Comparison Study of the Reactivity of 2-Acetyl Heterocyclic Compound toward Aldol Condensation with Benzaldehyde Derivatives

Abdulrahim M. Khlafulia¹, Mohamad F. Ali²*

¹Department of Chemistry, Faculty of Science, Azzytoa University, Libya
²Department of Chemistry, Faculty of Science, Benghazi University, Benghazi, Libya

Abstract

Some new chalcones have been synthesized by condensation of 2-acetyl pyrrol, 3-acetyl pyridine and 3-acetyl indole with various aromatic aldehydes in 25% alcoholic alkali. The synthesized compounds were identified by spectral and physical methods. From the time of reactions and the yield of the products, we can state that there were some obvious differences in the reactivity between the heterocyclic compounds used.

Keywords: Reactivity, chalcone, aldol condensation, heterocyclic compounds, benzaldehyde

*Author for Correspondence E-mail: fadelalla2001@yahoo.com

INTRODUCTION

Aldol condensation is an organic reaction in which an enol or enolate ion reacts with a carbonyl compound to form a β-hydroxyl aldehyde or β-hydroxyl ketone, followed by a dehydration to give conjugated enone.

![](image)

Ketone Aldehyde Aldol

O \(\text{R--C--}R_1\) \(\text{H--C--CH}_2R_2\) \(\text{R--C--CH--C--H}\) \(\text{R--C=C--C--H}\)

\(\text{R}_1\) \(\text{R}_2\) \(\text{R}_1\) \(\text{R}_2\)

Aldol condensations are important in organic synthesis, providing a good way to form carbon-carbon bonds, for example, the Robinson annulations reaction sequence features an aldol condensation; the Wieland-Miescher ketone product is an important starting material for many organic syntheses. Aldol condensations are also commonly discussed as good bond-forming reactions that demonstrate important reaction mechanisms [1–3].

In its usual form, it involves the nucleophilic addition of a ketone enolate to an aldehyde to form a β-hydroxyl ketone or aldol (aldehyde + alcohol), a structural unit found in many naturally occurring molecules and pharmaceuticals [4–6]. The name aldol condensation is also commonly used, especially in biochemistry, to refer to just the first (addition) stage of the process. The aldol reaction itself is catalyzed by aldolases. However, the aldol reaction is not formally a condensation reaction because it does not involve the loss of a small molecule. The reaction between an aldehyde/ketone and an aromatic carbonyl compound lacking an alpha hydrogen (cross Aldol condensation) is called the Claisen-Schmidt condensation [7–9].

The condensation of aldehydes/ketones with benzaldehyde leads to the formation of α, β-unsaturated ketones, called chalcones, which are known to have high biological activity and great pharmaceutical and medicinal applications [10]. They are used recently as anti-Aids agent [11], cytotoxic with antiangiogenic activity [12, 13], antimalerial [14, 15], anti-inflammatory [16, 17], and antitumor [18, 19].
In this work we intended to study the reactivity of different 2-acetyl heterocyclic compounds toward aldol condensation with aromatic aldehyde, therefore we have chosen three different heterocyclic compounds, five member, six member and fused rings to see which one is more reactive, the criteria we consider for that comparison will be the reaction time and the percent yield of the products. Also we consider the substituent effect of different groups, electron donating and electron withdrawing on the aromatic aldehyde. Chalcones obtained from the condensation of heterocyclic compounds with aromatic aldehydes in presence of a base represent one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices and soy-based food stuffs. Chalcones are suitable intermediates for the synthesis of biologically active heterocyclic compounds [20, 21].

EXPERIMENTAL

A number of chalcones derivatives were synthesized by condensation of 2-acetylpyrrol, 2-acetylpyridine and 3-acetylindole (Ia–d) with benzaldehyde derivatives (IIa–d). The scheme of the synthesis is shown below:

\[
\text{R--CO--CH}=\text{CH}-\text{C}_6\text{H}_4--\text{X} + \text{Ia} = \text{R} = \text{Pyrrol} \rightarrow \text{IIa} = \text{X} = \text{H} \rightarrow \text{IIIa-d}
\]

where R = Pyrrol, Pyridine, Indole, Acetyl pyrrol, Acetyl pyridine and Acetyl indole.

**Reaction scheme**

The melting points of the newly synthesized compounds were determined using visual melting point apparatus and were uncorrected. All chemicals were used as received; the reactions were followed by TLC. The microanalysis, the IR and \textsuperscript{1}HNMR were measured at Ain Shams University, Cairo, Egypt.

