Synthesis of Pyridone Derivatives

MICHAEL Condensation with Ethyl Cyanoacetate,
Cyanoacetamide and Acetoacetamide

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2-Cinnamoylbenzimidazole, Grignard Reagents, Azachromone, Pyrazole

MICHAEL condensation of 2-cinnamoylbenzimidazoles (1a–h) with ethyl cyanoacetate, cyanoacetamide and acetoacetamide led to the formation of 2(1H)pyridone derivatives (2a–e), (3a–e), (4a–e), and (5a–e). Compounds (2a–e) added Grignard reagents at the nitrile group to give 5a–e. CLAISEN condensation of 5a–e with ethyl acetate gave the corresponding diketo derivatives (6a–e), respectively. Cyclization of 6e with ethanolic hydrogen chloride gave the 8-azachromone (7). Both 6 and 7 gave the same pyrazole derivative (8) upon the reaction with phenylhydrazine.

In the present work the interest emphasized the synthesis of new compounds of 2-substituted benzimidazole derivatives. Since these types of compounds had demonstrated biological activity in different areas of chemotherapy1–7. For these considerations, a new series of heterocyclic binary systems including the 2-benzimidazole moiety as well as pyridone moiety were synthesized. The α,β-unsaturated ketones represent an active intermediate in the synthesis of heterocyclic compounds, hence we synthesized some chalcone analogues (1a–h) in which one or the two phenyl rings is replaced by heterocyclic rings

1a: Ar = 2-C6H4-2-Cl
1b: Ar = 2-C6H4-4-NO2
1c: Ar = C6H5
1d: Ar = C6H4-4-CH3
1e: Ar = C6H4-2-Cl-4-NO2
1f: Ar = C6H5
1g: Ar = C6H4-4-CH3
1h: Ar = C6H4-4-N(CH3)2

1a–h were prepared by CLAISEN–SCHMIDT condensation of the appropriate aldehyde namely, 2-thiophenecarboxaldehyde, furfural, salicylaldehyde, p-tolualdehyde, 2-chloro-4-nitrobenzaldehyde, anisaldehyde, and p-N-dimethylaminobenzaldehyde with 2-acetylbenzimidazoles8 using methanol as a solvent and piperidine as base.

1a–e were shown to be the arylidenes of 2-acetylbenzimidazole from their IR spectra. They show the stretching frequency in the range 1685–1665 cm\(^{-1}\) characteristic for conjugated carbonyl group9.

Here, we deal with the synthesis of 2-pyridones via the base catalyzed condensation of ethyl cyanoacetate and 2-cinnamoylbenzimidazole derivatives (11–h in the presence of ammonium acetate (molar ratio 1:1:6) at 150–170 °C for 10 hours. Treating the reaction mixture with ethanol yielded two fractions:

a) The ethanol insoluble part afforded the 3-cyanopyridones (2a–e).

b) The ethanol soluble part: gave on fractional crystallization (i) 3-cyanohexahydropyridones (3a–e).

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(ii) 3-Carbethoxy-2-aminopyridine (4a–c).

\[
\text{4a: } Ar = \text{C}_6\text{H}_5, \\
\text{4b: } Ar = \text{C}_6\text{H}_4-4-\text{OCH}_3, \\
\text{4c: } Ar = \text{C}_6\text{H}_4-4-\text{N(CH}_3)_2.
\]

In support for the structure assignment for 2a–c are the following:

a) Their correct molecular weights (osmotically).
b) Their IR spectra showed the carbonyl stretching frequency in the range 1706–1649 cm\(^{-1}\), NH frequency in the range 3080–2729 cm\(^{-1}\) (which are characterized for the stretching frequencies in 2(1H)pyridone\(^{11-13}\) and the C=N frequency at 2227 cm\(^{-1}\)).
c) Their correct analytical data.

Also, the structure of 4a–c was supported by their IR spectra. They showed well defined absorption bands attributable for –NH (3289 cm\(^{-1}\) broad), C=O (1684 cm\(^{-1}\)) and C=NH (1613–1577 cm\(^{-1}\)).

A possible explanation for the formation of 2, 3 and 4 via the reaction of ethyl cyanoacetate with 1 is the assumption that the reactants undergo MICHAEL addition, followed by cyclization to form the pyridone derivative. Moreover, these reactions are accompanied with dehydrogenation.

The structure of 2a–c was established by independent synthesis. Thus condensation of \(\text{1f-h} \) with cyanoacetamide in boiling butanol and few drops of piperidine as catalyst, gave 2a–c.

