Chapter I

Part 1  Barium hydroxide mediated condensation of cycloalkanones with aryl aldehydes

Part 2  Synthesis of chalcones and 2'-hydroxychalcones
CHAPTER-I

Part 1: Barium hydroxide mediated condensation of cycloalkanones with aryl aldehydes

Introduction

α,α'-Bis(arylidene)cycloalkanones (Fig. 3) constitute an important class of α,β-unsaturated carbonyl compounds as they play an important role in organic synthesis and are versatile starting materials for the synthesis of various saturated and partially saturated heterocyclic ring system. These are also important precursors for the synthesis of pyridazine derivatives, 2,7-disubstituted tropones, and synthetic intermediates to functionalize α-β position during the total synthesis of natural products such as cystodytins. These also find applications in the preparation of non linear optical materials, liquid crystalline polymers, and in the synthesis of various polydentate ligands. This class of compounds has been attracting attention of the chemists not only due to their synthetic applications but also due to immense biological activities.

Cytotoxicity of 2,6-bis(phenylmethylene)cyclohexanone (1) has already been disclosed. These also show biological activities such as antiangiogenic, quinine reductase inducer, cholesterol lowering activity. A number of compounds bearing arylidene cycloalkanone or α-β unsaturated ketonic unit in the structure have been reported to be biologically active. For example, natural products of curcumin family exhibit anticancer properties. Recently a series of cyclic analogues of curcumin (2), have been synthesised and reported to show in vitro cytostatic activity (3). 2-Arylidene-4-cyclopentene-1,3-diones (4) and 2-arylidene indan-1,3-diones (5) have also been reported to exhibit high degree of antitumour activity.
Part work on the synthesis of $\alpha,\alpha'$-bis(arylidene)cycloalkanones

Cross aldol condensation,\textsuperscript{55} which is a powerful tool for the formation of carbon-carbon bond, and is an important protocol for the synthesis of $\alpha,\alpha'$-bis(arylidene) cycloalkanones. Cross aldol condensation of cycloalkanones with aromatic aldehydes leading to the formation of $\alpha,\alpha'$-bis(arylidene)cycloalkanones has been catalysed by strong acids,\textsuperscript{56} more likely by bases\textsuperscript{57} using either traditional heating or microwave heating. However, in most of the cases reaction suffers from reverse and / or side reactions.\textsuperscript{58} So a variety of new reagents have been introduced as catalyst, replacing acid or base for the synthesis of $\alpha,\alpha'$-bis(arylidene)cycloalkanones, such as Cp$_2$ZrH$_2$,\textsuperscript{59} BMPTO,\textsuperscript{60} RuCl$_3$,\textsuperscript{61} SmI$_3$,\textsuperscript{62} K-F/Al$_2$O$_3$,\textsuperscript{63} FeCl$_3$,\textsuperscript{64} InCl$_3$,\textsuperscript{65} TMSI / NaI,\textsuperscript{66} Yb(OTf)$_3$,\textsuperscript{67} I$_2$,\textsuperscript{68} LiCl$_4$O$_4$ / Et$_3$N,\textsuperscript{69} CH$_3$COONa/CH$_3$COOH.\textsuperscript{70} Some of these modified approaches are briefly described below.

Gupta et al.\textsuperscript{57b} in 1995 obtained $\alpha,\alpha'$-bis(arylidene)cyclohexanone by condensation of cyclic ketones and aromatic aldehydes in the presence of sodium hydroxide in open borosil glass vessel under microwave irradiations using ethanol as energy transfer medium. Five derivatives were synthesized in a time period of 2 minutes (scheme 13).
Cycloalkanones triethylmethylsilyl enol ethers on condensation with aldehyde at room temperature using Sml₃ under nitrogen atmosphere condition produced bis(arylidene) cycloalkanones in a time period of 4 to 6 hours⁶² (scheme 14). Later on Sml₃ catalysed condensation of cycloalkanones with aldehyde in ionic liquid was also reported⁷¹.

\[
\text{O} \quad \text{SiMe}_3
\]
\[n = 1, 2\]
\[\begin{array}{c}
\text{OSiMe}_3 \\
\text{Sml}_3 / \text{THF} \\
\Delta \\
\end{array}
\]
\[\begin{array}{c}
\text{2 Ar CHO} \\
\end{array}
\]
\[\begin{array}{c}
\text{(scheme 14)} \\
71-85\%
\end{array}
\]

The bis(4-methoxyphenyl)telluroxide (BMPTO) catalyzed reaction of cyclopentanone or cyclohexanone with aldehyde produced cross aldol product i.e. 2,5-bis(substituted benzylidene)cyclopentanones or 2,6-bis(substituted benzylidene)cyclohexanones in 53 to 85% yield under microwave condition, in a time period of 5-10 minutes⁶⁰ (scheme 15).

\[
\begin{array}{c}
\text{O} \\
n = 0, 1, \text{Ar} \\
\end{array}
\]
\[\begin{array}{c}
\text{BMPTO} \\
\text{M.W.} \\
\end{array}
\]
\[\begin{array}{c}
\text{2 Ar CHO} \\
\end{array}
\]
\[\begin{array}{c}
\text{scheme 15} \\
53-85\%
\end{array}
\]

Iranpoor et al.⁶¹ studied the cross condensation of cyclopentanone and cyclohexanone with different aromatic aldehydes using anhydrous RuCl₃ (0.02 mol eq.) as a catalyst in a sealed tube under solvent free conditions and found that α,α'-bis(arylidene) cycloalkanones are formed selectively in a time period of 4 to 24 hours (scheme 16).

\[
\begin{array}{c}
\text{O} \\
n = 0, 1, \text{Ar} \\
\end{array}
\]
\[\begin{array}{c}
\text{Anhyd. RuCl₃, sealed tube} \\
120^\circ \text{C, 4-24 hrs.} \\
\end{array}
\]
\[\begin{array}{c}
\text{scheme 16} \\
\end{array}
\]

Later on expensive RuCl₃ was replaced by hydrated Indium chloride (InCl₃. 4H₂O) under the similar conditions to produce α,α'-bis(arylidene)cycloalkanones in 89 to 95% yield in a time period of 4 to 24 hours⁶⁵ (scheme 17).
Ultrasound irradiation have also been utilized for the synthesis of $\alpha,\alpha'$-bis(arylidene) cycloalkanones.\textsuperscript{72} When a mixture of aromatic aldehyde, cycloalkanone in methanol and KF-Al$_2$O$_3$ was irradiated with ultrasound for a period of 30 to 150 minutes products were obtained in 60 to 92\% yield (scheme 18).

Wang et al.\textsuperscript{87} in 2004 reported the use of rare earth metal triflate such as Yb(OTf)$_3$ as an efficient catalyst for the synthesis of $\alpha,\alpha'$-bis(arylidene)cycloalkanones by cross aldol condensation (scheme 19).

Sabitha et al.\textsuperscript{66} used iodosotrimethylsilane generated in situ from chlorotrimethylsilane and sodium iodide in acetonitrile, as catalyst in cross aldol condensation for the synthesis of title compound (scheme 20).

Cross aldol condensation in the present of lithium perchlorate and tertiary amine has also been reported to produce $\alpha,\alpha'$-bis(arylidene)cyclopentanones in 74-97\% yield.\textsuperscript{69} Time varied from few minutes (for aryl aldehydes) to hours and days (for aliphatic aldehydes) (scheme 21).
SiO₂-OK, a new solid base⁷⁄₃, when used as catalyst for condensation of cycloalkanones with aromatic aldehydes in ethanol under refluxing condition produced α,α′-bis(arylidene)cycloalkanones in good yield (scheme 22).

Das et al.⁶⁸ used molecular iodine catalysed cross-aldol condensation for the synthesis of α,α′-bis(arylidene)cycloalkanones at room temperature (scheme 23).

The potential of sodium acetate in glacial acetic acid as catalyst for cross aldol condensation of cycloalkanones and aromatic aldehydes has also been examined⁷⁰ and found as good catalyst which produced the title compound in 78-83% yield (scheme 24).

Recently use of polymer-supported sulphonic acid (NKC-9) has been reported as an efficient catalyst for the cross aldol condensation of aryl aldehydes and cycloalkanones to produce α,α′-bis(substituted benzylidene)cycloalkanones⁷⁴ (scheme 25).
Barium hydroxide

Barium hydroxide is a valuable reagent because of its textural properties and microcrystallines structures and also due to the nature and amount of strong basic sites. The octahydrate, Ba(OH)$_2$.8H$_2$O is its most common form and is commercially available. On dehydration at elevated temperature (200-500°C) it is converted to the anhydrous form, which is called activated barium hydroxide or C-200 (i.e. dehydrated at 200°C).

Use of barium hydroxide in organic synthesis

Barium hydroxide in its hydrated as well as anhydrous (commonly called as C-200) form has been used as a base catalyst in variety of organic reactions. Barium hydroxide reacts as a base or as a nucleophile in homogeneous or in heterogeneous conditions. A brief account of use of barium hydroxide in organic reactions is listed below.

Heterogeneous Claisen – Schmidt condensation

Activated barium hydroxide (C-200) was used as a heterogeneous catalyst in Claisen-Schmidt reaction for the synthesis of styryl ketones and 2-hydroxychalcones (scheme 26)

Michael addition

Partially dehydrated Ba(OH)$_2$ has been reported as an efficient catalyst for the Michael addition of active methylene compounds to chalcones in organic solvent media to produce addition product in 90% yield (scheme 27).
Cannizaro reaction\textsuperscript{80}

Varma et al. in 1998 reported a method for preparation of alcohols from aldehydes via microwave accelerated cross cannizaro reaction using barium hydroxide under solvent free conditions (scheme 28).

\[
\begin{align*}
\text{RCHO} + (\text{CH}_2\text{O})_n & \rightarrow \text{RCH}_2\text{OH} + \text{RCOOH} \\
\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O} & \text{MW} \\
\end{align*}
\]

scheme 28

Wittig–Horner reaction\textsuperscript{85,87}

The reactions of aryl aldehydes with triethyl phosphonoacetates in 1,4-dioxane in the presence of small amount of water have been carried using C-200 at 70°C to give the corresponding 3- substituted ethyl acrylates. The yield of the product with aromatic aldehydes range from 0 % for indole 3-carbaldehyde to 100% for furfural and m-nitrobenzaldehyde (scheme 29).

\[
\begin{align*}
\text{RCHO} + \text{EtO}_2\text{C} \rightarrow \text{RCH}_2\text{H} \rightarrow \text{RCO}_2\text{Et} \\
\text{Ba(OH)}_2 \cdot \text{dioxane, H}_2\text{O, 70 °C} \\
\end{align*}
\]

scheme 29

Suzuki coupling\textsuperscript{84,88}

Barium hydroxide has also been used in solvent media for Suzuki cross coupling of arenes bearing hindered or electron withdrawing group (scheme 30).

\[
\begin{align*}
\text{Br} & \rightarrow \text{CO}_2\text{Et} \\
\text{Pd (PPh}_3\text{)}_4 & \text{DmAc, 100°C} \\
\end{align*}
\]

scheme 30

\(\alpha\)-Arylation of diethyl malonate\textsuperscript{81}

\(\alpha\)-Arylation of diethyl malonate has been reported in quantitative yield by using an homogeneous catalyst and Ba(OH)_2 . H_2O as heterogeneous base (scheme 31).

\[
\begin{align*}
\text{Br} & \rightarrow \text{CO}_2\text{Et} \\
\text{DMf, 100 °C} & \text{Na}_2\text{PdCl}_4 \\
\end{align*}
\]

scheme 31
Addition of diethyl melonate to coumarin

Michael addition of diethyl melonate to coumarin has been attempted in presence of C-200 in ethanol medium to give an unusual 1,2-addition-elimination product (scheme 32).