**General Procedure for Preparation of Chalcones Derivatives (IIIa-d, IVa-d, V a-d)**

Acetyl heterocyclic compounds (Ia–d) (100 mmoles), aromatic aldehydes (IIa–d) (100 mmoles) were added to an aqueous solution of NaOH (100 mL, 0.5 M). The reaction mixture was vigorously stirred at room temperature for the duration reported in the table below; the reaction was monitored by TLC. The solid products were filtered and washed with water, dried and purified by recrystallization from appropriate solvent. All characterization data are shown in Tables 1–3.

**RESULTS AND DISCUSSION**

In continuing our studies about chalcones, we have decided to synthesize new chalcones using heterocyclic compounds, therefore we have chosen a five-membered ring, a six-membered ring and a fused ring derivatives, namely 2-acetylpyrrol, 2-acetylpyridine and 3-acetylindole, and for the benzaldehyde derivatives we used p-chloro, which is known as electron withdrawing group, and the p-methoxy, and p-N, N-dimethylamino groups which are both known as electron donating group to examine the effects of these groups on the time of the reaction and on the yield percent [22]. The detailed information is outlined in the table 1-3.

**The Spectral Data of Chalcone Derivatives**

In general the IR and the NMR spectra of these compounds are quite similar as they are expected, except for the minor differences due to the different substituents used on the aromatic aldehyde. The difference in the values of \(\nu\) and \(\delta\) in the IR and NMR spectra respectively does not represent a big issue as these spectra are very well known and we use them for elucidation of the product structures. Therefore and to avoid repeating the same
data, we sought giving one general IR spectrum and one general NMR spectrum which mainly shows the main peaks and bands and their υ and δ values together with the structures of the chalcone derivatives.

### Table 1: Physical Data of Chalcones Derived from 2-Acetylpyrrol.

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>Mol. Formula</th>
<th>Mol. Wt</th>
<th>Reaction Time/min</th>
<th>Yield %</th>
<th>M.P. (°C)</th>
<th>Microanalysis % Calc./Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>C_{12}H_{11}NO</td>
<td>197</td>
<td>90</td>
<td>85</td>
<td>136–8</td>
<td>79.18, 5.58, 7.18 (79.54), (5.36), (7.62)</td>
</tr>
<tr>
<td>IIIb</td>
<td>C_{12}H_{10}NOCl</td>
<td>231.5</td>
<td>120</td>
<td>82</td>
<td>154–5</td>
<td>67.38, 4.31, 6.04, 15.33 (67.82), (4.64), (5.88), (15.67)</td>
</tr>
<tr>
<td>IIIc</td>
<td>C_{12}H_{11}NO_{2}</td>
<td>227</td>
<td>75</td>
<td>88</td>
<td>166–7</td>
<td>74.00, 5.72, 6.16 (74.68), (5.21), (6.43)</td>
</tr>
<tr>
<td>IIId</td>
<td>C_{12}H_{10}N_{2}O</td>
<td>240</td>
<td>55</td>
<td>92</td>
<td>192–4</td>
<td>75.00, 6.66, 11.66 (75.58), (6.98), (11.44)</td>
</tr>
</tbody>
</table>

### Table 2: Physical Data of Chalcones Derived from 2-Acetylpyridine.

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>Mol. Formula</th>
<th>Mol. Wt</th>
<th>Reaction Time/min</th>
<th>Yield %</th>
<th>M.P. (°C)</th>
<th>Microanalysis % Calc./Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>C_{13}H_{11}NO</td>
<td>209</td>
<td>35</td>
<td>85</td>
<td>132–4</td>
<td>80.38, 5.28, 6.69 (80.54), (5.36), (7.02)</td>
</tr>
<tr>
<td>IVb</td>
<td>C_{13}H_{10}NOCl</td>
<td>243.5</td>
<td>40</td>
<td>80</td>
<td>103–5</td>
<td>68.99, 4.10, 5.74, 14.57 (68.72), (4.64), (5.38), (14.30)</td>
</tr>
<tr>
<td>IVc</td>
<td>C_{13}H_{11}NO_{2}</td>
<td>239</td>
<td>30</td>
<td>90</td>
<td>120–2</td>
<td>75.31, 5.42, 5.85 (75.68), (5.21), (5.43)</td>
</tr>
<tr>
<td>IVd</td>
<td>C_{13}H_{10}N_{2}O</td>
<td>252</td>
<td>25</td>
<td>92</td>
<td>146–8</td>
<td>76.14, 6.34, 11.11 (76.52), (5.98), (11.44)</td>
</tr>
</tbody>
</table>

