CHAPTER - 4

Nazarov Cyclisation and Consequent Fragmentations of Protonated Chalcones: Gas-Phase Proton Transport Catalysis.
4.1. Introduction

The acid catalyzed cyclisation of divinyl ketones to yield cyclopentenones is known as Nazarov cyclisation. Nazarov cyclisation has been recently reviewed [1-4]. Bronsted acids such as trifluoroacetic acid, superacids such as trifluoromethanesulfonic acid and Lewis acids such as BF$_3$ and AlCl$_3$ were employed for affecting the cyclisations. The mechanism of the reaction involves electrocyclic ring closure of the protonated ketone followed by deprotonation [1]. Substituted chalcones [5, 6] undergo acid catalyzed Nazarov cyclisation to produce 3-arylindanones, Scheme: 1. Typically, the cyclisation is performed by heating chalcone in anhydrous TFA solution at high temperatures (120-130 °C) for extended periods of time (4-24 h). A variety of indanone derivatives were synthesized by microwave-assisted Nazarov cyclisation of chalcones and are now considered as a general and efficient method for the synthesis of biologically active indanones [6]. A one pot synthesis of 3-phenylindanone from cinnamoyl chloride and benzene catalyzed by anhydrous AlCl$_3$ in presence of microwave involves Friedel-Crafts acylation followed by Nazarov cyclisation of chalcone [7], Scheme: 2. This chapter describes the investigation of attempted Nazarov cyclisation of chalcones in the gas-phase by using mass spectrometer as a reactor [8, 9].

Scheme: 1
The antimicrobial activity of substituted chalcones has been evaluated \[37a\] recently by biotechnologists while their fragmentation processes upon ionization has been studied by mass spectrometrists since 1960 \[10\]. Particularly, the formation and structures of the \([M-H]^{+}\) ion and \([M-H-CO]^{+}\) ions from the \(M^{+}\), were the focus of many investigations \[11-23\]. The structures of these fragment ions were investigated using CAD experiments in an ion trap mass spectrometer \[24\]. Recently, the mechanisms of the elimination of benzene as well as CO from the APCI generated \([M+H]^{+}\) ions of chalcones were investigated \[25\]. The three important fragment ions observed in the CAD mass spectrum of protonated chalcone are \([M+H-H_{2}O]^{+}\), \([M+H-CO]^{+}\) and \([M+H-C_{6}H_{6}]^{+}\). The structures proposed for the \([M+H-CO]^{+}\) ion and \([M+H-C_{6}H_{6}]^{+}\) ion are given in **Scheme: 3**. Based on the studies of the substituted chalcones it was shown that either of the phenyl rings can be eliminated as benzene \[25\].

\[\text{Scheme: 3}\]
Ionization methods such as CI and ESI are efficient for protonating organic molecules. Tandem mass spectrometric experiments combined with molecular modeling are widely used for the elucidation of the fragment ion structures and mechanism of fragmentations of protonated organic molecules in the gas-phase. A recent example is the investigation of the mechanism of cyclisation of 2-nitrophenyl phenyl ether [26] upon protonation by ESI. The proton induced gas-phase rearrangements may have close parallelism in solution chemistry as demonstrated by many mass spectrometric studies earlier, the acid catalyzed Claisen rearrangement in CI mass spectrometry is a classic example [27]. A recent example is the rearrangement of protonated 2-[N-benzoyloxyphenyl] benzamide both in gas-phase and solution phase [28]. Experimental and theoretical studies established that high-energy 1,3-H-shifts in the gas-phase take place when catalyzed by a base, the process has been termed Proton Transport Catalysis [29-31]. The catalysis of enolization of gaseous acetone radical cation by benzonitrile and methanol [32a-d] as well as the isomerization of ionized acetaldehyde by methanol has been investigated [32e-h].

The protonation of chalcones were attempted by using ESI or Chemical ionization, expecting that the protonation will occur at the carbonyl oxygen and the [M+H]^+ ions would undergo a Nazarov type cyclisation in the gas-phase. An important step in the solution phase Nazarov cyclisation is the deprotonation. A basic substituent such as OCH₃ or OH at the ortho position may cause deprotonation or proton transport. Since the OCH₃ (or OH) is capable of catalyzing proton migrations in the gas-phase [32]. We have synthesized chalcone (4.1), isomeric methoxy chalcones, 4.2, 4.3, 4.4 and 4.7 and hydroxy chalcones 4.5, 4.6 and 4.8 for this investigation. Benzhydrols 4.9, 4.10 and 4.11 were synthesized to generate reference ions. 3-phenylindanone was purchased form Aldrich Chemical Co. (USA).
4.2. Results and Discussion

4.2.1. Mass spectra of benzal acetophenone (4.1), (chalcone)

The CAD mass spectrum of the ESI generated [M+H]$^+$ ion (m/z 209) of chalcone, Fig.4.1, shows fragment ions of m/z 191, 181, 131 due to eliminations of H$_2$O, CO and C$_6$H$_6$ respectively [16]. The ion m/z 105 corresponds to benzoyl cation.