Ester hydrolysis

Recently a procedure for parallel ester hydrolysis has also been reported making use of barium hydroxide. In this method alkyl ester on treatment with barium hydroxide octahydrate in methanol followed by protonation with anhydrous hydrogen chloride afford carboxylic acid (scheme 33).

PRESENT WORK

α,α'-Bis(arylidene)cycloalkanones, a class of important intermediate compounds have been obtained by condensation between cycloalkanones and aromatic aldehydes using various bases and other reagents under variety of conditions i.e. in the presence of solvents, under solvent free conditions, using microwave radiations etc. (Table: 1).

Now a days as more emphasis is being laid on development of the reactions under eco-friendly conditions by eliminating the use of hazardous chemicals particularly solvents as they are more volatile in nature, therefore attempts have been made to carry out reaction in solid phase using microwave radiations or grinding technique.

Keeping these ideas in mind and as reactions using grinding condition have been found to be effective, it was proposed to study the condensation between cyclohexanones and aryl aldehydes under solvent free condition using grinding technique. Anhydrous barium hydroxide (C-200) was choosen as the base because it could also act as an effective solid support during the reaction because of its texture properties. Thus, a mixture of cyclohexanone, benzaldehyde and anhydrous barium hydroxide was ground together in a
mortar using a pestle at room temperature. The reaction mixture acquired a pale yellow colour almost immediately. The progress of the reaction was checked on TLC after grinding the mixture for 3 minutes when a solid yellow mass was found to be formed and it was observed that reactants had reacted almost completely. The reaction mixture was worked up after keeping at room temperature for 10 minutes and the solid product that had separated was identified as \( \alpha,\alpha'-\text{bis(benzylidene)cyclohexanone} \) from its IR & \(^1\text{H-}

NMR spectra.

This appeared to be a simple protocol for the preparation of \( \alpha,\alpha'-\text{bis(arylidene)} \)
cycloalkanones as it requires a very short period for reaction (3 minutes), yields are high and is totally eco-friendly as it does not require any organic solvent during the reaction or isolation of the product. A comparative account of the present method with the reported ones is highlighted in the following table (table: 1).

**Table 1:** Comparison of the results of the reactions carried out with different catalyst for the synthesis of \( \alpha,\alpha'-\text{bis(arylidene)cycloalkanones} \) and the present one.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>Time</th>
<th>Temp. ( ^\circ\text{C} )</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH/C(_2\text{H}_5\text{OH})</td>
<td>2-10 min.</td>
<td>MW</td>
<td>90-95</td>
<td>57b</td>
</tr>
<tr>
<td>2</td>
<td>SmI(_3)/THF</td>
<td>4-6 hrs.</td>
<td>room temp.-80</td>
<td>71-85</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>SmI(_3)/ionic liquid</td>
<td>3-4.5 hrs.</td>
<td>room temp.-60</td>
<td>80-98</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>BMPTO</td>
<td>5-10 min.</td>
<td>MW</td>
<td>53-85</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>RuCl(_3)</td>
<td>4-24 hrs.</td>
<td>120(sealed tube)</td>
<td>82-95</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>InCl(_3),4 H(_2\text{O})</td>
<td>4-24 hrs.</td>
<td>110(sealed tube)</td>
<td>89-95</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>KF/Al(_2\text{O}_3)</td>
<td>30-150 min.</td>
<td>ultra sound</td>
<td>60-92</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>Yb(OTF)(_3)</td>
<td>4-12 hrs.</td>
<td>90</td>
<td>88-97</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>LiClO(_4)/NaI</td>
<td>60-80 min.</td>
<td>room temp.</td>
<td>72-95</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>SiO(_2)/Et(_3\text{N})</td>
<td>1 min - 4 days</td>
<td>room temp.</td>
<td>74-97</td>
<td>69</td>
</tr>
<tr>
<td>11</td>
<td>AcONa, AcOH</td>
<td>1.5-4.5 hrs.</td>
<td>reflux</td>
<td>84-98</td>
<td>73</td>
</tr>
<tr>
<td>12</td>
<td>I(_2)/CH(_3)Cl(_2)</td>
<td>4.5-9.5 hrs.</td>
<td>room temp.</td>
<td>89-95</td>
<td>68</td>
</tr>
<tr>
<td>13</td>
<td>NKC-9</td>
<td>3-8 hrs.</td>
<td>120</td>
<td>78-83</td>
<td>70</td>
</tr>
<tr>
<td>14</td>
<td>Ba(OH)(_2)/Grinding*</td>
<td>3-5 min.</td>
<td>room temp.</td>
<td>84-93</td>
<td>----</td>
</tr>
</tbody>
</table>

* Present method
The success of the reaction was established by preparing various substituted \(\alpha,\alpha\)'-bis(arylidene)cyclohexanones and cyclopentanones. Details of the work are presented below.

**Reaction of cyclohexanone with benzaldehyde using anhydrous barium hydroxide (C-200) under grinding conditions: synthesis of 2,6-bis(benzylidene)cyclohexanone (8)**

A mixture of cyclohexanone (6; 4.8 mmol), benzaldehyde (7; 9.6 mmol) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with a pestle at room temperature for 3 minutes, till a light yellow solid mass was formed. The progress of the reaction was checked by TLC which showed the formation of product. For complete conversion the reaction mixture was left at room temperature and reactants were found to have reacted completely after 10 minutes. The reaction mixture was acidified with conc. HCl after diluting with ice cold water when a pale yellow solid separated out which was filtered and washed with water and recrystallised from ethanol (m.p. 117-18 °C, 90% yield). \(^1^H\)-NMR data of the compound showed a multiplet at \(\delta\) 1.72 - 1.88 for two protons (4\(^{-}\)CH\(^2\)). Two another multiplet, one at \(\delta\) 2.82 - 2.98 for four protons (3 & 5\(^{-}\)CH\(^2\)) and other at \(\delta\) 7.23 - 7.55 for ten protons (aromatic) were also appeared along with a singlet at \(\delta\) 7.80 for two protons (2\(^{\times}\) =CH). In IR, absorption at 1664 cm\(^{-1}\) showed the presence of \(\alpha,\beta\)-unsaturated carbonyl group. Based on this data the compound was identified as 2,6-bis(benzylidene)cyclohexanone (8).

\[
\begin{align*}
6 & \quad (+) \\
7 & \quad \text{anhydrous Ba(OH)\textsubscript{2}; r.t.} \\
\text{grinding 3 min.} & \quad \text{digestion 10 min.} \\
\end{align*}
\]

**Reaction of cyclopentanone with benzaldehyde using anhydrous barium hydroxide (C-200) under grinding conditions: synthesis of 2,5-bis(benzylidene)cyclopentanone (10)**

A mixture of cyclopentanone (9), benzaldehyde (7) and anhydrous barium hydroxide in a mortar was ground with a pestle at room temperature for 3 minutes till a light yellow solid mass was formed and then mixture was left at room temperature for
10 minutes. Completion of the reaction was confirmed by TLC. The reaction mixture on acidification in cold gave a solid m.p. 189-90 °C in 91% yield. $^1$H-NMR data of the compound showed a multiplet at δ 7.35-7.45 for ten protons (aromatic) and two singlet one at δ 3.10 for four protons (3 & 4 -CH$_2$) and another at δ 7.58 for two protons (2 × =CH). In IR it showed a peak at 1675 cm$^{-1}$ due to α,β-unsaturated ketonic group. Based on this data compound formed was identified as 2,5-bis(benzylidene) cyclopentanone (10).

$$
\begin{align*}
\text{Synthesis of 2,6-bis(4-methoxybenzylidene)cyclohexanone (12)}
\end{align*}
$$

A mixture of cyclohexanone (6), 4-methoxybenzaldehyde (11) and anhydrous barium hydroxide on grinding in a mortar with pestle for 3 minutes at room temperature and on working up as described earlier gave 2,6-bis(4-methoxybenzylidene) cyclohexanone (12) in 92% yield, whose structure was confirmed based on its IR and $^1$H-NMR.

$$
\begin{align*}
\text{Synthesis of 2,5-bis(4-methoxybenzylidene)cyclopentanone (13)}
\end{align*}
$$

A mixture of cyclopentanone (9), 4-methoxybenzaldehyde (11) and anhydrous barium hydroxide on grinding in a mortar with pestle for 3 minutes at room temperature followed by working up as described earlier gave 2,5-bis(4-methoxybenzylidene) cyclopentanone (13) in 93% yield whose structure was confirmed based on its IR and $^1$H-NMR.
Synthesis of 2,6-bis(4-methylbenzylidene)cyclohexanone (15)

A mixture of cyclohexanone (6), 4-methylbenzaldehyde (14) and anhydrous barium hydroxide on grinding in a mortar with pestle for 4 minutes followed by working up as described earlier gave 2,6-bis(4-methylbenzylidene)cyclohexanone (15) in 93% yield, whose structure was confirmed based on its IR and $^1$H-NMR data.

Synthesis of 2,5-bis(4-methylbenzylidene)cyclopentanone (16)

A mixture of cyclopentanone (9), 4-methylbenzaldehyde (14) and anhydrous barium hydroxide on grinding in a mortar with pestle for 4 minutes at room temperature followed by working up as described earlier gave 2,5-bis(4-methylbenzylidene)cyclopentanone (16) in 91% yield whose structure was confirmed based on its IR and $^1$H-NMR data.

Synthesis of 2,6-bis(4-chlorobenzylidene)cyclohexanone (18)

A mixture of cyclohexanone (6), 4-chlorobenzaldehyde (17) and anhydrous barium hydroxide on grinding in a mortar with pestle for 5 minutes at room temperature followed by working up as described earlier gave 2,6-bis(4-chlorobenzylidene)cyclohexanone (18) in 88% yield. Identity of the compound was confirmed by its IR and $^1$H-NMR data.
Synthesis of 2,5-bis(4-chlorobenzylidene)cyclopentanone (19)

A mixture of cyclopentanone (9), 4-chlorobenzaldehyde (17) and anhydrous barium hydroxide on grinding in a mortar with pestle for 5 minutes at room temperature followed by working up as described earlier gave 2,5-bis(4-chlorobenzylidene)cyclopentanone (19) in 85% yield whose structure was confirmed based on its IR and $^1$H-NMR spectral data.

