \text{Ar} = \text{C}_6\text{H}_4\text{OH}-o, \\
\text{e) } \text{Ar} = \text{C}_6\text{H}_3(\text{Cl})(\text{NO}_2)-2,4, \\
\text{f) } \text{Ar} = 2\text{-thienyl}. \)

As reported before 5, 2-cinnamoylbenzimidazole (1) reacts with thiourea to give 5,6-dihydro-4-(2-benzimidazolyl)-6-phenyl-2(1H)-pyrimidinethione (2a). Similarly, 1b-e reacted with thiourea in boiling alcoholic potassium hydroxide to give the pyrimidinethiones (2b-e), respectively.

The IR spectra of 2b-e showed absorption bands at 1310-1290 cm\(^{-1}\) assigned to the C=S group. The NMR spectrum (TFA) of 2 showed signals at \( \delta \) 3.9 ppm (s, 3, OCH\(_3\)), \( \delta \) 6.60 ppm (d, 4, pyrimidine ring protons) and \( \delta \) 7.00-7.78 ppm (m, 8, aromatic protons).

The analogous pyrimidones (3a-e) were respectively obtained by the reaction of 1a-e with urea in boiling ethanolic hydrogen chloride.

The IR spectrum of 3a showed bands assigned to NH (3210 cm\(^{-1}\)), C=O (1665 cm\(^{-1}\)) and C=N (1520 cm\(^{-1}\)).

The condensation of hydrazine hydrate with 1a-d in boiling ethanol yielded the unstable yellow pyrazoline derivatives, 3-(2-benzimidazolyl)-5-aryl-2-pyrazolines (4a-d).

As reported before 5, 2-cinnamoylbenzimidazole (1) reacts with thiourea to give 5,6-dihydro-4-(2-benzimidazolyl)-6-phenyl-2(1H)-pyrimidinethione (2a). Similarly, 1b-e reacted with thiourea in boiling alcoholic potassium hydroxide to give the pyrimidinethiones (2b-e), respectively.

Requests for reprints should be sent to Dr. H. H. Zoorob, Faculty of Science, Mansoura University, Chemistry Department, Mansoura, Egypt.
However, the rather stable N-acetyl derivatives (5a-d) were obtained when the reaction was carried out in boiling acetic acid.

The structure of 5a-d was confirmed by their independent synthesis. Thus on refluxing 4a-d in acetic anhydride for three hours, the colourless N-acetyl compounds 5a-d were obtained.

The IR spectrum of 5a showed absorption bands at 1650 cm⁻¹ (amide C=O) and at 1600 cm⁻¹ (C=N). Furthermore, the condensation of 1a-f with phenylhydrazine produced the corresponding N-phenylpyrazoline derivatives (6a-f), respectively.

\[ \text{N-acetylation} \]

\[ \text{Condensation with phenylhydrazine} \]

The analytical and spectral data favour the assignment of structure 6 to these products. Thus the IR spectrum of 6d exhibits bands attributable to OH (3450 cm⁻¹) and C=N (1620 cm⁻¹). The NMR spectrum (TFA) of 6c shows the following signals at δ 2.49 (for the \(-\text{N(CH}_3\text{)}_2\) group protons, singlet), δ 4.90 (methylene group protons, singlet), δ 7.00-8.40 (aromatic protons, multiplet) and δ 8.90 ppm (NH proton, singlet).

Compounds 4a, 5a and 6a, when exposed to bromine vapour, turned green conforming thus to the RAIFORD and PATerson test for pyrazolines.7

Apparently the formation of the pyrazoline ring in compounds 4-6 required initial formation of a hydrazone followed by the addition of this hydrazone to the ethylenic linkage. This is in accord with the formation of pyrazolines from vinylketones.8

The NH of the pyrazoline ring in 4 proved to be the active centre towards Mannich reaction. Thus, when a methanolic solution of 4d was treated with aqueous formaldehyde and morpholine the crystalline N-Mannich base, 1-morpholinomethyl-3-(2-benzimidazolyl)-5-(o-phenolyl)-2-pyrazoline (7) was obtained.