![Mass spectra of benzal acetophenone (4.1), (chalcone)](attachment:image.png)
A comparison of the CAD mass spectrum of chalcone with that of 3-phenylindanone, **Fig.4.2**, reveals that both compounds give same fragment ions (m/z 194, 191, 181 and 131) except for the ion of m/z 105, suggesting that chalcone may be isomerising, via Nazarov type cyclisation, to 3-phenylindanone at least to some extent. But the ratios of the abundances of the product ions are not the same. The presence of benzoyl cation in the CAD mass spectrum of chalcone probably indicates that a fraction of protonated chalcones did not cyclise, since the CAD mass spectrum of 3-phenylindanone does not contain an ion of m/z 105.

![Fig.4.2. The CAD mass spectrum of the ESI generated [M+H]+ ion of 3-phenylindanone](image)

We propose that protonated chalcone undergoes Nazarov type cyclisation i.e. electrophilic cyclisation followed H-migration to form protonated 3-phenylindanone. The eliminations of H₂O, CO and benzene occur from the resulting protonated 3-phenylindanone to yield the fragment ion of m/z 191, 181 and 131, **Scheme: 4.1**.
Scheme: 4.1. The elimination of CO, H_2O and benzene from [M+H]^+ of chalcone.

Fig. 4.3. CAD MS of ion of m/z 181 from (a) chalcone (b) 3-phenylindanone
The CAD mass spectra of the fragment ions of m/z 181 from chalcone and 3-phenylindanones were compared, **Fig.4.3a** and **b**. The two spectra are closely similar confirming the proposed cyclisation. It is proposed that the fragment ion of m/z 181 possesses 1,1-diphenylethyl cation structure. To generate a reference standard for 1,1-diphenylethyl cation a suitable precursor, 1,1-diphenyl ethanol (4.11) was synthesized. The ESI-CAD mass spectrum of the fragment ion of m/z 181 (ms/ms), **Fig.4.4a**, was compared with that of the ion of m/z 181 from the [M+H]+ ion of 4.11 (ms³ experiment), **Fig.4.4b**. The two spectra are similar indicating that the [M+H-CO]+ ions from chalcone possess 1,1-diphenylethylcation structure. The three important fragment ions observed in the CAD mass spectrum of the ion of m/z 181 are m/z 166, 153 and 103 due to eliminations of CH₃, C₂H₄ and C₆H₆ respectively.

![MGVS-55+181 #2-39 RT: 0.03-0.82 AV: 38 SM: 15G NL: 5.20E3
T: + p ESI Full ms³ 209.00@38.00 181.00@41.00 [ 70.00-200.00]
80 100 120 140 160 180 200
m/z
0
10
20
30
40
50
60
70
80
90
100
Relative Abundance 166 181 103 153](image)

**Fig.4.4a.** The CAD MS of the collision generated ion of m/z 181 from the [M+H]+ ion of chalcone, an ESI MS³ experiment.
Moreover, the CAD mass spectra of the fragment ions of m/z 131 from both chalcone and 3-phenylindanone show the ion of m/z 103 as the only fragment due to loss of CO.

**Fig. 4.5.** Similarly, the CAD mass spectra of the fragment ion of m/z 191 from both compounds are closely similar.
The feasibility of cyclisation of protonated chalcone was explored by molecular modeling by using DFT calculation. The estimated heats of formation of the intermediates relative to that of the protonated molecule are given in Table 4.1. The trans-isomer of protonated chalcone rearranges to the cis form and cyclization occurs by an electrophilic mechanism, Scheme 4.2. The enthalpy of the transition state for the important H-migration steps for aromatization is high, $\text{TS}_{\text{d-e}} = 61.4 \text{ kcal/mol}$, $\text{TS}_{\text{e-f}} = 51.1 \text{ kcal/mol}$ (two 1,2-shifts). This is probably the reason for the incomplete cyclisation of chalcone to 3-phenylindanone in the gas-phase (unimolecular process). But in the solution phase, the solvent assisted deprotonation and protonation can occur for the aromatization step (bimolecular process).

**Scheme: 4.2** Cyclisation of chalcone
Table 4.1. Heats of formations of the intermediates, products and transition states relative to that of \([M+H]^+\), 4.1.

<table>
<thead>
<tr>
<th>Species</th>
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<th>Species</th>
<th>Hf</th>
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<tbody>
<tr>
<td>4.1a; [M+H]^+</td>
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<td>TSb-c</td>
<td>13.2</td>
<td>TSc-d</td>
<td>13.2</td>
</tr>
<tr>
<td>4.1b</td>
<td>5.1</td>
<td>4.1d</td>
<td>29.5</td>
<td>4.1f</td>
<td>-2.4</td>
</tr>
<tr>
<td>TSa-b</td>
<td>33.5</td>
<td>TSe-f</td>
<td>51.1</td>
<td></td>
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<tr>
<td>4.1c</td>
<td>9.3</td>
<td>4.1e</td>
<td>46.3</td>
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4.2.2. Mass spectra of 2-methoxybenzal acetophenone (4.2)

Further, the CI and ESI mass spectra of 2-methoxy chalcone were investigated to determine feasibility of cyclisation. Being a catalyst for hydrogen migrations in the gas phase the methoxy group can potentially facilitate the cyclisation by lowering the transition state energy for the aromatization step (H-migration). The CI mass spectrum, Fig.4.6, of 4.2, shows \([M+H]^+\) ion of m/z 239 and fragment ions of m/z 207, 197, 161, 131 and 105 (benzoyl cation). The fragment ions of m/z 207, 161 and 131 are due to losses of methanol, benzene and methoxybenzene, respectively. The fragment ion of m/z 197, \([M+H-42]^+\), is due to an unusual elimination of ketene.