### Table 3: Physical Data of Chalcones Derived from 3-Acetylindole.

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>Mol. Formula</th>
<th>Mol. Wt</th>
<th>Reaction Time/min</th>
<th>Yield %</th>
<th>M.P. (°C)</th>
<th>Microanalysis % Calc./Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Va</td>
<td>C_{14}H_{13}NO</td>
<td>247</td>
<td>300</td>
<td>60</td>
<td>167–8</td>
<td>82.59, 4.85, 5.66 (82.54), (4.36), (6.02)</td>
</tr>
<tr>
<td>Vb</td>
<td>C_{15}H_{12}NOCl</td>
<td>281.5</td>
<td>350</td>
<td>55</td>
<td>193–5</td>
<td>72.46, 4.26, 4.97, 12.61 (72.82), (4.64), (5.38), (12.30)</td>
</tr>
<tr>
<td>Vc</td>
<td>C_{15}H_{13}NO_{2}</td>
<td>277</td>
<td>240</td>
<td>65</td>
<td>145–7</td>
<td>77.97, 5.41, 5.05 (77.68), (5.21), (5.43)</td>
</tr>
<tr>
<td>Vd</td>
<td>C_{15}H_{14}N_{2}O</td>
<td>290</td>
<td>200</td>
<td>75</td>
<td>186–8</td>
<td>78.62, 6.20, 0.96 (78.98), (5.98), (0.94)</td>
</tr>
</tbody>
</table>

**Structures of Chalcones III_{a-d} and their IR and NMR Spectra**

$$\text{NH} \quad \text{CH}=\text{CH}--\text{CO}--$$

III_{a}=X=\text{H}; III_{b}=X=\text{p}-\text{Cl}; III_{c}=X=\text{p}-\text{OMe}; III_{d}=X=\text{p}-\text{N(Me)}_{2}$

IR (KBr) υ cm\(^{-1}\): 1310 (C-N); 1520 (C=O); 1640 (C=O); 2918–3020 (CH); 3268 (NH)

\(^{1}\)H NMR (DMSO–d\(_{6}\)) δ ppm: 5.0 (NH); 6.01–6.60 (pyrrol-H); 7.22–7.48 (Ar-H); 7.57 (d, 1H, C=O), 7.90 (d, 1H, C=C)
Reactivity of 2-Acetyl Heterocyclic Compound

Ali and Khafulla

Structures of Chalcones IV<sub>a-d</sub> and their IR and NMR Spectra

IV<sub>a</sub> = X = H; IV<sub>b</sub> = X = p-Cl; IV<sub>c</sub> = X = p-OMe; IV<sub>d</sub> = X = p-N(Me)<sub>2</sub>
IR (KBr) v cm<sup>-1</sup>: 1568 (C=C); 1606 (C=N); 1677 (C=O); 3020 (CH)
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ ppm: 6.98–8.66 (pyridine-H); 7.22–7.99 (Ar-H); 8.19 (d, 1H, C=O), 8.13 (d, 1H, C=C)

Structures of Chalcones V<sub>a-d</sub> and their IR and NMR Spectra

V<sub>a</sub> = X = H; V<sub>b</sub> = X = p-Cl; V<sub>c</sub> = X = p-OMe; V<sub>d</sub> = X = p-N(Me)<sub>2</sub>
IR (KBr) v cm<sup>-1</sup>: 1310 (C=N); 1475 (C=C); 1662 (C=O); 3012 (Ar-CH); 3270 (NH)
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ ppm: 7.04–7.18 (indole-H); 7.22–7.48 (Ar-H); 1010 (NH); 7.57 (d, 1H, C=O), 7.88 (d, 1H, C=C).

CONCLUSION
Comparison of the reactivity of the acetyl-heterocyclic compounds toward aldol condensation with benzaldehyde derivatives, we can conclude from the results we obtained in this study, and by considering the duration of the reaction and the percent yield, that 2-acetylpyridine is the more reactive than 2-acetylpyrrol and 3-acetylindole (Tables 1–3), the only explanations we can offer may be that pyridine is more stable than the other two heterocyclic used in this study.

REFERENCES

Cite this Article