Assignment of structure 7 to the Mannich base is inferred from the correct analytical data for C₂₁H₂₉N₂O₂ and from its IR spectrum which shows a broad absorption band at 3500-3110 cm⁻¹ due to both OH and NH, and another band at 1640 cm⁻¹ due to C=N.

N-Alkylation took place also at the pyrazoline ring. Treatment of a methanolic solution of 4d with 2-diethylaminoethyl chloride gives a white precipitate of 1-(2-diethylaminoethyl)-3-(2-benzimidazolyl)-5-(o-phenolyl)-2-pyrazoline (8).

The formation of an isoxazoline ring could be effected by the reaction of 1 with hydroxylamine. When 1a, b, d, e were boiled with hydroxylamine hydrochloride in alcoholic sodium hydroxide solution, the corresponding isoxazolines, 3-(2-benzimidazolyl)-5-aryl-2-isoxazolines (9a-d) were obtained.

In view of the fact that halogens confer fungicidal activity, bromination of the 2-cinnamoylbenzimidazoles (1) was attempted. Thus, 1a-c were treated with bromine in carbon tetrachloride, where addition took place at the olefinic linkage, to give the dibromides (10a-c).

Attempted recrystallization of these dibromides from methanol or acetic acid effected cyclization to give the pyrrolo[1,2-a]benzimidazoles (11a-c). The structure assigned for 11 are inferred from their IR spectra which have no absorption bands characteristic for the NH group.
Experimental

All melting points are uncorrected and were taken in a Gallenkamp electric melting point apparatus and Boetius melting point microscope. The IR spectra were performed on a Carl Zeiss Infracord spectrophotometer model “UR 10” using KBr. The NMR spectra were obtained in deuterotrifluoroacetic acid solution with a Varian Associates model “A-60” spectrometer.

Reaction of 1b-e with thiourea

The same procedure described for the preparation of 2a⁵ was followed and the products 2b-e are listed in Table I.

Reaction of 1a-e with urea

To a mixture of urea (2 g; 0.033 mole) and ethanol (20 ml) was added enough hydrochloric acid to get a clear solution. 0.02 mole of 1a-e was then added and the mixture refluxed on a steam bath for 8 hours.

The reaction mixture was then concentrated, cooled and made alkaline with ammonium hydroxide. The product was filtered off and crystallized from the proper solvent to give 3a-e (Table I).

Table I. Products from the reaction of 1 with thiourea and urea.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Solvent of crystals</th>
<th>Formula</th>
<th>Carbon Analysis [%]</th>
<th>Hydrogen</th>
<th>Nitrogen</th>
<th>Sulphur</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>260</td>
<td>64</td>
<td>AcOH</td>
<td>C₁₃H₁₆N₄O₅</td>
<td>64.25</td>
<td>4.78</td>
<td>4.87</td>
<td>16.66</td>
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<tr>
<td>2c</td>
<td>235</td>
<td>76</td>
<td>Methanol-water</td>
<td>C₁₉H₁₉N₅S</td>
<td>65.30</td>
<td>5.48</td>
<td>5.60</td>
<td>20.05</td>
</tr>
<tr>
<td>2d</td>
<td>230</td>
<td>80</td>
<td>AcOH</td>
<td>C₁₇H₁₄N₅O₅</td>
<td>63.33</td>
<td>4.38</td>
<td>4.24</td>
<td>17.38</td>
</tr>
<tr>
<td>2e</td>
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<td>63</td>
<td>AcOH</td>
<td>C₁₇H₁₂Cl₅N₅O₅*</td>
<td>52.92</td>
<td>3.14</td>
<td>3.10</td>
<td>18.16</td>
</tr>
<tr>
<td>3a</td>
<td>240</td>
<td>79</td>
<td>Ethylene chloride</td>
<td>C₁₇H₁₉N₅O₇</td>
<td>70.32</td>
<td>4.86</td>
<td>4.90</td>
<td>19.30</td>
</tr>
<tr>
<td>3b</td>
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<td>74</td>
<td>AcOH</td>
<td>C₁₈H₂₀N₅O₂</td>
<td>67.48</td>
<td>5.94</td>
<td>4.80</td>
<td>17.49</td>
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<tr>
<td>3c</td>
<td>185</td>
<td>72</td>
<td>Benzene</td>
<td>C₁₉H₁₈N₅O₂</td>
<td>68.44</td>
<td>5.74</td>
<td>5.94</td>
<td>21.01</td>
</tr>
<tr>
<td>3d</td>
<td>245</td>
<td>65</td>
<td>AcOH</td>
<td>C₁₇H₁₉N₅O₂</td>
<td>66.65</td>
<td>4.61</td>
<td>4.50</td>
<td>18.29</td>
</tr>
<tr>
<td>3e</td>
<td>248</td>
<td>81</td>
<td>AcOH</td>
<td>C₁₇H₁₂Cl₅N₅O₂**</td>
<td>55.22</td>
<td>3.27</td>
<td>3.19</td>
<td>18.94</td>
</tr>
</tbody>
</table>

