Reactions with 2-Acylbenzimidazole  
Preparation of 2-Cinnamoylbenzimidazoles, their Reactions towards  
Grignard Reagents and Thiourea  

MOHAMED I. ALI, ABD-ELSAMIEI M. ABD-ELFATTAH, and HAMDY A. HAMMOUNDA  
Chemistry Department, Faculty of Science, Cairo University, Egypt  
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2-Acylbenzimidazole, 2-Cinnamoylbenzimidazoles, Grignard Reagents, Benimidazolylpyrimidine  

2-Acetylbenzimidazole condensed with aldehydes to afford the 2-cinnamoyl derivatives (1a–e). Whereas 2-acetyl- and 2-benzoylbenzimidazole added Grignard reagents at the carbonyl group, the 2-cinnamoyl derivatives (1a, b) suffered addition at the olefinic double bond to give 2a, b. Condensation of amines with 2-acetyl and 2-benzoylbenzimidazole yielded the imino compounds (4a–e). 1a reacted with thiourea to furnish the pyrimidine (5).  

The presence of a benzimidazole moiety in various biologically active drugs led us as many other investigators1–6 to synthesize and study the properties of new benzimidazole derivatives.  

2-Acetylbenzimidazole7 condensed with aromatic aldehydes in boiling ethanol in the presence of fused sodium acetate to give 2-cinnamoylbenzimidazoles (1a–e).  

\[
\text{a) } \text{Ar} = \text{C}_6\text{H}_5, \\
\text{b) } \text{Ar} = \text{C}_6\text{H}_4\text{OCH}_3-\text{p}, \\
\text{c) } \text{Ar} = \text{C}_6\text{H}_4\text{Cl}-\text{p}, \\
\text{d) } \text{Ar} = \text{C}_6\text{H}_4\text{NO}_2-\text{p}, \\
\text{e) } \text{Ar} = \text{C}_6\text{H}_4\text{N}-(\text{CH}_3)_2-\text{p}. 
\]

The IR spectrum of 1a shows NH absorption at 3320 cm\(^{-1}\) and CO absorption at 1695 cm\(^{-1}\), with almost no significant shift from the CO absorption of the acetyl compound (1685 cm\(^{-1}\)).  

The absorption of the cinnamoyl carbonyl at an apparent high wave number may be attributed to that the acetyl compound exhibits a higher degree of intramolecular hydrogen bonding.  

The addition of Grignard reagents to the cinnamoyl derivatives (1a, b) afforded the 2-(3,3-diarylp propane)benzimidazoles (2a, b).  

The structures assigned to the products (2a, b) were based on the following facts:  

a) Unlike the cinnamoyl derivatives, these products are colourless, and they give the correct analytical values,  

b) the absence of an OH group and the presence of a carbonyl group as revealed from the IR spectrum of 2a, taken as example, \(\delta\text{CO}; 1695\text{cm}^{-1}\),  

c) the formation of the same product 2b either from \(p\)-methoxyphenylmagnesium bromide and 1a, or from phenylmagnesium bromide and 1b.  

This conforms with the conjugate addition of Grignard reagents cited in literature9,10.  

On the other hand, Grignard reagents added to the carbonyl group in 2-acetylenylbenzimidazole and 2-benzoylbenzimidazole11 with the formation of the carbinols (3a–e).  

Requests for reprints should be sent to Dr. H. A. HAMMOUNDA, Chemistry Department, Faculty of Science, Cairo University, Giza, A.R. Egypt.
The IR spectra of 3\(\text{a-c}\) show absorption bands at 3400 cm\(^{-1}\) (OH) and at 3320 cm\(^{-1}\) (NH). Furthermore, that the addition of phenylmagnesium bromide to the 2-acetylbenzimidazole led to the formation of the same compound (3\(\text{c}\)) obtained from the 2-benzoylbenzimidazole and methylmagnesium iodide, is in favour of the structure 3.

2-Acetyl and 2-benzoylbenzimidazoles condensed with aniline and \(p\)-toluidine at 140 °C to afford the corresponding imino derivatives (4\(\text{a-c}\)).

![Diagram](image)

The structure of compounds 4\(\text{a-c}\) was inferred from their analytical data and from the absence of carbonyl absorption in the IR spectra of compounds 4\(\text{a,b}\).

\(\alpha,\beta\)-Unsaturated ketones react with thiourea to give 2-thiopyrimidine derivatives\(^{12-14}\). Thus, when the 2-cinnamoyl derivative (1\(\text{a}\)) was heated with thiourea in boiling ethanol in the presence of potassium hydroxide, it gave 5,6-dihydro-4(2-benzimidazoyl)-6-phenyl-2(1H)-pyrimidinethione (5).