Synthesis of 2,6-bis(4-nitrobenzylidene)cyclohexanone (21)

A mixture of cyclohexanone (6), 4-nitrobenzaldehyde (20) and anhydrous barium hydroxide on grinding in a mortar followed by working up as described earlier gave 2,6-bis(4-nitrobenzylidene)cyclohexanone (21) in 87% yield. Identity of the compound was confirmed by IR and $^1$H-NMR spectral data.

Synthesis of 2,5-bis(4-nitrobenzylidene)cyclopentanone (22)

A mixture of cyclopentanone (9), 4-nitrobenzaldehyde (20) and anhydrous barium hydroxide was ground in a mortar with pestle at room temperature followed by working up as described earlier gave 2,5-bis(4-nitrobenzylidene)cyclopentanone (22) in 84% yield. Structure of the compound was confirmed based on its IR and $^1$H-NMR spectral data.
Synthesis of 2,6-bis(cinnamylidene)cyclohexanone (24)

A mixture of cyclohexanone (6), cinnamaldehyde (23) and anhydrous barium hydroxide on grinding in a mortar followed by working up as described earlier gave 2,6-bis(cinnamylidene)cyclohexanone (24) in 89% yield. Identity of the compound was confirmed by its IR and $^1$H-NMR spectral data.

Synthesis of 2,5-bis(cinnamylidene)cyclopentanone (25)

A mixture of cyclopentanone (9), cinnamaldehyde (23) and anhydrous barium hydroxide on grinding in a mortar with pestle at room temperature followed by working up as described earlier gave 2,5-bis(cinnamylidene)cyclopentanone (25) in 88% yield. Structure of the compound was confirmed based on its IR and $^1$H-NMR spectral data.
Experimental

2,6-Bis(benzylidene)cyclohexanone (8)

A mixture of cyclohexanone (6; 0.5 ml), benzaldehyde (7; 0.98 ml) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 3 minutes, till a light yellow solid mass was formed. The reaction mixture was left at room temperature for 10 minutes. Progress of the reaction was checked on TLC and reactants were found to have reacted completely. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Pale yellow coloured solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2,6-bis(benzylidene)cyclohexanone (8; 1.20 g), m.p. 117-18°C (lit. m.p. 117-18°C). IR (KBr): 1664 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 1.72-1.88 (m, 2H, 4-CH₂), 2.82-2.98 (m, 4H, 3 & 5 -CH₂) 7.23-7.55 (m, 10H, Ar-H), 7.80 (s, 2H, 2 x = CH).

2,5-Bis(benzylidene)cyclopentanone (10)

A mixture of cyclopentanone (9; 0.5 ml), benzaldehyde (7; 1.15 ml) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 3 minutes till a light yellow solid mass was formed. The reaction mixture was left at room temperature for 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Pale yellow coloured solid that separated out was filtered, washed with water, and recrystallised from ethanol to give 2,5-bis(benzylidene)cyclopentanone (10; 1.38 g), m.p. 189-90°C (lit. 188-89°C). IR (KBr): 1675 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 3.10 (s, 4H, 3 & 4-CH₂), 7.35-7.45 (m, 10H, Ar-H), 7.58 (s, 2H, 2 x = CH).

2,6-Bis(4-methoxybenzylidene)cyclohexanone (12)

Cyclohexanone (6; 0.5 ml), 4-methoxybenzaldehyde (11; 1.18 ml) and anhydrous barium hydroxide (2.5 g) were taken in mortar and the reaction mixture was ground well with pestle for 3 minutes and the reaction mixture was kept at room temperature for 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated
out was filtered, washed with water and recrystallised from ethanol to give 2,6-bis(4-methoxybenzylidene)cyclohexanone (12; 1.48 g), m.p. 202-03°C (lit. m.p. 203-04°C). IR (KBr): 1661cm⁻¹(C=O).

1H-NMR (CDCl₃): δ 1.72-1.84 (m, 2H, 4-CH₂), 2.91 (t, J= 5.4 Hz, 4H, 3 & 5-CH₂), 3.78 (s, 6H, 2 x OCH₃), 6.96-7.48 (m, 8H, Ar-H), 7.75(s, 2H, 2 x = CH).

2.5-Bis(4-methoxybenzylidene)cyclopentanone (13)

A mixture of cyclopentanone (9; 0.5 ml), 4-methoxybenzaldehyde (11; 1.37 ml) and anhydrous barium hydroxide (2.5 g) was ground in a mortar with pestle and reaction mixture was left at room temperature for 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2,5-bis(4-methoxybenzylidene)cyclopentanone (13; 1.68 g), m.p. 210-11°C (lit. m.p. 212°C). IR (KBr): 1692 cm⁻¹(C=O).

1H-NMR (CDCl₃): δ 3.08 (s, 4H, 3 & 4-CH₂), 3.80 (s, 6H, 2 x OCH₃), 6.92 - 7.57 (m, 10H, 8 Ar-H & 2 x = CH).

2,6-Bis(4-methylbenzylidene)cyclohexanone (15)

Cyclohexanone (6; 0.5 ml), 4-methylbenzaldehyde (14; 1.14 ml) and anhydrous barium hydroxide (2.5 g) were ground in a mortar with pestle for 4 minutes till light yellow solid mass was formed and the reaction mixture was left at room temperature for 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2,6-bis(4-methylbenzylidene)cyclohexanone (15; 1.40 g), m.p. 169-70°C (lit. m.p. 172-73°C). IR (KBr): 1661 cm⁻¹(C=O).

1H-NMR (CDCl₃): δ 1.72-1.77 (m, 2H, 4-CH₂), 2.35 (s, 6H, 2 x CH₃), 2.92 (t, J= 5.6 Hz, 4H, 3 & 5 -CH₂), 7.18-7.43 (m, 8H, Ar-H), 7.76 (s, 2H, 2 x = CH).

2,5-Bis(4-methylbenzylidene)cyclopentanone (16)

A mixture of cyclopentanone (9; 0.5 ml), 4-methylbenzaldehyde (14; 1.33 ml) and anhydrous barium hydroxide(2.5 g) was ground well in a mortar with pestle for 4 minutes
and the reaction mixture was left at room temperature for another 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2,5-bis(4-methylbenzylidene) cyclopentanone (16; 1.48 g), m.p. 184-85°C (lit. m.p. 183-84°C).62

IR (KBr): 1700 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 2.35 (s, 6H, 2 x CH₃), 3.06 (s, 4H, 3 & 4 -CH₂), 7.12-7.57 (m, 10H, Ar-H, & 2 x = CH).

2,6-Bis(4-chlorobenzylidene)cyclohexanone (18)

Cyclohexanone (6; 0.5 ml), 4-chlorobenzaldehyde (17; 1.36 g) and anhydrous barium hydroxide (2.5 g) were ground in a mortar by a pestle for 5 minutes and the reaction mixture was left at room temperature of another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The pale yellow solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2,6-bis(4-chlorobenzylidene) cyclohexanone (18; 1.46 g), m.p. 146-47°C (lit. m.p. 147-48°C).91

IR (KBr): 1667 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 1.81 -1.85 (m, 2H, 4-CH₂), 2.86-2.93 (t, J=6.0 Hz, 4H, 3 & 5 -CH₂), 7.36-7.39 (m, 8H, Ar-H), 7.73 (s, 2H, 2 x = CH).

2,5-Bis(4-chlorobenzylidene)cyclopentanone (19)

A mixture of cyclopentanone (9; 0.5 ml), 4-chlorobenzaldehyde (17; 1.58 g) and anhydrous barium hydroxide (2.5 g) was ground in a mortar by a pestle for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes, and reaction was found to be completed when checked on TLC. Ice cold water (30 ml) was added to the reaction mixture, acidified with conc. HCl. The solid product that separated out was filtered, washed with water and recrystallised from ethanol to give 2,5-bis(4-chlorobenzylidene)cyclopentanone (19; 1.58 g), m.p. 225-26°C (lit. m.p. 224-25°C).62

IR (KBr): 1620 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 3.11 (s, 4H, 3 & 4 -CH₂), 7.29-7.65 (m, 10H, Ar-H & 2 x = CH).
2,6-Bis(4-nitrobenzylidene)cyclohexanone (21)

A mixture of cyclohexanone (9; 0.5 ml), 4-nitrobenzaldehyde (20; 1.46 g) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes, and the reaction mixture was left at room temperature for another 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The light yellow solid product that separated out was filtered, washed with water and recrystallised from ethanol to give 2,6-bis(4-nitrobenzylidene)cyclohexanone (21; 1.53 g), m.p. 158-59°C (lit. m.p.159°C). IR (KBr): 1669 cm\(^{-1}\) (C=O). 
\[^1\text{H-NMR (CDCl}_3\text{): }\delta 1.85-1.87 \text{ (m, 2H, 4-CH}_2\text{), 2.94 \text{ (t, J = 6.0 Hz, 4H, 3 & 5 -CH}_2\text{), 7.56-8.20 \text{ (m, 8H, Ar-H), 8.30 (s, 2H, 2 = CH).}\]

2,5-Bis(4-nitrobenzylidene)cyclopentanone (22)

A mixture of cyclopentanone (9; 0.5 ml), 4-nitrobenzaldehyde (20; 1.71 g) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. The reaction was found to be completed when checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The light yellow solid product that separated out was filtered, washed with water, and recrystallised from ethanol to give 2,5-bis(4-nitrobenzylidene)cyclopentanone (22; 1.66 g), m.p. 228-30°C (lit. m.p. 230-31°C). IR (KBr): 1686 cm\(^{-1}\) (C=O). 
\[^1\text{H-NMR (CDCl}_3\text{): }\delta 3.20 \text{ (s, 4H, 3 & 4 -CH}_2\text{), 7.65-8.30 \text{ (m, 10H, Ar-H), 2 = CH).}\]

2,6-Bis(cinnamylidene)cyclohexanone (24)

A mixture of cyclohexanone (6; 0.5 ml), cinnamaldehyde (23; 1.22 ml), and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 4 minutes till a yellow coloured solid mass was formed. The reaction mixture was then left at room temperature for 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture, acidified with conc HCl, the yellow solid that separated out was filtered, washed with water and recrystallised
from ethanol to give 2,6-bis(cinnamylidene)cyclohexanone (24; 1.40 g), m.p. 179-80°C (lit. m.p. 180°C).\textsuperscript{60}

IR (KBr): 1690 cm\(^{-1}\)(C=O).

\(\text{H-NMR (CDCl}_3\text{): } \delta 1.75 (m, 2H, 4-CH}_2\text{), 2.72-275 (t, J = 5.6 Hz, 4H, 3 \& 5 -CH}_2\text{), 6.96-7.44 (m, 16H, Ar-H, 6 \times = CH}).\)

2,5-Bis(cinnamylidene)cyclopentanone (25)

Cyclopentanone (9; 0.5 ml), cinnamaldehyde (23; 1.42 ml) and anhydrous barium hydroxide (2.5 g) were ground in a mortar with a pestle for 4 minutes and the reaction mixture was left at room temperature for another 10 minutes, when reaction was found to be completed on TLC. Ice cold water (30 ml) was added to the reaction mixture, acidified with conc. HCl. The pale yellow solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2, 5-bis(cinnamylidene)cyclopentanone (25; 1.55 g), m.p. 223-240°C (lit. m.p. 222-240°C).\textsuperscript{60}

IR (KBr): 1670 cm\(^{-1}\)(C=O).