* Cl: Calcd 9.19, Found 9.11%.
** Cl: Calcd 8.48, Found 8.40%.

Table II. Condensation products of 1 with hydrazine hydrate and phenylhydrazine.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Solvent of crystals</th>
<th>Formula</th>
<th>Carbon Analysis [%]</th>
<th>Hydrogen</th>
<th>Nitrogen</th>
<th>Sulphur</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>248</td>
<td>70</td>
<td>Ethylene chloride</td>
<td>C₁₈H₁₅N₄O₄</td>
<td>71.03</td>
<td>5.50</td>
<td>5.21</td>
<td>18.41</td>
</tr>
<tr>
<td>5b</td>
<td>254</td>
<td>67</td>
<td>Ethylene chloride</td>
<td>C₁₉H₁₆N₅O₅</td>
<td>68.24</td>
<td>5.43</td>
<td>5.61</td>
<td>16.76</td>
</tr>
<tr>
<td>5c</td>
<td>350</td>
<td>75</td>
<td>AcOH</td>
<td>C₂₀H₂₁N₅O₅</td>
<td>69.14</td>
<td>6.09</td>
<td>5.90</td>
<td>20.16</td>
</tr>
<tr>
<td>5d</td>
<td>317</td>
<td>80</td>
<td>AcOH</td>
<td>C₁₉H₁₆N₅O₄</td>
<td>67.48</td>
<td>5.04</td>
<td>5.17</td>
<td>17.49</td>
</tr>
<tr>
<td>6a</td>
<td>268</td>
<td>74</td>
<td>AcOH</td>
<td>C₂₂H₂₃N₅O₅</td>
<td>78.07</td>
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<td>5.17</td>
<td>16.56</td>
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<td>6b</td>
<td>263</td>
<td>71</td>
<td>Cyclohexane</td>
<td>C₂₂H₂₃N₅O₅</td>
<td>74.87</td>
<td>5.47</td>
<td>5.30</td>
<td>15.21</td>
</tr>
<tr>
<td>6c</td>
<td>273</td>
<td>81</td>
<td>AcOH</td>
<td>C₂₂H₂₃N₅O₅</td>
<td>75.56</td>
<td>6.08</td>
<td>5.85</td>
<td>18.36</td>
</tr>
<tr>
<td>6d</td>
<td>275</td>
<td>71</td>
<td>AcOH</td>
<td>C₂₂H₂₃N₅O₅</td>
<td>74.55</td>
<td>5.12</td>
<td>5.10</td>
<td>15.81</td>
</tr>
<tr>
<td>6e</td>
<td>255</td>
<td>77</td>
<td>Ethylene chloride</td>
<td>C₂₂H₁₈Cl₅N₅O₅*</td>
<td>63.23</td>
<td>3.86</td>
<td>3.75</td>
<td>16.76</td>
</tr>
<tr>
<td>6f</td>
<td>227</td>
<td>78</td>
<td>Ethanol-water</td>
<td>C₂₂H₁₈N₄O₄**</td>
<td>69.74</td>
<td>4.68</td>
<td>4.45</td>
<td>16.27</td>
</tr>
</tbody>
</table>

* Cl: Calcd 8.48, Found 8.40%.
** S: Calcd 9.31, Found 9.27%.
Condensation of 1a-d with phenylhydrazine

**General procedure:**

A mixture of 0.005 mole of 1a-d, phenylhydrazine (0.005 mole) and 15 ml of acetic acid was refluxed for 8 hours. The yellow crystalline product separated after cooling was filtered off and recrystallized from the proper solvent (Table II).