Fig: 4.6. CI mass spectrum of 2-methoxybenzal acetophenone (4.2)
The MI mass spectrum, Fig. 4.7a, of [M+H]^+ shows fragment ions of m/z 207, 197, 161, 131 and 105. Upon collision activation the abundance of the ions of m/z 207, 161, 131 and 105 increases compared to that of the ion of m/z 197, Fig. 4.7b. This suggests that the ions of m/z 207, 161, 131 and 105 are formed by high energy processes where as the ions of m/z 197 are formed by low energy rearrangement process. The ions of m/z 207, 161 and 105 probably corresponds to the fraction of 4.2 that did not undergo Nazarov cyclisation, whereas the ions of m/z 197, 131 may be arising from the cyclised form of 2-methoxychalcone.

![Fig. 4.7. (a) MI and (b) CAD spectra of [M+H]^+ of 4.2 (CI).]

The ion of m/z 207 may have flavylium cation structure. To confirm this, the CAD mass spectrum, Fig: 4.8a, of the ion of m/z 207 from 4.2, was compared with that of flavylium cation, Fig: 4.8b. The two spectra are closely similar indicating that the [M+H-
CH$_3$OH$^+$ ion possesses flavylum cation structure. The formation of ion of m/z 207 probably involves a nucleophilic displacement of the protonated methoxy group by the carbonyl oxygen.

![Fig: 4.8. The CAD mass spectra of the ion of m/z 207 from (a) compound 4.2 and (b) flavylum chloride.](image)

**Scheme: 4.3.** Elimination of methanol from 4.2

The interesting fragmentation of 4.2 upon protonation is the unusual elimination of ketene. The base peak in the CAD mass spectrum, Fig.4.9, of the ion of m/z 197 is due to benzyl cation (m/z 91). In addition, the CAD mass spectrum exhibits major fragment ions of m/z 181 and m/z 165 (may be fluorenyl cation) due to the eliminations of methane and
methanol, respectively. Molecular orbital calculation (DFT theory) showed that the formation of the fragment ions of m/z 91 can be explained by assuming 2-methoxyphenyl phenyl methyl cation structure for the ion of m/z 197 from 4.2, Scheme: 4.4. The enthalpies of the intermediates and sum of the energies of the products are given relative to that of the ion of m/z 197.

Scheme: 4.4

Relative abundance

Fig: 4.9. The CAD mass spectrum of the ion of m/z 197 from 4.2
Further, the CI experiment was repeated with CD$_4$ and the MI mass spectrum of [M+D]$^+$ ion (m/z 240) of 4.2 was recorded. The CAD mass spectrum, Fig.4.10, of [M+D]$^+$ shows fragment ion of m/z 198 corresponding to [M+H-Ketene]$^+$ indicating that the deuterium is retained in the product ion during the elimination of ketene.

![Fig: 4.10. MI mass spectrum of [M+D]$^+$ ion of compound 4.2](image1)

![Fig: 4.11. CAD spectrum of ion of m/z 198 from (CI) [M+D]$^+$ of 4.2](image2)
The CAD mass spectrum of the ion of m/z 198 was examined. A comparison of the CAD mass spectra of the ions of m/z 197, **Fig.4.9**, and 198, **Fig.4.11**, reveals that the masses of all the major fragments ions of m/z 181, 165 and 91, are shifted by one mass unit in the latter spectrum. This probably indicates that, in the ion of m/z 198, the D is part of the phenyl ring that does not contain the OCH₃ group. The formation of the fragment ions from the ion of m/z 198 can be explained by extending the mechanism for the fragmentation of the ion of m/z 197, **Scheme: 4.5**.

![Scheme: 4.5](image)

**Fig.4.12a.** The ESI MS of 4.2  
**Fig.4.12b.** The ESI-CAD MS of 4.2
The ESI- spectrum, Fig.4.12a, of compound 4.2 shows the [M+H]^+ ion of m/z 239 and the ESI- CAD spectrum, Fig.4.12b, (Q-Tof, resolution 15000) shows ion of m/z 197 as the only fragment. The measured accurate mass of the fragment ion of m/z 197 from the CAD mass spectrum, 197.0965 corresponds to the elemental composition C_{14}H_{13}O (calculated = 197.0966) which is in good agreement with the proposed elimination of ketene. The CAD mass spectrum does not show the fragment ions of m/z 207, 161 and 131 but these fragments were present in the CAD (high-energy collisions in a four sector instrument) mass spectrum of the [M+H]^+ ion generated by CI. This indicates that the formation of ions of m/z 207, 161 and 131 require high-energy but the production of ion of m/z 197 is a low energy process. Hence, the low energy [M+H]^+ ions produced by ESI ionization of 4.2 produces the fragment ion of m/z 197 more efficiently than the ions produced by CI probably indicate that Nazarov cyclisation takes place to a greater extent in the ESI produced [M+H]^+ ions.