\(\text{H-NMR (CDCl}_3\text{): } \delta 2.93 (s, 4H, 3 \& 4 -CH}_2\text{), 6.98-7.53 (m, 16H, Ar-H, 6 \times = CH}).\)
Part 2: Synthesis of chalcones and 2'-hydroxychalcones

Introduction

Chalcone is a generic term given to the compounds bearing the 1,3-diphenyl-2-propen-1-one framework and possess C-15 skelton\textsuperscript{92} (Fig. 4). These compounds constitute an important class of natural products belonging to the flavonoid family.\textsuperscript{92} Naturally occurring chalcones are all hydroxylated to greater or lesser extent, however, the parent compound chalcone (26) itself is not known as a natural product. In nature chalcones are found in many plant organs, most conspicuously in flowers. Generally carotenoids are responsible for the yellow colour of the flower in most of the cases but in the case of certain members of the Compositae, Oxalidaceae, Scrophulariaceae, Gesneriaceae, Acanthaceae and Liliaceae, chalcones contribute significantly to the corolla pigmentation\textsuperscript{93}. Few examples of naturally occurring chalcones are.

(i) 2', 4'-dihydroxychalcone (27) isolated from Flemingia chapper.\textsuperscript{94}
(ii) 2, 4', 4-trihydroxychalcone (28) isolated from the bark of leguminous trees.\textsuperscript{95}
(iii) 2',4',3,4-tetrahydroxychalcone (Butein,29) isolated from the bark of acacia trees.\textsuperscript{96}
(iv) 2',4',3,4,5-pentahydroxychalcone (Robtein,30) isolated from the heartwood of acacia.\textsuperscript{97}
(v) 2'-hydroxy-3',4',6'-trimethoxychalcone (31), 2',3',4',6'-tetramethoxychalcone (32), 2',4-dihydroxy-3',4',6'-trimethoxychalcone (33) isolated from the whole stem of popowia cauliflora.\textsuperscript{98a}

(vi) cryptocaryone (34) isolated from Cryptocarya bourdillonii (Lauraceae) is among the rare group of flavonoids having partially reduced A ring.\textsuperscript{98b}

The most common chalcones found in food are phloretin (35) and phloridzin (36) in apples, chalconaringenin (37) in tomatoes.\textsuperscript{99}

2'-Hydroxychalcones are the key intermediates for the synthesis of variety of biologically active oxygen heterocyclic compounds\textsuperscript{93,100} such as, flavanones, flavones, homoiso flavones, aurones and flavanols etc. (Fig. 5).

\textsuperscript{98a}
Chalcone is a unique template that is associated with several biological activities. The compounds with chalcone backbone have been reported to possess varied biological and pharmacological activities including antimicrobial, \textsuperscript{101} anti-inflammatory, \textsuperscript{102} analgesic, \textsuperscript{103} cytotoxic, \textsuperscript{104} antimalarial, \textsuperscript{105} antiviral, \textsuperscript{106} anti HIV, \textsuperscript{107} antioxidant, \textsuperscript{108} antihistaminic, \textsuperscript{109} antihyperglycemic \textsuperscript{110} and antiplatelet activities. \textsuperscript{111} Infact the presence of reactive $\alpha,\beta$-unsaturated keto group in chalcones is found to be responsible for their biological activities. There are also evidences that biological activities of the chalcones are correlated to their antioxidant potential \textsuperscript{112}. The antioxidant properties of the chalcones are known to be influenced to a greater extent by the two aryl structure i.e. the substituents on two aryl rings of chalcone molecule and their substitution patterns, especially the hydroxyl substituent is one of the key group to enhance greatly the antioxidant activity of chalcone mainly due to its easy conversion to phenoxy radicals.
through the hydrogen atom transfer mechanism. This phenoxy radical formation may be central to the antioxidant properties which are assessed primarily as radical scavenging potential of phenolic chalcones\textsuperscript{113}. Synthesis of large number of chalcones derivative have been reported in the literature along with the evaluation of their diverse and potent biological activities\textsuperscript{114}. Recently Hwang et al.\textsuperscript{115} have reported the synthesis of a series of dihydroxylated chalcones (Fig. 6) along with evaluation of their radical scavenging activities (ranging from 25\% to 90\% control at the concentration of 50 \(\mu\)m, depending on the substitution pattern of two hydroxyl groups).

\begin{figure}[h]
\centering
\includegraphics[width=0.4\textwidth]{fig6}
\caption{Fig. 6}
\end{figure}

Khan et al.\textsuperscript{116} have reported the synthesis of some chalcone derivatives containing 1,4-dioxane ring. Two of these derivatives (38, 39) showed potent antihepatotoxic activity, where as other compounds exhibited moderate activity w.r.t. standard drug silybon-70.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig3839}
\caption{38, 39}
\end{figure}

Beside pharmacological activities, chalcones and their derivatives also find application as artificial sweetners\textsuperscript{117}, scintillators\textsuperscript{118}, sunscreen agents\textsuperscript{119} and for the synthesis of photoreactive materials\textsuperscript{120}.
Past work on the synthesis of chalcones

By Claisen Schmidt condensation of acetophenones and benzaldehydes

There are different methods, which have been reported in the literature for the synthesis of chalcones, but these are commonly synthesised via Claisen-Schmidt condensation between acetophenones and benzaldehydes. The Claisen Schmidt condensation, for the synthesis of chalcones have been carried out using different condensing agents like aqueous alkali, hydrogen chloride, aluminium oxide, alkali metal alkoxide, phosphorus oxychloride, lewis acids such as boron trifluoride, aluminium trichloride, metal phosphate etc. but out of these, base catalysed condensation of acetophenones and benzaldehydes has proved to be most popular because of its simplicity and ready accessibility of starting materials (scheme 34).

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 & \quad \text{OHC} & \quad \text{Base} & \quad \text{O} \\
\text{scheme 34} \\
\end{align*}
\]

Dhar et al. obtained 2',4'-dihydroxychalcone by condensation of resacetophenone and benzaldehyde in presence of 40% aqueous ethanolic potassium hydroxide at room temperature for seven days. Beside the expected chalcone, small quantity of 7-hydroxyflavanone, benzyl alcohol and benzoic acid was also obtained (scheme 35). Higher temperature was found to favour the formation of chalcone over that of flavanone. Due to the accompanying cannizaro and cyclisation reaction the yield of product was low.

\[
\begin{align*}
\text{OH} & \quad \text{OH} & \quad \text{OHC} & \quad 40\% \text{alkali} & \quad \text{room temp., 7 days} & \quad \text{HO} & \quad \text{HO} & \quad \text{CH}_3 & \quad \text{O} \\
\text{scheme 35} \\
\end{align*}
\]
Later on Roux et al.\textsuperscript{129} found that protection of o-hydroxy group of acetophenone prior to condensation with benzaldehyde prevent the cyclisation of chalcone. Grover et al.\textsuperscript{130} modified the above procedure by carrying out the condensation under phase transfer catalysed condition. When acetophenones were condensed with aryl aldehydes in aqueous ethanolic medium containing potassium hydroxide in presence of triethylbenzyl ammonium chloride as phase transfer catalyst, desired chalcones were obtained in 64-93\% yield after stirring the reaction mixture for 24 hours (scheme 36).

\[
\begin{array}{cccccc}
R_2 & R_3 & O & C_3H_7 & \text{H} & \text{O} \\
\text{H} & \text{OH} & \text{CH}_3 & \text{OH} & \text{H} & \text{OH} \\
\end{array}
\]

\[
\text{OHC-} - \text{C}_6\text{H}_4\text{R} \quad \text{C}_2\text{H}_5\text{OH} / \text{H}_2\text{O} / \text{OH}^+ \\
(C_2H_3)_NCH_2C_6H_5\text{Cl}^- \quad \text{R}_2 \quad \text{R}_3 \quad \text{R}_4 \quad \text{R}_5 \quad \text{R}_6
\]

\text{scheme 36}

Gupta et al.\textsuperscript{47b} synthesised different chalcones by condensation of acetophenones with benzaldehydes using catalytic amount of sodium hydroxide in dry ethanol, using microwave irradiations when time period for reaction was drastically reduced (scheme 37).

\[
\text{R}_3 \quad \text{O} \quad \text{CH}_3 \quad \text{NaOH (s)} \quad \text{M.W.} \quad \text{O} \\
\text{OHC-} - \text{C}_6\text{H}_4\text{R} \quad \text{R} \quad \text{R}_2
\]

\text{scheme 37}

Synthesis of chalcones has also been reported in interfacial solid-liquid condition under thermochemical and sonochemical conditions in ethanol medium. The required chalcones were obtained in 24-89\% yield after 5 hours of refluxing in thermochemical\textsuperscript{86b} and in 5-80\% after 24 hours in sonochemical\textsuperscript{131} conditions (scheme 38).

\[
\text{R}_1 \quad \text{O} \quad \text{CH}_3 \quad \text{O} \quad \text{R} \\
\text{R} \quad \text{R}_2 \quad \text{C-200} \quad \triangle, \text{or Ultrasound} \quad \text{R} \quad \text{R}_2
\]

\text{R} = \text{H, OH}

\text{scheme 38}
Varma et al.\textsuperscript{124} synthesised chalcones by condensing benzaldehydes with ketones over basic alumina. Reaction mixture was agitated at room temperature for 2.5 hours using a Fisher Vortex mixer (scheme 39).

![Scheme 39](image)

A simple heterogeneous procedure for the synthesis of chalcones has also been developed using Mg-Al-O\textsuperscript{1}-Bu hydrotalcite as solid base catalyst\textsuperscript{132} (scheme 40).

![Scheme 40](image)

Besides the base catalysed condensation, use of other catalysts have also been reported for the synthesis of chalcones via Claisen Schmidt condensation. Breslow \& Hauser\textsuperscript{127a} reported the use of boron trifluoride whereas Rao et al.\textsuperscript{133} synthesised simple chalcones by irradiating the mixture of acetophenones and aryl aldehydes in presence of anhydrous zinc chloride using microwave heating (scheme 41).

![Scheme 41](image)

Sebti et al.\textsuperscript{134} synthesised chalcones at room temperature using catalytic amount of natural phosphate (NP) modified with sodium nitrate by calcination procedure, in time period of 24 hours (scheme 42).

