CHAPTER : FIVE - PREPARATION OF CHALCONES

Chalcone is a condensed product of the reaction between an aromatic aldehyde and an aromatic ketone in the presence of an alkali. Generally acetophenone or substituted acetophenone and benzaldehyde or substituted benzaldehyde are condensed. Sometimes methyl naphthyl ketone, methyl phenanthryl ketone or their substituted ketones may also be used.

Claisen Reaction\textsuperscript{1,2}

The condensation of aromatic aldehydes with aliphatic or aromatic aldehyde and ketone or esters bearing active hydrogen in the presence of alkali solution to give unsaturated aldehydes or ketones is known as 'Claisen Reaction'. Sometimes it is also known as 'Claisen Schmidt reaction' or aldol condensation reaction.

\[
\text{C}_6\text{H}_5\text{-CHO} + \text{CH}_3\text{C}-\text{C}_6\text{H}_5 \xrightarrow{\text{NaOH}} \text{C}_6\text{H}_5\text{-CH=CH-C}_6\text{H}_5
\]

Aldehydes used for the reaction must not have any \(\alpha\)-hydrogen atom because they preferentially undergo self condensation.

Mechanism

The mechanism of the Claisen reaction is given by Nayce and Stiles \textit{et al.} in 1959. It is similar to the aldol
condensation and can be summarised as below:

\[
\text{Ar-C-CH}_2\text{OH}^{-} + \text{Ar-C-CH}_2\text{H}_2\text{O} \rightarrow \text{Ar-C-CH}_2\text{H}_2\text{O} + \text{H}_2\text{O}
\]

\[
\text{Ar-C-CH}_2\text{H}_2 + \text{C-Ar} \rightarrow \text{Ar-C-CH}_2\text{C-Ar}
\]

\[
\text{H}_2\text{O} \rightarrow \text{Ar-C-CH}_2\text{C-OH} \rightarrow \text{Ar-C-CH=CH-Ar}
\]

Claisen reaction is successfully used for the synthesis of \( \alpha: \beta \) unsaturated carbonyl compounds, for example: cinnamaldehyde, benzyldiene acetone and synthesis of natural products like: \( \beta \)-ionone, piperine, flavones, flavonol, etc.

At first Jeiger and Conn\(^3\) in 1945 and Kmoda and Ito\(^4\) in 1945 reported that \( \alpha: \beta \) unsaturated ketones possess antibacterial activity. After that Schraufstatter\(^5,6\) in 1948 and Eaton and Devies\(^7\) in 1950 observed that chalcones are capable of destroying the disease germs. Wilson and coworkers\(^8\) have reported that destruction of adrenalin can be checked up by the use of chalcones due to the presence of (-CO-CH=CH-) group which can react with bacterial protoplasm\(^9,10\). Promising usefulness of various chalcones and their analogous compounds have been studied against various bacterial infections\(^11,12\). Misra has reported germicidal properties of some chalcones.
derived from 4-hydroxy-5-nitro acetophenone, acetyl phenanthrene, 2-methoxy-1-acetonaphthone, 1-hydroxy-2-acetonaphthone, 2-aceto-naphthone, acetyl naphthalene, etc. Antifertilitic property of the phenanthrene chalcones and some other chalcones have also been reported. Besides antimicrobial and antifertilitic properties, chalcones also possess sedative, antihistaminic and carcinogenic activities.

A wide range of sulphonamides have been reported to be pharmacodynamic versatile compounds for the diseases like - cancer, tuberculosis, malaria, leprosy, convulsant action and bacterial infections.

Antimicrobial activity of some chalcones derived from 4-(p-tolyl sulphonamido) acetophenone have also been reported. Joshi and Naik have studied the antibacterial properties of some chalcones derived from 2-hydroxy-4-ethoxy-5-nitro acetophenone against Staphylococcus aureus and Escherichiacoli. Some chalcones from 2-hydroxy-3-bromo-4-n-propoxy-5-nitroacetophenone have also been found to be very good antimicrobial agents.

Keeping in view their microbiological activities, some new chalcone derivatives were prepared from 2,4-hydroxy acetophenone with a view to test their antimicrobial, insecticidal and anthelmintic activities.
Synthesis of chalcones from 2,4-dihydroxy acetophenone:

It has been done in two parts. Part I- deals with the preparation of 2,4-dihydroxy acetophenone and Part-II is the condensation of this acetophenone with different aromatic aldehydes.

**Part I: Preparation of 2,4-dihydroxy acetophenone**

\[
\text{OH} + \text{CH}_3-\text{C}=\text{N} \xrightarrow{\text{AlCl}_3} \text{CH}_3-\text{CO}=\text{O}
\]

In a 250 ml conical flask, 10 gm of resorcinol and 7 ml acetonitrile were shaken with 60 ml of ether. To the clear solution of resorcinol, 5 gm of pulverised aluminium chloride was added and then the flask was cooled in an icebath. A stream of hydrogen chloride gas was passed into the solution for 15 minutes and flask was left for 24 hours. The product was filtered and washed with ether. To remove excess of aluminium chloride, it was refluxed with 50 ml of dilute hydrochloric acid for half an hour. On cooling the above solution in an ice bath, pinkish brown coloured crystals were separated by filtration.

m.p. 149°

yield-51%.
Part II: Preparation of 2',4'-dihydroxy chalcone

\[
\text{OH} \quad + \quad \text{C}_6\text{H}_5-\text{CHO} \quad \xrightarrow{\text{NaOH}} \quad \begin{array}{c}
\text{OH} \\
\text{C-CH=CH-C}_6\text{H}_5
\end{array}
\]

2',4'-dihydroxy chalcone

In a 100 ml, conical flask 1.52 gm (0.01 M) of 2,4-dihydroxy acetophenone was dissolved in minimum quantity of ethanol and 50% sodium hydroxide solution was added with continuous stirring and then 1.06 gm (0.01 M) of benzaldehyde was also added with stirring. The mixture was kept at room temperature for 12 hours and the separated product was decomposed by a mixture of ice and dilute hydrochloric acid and then filtered.