To generate a reference standard for the ion of m/z 197 having 2-methoxyphenyl phenyl methyl cation structure, 2-methoxybenzhydrol (4.9) was synthesized and its ESI mass spectrum was recorded, Fig: 4.13a. The ESI- MS of compound 4.9 showed abundant ions of m/z 237, the [M+Na]^+ ion. The CAD mass spectrum of the [M+Na]^+ ion, Fig.4.13b, shows that the only fragment ion formed is the ion of m/z 197. The formation of fragment ion of m/z 197, from [M+Na]^+ ion of 4.9 is shown in, Scheme: 4.6. The structure of the ion of m/z 197 from 4.9 and its OCD$_3$ analogue upon CI and its CAD mass spectrum using an ion trap instrument have been discussed [33]. This ion is stable in solution so that its $^{13}$C-NMR spectrum could be explored [34]. It has been demonstrated that the CH$_2$ group of benzyl cation fragment is derived from the OCH$_3$ group by recording the CAD mass spectrum of the OCD$_3$ analogue, the ion of m/z 200 generated from 2-methoxybenzhydrol-d$_3$. 

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Scheme: 4.6. The formation of fragment ion of m/z 197 from 4.9

Further, the CAD spectrum, Fig.4.14a, of the collision-generated fragment ion of m/z 197 (MS\textsuperscript{3} experiment) of 4.2 was compared with that of m/z 197 (MS\textsuperscript{3} experiment) from 4.9, Fig.4.14b. The two spectra are closely similar indicating that the [M+H-CH\textsubscript{2}CO]\textsuperscript{+} ion from 4.2 has indeed 2-methoxyphenyl phenyl methyl cation structure. The CAD mass spectrum of the fragment ion of m/z 197 obtained by low energy collisions (MS\textsuperscript{3} experiment on the collision generated ion of m/z 197) in an ion-trap instrument, Fig. 4.14a, (the spectrum is closely similar to that reported in ref. 33) is different from that obtained by high energy (4
Kilovolts, ms/ms experiment on the source generated ion of m/z 197) collisions in a sector instrument. **Fig 4.9.** The fragment ion of m/z 91, however, is common in both mass spectra suggesting that the collision generated ion has the same structure as the source generated fragment ion. The fragment ions of m/z 195 (H₂ loss) 182 (CH₃ loss), m/z 179 (H₂O loss) and m/z 169 (loss of 28 u, CO or C₂H₄) are observed in the CAD mass spectrum, **Fig. 4.14a.**

The structure of the fragment ion of m/z 197 indicates that upon protonation 2-methoxy chalcone (4.2) rearranges to a structure in which both the phenyl rings in the molecule are attached to the same carbon atom before elimination of ketene. A mechanism, based on molecular orbital calculation (DFT theory), is proposed for the elimination of ketene from 4.2, **Scheme: 4.7, 4.8 and 4.9.** The estimated values of the heats of formation of the intermediates and transition states relative to that of the [M+H]^+ ion is given in **Table 4.2.**

The protonated molecule, 4.2a, isomerizes to the cis configuration, 4.2b, which to form the intermediate, 4.2d (cis) or 4.2d1 (trans). A 1,3-H shift could generate the intermediate 4.2f.
which can rearrange (C-C rotation) to 4.2g {protonated 3-(2-methoxyphenyl) indanone} from 4.2d but this is a forbidden process. A possible route 4.2d to 4.2f is two 1,2-H shifts via 4.2e, Scheme: 4.8. The conversion of 4.2a to 4.2f may be considered as the gas-phase equivalent of Nazarov type cyclisation, analogous to 4.1. The enthalpies of the transition states involved in the transformation of 4.2d to 4.2f is very high (62.0 kcal/mol) and hence does not explain the facile cyclisation of 2-methoxychalcone (4.2).

| Table 4.2. Heats of formations of the intermediates, products and transition states relative to that of the [M+H]^+ ion in Kcal/mol. Scheme 4.7, 4.8 & 4.9. |
|--------------------------|------------------|------------------|
| Species                  | ∆Hf             | Species          | ∆Hf             |
| 4.2a, [M+H]^+            | 0.0             | TSa-b            | 28.6            |
| 4.2b                     | 5.3             | TSB-c            | 16.0            |
| 4.2c                     | 9.8             | TSc-d            | 37.4            |
| 4.2d                     | 32.1            | TSD-e            | 62.0            |
| 4.2e                     | 45.7            | TSe-f            | 47.4            |
| 4.2f                     | 0.3             | Tsf-g            | 10.1            |
| 4.2g                     | -0.8            | TSb-c1           | 30.9            |
| 4.2c1                    | 29.8            | TSc1-d1          | 36.2            |
| 4.2d1                    | 28.1            | TSD1-d2          | 30.5            |
| 4.2d2                    | 28.6            | TSD2-g           | 32.0            |
| 4.2h                     | 28.4            | TSG-h            | 29.2            |
| 4.2i                     | 27.9            | TSh-i            | 31.8            |
| 4.2j                     | 25.5            | TSj-j            | 30.0            |
| 4.2k+m                   | 27.0            | TSj-(k+m)        | 33.6            |

Therefore an alternate route from intermediate 4.2d1 (trans-isomer of 4.2d) involving proton transport catalysis was considered for the formation 4.2g, Scheme: 4.7. The activation energy for the rearrangement is considerably lower (the highest energy transition state is 36.2 kcal/mol) in transferring the proton via the methoxy group to the required site via 4.5d2 to afford intermediate 4.2g. Low activation energy for the cyclisation must bring about the cyclisation to greater extends. The very low abundance for the benzoyl cation fragment (m/z 105) in the ESI-CAD mass spectrum of 2-methoxychalcone in comparison to
that of 4-methoxychalcone, Fig.4.32 (under identical instrument conditions), indicate that the cyclisation is nearly complete, Fig.4.15a.