Furthermore, Grignard reaction on 2a–c with subsequent decomposition and hydrolysis was studied. Optimum result have been found with the use of four moles of Grignard reagents to one mole of 3-cyanopyridone derivatives (2a–c). Thus, treatment of 2a–c with methylmagnesium iodide yielded the corresponding 3-acetylpyridone derivatives (5a–c), respectively.

\[
\text{5a: } Ar = \text{C}_6\text{H}_5, \\
\text{5b: } Ar = \text{C}_6\text{H}_4-4-\text{OCH}_3, \\
\text{5c: } Ar = \text{C}_6\text{H}_4-4-\text{N(CH}_3)_2.
\]

In support for the products 5a–c are the following: The IR spectra of 5a–c are characterized by the band (strongest in the spectrum) at 1640–1620 cm\(^{-1}\) attributed to C=O (amide), a relatively weak band at the range 1525–1505 cm\(^{-1}\) is present and is probably due to the skeletal C=C stretching frequency and at the range 3200–3000 cm\(^{-1}\) due to NH group.

The NMR spectrum of 5a showed the following assignments:

a) \(\tau = 2.35\) (for the acetyl-CH\(_3\) protons, singlet),
b) \(\tau = 8.37–7.60\) (for the aromatic protons, multiplet),
c) \(\tau = 8.55\) (for the NH protons, singlet).

The structure of 5a–c, however, was rigidly established by independent synthesis. Thus condensation of 1f–h with acetoacetamide in boiling alcoholic hydrogen chloride yielded 5a–c, respectively.

Derivatives of 8-azachromone (4-oxo-4H-pyrano[2,3-b]-pyridine are of interest as aza-analogue of chromone, since many chromones possess pharmacological activity.

Claissen condensation of 5a–c with ethyl acetate in presence of sodium hydride or sodium dust gave the corresponding acetoacetyl derivatives (6a–c).

\[
\text{6a: } Ar = \text{C}_6\text{H}_5, \\
\text{6b: } Ar = \text{C}_6\text{H}_4-4-\text{OCH}_3, \\
\text{6c: } Ar = \text{C}_6\text{H}_4-4-\text{N(CH}_3)_2.
\]

The IR spectrum of the acetoacetyl derivative (6a) is characterized by the bands at 1620 cm\(^{-1}\) (C=O amide) and at 1580 cm\(^{-1}\) (C=C).

Cyclization of 6b with ethanolic hydrogen chloride gave 2-methyl-5-(2-anisyl)-7-(2-benzimidazolyl)-4H-pyrano-[2,3-b]pyridine-4-one (7).

Both 6b and 7 gave the same pyrazole derivative (8) on reaction with phenylhydrazine.
The building of the pyrazole structure is expected in such reaction. The product 8 is soluble in alkali indicating a pyridine nucleus.

The NMR spectrum of 8 reveals the presence of three methyl protons which appeared as singlet at \( \tau = 7.61 \) ppm.

**Experimental**

All melting points were 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 Jena Infracord Spectrophotometer model “UR 10” using KBr.

The NMR spectra were obtained in deuterotri-fluoroacetic acid solution with the Varian Associates model “A-60”.

2-(3-Substituted acryloyl)benzimidazoles (1a-h)

To a mixture of 2-acetylbenzimidazole (1.60 g, 0.01 mole), methanol (20 ml) and aldehyde (0.01 mole), four drops of piperidine were added. * The nomenclature of the compounds described in this paper follows the rules of the American Chemical Society and the Chemical Abstracts.

The reaction mixture was refluxed for 6 hours. The precipitated crystalline mass upon cooling was filtered off, recrystallized from the proper solvent to give 1a-h (cf. Table I).

1,2-Dihydro-2-oxo-4-(substituted)-6-(2-benzimidazolyl)nicotinonitrile (2a-c)

3-Cyano-4-(substituted)-6-(2-benzimidazolyl)hexahydro-2-pyridone (3a-c)

Ethyl 2-amino-4-(substituted)-6-(2-benzimidazolyl)nicotinic acid (4a-e)

Method (A): (without solvent):

A mixture of ethyl cyanoacetate (4.5 g, 0.04 mole), chalcone analogues (1f-h) (0.04 mole) and ammonium acetate (17.48 g, 0.24 mole) was heated at 160-170 °C for 8 hours (oil bath) and then allowed to cool. The yellow precipitate that obtained was washed with water, dried and then triturated with ethanol to give two parts:

i) Ethanol insoluble part which was isolated and recrystallized from the proper solvent to give 2a-e (cf. Table II).

ii) Ethanol soluble part was concentrated and allowed to stand overnight at room temperature. An oily product was separated and triturated with cold ether, the resulting precipitate was crystallized from the proper solvent to give 3a-c (cf. Table III).