![Scheme 42](image)
Claisen Schmidt condensation of acetophenones with aromatic aldehydes catalysed by KF- Al₂O₃ has provided chalcones (83-98%) in alcoholic medium under ultrasound irradiations\(^\text{135}\) (scheme 43).

\[
\text{R}^1\text{CCH}_3 + \text{OHC} - \text{C} = \text{O} \xrightarrow{\text{KF- AI}_2\text{O}_3 / C_2\text{H}_5\text{OH}} \text{Ultrasound} \xrightarrow{} \text{R}^1\text{CH} = \text{CH} - \text{C} = \text{O} \text{R}^2
\]

(scheme 43)

Use of amino graphed zeolites has also been reported under ultrasound condition, which has produced simple chalcones in a period of three hours\(^\text{136}\) (scheme 44).

\[
\text{OCH}_3 + \text{OHC} - \text{C} = \text{O} \xrightarrow{\text{Basic Zeolite}} \xrightarrow{\text{Ultrasound irradiation}} \text{OCH} = \text{CH} - \text{C} = \text{O}
\]

(scheme 44)

Recently Aranda et al.\(^\text{137}\) have also utilised ultrasound acceleration for the synthesis of title compounds using two basic activated carbons (Na and Cs-Norit) as catalyst. Though Claisen Schmidt condensation of acetophenones with benzaldehydes is very convenient and reliable approach for the synthesis of chalcones, but it is not the only route reported, some other methods for the synthesis of chalcones are listed below.

**Other methods**

**Friedel-Craft reaction\(^\text{138}\)**

Friedel Craft reaction between cinnamoyl chloride and resorcinol in nitrobenzene medium in presence of anhydrous aluminium chloride have been found to give 2',4'-dihydroxychalcone (scheme 45).

\[
\text{OH} \text{OH} + \text{CH}=\text{CH}-\text{C}=\text{Cl} \xrightarrow{\text{AlCl}_3} \xrightarrow{\text{C}_6\text{H}_5\text{NO}_2} \text{HO} \text{HO} \text{KH}
\]

(scheme 45)

Later on Kochetkou et al.\(^\text{139}\) reinvestigated the above reaction and obtained chalcones by reacting β-chlorovinyl ketones with substituted benzene (scheme 46).
2'-Hydroxychalcones have also been obtained by ring opening of the hetero ring of flavones using alkali\textsuperscript{57a} or the micro organism\textsuperscript{141} \textquoteleft Gibberella fukikuroi\textquoteright or U.V. Irradiations\textsuperscript{142} (scheme 48).

Saito et al. have synthesised chalcones from phenyl acetylene and aromatic aldehydes using triton B in DMSO\textsuperscript{143} (scheme 49).

\textbf{PRESENT WORK}

2'-Hydroxychalcones are the important class of compounds as they are used as intermediates for the synthesis of various class of flavanoids and other heterocyclic compounds. Till date these compounds are prepared by Claisen Schmidt reaction between acetophenones and aryl aldehydes in the presence of alcoholic potassium hydroxide at
room temperature (24 to 72 hours). Though number of attempts have been made to reduce the reaction time (Table: 2) and use of microwave is one step in this direction when the reaction is completed in 2 minutes.

**Table: 2** Comparison of the results of the present method used for the synthesis of chalcones with the reported ones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time</th>
<th>Temp.</th>
<th>% Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH</td>
<td>24-47 hrs.</td>
<td>room temp.</td>
<td>41-50</td>
<td>122b</td>
</tr>
<tr>
<td>2</td>
<td>Basic Al₂O₃</td>
<td>2.5 hrs.</td>
<td>room temp.</td>
<td>72-83</td>
<td>124</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl₂</td>
<td>5 min.</td>
<td>M.W.</td>
<td>75-90</td>
<td>133</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl₂</td>
<td>6 hrs.</td>
<td>M.W.</td>
<td>75-90</td>
<td>133</td>
</tr>
<tr>
<td>5</td>
<td>AlCl₃/CS₂</td>
<td>6 hrs.</td>
<td>room temp.</td>
<td>91</td>
<td>127b</td>
</tr>
<tr>
<td>6</td>
<td>BF₃</td>
<td>3 hrs.</td>
<td>room temp.</td>
<td>61</td>
<td>127a</td>
</tr>
<tr>
<td>7</td>
<td>KOH/TEBA/C₂H₅OH/H₂O</td>
<td>24 hrs.</td>
<td>30 °C</td>
<td>71-92</td>
<td>130</td>
</tr>
<tr>
<td>8</td>
<td>Mg-Al-O'Bu</td>
<td>1-8 hrs.</td>
<td>reflux</td>
<td>77-93</td>
<td>132</td>
</tr>
<tr>
<td>9</td>
<td>NaNO₃/NP/CH₃OH</td>
<td>16-48 hrs.</td>
<td>room temp.</td>
<td>40-98</td>
<td>134</td>
</tr>
<tr>
<td>10</td>
<td>KOH/ C₂H₅OH</td>
<td>4-300 min.</td>
<td>ultrasound irradiation</td>
<td>52-97</td>
<td>135</td>
</tr>
<tr>
<td>11</td>
<td>KF/ Al₂O₃</td>
<td>4-960 min.</td>
<td>ultrasound irradiation</td>
<td>83-98</td>
<td>135</td>
</tr>
<tr>
<td>12</td>
<td>NaOH/ C₂H₅OH/</td>
<td>2 min.</td>
<td>M.W.</td>
<td>85-96</td>
<td>57b</td>
</tr>
<tr>
<td>13</td>
<td>Ba(OH)₂/C₂H₅OH</td>
<td>4 hrs.</td>
<td>reflux</td>
<td>24-89</td>
<td>86</td>
</tr>
<tr>
<td>14</td>
<td>Ba(OH)₂/C₂H₅OH</td>
<td>10 min.+24 hrs.</td>
<td>ultrasound irradiation</td>
<td>5-80</td>
<td>131</td>
</tr>
<tr>
<td>15</td>
<td>Ba(OH)₂ Grinding*</td>
<td>2 to 5 min.</td>
<td>room temp.</td>
<td>83-92</td>
<td>-</td>
</tr>
</tbody>
</table>

* Present method.

But one serious limitation with this method is the formation of side products aurones and flavanones along with the required 2'-hydroxylchalcones, thus reducing the yields. Having met with the success of the condensation reaction between cyclohexanone or cyclopentanone with various aromatic aldehydes in the presence of anhydrous barium hydroxide using grinding technique, it was proposed to synthesise 2'-hydroxylchalcones from 2-hydroxyacetophenones and various aromatic aldehydes. Thus a mixture of acetophenone, benzaldehyde and anhydrous barium hydroxide was ground in a mortar with a pestle and reactants were found to have reacted completely after 4 minutes of grinding. The reaction mixture on working up gave chalcone in 87% yield whose identity was confirmed by its ¹H-NMR and by direct comparison with the authentic sample.
Using this method, various substituted chalcones and 2'-hydroxychalcones were prepared.
This method was next successfully used for the synthesis of various substituted
\( \omega \)-cinnamylidene-2-hydroxyacetophenones, the required intermediates for synthesis of
2-styrylchromones, by carrying out reaction of 2-hydroxyacetophenones with
cinnamaldehyde.
In conclusion is can be stated that the present method has an edge over the other
previously known methods as it gives the required chalcones in high yield in very short
duration of time and is totally eco-friendly. Moreover, by this method 2'-hydroxy
chalcones are obtained selectively with no cyclised product. Details of the present work
are given below.

**Condensation of acetophenone and benzaldehyde: synthesis of chalcone (41)**

A mixture of acetophenone (40; 4 mmol), benzaldehyde (7; 4.1 mmol) and
anhydrous barium hydroxide (2 g) was ground well in a mortar with pestle at room
temperature for 4 minutes, till the reaction mixture was transformed into a yellow solid
mass. The reaction mixture was left at room temperature and the progress of the reaction
was monitored on TLC. Starting acetophenone was found to have reacted completely
after 10 minutes of standing at room temperature. The reaction mixture was acidified
with conc. HCl in cold after diluting the reaction mixture with ice-cold water to give pale
yellow solid (m.p. 55-56\(^\circ\)C) in 90% yield. The compound in its \(^1\)H-NMR showed a
multiplet at \( \delta 7.34-7.52 \) for seven protons (H-2, H-3, H-5, H-6, H-3', H-5' & H-\( \beta \)),
another multiplet at \( \delta 7.56 \) for two protons (H-4 & H-4'), along with doublets at \( \delta 7.81 \)
for one proton (J = 15.0 Hz, H-\( \alpha \)) and \( \delta 7.98 \) for two protons (J = 9.0 Hz, 2H, H-2' &
H-6'). In IR it showed an absorption peak at 1651 cm\(^{-1}\) due to \( \alpha,\beta \)-unsaturated carbonyl
functional group. Based on this data the compound was identified as chalcone (41) and its
structure was finally confirmed by comparison with authentic sample\(^{144}\).

\[
\begin{align*}
\text{CH}_3 & \quad + \quad \text{OHC-} \\
40 & \quad \quad \quad 7 \\
\quad \quad \quad \quad \quad \quad \text{anhydrous Ba(OH)_2; r.t.} \\
\quad \quad \quad \quad \text{grinding 4 min.} \\
\quad \quad \quad \quad \text{digestion 10 min.} \\
\end{align*}
\]

\[ \text{41} \]
Synthesis of 4-methoxychalcone (42)

A mixture of acetophenone (40), anisaldehyde (11) and anhydrous barium hydroxide was ground in a mortar with pestle for 3 minutes and reaction mixture was left at room temperature for 10 minutes. The reaction mixture on working up as described above gave 4-methoxychalcone (42) in 91% yield. The structure of the compound was confirmed by $^1$H-NMR and comparison with authentic sample (Co-IR, m.m.p.).

\[
\text{苯} + \text{OHC-苯} \xrightarrow{\text{研磨3 min.}} \text{OCH}_3
\]

Synthesis of 4-methylchalcone (43)

Acetophenone (40) and 4-methylbenzaldehyde (14) were ground well in presence of anhydrous barium hydroxide in a mortar with pestle and worked up as described above to give 4-methylchalcone (43) in 88% yield. The structure of the compound was confirmed by $^1$H-NMR and comparison with authentic sample (Co-IR, m.m.p.).

\[
\text{苯} + \text{OHC-苯} \xrightarrow{\text{研磨4 min.}} \text{CH}_3
\]

Synthesis of 4-chlorochalcone (44)

A mixture of acetophenone (40), 4-chlorobenzaldehyde (17) and anhydrous barium hydroxide on grinding in mortar with pestle for 5 minutes and then leaving it at room temperature for 10 minutes gave 4-chlorochalcone (44) in 85% yield, after working up the reaction mixture as described above. Structure of the compound was confirmed by $^1$H-NMR and comparison with authentic sample (Co-IR, m.m.p.).
Synthesis of 4-nitrochalcone (45)

A mixture of acetophenone (40), 4-nitrobenzaldehyde (20) and anhydrous barium hydroxide on grinding in mortar with pestle and working up as described above gave a yellow solid in 87% yield, which was identified as 4-nitrochalcone (45) based on \(^1\)H-NMR spectral data and comparison with authentic sample (Co-IR, m.m.p.).

\[
\begin{align*}
\text{CH}_3 \text{C} & + \text{OHC} - \text{NO}_2 \\
40 & \quad 20 \\
& \quad \text{anhydrous Ba(OH)}_2; \text{r.t.} \\
& \quad \text{grinding 5 min.} \\
& \quad \text{digestion 10 min.}
\end{align*}
\]

Synthesis of 4'-bromo-4-methoxychalcone (47)