Once again for the ketene elimination, the OCH$_3$ group acts as a catalyst by providing an alternate pathway and lowers the activation energy for a 1,3-H-migration from the carbonyl oxygen to the aromatic ring in structure 4.2g, Scheme: 4.9. First the H$^+$ shifts to the methoxy group and then to the ring carbon to afford 4.2i, which ring opens and closes to generate the intermediate 4.2j, the precursor for the expulsion of ketene. The ionizing proton reaches the ortho position of the phenyl group in the product ion (m/z 197). The ketene loss via proton transport catalysis suppresses any other fragmentations routes for the 3-(2-methoxy) phenyldanone intermediate.

Scheme: 4.8  Cyclisation catalyzed by OCH$_3$ group


In addition, the CAD mass spectrum of the [M+D]$^+$ ion generated by ESI ionization was recorded, Fig.4.15a. The spectrum showed that the [M+D]$^+$ ion exclusively losses ketene (no loss of ketene-d) giving rise to a fragment ion of m/z 198. The mechanism proposed in Scheme: 4.7 to 4.9 predict that during the fragmentation of the [M+D]$^+$ ion,
deuterium is retained by the [M+D-ketene]$^+$ fragment as part of the phenyl ring. To determine the position of D in the [M+D-ketene]$^+$ fragment the CAD mass spectrum of the collision generated ion of m/z 198 was recorded, Fig.4.15b. The CAD mass spectrum shows an ion of m/z 92 due to benzyl cation containing D, clearly substantiate the proposal that D is present in the phenyl ring of the [M+D-ketene]$^+$ fragment.

**Fig.4.15a.** CAD MS of the [M+D]$^+$ ion of 4.2 generated by ESI

**Fig.4.15b.** CAD MS of the fragment ion of m/z 198 of 4.2 ms$^3$ experiment.
4.2.3. Mass spectra of 2-methoxybenzal propiophenone (4.3)

The proposed mechanism for the elimination of ketene from 2-methoxychalcone envisages that carbon-2 of the propene moiety is eliminated, along with the hydrogen attached to it, as ketene. To test this hypothesis the CI and ESI mass spectra of 2-methyl analogue, 3-(2-methoxyphenyl)-2-methyl-1-phenylprop-2-en-1-one, 4.3, was examined. The CI mass spectrum, Fig: 4.16, of 4.3 show the [M+H]⁺ ion of m/z 253 and the fragment ion of m/z 197 due to the loss of methyl ketene.

The MI and CAD mass spectra of [M+H]⁺ of 4.3 (Fig.4.17) exhibit fragment ions of m/z 235, 197 and 145 formed by the expulsions of H₂O, methyl ketene (56u) and methoxy benzene (108 u) from the molecular ion respectively. The elimination of methoxy benzene is preferred over the elimination of benzene. Moreover, a comparison between the CAD mass spectra (Fig.4.18a and b) of the fragment ions of m/z 197 obtained from 4.2 and 4.3, obtained by CI experiments, showed that the two spectra are closely similar indicating that the fragment ions of m/z 197 from both compounds 4.2 and 4.3 have the same structure.
These observations indicate that the [M+H]^+ ion of 4.3 eliminates methylketene by a mechanism analogous to that for 4.2 and carbon-2 of the propene moiety is eliminated as part of ketene, Scheme: 4.10. The ESI mass spectrum of 4.3, Fig.4.19a shows the molecular ion of m/z 253 and the CAD mass spectrum, Fig.4.19b, shows the fragment ions of m/z 197 and 235 due to the eliminations of methyl ketene and H2O, respectively, from the [M+H]^+. The measured accurate masses 197.0964 and 235.1129 correspond to C14H13O, {[M+H-CH2CO]^+}, calculated 197.0966} and C16H13O (calculated 235.1123), respectively.
It is proposed that the elimination of methylketene occurs from 4.3, as a result of cyclisation analogous to the elimination of ketene from 4.1., Scheme: 4.10.
Scheme: 4.10. The formation of fragment ion of m/z 197 from 4.3


Further, the ESI mass spectrum of the isomeric benzal-2-methoxyacetophenone was investigated to explore the possibility of ketene elimination from the [M+H]^+. However, the CAD mass spectrum of the [M+H]^+ ion of m/z 239 of benzal-2-methoxyacetophenone generated by ESI shows fragment ions of m/z 224 and 135, Fig. 4.20a. The ion of m/z 224 is formed by the elimination of methyl radical while the fragment ion of m/z 135 is due to methoxy benzoyl cation formed by simple cleavage reaction. The absence of [M+H-ketene]^+ ion in the CAD mass spectrum of 2'-methoxychalcone reveals the requirement of the OCH₃ group at the 2-position of chalcone for the elimination of ketene.

\[ \text{Fig. 4.20. The CAD MS of the (a) [M+H]^+ ion of m/z 239 (b) ion of m/z 224 (ms}^3) \text{ (c) fragment ion of m/z 135 (ms}^3) 4.4 \text{ generated by ESI} \]
4.2.5. Mass spectra of 2-hydroxybenzal acetophenone (4.5)

The proposed mechanism for the fragmentation of protonated methoxybenzal acetophenone suggests that the oxygen atom of the methoxy group (rather than the methyl group) plays an important role in the cyclisation and elimination of ketene. Therefore the CI and ESI mass spectra of 2-hydroxybenzal acetophenone, 4.5, a molecule in which a hydrogen atom is present in the place of the methyl group, was investigated.