For the present studies, chalcones have been prepared by condensing 4-chlorobenzaldehyde, 4-hydroxy-3-methoxy benzaldehyde, 3,4-dimethoxy benzaldehyde, 3,4-dihydroxy benzaldehyde, 2-nitrobenzaldehyde, 4-methoxy benzaldehyde and 2-hydroxybenzaldehyde.

The yields and melting points of the chalcones are given in Table I.

The molecular formulae of these chalcones were calculated from their elemental analysis and are reported in Table II.
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the compound</th>
<th>Yield (%)</th>
<th>m.p.</th>
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<tbody>
<tr>
<td>1</td>
<td>2',4'-dihydroxy chalcone</td>
<td>68</td>
<td>125</td>
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<tr>
<td>2</td>
<td>2,2',4'-trihydroxychalcone</td>
<td>72</td>
<td>285</td>
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<td>3</td>
<td>4-chloro-2',4'-dihydroxy chalcone</td>
<td>80</td>
<td>279</td>
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<td>4</td>
<td>2-nitro-2',4'-dihydroxy chalcone</td>
<td>75</td>
<td>271</td>
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<td>4-methoxy-2',4'-dihydroxy chalcone</td>
<td>83</td>
<td>245</td>
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<td>6</td>
<td>3-methoxy-4,2',4'-trihydroxy chalcone</td>
<td>86</td>
<td>223</td>
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<td>7</td>
<td>3,4,2',4'-tetrahydroxy chalcone</td>
<td>77</td>
<td>214</td>
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<td>8</td>
<td>3,4-dimethoxy-2',4'-dihydroxy chalcone</td>
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<td>265</td>
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<tr>
<td>S.No.</td>
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<td>Molecular formula</td>
<td>C %</td>
</tr>
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<td>-----------------------------------------------</td>
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<td>1</td>
<td>2',4'-dihydroxy chalcone</td>
<td>C_{15}H_{12}O_{3}</td>
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<td>2</td>
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<td>C_{15}H_{12}O_{4}</td>
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<td>4-chloro-2',4'-dihydroxy chalcone</td>
<td>C_{15}H_{11}O_{2}Cl</td>
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<td>4</td>
<td>2-nitro-2',4'-dihydroxy chalcone</td>
<td>C_{15}H_{11}O_{5}N</td>
<td>63.06</td>
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<td>4-methoxy-2',4'-dihydroxy chalcone</td>
<td>C_{16}H_{14}O_{4}</td>
<td>71.03</td>
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<tr>
<td>6</td>
<td>3-methoxy-4,2',4'-trihydroxy chalcone</td>
<td>C_{16}H_{14}O_{5}</td>
<td>66.95</td>
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<tr>
<td>7</td>
<td>3,4,2',4'-tetrahydroxy chalcone</td>
<td>C_{15}H_{12}O_{5}</td>
<td>66.02</td>
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<tr>
<td>8</td>
<td>3,4-dimethoxy-2',4'-dihydroxy chalcone</td>
<td>C_{17}H_{16}O_{5}</td>
<td>67.72</td>
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</table>
The structure for the chalcones was confirmed by their IR spectra. IR-spectra has shown (Fig 1-8 )-C-H (bending) 710 cm\(^{-1}\); O-H (bending) and C-O (stretching) 1380 cm\(^{-1}\); C-H (bending) 1460 cm\(^{-1}\); \(\alpha,\beta\) unsaturated cyclic 1600 cm\(^{-1}\), C=O (stretching) 1720 cm\(^{-1}\); C-H (stretching) 2850-2975 cm\(^{-1}\).

The prepared chalcones were screened for their antimicrobial (Chapter VII); anthelmintic (Chapter VIII) and insecticidal (Chapter IX) properties.
Fig. 2: 3,4,2'-4'-tetrahydroxychalkone

Probe Nr.
Datum, Name

Konzentration
Schichtdicke
Vergleichsprobe

Maßstab 75 mm/100 cm²
Spalt 3
Registrierzeit 4.4 min
Verstärkung 4
Zeitkonstante 5
Verzögerer 2

mit/ ohne AVR
Fig. 3:

Probe: 4-chloro-2,4'-dihydroxy Chalcone
Konzentration
Schichtdicke
Vergleichsprobe

Maßstab: 7,5 mm/100 cm²
Verstärkung: 1
Zeitkonstante: 3
Verzögerer: 0,3 s

Datum, Name

mit/ohne AVR
Fig. 4

Probe B4
Nr. 2', 4'-dihydroxy chalcone
Datum, Name

Konzentration
Schichtdicke
Vergleichsprobe

Maßstab 7.5mm/100cm²
Spalt 3
Registrierzeit 4.4 min
Verstärkung 1
Zeitkonstante 3
Verzögerer 0.3 s

mit/ohne AVR
Fig. 7: 2-methyl-2',4'-dihydroxy chalcone

Probe: 5
Nr.
Datum: Name

Konzentration
Schichtdicke
Vergleichsprobe

Maßstab: 7.1. mm/100 cm⁻¹
Spalt: 3
Registrierzeit: 4.4 ms

Verstärkung: 1
Zeitkonstante: 5
Verzögerer: 0.5 s

mit/ohne AVR
REFERENCES


15. Ibid., 1974, 51, 909.
16. Ibid., 1975, 52, 651.
17. Ibid., 1095.
18. Ibid., 576.