The mother liquor was diluted with water and the formed precipitate was recrystallized from the proper solvent to give 4a-e (cf. Table IV).

Method (B): (in butanol):

A mixture of ethyl cyanoacetate (4.5 g, 0.04 mole), chalcone analogues (1f-h) (0.04 mole) and am-

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<tr>
<td>1a</td>
<td>222</td>
<td>71</td>
<td>ethanol</td>
<td>C_{14}H_{15}N_{4}SO</td>
<td>66.14</td>
<td>66.05</td>
<td>3.99</td>
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<td>1b</td>
<td>216</td>
<td>69</td>
<td>methanol</td>
<td>C_{14}H_{15}N_{4}O_{2}</td>
<td>70.58</td>
<td>70.57</td>
<td>4.50</td>
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<td>1c</td>
<td>105</td>
<td>73</td>
<td>chloroform/pet.</td>
<td>C_{17}H_{14}N_{2}O</td>
<td>71.86</td>
<td>71.50</td>
<td>5.34</td>
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<td>205</td>
<td>82</td>
<td>1,2-dichloro ether</td>
<td>C_{16}H_{16}N_{2}O_{2}</td>
<td>71.42</td>
<td>70.96</td>
<td>5.26</td>
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<tr>
<td>1e</td>
<td>244</td>
<td>78</td>
<td>methanol</td>
<td>C_{16}H_{16}N_{3}O_{Cl}</td>
<td>58.71</td>
<td>58.74</td>
<td>3.05</td>
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<tr>
<td>2a</td>
<td>above 25</td>
<td>350</td>
<td>acetic acid</td>
<td>C_{18}H_{12}N_{2}O</td>
<td>73.07</td>
<td>72.98</td>
<td>3.84</td>
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<tr>
<td>2b</td>
<td>above 22</td>
<td>350</td>
<td>acetic acid</td>
<td>C_{20}H_{14}N_{2}O</td>
<td>70.17</td>
<td>70.47</td>
<td>4.09</td>
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<td>2c</td>
<td>above 28</td>
<td>350</td>
<td>D.M.F.</td>
<td>C_{21}H_{17}N_{2}O</td>
<td>70.98</td>
<td>70.61</td>
<td>4.78</td>
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Table I. 2-(3-Substituted acryloyl)benzimidazoles (1a-e).

Table II. 1,2-Dihydro-2-oxo-4-substituted-6-(2-benzimidazolyl)nicotinonitrile (2a-c).
monium acetate (17.48 g, 0.24 mole) in 20 ml butanol was refluxed for 10 hours. The yellow precipitate that obtained on cooling was separated and recrystallized from the proper solvent to give 2a-c (cf. Table II).

Method (C): A mixture of cyanoacetamide (0.84 g, 0.01 mole), chalcone analogues (1f-h) (0.01 mole) and two drops of piperidine in 10 ml butanol was refluxed for 10 hours. The most of the alcohol was evaporated, the yellow crystalline mass that separated after cooling was filtered off and dried, recrystallized from the appropriate solvent to give 2a-c (cf. Table II).

No depression occurs in the admixed m.p. between both of each products 2a-c obtained by methods (B) and (C) and that obtained from method (A).

3-Acetyl-4-substituted-6-(2-benzimidazolyl)-2-[1H]pyridones (5a-c)

A mixture of 2a, b and c (0.0072 mole) in dry benzene (50 ml) was added dropwise to an etherial solution of methylmagnesium iodide (prepared from 0.9 g magnesium, 7 g methyl iodide and 40 ml dry ether) the reaction mixture was refluxed on a steam bath for two hours, set aside at room temperature, and then decomposed with a cold solution of hydrochloric acid (10%). The yellow solid obtained was crystallized from the proper solvent to give 5a-c (cf. Table V).

Preparation of an authentic samples of 5a-c
A mixture of acetoacetamide (2.02 g, 0.02 mole), 1f-h (0.02 mole) and (20 ml of 10%) ethanolic hydrochloric acid was heated under reflux for 30 minutes. The reaction mixture was cooled and treated with ammonium hydroxide solution (25%), the solid product was collected and recrystallized from the proper solvent to give 5a-c (cf. Table V).

No depression occurs in the admixed m.p. between both of each products 5a-c obtained by the two methods.

1-[1,2-Dihydro-2-oxo-4-substituted-6-(2-benzimidazolyl)-3-pyridyl]-1,3-butanones (6a-c)

Method (a): A mixture of 5a-c (0.0033 mole), ethyl acetate (3 ml; 0.0031 mole), dry dioxane (20 ml) and 50% suspension of sodium hydride in oil (1.2 g) was refluxed for 30 minutes. The mixture was cooled, then stirred into water (50 ml) and 2 N hydrochloric acid (5 ml) was added to give 6a-c (cf. Table VI).