4-Bromoacetophenone (46), anisaldehyde (11) and anhydrous barium hydroxide on grinding together in a mortar with pestle and working up as described earlier gave 4'-bromo-4-methoxychalcone (47) in 92% yield. Identity of the compound was confirmed based on \(^1\)H-NMR and comparison with authentic sample (Co-IR, m.m.p.).

\[
\begin{align*}
\text{Br} \text{C} & + \text{OHC} - \text{OCH}_3 \\
46 & \quad 11 \\
& \quad \text{anhydrous Ba(OH)}_2; \text{r.t.} \\
& \quad \text{grinding 2 min.} \\
& \quad \text{digestion 10 min.}
\end{align*}
\]

Synthesis of 3'-nitro-4-methoxychalcone (49)

A mixture of 3-nitroacetophenone (48), anisaldehyde (11) and anhydrous barium hydroxide on grinding in a mortar with pestle and working up as described earlier gave 3'-nitro-4-methoxychalcone (49) in 85% yield, structure of which was confirmed based on its IR and \(^1\)H-NMR spectral data.

\[
\begin{align*}
\text{NO}_2 \text{C} & + \text{OHC} - \text{OCH}_3 \\
48 & \quad 11 \\
& \quad \text{anhydrous Ba(OH)}_2; \text{r.t.} \\
& \quad \text{grinding 5 min.} \\
& \quad \text{digestion 10 min.}
\end{align*}
\]
Reaction of 2-hydroxyacetophenone with benzaldehyde: synthesis of 2'-hydroxychalcone (51)

A mixture of 2-hydroxyacetophenone (50; 4 mmol), benzaldehyde (7; 4.1 mmol) and anhydrous barium hydroxide (2 g) was ground well in a mortar with pestle, till the reaction mixture transformed into a yellow solid mass (4 minutes). Reaction mixture was left at room temperature for 10 minutes. The reactants were found to have reacted completely when checked on TLC. Reaction mixture on working up as described earlier gave a yellow solid (m.p. 89-90°C) in 87% yield. In $^1$H-NMR it showed a complex multiplet at $\delta$ 6.80-7.98 for 11H (H-3', H-4', H-5', H-6', H-2, H-3, H-4, H-5, H-6, H-α & H-β) and a singlet at $\delta$ 13.20 due to chelated OH, and in IR it showed an absorption peak at 1642 cm$^{-1}$ due to α,β-unsaturated carbonyl functional group. Based on this data compound was identified as 2'-hydroxychalcone (51). It was further confirmed by comparison with authentic sample.86b

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]  
50 + \begin{align*}
\text{OHC} & \quad \text{O} \quad \text{OCH}_3 \\
\text{H} & \quad \text{H}
\end{align*}
7 \quad \text{anhydrous Ba(OH)$_2$; r.t.}
\quad \text{grinding 4 min.}
\quad \text{digestion 10 min.}
\rightarrow
\begin{align*}
\text{OH} & \quad \text{O} \\
& \quad \text{OCH}_3
\end{align*}
51

Synthesis of 2'-hydroxy-4-methoxychalcone (52)

A mixture of 2-hydroxyacetophenone (50), anisaldehyde (11) and anhydrous barium hydroxide on grinding in a mortar with a pestle and working up as described earlier gave 2'-hydroxy-4-methoxychalcone (52) in 83% yield whose structure was confirmed by $^1$H-NMR spectral data and by comparison with authentic sample (Co-IR, m.m.p.).86b

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]  
50 + \begin{align*}
\text{OHC} & \quad \text{O} \quad \text{OCH}_3 \\
\text{H} & \quad \text{H}
\end{align*}
11 \quad \text{anhydrous Ba(OH)$_2$; r.t.}
\quad \text{grinding 2 min.}
\quad \text{digestion 10 min.}
\rightarrow
\begin{align*}
\text{OH} & \quad \text{O} \\
& \quad \text{OCH}_3
\end{align*}
52

Synthesis of 2'-hydroxy-4-methylchalcone (53)

A mixture of 2-hydroxyacetophenone (50), 4-methylbenzaldehyde (14) and anhydrous barium hydroxide on grinding in a mortar with a pestle and working up as
described earlier gave 2'-hydroxy-4-methylchalcone (53) in 86% yield, whose structure was confirmed based on its IR and $^1$H-NMR data.

![Chemical structure](image1)

**Synthesis of 2'-hydroxy-4-chlorochalcone (54)**

A mixture of 2-hydroxyacetophenone (50), 4-chlorobenzaldehyde (17) and anhydrous barium hydroxide on grinding in a mortar with a pestle and working up as described earlier gave 2'-hydroxy-4-chlorochalcone (54) in 84% yield, whose structure was confirmed based on its IR and $^1$H-NMR spectral data.

![Chemical structure](image2)

**Synthesis of 2'-hydroxy-3,4-dimethoxychalcone (56)**

A mixture of 2-hydroxyacetophenone (50), 3,4-dimethoxybenzaldehyde (55) and anhydrous barium hydroxide on grinding and working up as described earlier gave 2'-hydroxy-3,4-dimethoxychalcone (56) in 88% yield, whose structure was confirmed based on its $^1$H-NMR spectral data and comparison with authentic sample (Co-IR, m.m.p.).

![Chemical structure](image3)

**Synthesis of 2'-hydroxy-4'-methoxychalcone (60)**

2-Hydroxy-4-methoxyacetophenone (59) obtained from resorcinol (57), on grinding with benzaldehyde (7) and anhydrous barium hydroxide in a mortar with a
pestle and working up as described earlier gave 2'-hydroxy-4'-methoxychalcone (60) in 89% yield, whose structure was confirmed based on its IR and \( ^1H \)-NMR spectral data and on comparison with authentic sample (Co-IR, m.m.p.).

**Synthesis of 2'-hydroxy-4,4'-dimethoxychalcone (61)**

2-Hydroxy-4-methoxyacetophenone (59) on grinding with anisaldehyde (11) and anhydrous barium hydroxide in a mortar with pestle for 5 minutes and working up as described earlier gave 2'-hydroxy-4,4'-dimethoxychalcone (61) in 90% yield, whose structure was confirmed based on its IR and \( ^1H \)-NMR data.

**Synthesis of 2'-hydroxy-5'-methylchalcone (64)**

2-Hydroxy-5-methylacetophenone (63) obtained from p-tolylacetate (62) by Fries rearrangement on grinding with benzaldehyde (7) and anhydrous barium hydroxide in a mortar at room temperature followed by working up as described earlier gave 2'-hydroxy-5'-methylchalcone (64) in 82% yield, whose structure was confirmed based on IR and \( ^1H \)-NMR spectral data.

**Synthesis of 2'-hydroxy-4-methoxy-5'-methylchalcone (65)**

2-Hydroxy-5-methylacetophenone (63) on grinding with anisaldehyde (11) and anhydrous barium hydroxide in a mortar at room temperature followed by working up as
described earlier gave 2'-hydroxy-4-methoxy-5'H-methylchalcone (65) in 84% yield, whose structure was confirmed based on IR and $^1$H-NMR spectral data.

Reactivity of 2-hydroxyacetophenone with cinnamaldehyde: synthesis of $\omega$-cinnamylidene-2-hydroxyacetophenone (67)

2-Hydroxyacetophenone (50; 4 mmol), cinnamaldehyde (66; 4.1 mmol) and anhydrous barium hydroxide (C-200, 2 g) taken in a mortar were ground well by pestle for 5 minutes when reaction mixture was transformed to a yellow solid mass. Reaction mixture was left at room temperature for 10 minutes and the progress of the reaction was checked on TLC, when the reactants were found to have reacted completely. Reaction mixture on working up as described earlier gave a pale yellow solid m.p. (153-54°C) in 90% yield. The compound in its $^1$H-NMR showed a multiplet for twelve protons at $\delta$ 6.97-7.90 (C$_6$H$_5$, H-3', H-4', H-5' & CH = CH – CH = CH), a doublet for one proton at $\delta$ 8.02 (H-6') and singlet for one proton at $\delta$ 13.80 (OH). In IR it showed an absorption band at 1632 cm$^{-1}$ due to $\alpha,\beta$-unsaturated carbonyl functional group. Based on the above data compound was identified as $\omega$-cinnamylidene-2-hydroxyacetophenone (67) whose structure was further confirmed by comparison with authentic sample (Co-IR, m.m.p.).

Synthesis of $\omega$-cinnamylidene-2-hydroxy-4-methoxyacetophenone (68)

A mixture of 2-hydroxy-4-methoxyacetophenone (59) on grinding with cinnamaldehyde (66) and anhydrous barium hydroxide in a mortar with pestle at room temperature followed by working up as described earlier gave $\omega$-cinnamylidene-2-hydroxy-4-methoxyacetophenone (68) in 86% yield, whose structure was confirmed based on its IR and $^1$H-NMR data.
Synthesis of ω-cinnamylidene-2-hydroxy-5-methylacetophenone (69)

A mixture of 2-hydroxy-5-methylacetophenone (63), cinnamaldehyde (66) and anhydrous barium hydroxide on grinding followed by working up as described earlier gave ω-cinnamylidene-2-hydroxy-5-methylacetophenone (69) in 80% yield, whose structure was confirmed based on its IR and $^1$H-NMR spectral data.

Synthesis of ω-cinnamylidene-2-hydroxy-3,4-dimethoxyacetophenone (73)

2-Hydroxy-3,4-dimethoxyacetophenone (72) obtained from pyragallol (70), on grinding with cinnamaldehyde (66) and anhydrous barium hydroxide in a mortar with a pestle followed by working up as described earlier gave title compound (73) in 75% yield, whose structure was confirmed based on its IR and $^1$H-NMR spectral data.
Experimental

Chalcone (41)

A mixture of acetophenone (40; 0.47 ml), benzaldehyde (7; 0.42 ml) and anhydrous barium hydroxide (2.0 g) was finely ground in a mortar by pestle for 4 minutes at room temperature, till it was transformed into a yellow solid mass. The reaction mixture was left at room temperature for another 10 minutes. The reactants were found to have reacted completely on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl, when a pale yellow solid separated out, which was filtered, washed with water and recrystallised from ethanol to give chalcone (41; 0.75 g), m.p. 55-56°C (lit. m.p. 55°C).144

IR (KBr): 1651 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 7.34-7.52 (m, 7H, H-3', H-5', H-2, H-3, H-5, H-6 & H-β) 7.56, (m, 2H, H-4 & H-4'), 7.81 (d, J = 15.0 Hz, 1H, H-α) 7.99 (d, J = 9.0 Hz, 2H, H-2' & H-6').

4-Methoxychalcone (42)

A mixture of acetophenone (40; 0.47 ml), anisaldehyde (11; 0.5 ml) and anhydrous barium hydroxide (2.0 g) was ground well in a mortar with pestle for 3 minutes and the reaction mixture was left at room temperature for 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The yellow solid that separated out was filtered, washed with water and recrystallised from ethanol to give 4-methoxychalcone (42; 0.87 g), m.p. 74-75°C (lit. m.p. 76°C).133

IR (KBr): 1654 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 3.82 (s, 3H, OCH₃), 6.92 (d, J = 8.0 Hz, 2H, H-3 & H-5), 7.40 (d, J = 14.0 Hz, 1H, H-β), 7.43-7.50 (m, 3H, H-3', H-4', H-5'), 7.58 (d, J = 8.0 Hz, 2H, H-2 & H-6), 7.78 (d, J = 14.0 Hz, 1H, H-α) and 8.0 (d, J = 8.0 Hz, 2H, H-2' & H-6').