![Mass spectrum of 2-hydroxybenzal acetophenone](image)

**Fig: 4.21.** CI mass spectrum of 2-hydroxybenzal acetophenone (4.5)

The CI mass spectrum, **Fig: 4.21**, of 2-hydroxybenzal acetophenone (2-hydroxy chalcone, 4.5) shows molecular ion, [M+H]⁺, of m/z 225 and fragment ions of m/z 207, 183, 147 and 105 (benzoyl cation). The fragment ions of m/z 207 and 147 correspond to the losses of H₂O and benzene, respectively, from the protonated molecule. The structure of the ion of m/z 147 was discussed in chapter 2. The fragment ion of m/z 183 arises due to the elimination of ketene (42 u) from the molecular ion. The MI and CAD mass spectra, **Fig.4.22a** and **b**, of [M+H]⁺ of compound 4.5 exhibit peaks corresponding to the ions of m/z 207, 183, 147 and 105. The ion of m/z 183 has lower abundance in the CAD mass spectrum compared to the MI mass spectrum indicating that its formation involves rearrangement.
The ESI mass spectrum of 2-hydroxychalcone, **Fig.4.23a**, showed the molecular ion of m/z 225. The CAD mass spectrum, **Fig.4.23b**, of the [M+H]^+ ion shows the fragment ion of m/z 183 formed by the elimination of ketene but the fragment ions of m/z 207 and 147 are not observed (these fragments were present in the CI-MS and CAD mass spectra). This indicates that the formation of fragment ions of m/z 207 and 147 are high-energy processes where as the production of fragment ion of m/z 183 is a low energy process. The high abundance of the ion of m/z 183 and the absence of m/z 207 and 147 probably indicate that the Nazarov cyclisation takes place to a greater extend upon ionization by ESI, a technique which produces ions of lower energy compared to CI.
Scheme: 4.11. Ketene loss from 2-hydroxychalcone

Analogous to the structure of the [M+H-ketene]$^+$ fragment ion of 2-methoxy chalcone, 2-hydroxyphenyl phenylmethyl cation [35] structure is proposed for the fragment ion of m/z 183 from 2-hydroxy chalcone. To generate a reference standard for the ion of m/z 183, a suitable precursor 2-hydroxybenzhydrol, 4.10, was synthesized. The CAD mass spectrum, Fig.4.24, of the ESI generated [M+H]$^+$ ion of 2-hydroxybenzhydrol shows a fragment ion of m/z 183.
Fig. 4.24. The ESI mass spectrum of 4.10

Scheme: 4.12.

The formation of fragment ion of m/z 183 from 4.10 involves the elimination of H₂O as shown in Scheme: 4.12. The CAD mass spectrum of the fragment ion of m/z 183, [M+H-Ketene], Fig. 4.25a, from compound 4.5 was obtained by MS³ experiment using an ion trap instrument on the molecular ion of m/z 225. The CAD mass spectrum, Fig. 4.25b, of the [M+H-H₂O]⁺ fragment of compound 4.10 was also obtained by MS³ experiment. The two spectra are closely similar indicating that the ions of m/z 183 obtained from both compounds 4.5 and 4.10 have the same structure, 2-hydroxyphenyl phenyl methyl cation. This evidences that the proposed structure for the [M+H-Ketene]⁺ is correct and supports the proposed Nazarov cyclisation prior to the elimination of ketene from 2-hydroxychalcone.
The structure of the [M+H-ketene]+ fragment indicates that the elimination of ketene from 2-hydroxy chalcone (4.5) follows a mechanism analogous to that for the elimination of ketene from 4.2. The enthalpies of the intermediates, transition states and product ions were estimated, by molecular orbital calculations (DFT theory), relative to that of the protonated molecule, Table 4.3. The mechanism for cyclisation is presented in Scheme: 4.13 and Scheme: 4.14 that for the elimination of ketene is given in Scheme: 4.15.
### Table 4.3. Heats of formations of the intermediates, products and transition states relative to that of the [M+H]^+ ion in Kcal/mol. Scheme 4.13, 4.14 & 4.15.

<table>
<thead>
<tr>
<th>Species</th>
<th>ΔHf</th>
<th>Species</th>
<th>ΔHf</th>
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</thead>
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<tr>
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<td>5.6</td>
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<td>9.9</td>
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<td>31.2</td>
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<td>46.5</td>
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<td>27.4</td>
<td>TSc1-d2</td>
<td>32.9</td>
</tr>
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<td>4.5d2</td>
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<td>27.0</td>
<td>TSj-(k+m)</td>
<td>33.6</td>
</tr>
</tbody>
</table>

### Scheme: 4.13. Cyclisation of 2-hydroxy chalcone
Scheme: 4.14. Cyclisation catalyzed by OH group

Scheme: 4.15. Ketene elimination catalyzed by OH group.