**Mannich reaction with 4d**

To 1.4 g (0.005 mole) of 4d in 10 ml of methanol was added 1.5 ml of 35% aqueous formaldehyde solution followed by 0.85 g (0.01 mole) of morpholine. The mixture was boiled on a steam bath for 5 hours and then kept overnight at room temperature. The precipitated solid was collected and crystallized from dilute ethanol to give 7, m.p. 270 °C; 75% yield.

Analysis: C27H25ClN7O2
Calcd C 69.99 H 7.21 N 18.55
Found C 70.32 H 7.02 N 18.22.

**Reaction of 4d with 2-diethylaminoethyl chloride**

A mixture of 4d (2.8 g; 0.01 mole) and 2-diethylaminoethyl chloride (1.7 g; 0.01 mole) was refluxed with a solution of 1.6 g of bromine in 20 ml of carbon tetrachloride and the mixture was left overnight. The product was filtered off and washed with methanol to give the crude dibromides 10a-c.

**Reaction of 1a, b, d, e with hydroxylamine**

**General procedure:**

A mixture of 1a, b, d, e (0.01 mole), hydroxylamine hydrochloride (0.7 g; 0.01 mole), sodium hydroxide (1 g) and ethanol (30 ml) was refluxed for 3 hours. The solid which separated on cooling was filtered off and crystallized from the proper solvent to give 9a-d (Table III).

2-(3-Aryl-2,3-dibromopropanoyl)benzimidazoles (10a-c)

**General procedure:**

A solution of 0.01 mole of 1a-c in 60 ml of carbon tetrachloride was treated portionwise while shaking, with a solution of 1.6 g of bromine in 20 ml of carbon tetrachloride and the mixture was left overnight. The product was filtered off and washed with methanol to give the crude dibromides 10a-c.

1-Aryl-2-bromo-2,3-dihydro-1H-pyrrolo[1,2-a]-benzimidazol-3-ones (11a-c)

Recrystallization of the dibromides 10a-c from acetic acid gave 11a-c, respectively, in ca. 85% yields.

11a was crystallized from ethylene chloride, m.p. 195 °C.

Analysis: C16H11BrN2O
Calcd C 58.73 H 3.39 Br 24.42 N 8.56
Found C 59.05 H 3.39 Br 24.72 N 8.71.

11b was crystallized from methanol, m.p. 250 °C.

Analysis: C17H13BrN2O2
Calcd Br 22.37 N 7.84,
Found Br 22.59 N 8.10.

11c was crystallized from ethanol, m.p. 252 °C.

Analysis: C18H16BrN3O
Calcd Br 22.59 N 11.35,
Found Br 22.81 N 11.39.

### Table III. Reaction of 1 with hydroxylamine.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Solvent of crystals</th>
<th>Formula</th>
<th>Carbon</th>
<th>Hydrogen</th>
<th>Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>248</td>
<td>71</td>
<td>Ethylene chloride</td>
<td>C16H12N2O</td>
<td>72.98</td>
<td>4.98</td>
<td>15.96</td>
</tr>
<tr>
<td>9b</td>
<td>245</td>
<td>69</td>
<td>Cyclohexane</td>
<td>C17H14N2O2</td>
<td>69.61</td>
<td>5.15</td>
<td>13.33</td>
</tr>
<tr>
<td>9c</td>
<td>233</td>
<td>61</td>
<td>Ethylene chloride</td>
<td>C16H12N2O2</td>
<td>68.80</td>
<td>4.49</td>
<td>15.05</td>
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<tr>
<td>9d</td>
<td>305</td>
<td>68</td>
<td>Butanol</td>
<td>C18H11ClN4O2*</td>
<td>36.07</td>
<td>3.23</td>
<td>16.35</td>
</tr>
</tbody>
</table>

* CI: Calcd 13.43, Found 13.31%.

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2 R. C. Clapp and R. O. Roblin (Jr.) (to American Cyanamid Company); U.S. Pat. 2,418,925; C. A. 42, 619 [1948].
4 J. P. Skilеr and H. Limachеr, Chimia 27 (2), 68 [1973]; C. A. 78, 136171z [1972].