4-Methylchalcone (43)

A mixture of acetophenone (40; 0.47 ml), 4-methylbenzaldehyde (14; 0.49 ml) anhydrous barium hydroxide (2.0 g) in a mortar was ground well with pestle for 4 minutes and left at room temperature for another 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture, and acidified with conc. HCl. Solid that separated out, was filtered, washed with water
and recrystallised from ethanol to give 4-methylchalcone (43, 0.78 g), m.p. 94-95°C (lit. m.p. 96°C). IR (KBr): 1650 cm⁻¹ (C=O).

1H-NMR (CDCl₃): δ 2.42 (s, 3H, CH₃), 6.93 (d, J = 8.0 Hz, 2H, H-3 & H-5), 7.38 (d, J = 14.0 Hz, 1H, H-β), 7.43-7.52 (m, 3H, H-3', H-4', & H-5'), 7.59 (d, J = 8.0 Hz, 2H, H-2 & H-6), 7.78 (d, J = 14.0 Hz, 1H, H-α) and 8.2 (d, J = 8.0 Hz, 2H, H-2' & H-6').

4-Chlorochalcone (44)

A mixture of acetophenone (40; 0.47 ml), 4-chlorobenzaldehyde (17; 0.58 g) and anhydrous barium hydroxide (2.0 g) was ground well with pestle for 5 minutes. The reaction mixture was left at room temperature for another 10 minutes when reaction was found to be completed when checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid product that separated out was filtered, washed with water and recrystallised from ethanol to give 4-chlorochalcone (44; 0.82 g), m.p. 112-13°C (lit. m.p. 112°C). IR (KBr): 1654 cm⁻¹ (C=O).

1H-NMR (CDCl₃): δ 6.95 (d, J = 7.6 Hz, 2H, H-3, H-5), 7.40 (d, J = 14.0 Hz, 1H, H-β), 7.40-7.48 (m, 3H, H-3', H-4', & H-5'), 7.55 (d, J = 8.0 Hz, 2H, H-2 & H-6), 7.75 (d, J = 14.0 Hz, 1H, H-α), 8.0 (d, J = 7.8 Hz, 2H, H-2' & H-6').

4-Nitrochalcone (45)

A mixture of acetophenone (40; 0.47 ml), 4-nitrobenzaldehyde (20; 0.62 g) and anhydrous barium hydroxide (2.0 g) was ground well in a mortar with pestle for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on the TLC when reaction was found to be completed. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl, when a yellow solid was separated out, which was filtered, washed with water and recrystallised from ethanol to give 4-nitrochalcone (45; 0.88 g), m.p. 160-61°C (lit. m.p. 160°C). IR (KBr): 1650 cm⁻¹ (C=O).

1H-NMR (CDCl₃): δ 7.02 (d, J = 8.0 Hz, 2H, H-3, H-5), 7.42 (d, J = 14.0 Hz, 1H, H-β), 7.42-7.49 (m, 3H, H-3', H-4', & H-5'), 7.62 (d, J = 8.0 Hz, 2H, H-2 & H-6), 7.76 (d, J = 14.0 Hz, 1H, H-α), 8.0 (d, J = 7.8 Hz, 2H, H-2', H-6').
**4'-Bromo-4-methoxychalcone (47)**

4-Bromoacetophenone (46; 0.8 g) anisaldehyde (11; 0.5 ml) and anhydrous barium hydroxide (2.0 g) taken in a mortar were ground well with pestle for 2 minutes. The reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid product that separated out, was filtered, washed with water and recrystallised from ethanol to give 4'-bromo-4-methoxychalcone (47; 1.18 g), m.p. 145-47°C (lit. m.p. 145-46°C).

IR (KBr): 1650 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 3.86 (s, 3H, OCH₃), 6.96 (d, J = 8.0 Hz, 2H, H-3, H-5), 7.38 (d, J = 16.0 Hz, 1H, H-β), 7.60 (d, J = 8.0 Hz, 2H, H-2 & H-6), 7.65 (d, J = 8.0 Hz, 2H, H-3' & H-5'), 7.80 (d, J = 16.0 Hz, 1H, H-α), 7.88 (d, J = 8.0 Hz, 2H, H-2' & H-6').

**3'-Nitro-4-methoxychalcone (49)**

A mixture of 3-nitroacetophenone (48; 0.66 g), anisaldehyde (11; 0.5 ml), and anhydrous barium hydroxide (2.0 g) was ground well with pestle in a mortar for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl, when a yellow solid was separated out which was filtered washed with water and recrystallised from ethanol to give 3'-nitro-4-methoxychalcone (49; 0.96 g), m.p. 167-69°C (lit. m.p. 167-68°C).

IR (KBr): 1672 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 3.80 (s, 3H, OCH₃), 6.90 (d, J = 8.0 Hz, 2H, H-3 & H-5), 7.35 (d, J = 16.0 Hz, 1H, H-β), 7.58 (d, J = 8.0 Hz, 2H, H-2 & H-6), 7.65 (d, J = 8.0 Hz & 8.0 Hz, 1H, H-5'), 7.80 (d, J = 16.0 Hz, 1H, H-α), 8.29 (ddd, J = 8.0 Hz, 1.5 & 1.5 Hz, 1H, H-6'), 8.39 (ddd, J = 8.0 Hz, 1.5 & 1.5 Hz, 1H, H-4'), 8.76 (dd, J = 1.5 & 1.5 Hz, 1H, H-2').

**2'-Hydroxychalcone (51)**

A mixture of 2-hydroxyacetophenone (50; 0.48 ml), benzaldehyde (7; 0.42 ml) and anhydrous barium hydroxide (2.0 g) was ground well in a mortar with pestle for 4 minutes and the reaction mixture was left at room temperature for another 10 minutes. Progress of the reaction was monitored on TLC, when reactants were found to have
reacted completely. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl, when a pale yellow solid was separated out, which was filtered, washed with water and recrystallised from ethanol to give 2'-hydroxychalcone (51; 0.77 g) m.p. 89-90°C (lit. m.p. 88°C).\textsuperscript{86b}

IR (KBr): 1642 cm\(^{-1}\) (C=O).

\(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 6.80 – 7.98 (m, 11H, H-3', H-4', H-5', H-6', H-2, H-3, H-4, H-5, H-6, H-\(\alpha\), and H-\(\beta\)), 13.20 (s, 1H, OH).

\textbf{2'-Hydroxy-4-methoxychalcone (52)}

A mixture of 2-hydroxyacetophenone (50; 0.48 ml), 4-methylbenzaldehyde (11; 0.5 ml) and anhydrous barium hydroxide (2.0 g) was ground well with pestle in a mortar for 2 minutes and reaction mixture was left at room temperature from another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl, when a yellow solid was separated out which was filtered, washed with water and recrystallised from ethanol to give 2'-hydroxy-4-methoxychalcone (52; 0.84 g), m.p. 90-92°C (lit. m.p. 92°C).\textsuperscript{86b}

IR (KBr): 1640 cm\(^{-1}\) (C=O).

\(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 3.80 (s, 3H, OCH\(_3\)), 6.70-8.0 (m, 10H, H-3', H-4', H-5', H-6', H-2, H-3, H-5, H-6, H-\(\alpha\), H-\(\beta\)), 13.30 (s, 1H, OH).

\textbf{2'-Hydroxy-4-methylchalcone (53)}

A mixture of 2-hydroxyacetophenone (50; 0.48 ml), 4-methylbenzaldehyde (14; 0.48 ml) and anhydrous barium hydroxide (2.0 g) was ground well with pestle in a mortar for 4 minutes and reaction mixture was left at room temperature from another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. A pale yellow solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2'-hydroxy-4-methylchalcone (53; 0.81 g), m.p. 105-06°C (lit m.p. 108°C).\textsuperscript{86b}

IR (KBr): 1640 cm\(^{-1}\) (C=O).

\(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 2.44 (s, 3H, CH\(_3\)), 6.72-8.1 (m, 10H, H-3', H-4', H-5', H-6', H-2, H-3, H-5, H-6, H-\(\alpha\), H-\(\beta\)), 13.32 (s, 1H, OH).
2'-Hydroxy-4-chlorochalcone (54)

A mixture of 2-hydroxyacetophenone (50; 0.48 ml), 4-chlorobenzaldehyde (17; 0.58 g) and anhydrous barium hydroxide (2.0 g) was ground well in a mortar with pestle for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid product that separated out was filtered, washed with water and recrystallised from ethanol to give 2'-hydroxy-4-chlorochalcone (54; 0.86 g), m.p. 148-50°C (lit. m.p. 150°C). IR (KBr): 1640 cm⁻¹ (C=O).

H-NMR (CDCl₃): δ 6.94-7.85 (m, 10H, H-3', H-4', H5', H-6', H-2, H-3, H-5, H-6, H-α, H-β), 12.85 (s, 1H, OH).

2'-Hydroxy-3,4-dimethoxychalcone (56)

2'-Hydroxyacetophenone (50; 0.48 ml), 3,4-dimethoxybenzaldehyde (55; 0.68 g) and anhydrous barium hydroxide (2.0 g) taken in a mortar were ground well with pestle for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was confirmed by TLC. Ice cold water (30 ml) was added to the reaction mixture, and acidified with conc. HCl. The yellow solid that separated out was filtered, washed with water, and recrystallised from ethanol to give 2'-hydroxy-3,4-dimethoxychalcone (56; 1.0 g), m.p. 113-14°C, (lit. m.p. 114-15°C). IR (KBr): 1642 cm⁻¹ (C=O).

H-NMR (CDCl₃): δ 3.85 & 3.90 (each s, 6H, 2×OCH₃), 6.82-7.92 (m, 9H, H-3’, H-4’, H-5’, H-6’, H-2, H-5, H-6, H-α & H-β), 13.20 (s, 1H).