The mechanism involves isomerization of the protonated trans-2-hydroxychalcone (4.5a) to the cis-conformation (4.5b) followed by electrophilic cyclisation to form the intermediate 4.5d cis-isomer or trans-isomer 4.5d1. There are two pathways to form 4.5g. The first pathway involves the cis-isomer 4.5d which undergoes two 1,2-H-shifts followed
by C-C bond rotation (highest energy transition state = 61.7 kcal/mol). The second (from 4.5d1) is shown in Scheme: 4.14 in which the OH group acts as a catalyst and provides a lower energy pathway (34.4 kcal/mol) (this is equivalent to the role of solvent in the condensed phase Nazarov cyclisation). The proton first shifts to the OH before going to the required carbon (through intermediates 4.5d1 and 4.5d2) to form 4.5g. Subsequent proton shift from the carbonyl oxygen to the aromatic ring carbon via the oxygen atom of the hydroxyl group leads to the elimination of ketene. The role of the OH group is to reduce the energy for the H-migrations by providing an alternate pathway, i.e. it is acting as a catalyst.

![Figure 4.26](image)

**Fig: 4.26.** CI-CAD spectrum of [M+D]^+ ion of 4.5

The [M+H]^+ ion, 4.5a, has two OH groups and hence H/D is possible in the corresponding [M+D]^+ ion so that part of the D will be present in the phenolic OH. **Scheme:**
4.13. Since the H-shifts are mediated by the oxygen atom of the phenolic OH group, both retention and loss of deuterium with the product ion is expected during the elimination of ketene from the [M+D]+ ion. The CI-CAD mass spectrum, Fig 4.26, of [M+D]+ ion of m/z 226 of compound 4.5, generated by CI by using methane-d4 as the reagent gas, shows peaks corresponding to the ions of m/z 183 and 184 in the ratio 1:2 due to eliminations of ketene-d and ketene. The CAD mass spectrum of [M+D]+ ion 2-hydroxychalcone-d, Fig 4.27, generated by ESI, showed fragment ions of m/z 185, 184 and 183 due to eliminations of ketene-d2, ketene-d and ketene indicating H/D scrambling prior to the elimination of ketene. The fragmentation process of the [M+D]+ ion supports the proposed participation of the OH group in the cyclisation and elimination of ketene. In addition, the formation of benzoyl cation also involves partial H/D mixing.

![Fig.4.27. CAD mass spectrum of [2-hydroxychalcone-OD+D]+ (m/z 227)](image)
The high abundance of the ion of m/z 105 in the ESI-CAD mass spectrum of \textbf{4.5 Fig.4.27}, compared to that of 2-methoxychalcone under identical conditions (same instrument and collision energy), \textbf{Fig.4.15a}, is attributed to a 1,3-H-shift from the carbonyl oxygen to the α-carbon atom, catalyzed by the OH group, \textbf{Scheme: 4.16}, that provides a low energy pathway for the formation of benzoyl cation. The same process is not feasible for 2-methoxychalcone as shown by molecular orbital calculations.

\textbf{Scheme: 4.16}. Formation of benzoyl cation from \textbf{4.5}

\textbf{4.2.6. Mass spectra of benzal-2-hydroxyacetophenone (4.6)}

To establish the importance of the position of the OH group in the ketene elimination the ESI mass spectrum of benzal-2-hydroxyacetophenone, \textbf{Fig.4.28}, was investigated. The CAD mass spectrum of the [M+H]$^+$ ion does not show fragment ion of m/z 183 corresponding to elimination of ketene. All fragment ions arise due to the rearrangement mainly into flavanone, \textbf{Scheme: 4.17}. The EI mass spectra of flavanone and benzal-2-hydroxychalcone are reported to be identical [12].
Fig. 4.28. The CAD MS of the [M+H]$^+$ ion of m/z 225, compound 4.6

Scheme: 4.17.

4.2.7. Mass spectra of 4-methoxybenzal acetophenone (4.7)

Further, the CI and ESI mass spectra of 4-methoxybenzal acetophenone, 4.7, were examined to explore the possibility of cyclisation. The CI mass spectrum, Fig. 4.29, of 4.7 shows molecular ions, [M+H]$^+$ of m/z 239 and fragment ions of m/z 161 and 105. The formation of the ions of m/z 161 involves the elimination of a benzene molecule. But the fragment ion of m/z 197 is not observed indicating that the elimination of ketene from protonated methoxychalcone requires the presence of methoxy group at the ortho position.
Further, the CAD spectrum of [M+H]$^+$ of 4.7 (Fig.4.30) does not show fragment ion of m/z 197 but exhibits peaks corresponding to ions of m/z 161, 131 and 105.

The ESI mass spectrum of compound 4.7, Fig.2.31a shows the molecular ion of m/z 239 and the CAD mass spectrum, Fig.2.31b, shows fragment ions of m/z 221, 211 and 161.
formed by the eliminations of H$_2$O, CO and C$_6$H$_6$, respectively. The measured accurate masses obtained from the CAD mass spectrum are in good agreement with the calculated masses for the expected molecular formulae, **Table. 4.4.** At higher collision energy the intensities of the fragment ions in the CAD mass spectrum increase, **Fig.4.32.**

**Table.4.4.** High-resolution data for the ions of m/z 211 and 161 of compound 4.7.

<table>
<thead>
<tr>
<th>Nominal mass</th>
<th>Measured mass</th>
<th>Mol. formula</th>
<th>Calculated mass</th>
<th>Neutral lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>211</td>
<td>211.1141</td>
<td>C$<em>{15}$H$</em>{15}$O</td>
<td>211.1123</td>
<td>CO</td>
</tr>
<tr>
<td>161</td>
<td>161.0601</td>
<td>C$_{10}$H$_9$O$_2$</td>
<td>161.0602</td>
<td>C$_6$H$_6$</td>
</tr>
</tbody>
</table>