![Diagram](image)

The structure of compound 5 was established from its analytical data and from the consideration of its IR spectrum whereas no absorption appeared at the C=O region nor at the SH region; there is only one band at 3330 cm\(^{-1}\) assigned to an NH group.

**Experimental**

Melting points are not corrected. IR spectra were recorded on a Carl Zeiss Infracord Spectrophotometer “UR 10”.

**Preparation of 2-cinnamoylbenzimidazoles (1\(\text{a-e}\))**

**General procedure**

A mixture of 2-acetylbenzimidazole (1.6 g; 0.01 mole), fused sodium acetate (3 g) and 0.01 mole of the appropriate aromatic aldehyde was refluxed in 30 ml of ethanol for 3 hours. The reaction mixture was then cooled and poured into cold water, the precipitate that formed was collected, washed with water and crystallized from the proper solvent (cf. Table I).

The derivatives 1\(\text{a-e}\) are yellow to orange in colour but they all give blood-red colour with concentrated sulphuric acid.

**Action of Grignard reagents on 1\(\text{a,b}\)**

To an ethereal solution of phenylmagnesium bromide (obtained from 1 g of magnesium metal and 9 g of bromobenzene in ca. 50 ml of dry ether) was added 2 g of 1\(\text{a}\) or 1\(\text{b}\) dissolved in ca. 50 ml of dry ether. The reaction mixture was gently heated on a water bath using a calcium chloride tube for 45 min. After cooling it was hydrolyzed by a saturated ammonium chloride solution (ca. 300 ml) and extracted with ether. The ethereal layer, after drying over anhydrous sodium sulphate, was allowed to evaporate. The oily residue left behind was triturated with petroleum ether. The solid, so obtained, was collected and crystallized. 1\(\text{a}\) gave 2\(\text{a}\), crystallized from ethanol, m.p. 214 °C; yield 71%.

Analysis: C\(_{22}\)H\(_{18}\)N\(_2\)O

Calcd C 80.94 H 5.57 N 8.58,

Found C 80.81, H 5.49, N 8.68.

1\(\text{b}\) gave 2\(\text{b}\)*, crystallized from ethanol, m.p. 187 °C; yield 66%.

* 2\(\text{b}\) could also be obtained from 1\(\text{a}\) and \(p\)-methoxyphenylmagnesium bromide in 58% yield.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Solvent of cryst.</th>
<th>Formula</th>
<th>Carbon Caled</th>
<th>Carbon Found</th>
<th>Hydrogen Caled</th>
<th>Hydrogen Found</th>
<th>Nitrogen Caled</th>
<th>Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(\text{a})</td>
<td>208</td>
<td>78</td>
<td>Ethanol</td>
<td>C(<em>{16})H(</em>{12})N(_2)O</td>
<td>77.39</td>
<td>77.15</td>
<td>4.88</td>
<td>5.02</td>
<td>11.28</td>
<td>11.03</td>
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<tr>
<td>1(\text{b})</td>
<td>195</td>
<td>83</td>
<td>AcOH</td>
<td>C(<em>{17})H(</em>{14})N(_2)O(_2)</td>
<td>73.35</td>
<td>73.23</td>
<td>5.08</td>
<td>5.28</td>
<td>10.06</td>
<td>9.88</td>
</tr>
<tr>
<td>1(\text{c})</td>
<td>229</td>
<td>86</td>
<td>AcOH</td>
<td>C(<em>{16})H(</em>{11})ClN(_2)O(*)</td>
<td>67.96</td>
<td>68.24</td>
<td>3.93</td>
<td>3.91</td>
<td>9.91</td>
<td>9.70</td>
</tr>
<tr>
<td>1(\text{d})</td>
<td>244</td>
<td>81</td>
<td>AcOH</td>
<td>C(<em>{16})H(</em>{11})N(_3)O(_3)</td>
<td>65.51</td>
<td>65.39</td>
<td>3.79</td>
<td>3.98</td>
<td>14.33</td>
<td>14.28</td>
</tr>
<tr>
<td>1(\text{e})</td>
<td>226</td>
<td>72</td>
<td>Ethanol</td>
<td>C(<em>{18})H(</em>{17})N(_3)O</td>
<td>74.19</td>
<td>73.89</td>
<td>5.89</td>
<td>5.72</td>
<td>14.43</td>
<td>14.41</td>
</tr>
</tbody>
</table>

* Cl: Caled 12.53, Found 12.45%
Analysis: C_{23}H_{20}N_{2}O_{2}
Calcd C 77.49 H 5.66 N 7.86, Found C 77.31 H 5.54 N 7.98.