Method (b): A mixture of 5a-c (0.0033 mole), ethyl acetate (excess) (as a solvent and reactant) and granulated

Table V. 3-Acetyl-4-substituted-6-(2-benzimidazolyl)-2-[1H]pyridones (5a-c).

<table>
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<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Solvent of Cryst.</th>
<th>Formula</th>
<th>Carbon Caled Found</th>
<th>Analysis [%]</th>
<th>Hydrogen Caled Found</th>
<th>Nitrogen Caled Found</th>
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<tbody>
<tr>
<td>5a</td>
<td>320</td>
<td>92</td>
<td>methanol</td>
<td>C_{20}H_{13}N_{3}O_{2}</td>
<td>72.92</td>
<td>72.90</td>
<td>4.55</td>
<td>4.32</td>
</tr>
<tr>
<td>5b</td>
<td>325</td>
<td>95</td>
<td>ethanol</td>
<td>C_{21}H_{17}N_{3}O_{3}</td>
<td>70.19</td>
<td>69.96</td>
<td>4.73</td>
<td>5.16</td>
</tr>
<tr>
<td>5c</td>
<td>327</td>
<td>89</td>
<td>acetone</td>
<td>C_{22}H_{20}N_{4}O_{2}</td>
<td>70.43</td>
<td>70.18</td>
<td>5.37</td>
<td>5.40</td>
</tr>
</tbody>
</table>
Table VI. 1-(1,2-Dihydro-2-oxo-4-substituted-6-(2-benzimidazolyl)-3-pyridyl)-1,3-butandiones (6a–c).

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Solvent</th>
<th>Formula</th>
<th>Carbon [%]</th>
<th>Hydrogen [%]</th>
<th>Nitrogen [%]</th>
</tr>
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<tbody>
<tr>
<td>6a</td>
<td>330</td>
<td>81</td>
<td>ethanol</td>
<td>C₂₂H₁₇N₃O₃</td>
<td>71.15</td>
<td>71.25</td>
<td>4.58</td>
</tr>
<tr>
<td>6b</td>
<td>228</td>
<td>78</td>
<td>acetone</td>
<td>C₂₂H₁₅N₃O₄</td>
<td>68.82</td>
<td>68.76</td>
<td>4.73</td>
</tr>
<tr>
<td>6c</td>
<td>280</td>
<td>72</td>
<td>ethanol</td>
<td>C₂₄H₂₂N₄O₃</td>
<td>69.56</td>
<td>69.29</td>
<td>5.31</td>
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</table>

Sodium (0.1 g) were refluxed for three hours. The reaction mixture was cooled and treated with 2 N hydrochloric acid, the formed precipitate was re-crystallized from the proper solvent to give 6a–e (cf. Table VI).

No depression in the admixed melting points.

2-Methyl-5-(4-anisyl)-7-(2-benzimidazolyl)-4H-pyrano-[2,3-b]-pyridin-4-one (7)

A mixture of 6b (1.2 g, 0.003 mole) was heated under reflux for one hour with (10% ethanolic solution of hydrogen chloride) 10 ml. The mixture was cooled and neutralized with aqueous ammonium hydroxide (25%). The solid obtained was re-crystallized from methanol to give 7 as redish brown crystals of m.p. 310 °C (yield 86%).

Analysis: C₂₃H₁₇N₃O₃
Calcd C 72.06 H 4.43 N 10.96
Found C 72.33 H 4.33 N 10.56

3-(5-Methyl-1-phenyl-2-pyrazol-3-yl)-4-(4-anisyl)-6-(2-benzimidazolyl)-2-[1H]pyridone (8)

Method (a):
A mixture of phenylhydrazine (0.5 ml, 0.0051 mole) in 10 ml acetic acid and 7 (0.55 g, 0.0015 mole) was refluxed for 8 hours. The precipitate formed after cooling was filtered off and recrystallized from acetic acid to give 8 as yellow crystals, m.p. 335 °C (yield 83%).

Analysis: C₂₉H₂₇N₅O
Calcd C 75.48 H 5.85 N 15.18
Found C 75.34 H 5.73 N 14.93

Method (b):
A mixture of phenylhydrazine (0.5 ml, 0.0051 mole) in 15 ml acetic acid and 6b (0.6 g, 0.0015 mole) was refluxed for 3 hours. The formed precipitate upon cooling was filtered off, recrystallized from acetic acid to give 8.

No depression in the admixed melting points.