2,4-Dihydroxyacetophenone (Resacetophenone) (58)

Anhydrous zinc chloride (33 g) was dissolved in glacial acetic and (32 ml). To this hot mixture at 110⁰C, was added dry resorcinol (57; 22 g) in small lots with stirring. The solution was heated on a sand bath at 140 to 150⁰C for 20 minutes. Dilute hydrochloric acid (1:1, 100 ml) was added to the reaction mixture and the resulting solution was left overnight at room temperature. The solid that separated out was filtered, washed with water and recrystallised form hot dilute hydrochloric acid (1:10) as light yellow solid (58; 22 g), m.p. 144-46⁰C (lit. m.p. 147⁰C).
2-Hydroxy-4-methoxyacetophenone (59)

A solution of 2,4-dihydroxyacetophenone (58; 15 g) in acetone (200 ml) was refluxed with dimethylsulphate (10 ml) and anhydrous potassium carbonate (40 g) using calcium chloride guard tube on a water bath for 1.0 hour. The acetone solution was filtered and residue was washed with acetone. The solvent was removed from the combined acetone solution by distillation and ice cold water (200 ml) was added to the residue and was cooled in ice bath. The solid that separated out was filtered, washed with water, and dried. The dry solid on crystallization from ether-petroleum ether mixture gave 2-hydroxy-4-methoxyacetophenone (59) as colourless needles (13 g), m.p. 50-51°C (lit. m.p. 52-53°C).\textsuperscript{150}

2'-Hydroxy-4'-methoxychalcone (60)

A mixture of 2-hydroxy-4-methoxyacetophenone (59; 0.66 g), benzaldehyde (7; 0.42 ml), anhydrous barium hydroxide (2.0 g) was ground well with pestle in a mortar for 4 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2'-hydroxy-4'-methoxychalcone (60; 0.9 g), m.p. 104-105°C (lit. m.p. 105°C).\textsuperscript{151}

IR (KBr): 1639 cm\(^{-1}\)(C=O).

\textsuperscript{1}H-NMR(CDCl\(_3\)): \(\delta\) 3.85 (s, 3H, OCH\(_3\)), 6.41 (m, 2H, H-3', H-5'), 7.38 (d, J=14.0 Hz, 1H, H-\(\alpha\)), 7.49 (m, 5H, C\(_6\)H\(_5\)), 7.71 (d, J = 9.0 Hz 1H, H-6'), 7.80 (d, J = 14.0 Hz, 1H, H-\(\beta\)), 13.70 (s,1H, , OH).

2'-Hydroxy-4,4'-dimethoxychalcone (61)

A mixture of 2-hydroxy-4-methoxyacetophenone (59; 0.66 g), anisaldehyde (11; 0.5 ml) and anhydrous barium hydroxide (2.0 g) was ground well with pestle in a mortar for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2'-hydroxy-4,4'-dimethoxychalcone (61; 1.0 g), m.p. 112-114°C (lit. m.p. 113-14°C).\textsuperscript{151}

IR (KBr): 1638 cm\(^{-1}\)(C=O).
$^1$H-NMR (CDCl$_3$): $\delta$ 3.87 (s, 6H, 2 x OCH$_3$), 6.45 (m, 2H, H-3', H-5'), 6.82-7.58 (4H, H-2, H-3, H-5, H-6), 7.36 (d, J = 14.0 Hz, 1H, H-$\alpha$), 7.72 (d, J = 9.0 Hz, 1H, H-6'), 7.79 (d, J = 14.0 Hz, 1H, H-\(\beta\)), 13.80 (s, 1H, OH).

**P-Tolylacetate (62)**

A mixture of p-cresol (25 ml), acetic anhydride (50 ml) and anhydrous sodium acetate (40 g) was refluxed for 4.0 hours using calcium chloride guard tube. The reaction mixture was poured over crushed ice and kept overnight. The reaction mixture was extracted with ethylacetate. Organic layer was washed with water, dried over calcium chloride and solvent was removed by distillation. The residue was distilled to get p-tolylacetate as colourless liquid (62; 17 ml), b.p. 210-120°C (lit. b.p. 212-130°C).

**2-Hydroxy-5-methylacetophenone (63)**

Powdered aluminum chloride (30 g) was added to p-tolylacetate (62; 10.0 g) at 0°C in 250 ml round bottom flask fitted with an air condenser and calcium chloride guard tube. The temperature was slowly raised to 120°C for 30 minutes and maintained at 160°C in an oil bath for 2.0 hours. The reaction mixture was cooled and aluminum chloride complex was decomposed with crushed ice (150 g) and conc. HCl (100 ml). The solid that separated out was filtered, washed with water, dried and crystallized form petroleum ether to afford 2-hydroxy-5-methylacetophenone (63) as colourless needles (10.0 g), m.p. 48-50°C (lit. m.p. 50°C).

**2'-Hydroxy-5'-methylchalcone (64)**

A mixture of 2-hydroxy-5-methylacetophenone (63; 0.6 g), benzaldehyde (7; 0.42 ml) and anhydrous barium hydroxide (2.0 g) was ground well with pestle in a mortar for 4 minutes and the reaction mixture was left at room temperature for another 10 minutes completion of the reaction was confirmed by TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid product that separated out was filtered, washed with water and recrystallised from ethanol to give 2'-hydroxy-5'-methylchalcone (64) as yellow solid (0.78 g), m.p. 104-105°C (lit. m.p. 105-106°C).

IR (KBr): 1645 cm$^{-1}$ (C=O).

$^1$H-NMR. (CDCl$_3$): $\delta$ 2.30 (s, 3H, CH$_3$), 6.85-7.85 (m, 10H, H-3', H-4', H-6', C$_6$H$_5$, H-$\alpha$, H-\(\beta\)), 13.80 (s, 1H, OH).
2'-Hydroxy-4-methoxy-5'-methylchalcone (65)

A mixture of 2-hydroxy-5-methylacetophenone (63; 0.6 g), anisaldehyde (11; 0.42 ml) and anhydrous barium hydroxide (2.0 g) was ground well with pestle in a mortar for 4 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallised from ethanol to give 2'-hydroxy-4-methoxy-5'-methylchalcone (65: 0.72 g) as yellow solid m.p. 99-100°C (lit. m.p. 98-99°C).\textsuperscript{153}

IR (KBr): 1645 cm\textsuperscript{-1} (C=O).

$^1$H-NMR (CDCl\textsubscript{3}): $\delta$ 3.84 (s, 3H, OCH$_3$), 6.72-7.84 (m, 9H, H-3', H-4', H-6', H-2, H-3, H-5, H-6, H-\alpha, H-\beta), 13.80 (s, 1H, OH).

$\omega$-Cinnamylidene-2-hydroxyacetophenone (67)

A mixture of 2-hydroxyacetophenone (50; 0.48 ml), cinnamaldehyde (66; 0.52 ml) and anhydrous barium hydroxide (2.0 g) was ground well with pestle for 5 minutes, when the reaction mixture was transformed to a yellow solid mass. The reaction mixture was left at room temperature for another 10 minutes, and the reactants were found to have reacted completely, when checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. A pale yellow solid that separated out, was filtered, washed with water and recrystallised from ethanol to give $\omega$-cinnamylidene-2-hydroxyacetophenone (67; 0.96 g), m.p. 152-53°C (lit. m.p. 154-55°C).\textsuperscript{145}

IR (KBr): 1632 cm\textsuperscript{-1} (C=O).

$^1$H-NMR: (CDCl\textsubscript{3}): $\delta$ 6.97-7.90 (m, 12H, C$_6$H$_5$, H-3', H-4', H-5', H-2, H-3, H-5, H-6, H-\alpha, H-\beta), 8.02 (d, J = 9.0 Hz, 1H, H-6') and 13.80 (s, 1H, OH).

$\omega$-Cinnamylidene-2-hydroxy-4-methoxyacetophenone (68)

A mixture of 2-hydroxy-4-methoxyacetophenone (59; 0.66 g), cinnamaldehyde (66; 0.52 ml) and anhydrous barium hydroxide (2.0 g) was ground well with pestle in a mortar for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was
added to the reaction mixture and acidified with conc. HCl. The yellow solid that separated out was filtered, washed with water and recrystallised from ethanol to give o-cinnamylidene-2-hydroxy-4-methoxyacetophenone (68; 0.96 g), m.p. 144° C (lit. m.p. 144° C). IR (KBr): 1630 cm⁻¹ (C=O).

^1H-NMR (CDCl₃): δ 3.92 (s, 3H, OCH₃), 6.45-6.80 (m, 2H, H-3', & H-5'), 7.10-8.10 (m 10H, C₆H₅, H-6', -CH = CH – CH = CH-).

o-Cinnamylidene-2-hydroxy-5-methylacetophenone (69)

A mixture of 2-hydroxy-5-methylacetophenone (63; 0.6 g), cinnamaldehyde (66; 0.52 ml) and anhydrous barium hydroxide (0.2 g) was ground well with pestle in a mortar for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was confirmed by TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The yellow solid that separated out was filtered, washed with water and recrystallised from ethanol to give o-cinnamylidene-2-hydroxy-5-methylacetophenone (69; 0.85 g) m.p. 114-15° C (lit. m.p. 115° C).

IR (KBr): 1635 cm⁻¹ (C=O).

^1H-NMR (CDCl₃): δ 2.30 (s, 3H, CH₃), 7.0-7.85 (m, 12H, C₆H₅, H-3', H-4', H-6', -CH = CH – CH = CH-), 13.80 (s, 1H, OH).

2,3,4-Trihydroxyacetophenone (71)

Freshly fused zinc chloride (28 g) was dissolved in glacial acetic acid (38 ml) by heating at 135-40° C in an oil bath. To the clear pale yellow solution was added, acetic anhydride (40 ml) followed by pyrogallol (70; 50 g) in one lot. The mixture was heated at 140-45° C on an oil bath for 45 minutes with frequent shaking. Excess of acetic anhydride and acetic acid were removed by distillation under reduced pressure. Water (300 ml) was added and mixture was cooled in ice, the solid so obtained was filtered and washed well with cold water. It was crystallized from hot water (500 ml) saturated with sulphur dioxide to yield 2,3,4-trihydroxyacetophenone (71; 38 g) as straw-coloured solid m.p. 171-72° C (lit. m.p. 173° C).
2-Hydroxy-3,4-dimethoxyacetophenone (72)

A solution of 2,3,4-trihydroxyacetophenone (71; 10 g) in dry acetone (150 ml) was refluxed with dimethyl sulphate (11.8 ml) and ignited potassium carbonate (70 g) for 8 hours. Acetone was filtered and residue was washed with acetone. Acetone was distilled off from combined filtrate and residue was treated with ice cold water (150 ml). The solid that separated out was filtered washed well with water and recrystallised from methanol to give 2-hydroxy-3,4-dimethoxyacetophenone (72; 9.0 g) as colourless needles m.p. 83-84°C (lit. m.p. 83°C).155

ω-Cinnamylidene-2-hydroxy-3,4-dimethoxyacetophenone (73)

2-hydroxy-3,4-dimethoxy acetophenone (72; 0.78 g), cinnamaldehyde (66; 0.52 ml) and anhydrous barium hydroxide (2.0 g) were ground well in mortar with pestle for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was confirmed by TLC. Ice cold water (30 ml) was added to the reaction mixture, The yellow solid that separated out was filtered, washed with water and recrystallised from ethanol to given ω-cinnamylidene-2-hydroxy-3,4-dimethoxy acetophenone (73; 0.92 g), m.p. 142-143°C (lit. m.p. 142°C).145

IR (KBr): 1630 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 4.0 (s, 6H, 2 x OCH₃), 6.70 (d, J = 9.0 Hz, 1H, H-5''), 7.1-8.1 (m, 10H, C₆H₅, H-6', CH = CH – CH = CH), 13.55 (s, 1H, OH).
References


77 *Sigma-Aldrich*, 2005-06, 21, 757-3.

60