Action of Grignard reagents on 2-acylbenzimidazoles

2-Acetylbenzimidazole and 2-benzoylbenzimidazole were reacted with Grignard reagents by the above procedure used for the preparation of 2a,b. The products 3a-e are listed in Table II.

Action of amines on 2-acylbenzimidazoles

General procedure

0.01 Mole of 2-acetylbenzimidazole or 2-benzoylbenzimidazole was heated with 0.015 mole of the amine for 2 hours at 140 °C (bath temperature). The product was triturated with little ethanol and the solid obtained was filtered off and crystallized from the proper solvent.

4a was obtained from 2-acetylbenzimidazole and aniline, crystallized from ethanol, m.p. 218 °C; yield 70%.

Analysis: C_{15}H_{13}N_{3}
Calcd C 76.57 H 5.58 N 17.85, Found C 76.73 H 5.67 N 17.85.

4b was obtained from 2-benzoylbenzimidazole and aniline, crystallized from dilute ethanol, m.p. 181 °C; yield 77%.

Analysis: C_{17}H_{14}N_{4}S
Calcd C 66.82 H 4.72 N 18.03 S 10.44, Found C 66.81 H 4.72 N 18.03 S 10.44.

4c was obtained from 2-acetylbenzimidazole and p-toluidine, crystallized from dilute acetic acid, m.p. 217 °C; yield 83%.

Analysis: C_{20}H_{15}N_{3}

4e was obtained from 2-benzoylbenzimidazole and p-toluidine, crystallized from dilute acetic acid, m.p. 217 °C; yield 83%.

Analysis: C_{20}H_{15}N_{3}
Calcd C 80.77 H 5.09 N 14.13, Found C 80.60 H 4.92 N 14.00.

Reaction of 1a with thiourea

A mixture of 0.01 mole of 1a and 0.01 mole of thiourea was refluxed in a solution of 2 g of sodium hydroxide in 100 ml of ethanol and 2 ml of water for 12 hours and then left overnight. The resulting solution was concentrated under vacuum and the solid precipitated was filtered off, washed with little ethanol and dried well. It was crystallized from acetic acid as yellow crystals of 5, m.p. 305 °C, yield 61%.

Analysis: C_{15}H_{14}N_{3}S
Calcd C 68.14 H 4.72 N 18.03 S 10.44, Found C 68.12 H 4.72 N 18.03 S 10.44.

Table II. 2-(Disubstituted hydroxymethyl)benzimidazole (3a-e).

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Solvent of cryst.</th>
<th>Formula</th>
<th>Analysis [%]</th>
<th>Carbon Caled Found</th>
<th>Hydrogen Caled Found</th>
<th>Nitrogen Caled Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>218</td>
<td>72</td>
<td>Xylene</td>
<td>C_{10}H_{12}N_{2}O</td>
<td></td>
<td>68.14  68.40</td>
<td>6.87  7.03</td>
<td>15.90  16.11</td>
</tr>
<tr>
<td>3b</td>
<td>196</td>
<td>72</td>
<td>Xylene</td>
<td>C_{11}H_{14}N_{2}O</td>
<td></td>
<td>69.43  69.53</td>
<td>7.43  7.49</td>
<td>14.73  14.87</td>
</tr>
<tr>
<td>3c*</td>
<td>185</td>
<td>79</td>
<td>Ethanol</td>
<td>C_{13}H_{14}N_{2}O</td>
<td></td>
<td>75.59  75.74</td>
<td>5.92  6.13</td>
<td>11.76  11.90</td>
</tr>
<tr>
<td>3d</td>
<td>222</td>
<td>76</td>
<td>Ethanol</td>
<td>C_{20}H_{16}N_{2}O</td>
<td></td>
<td>79.96  80.21</td>
<td>5.37  5.51</td>
<td>9.32  9.44</td>
</tr>
<tr>
<td>3e</td>
<td>220</td>
<td>64</td>
<td>Ethanol</td>
<td>C_{21}H_{18}N_{2}O</td>
<td></td>
<td>80.21  80.50</td>
<td>5.78  5.95</td>
<td>8.91  9.09</td>
</tr>
</tbody>
</table>

* Prepared by the action of phenylmagnesium bromide on 2-acetylbenzimidazole, or by the action of methylmagnesium iodide on 2-benzoylbenzimidazole (65%).

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