**Fig.4.31a.** The ESI MS of 4.7

**Fig.4.31b.** The ESI-CAD MS of 4.7. (The abundances of ions of m/z 105 and 131 are very small-QToF).

**Fig.4.32.** The CAD MS of the ESI produced [M+H]$^+$ ion of 4.7 at high collision energy by using Thermo Finnigan LCQ Advantage ion trap instrument.
The low energy ESI-CAD mass spectra, Fig. 4.31b and Fig. 4.32, show fragment ions of m/z 221 and 211 due to elimination of CO and H$_2$O characteristic of 3-aryldanone (unlike in the high-energy CI-CAD mass spectrum) suggest that protonated 4-methoxychalcone undergoes cyclisation. In addition the abundances of the ions of m/z 221, 211, 161 and 131 are considerably higher relative to the ion of m/z 105 in the ESI-CAD mass spectrum compared to the CI-CAD mass spectrum, Fig.4.30, indicating that the cyclisation takes place to a greater extend upon protonation by ESI.

Scheme: 4.18. Mechanism of CO loss from protonated 4-methoxybenzal acetophenone (4.7)

The formation of fragment ion of m/z 211 can be explained by invoking electrophilic cyclisation in the [M+H]$^+$ ion of compound 4.7 (analogous to that of 2-methoxychalcone) to yield, 4.7d, protonated 3-(4-methoxyphenyl) indanone, Scheme: 4.18. The 1,3-H-shift from the carbonyl oxygen to the aromatic ring carbon is not possible since the methoxy group being at the para position cannot interact with the proton (i.e. the methoxy group cannot catalyze the H-shift). Hence, being a protonated cyclic ketone (4.7d), elimination of CO
occurs instead of ketene to afford the ion of m/z 211, 4.7e. The CAD mass spectrum of the ion of m/z 211, Fig. 4.33, shows major fragmentations due to losses of CH₃, C₂H₄, CH₂O and methanol to yield ion of m/z 196, 183, 181 and 179 respectively. The loss of CH₃ from the fragment ion of m/z 211 [M+H-CO]⁺ is similar to that from the m/z 181 [M+H-CO]⁺ fragment from chalcone (4.1) may be indicative of a similarity in structure.

**Fig. 4.33.** The CAD mass spectrum of the fragment ion of m/z 211 (MS³ Experiment) of 4.7.

### 4.2.8. Mass spectra of 4-hydroxybenzal acetophenone (4.8)

![CI MS of 4-hydroxybenzal acetophenone (4.8)](image)
Further the CI and ESI mass spectra of 4-hydroxybenzal acetophenone (4.8), a para analogue of 2-hydroxybenzal acetophenone, were examined. The CI mass spectrum, Fig.4.34, shows the molecular ion of m/z 225. The MI, Fig.4.35, and CAD, Fig.4.36, mass spectra of the ion of m/z 225 show fragment ions of m/z 207, 147 and 131 formed by the eliminations of H$_2$O, benzene and phenol respectively.

But the MI and CAD mass spectra do not show fragment ion of m/z 183, unlike the ortho isomer 4.5, indicating that the elimination of ketene from the [M+H]$^+$ of 4.8 is not
possible. The abundance of the fragment ion of m/z 105 is high compared to the ion of m/z 147. The ESI mass spectrum, Fig.4.37a, shows peak corresponding to the molecular ion of m/z 225 and the ESI-CAD mass spectrum, Fig.4.37b shows fragment ions of m/z 207, 197 and 147 corresponding to the eliminations of H₂O, CO and benzene respectively.

![Fig.4.37a. The ESI MS of 4.8](image1)

![Fig.4.37b. The ESI-CAD mass spectrum of 4.8](image2)

| Table.4.5. High-resolution data for the fragment ions formed from [M+H]^+ of 4.8. |
|---|---|---|---|---|
| Nominal mass | Measured mass | Mol. formula | Calculated mass | Neutral lost |
| 207 | 207.0801 | C₁₅H₁₁O | 207.0809 | H₂O |
| 197 | 197.0971 | C₁₄H₁₃O | 197.0966 | CO |
| 147 | 147.0440 | C₉H₇O | 147.0445 | C₆H₆ |

The fragment ion of m/z 197 is due to the elimination of CO from the [M+H]^+ of 4.8 analogous to the fragmentation of 4-methoxybenzal acetophenone. It is proposed that the [M+H]^+ ion rearranges to protonated 3-(4-hydroxyphenyl) indanone, 4.8d, Scheme: 4.19. The hydroxyl group present at the para position cannot facilitate the transfer of H-atom from the carbonyl oxygen to the ring carbon and hence elimination of CO yielding ion of m/z 197 occurs from 4.8d rather than ketene. Moreover, the higher abundances of the ions of m/z 207, 197, 147 compared to that of the ion of 105 in the ESI-CAD mass spectrum, unlike in
the CI-CAD mass spectrum, indicates cyclisation of the protonated molecule to indanone takes place to a greater extend in the low energy ESI generated [M+H]\(^+\) ion.

\[ \text{Scheme: 4.19. Elimination CO from protonated 4-hydroxybenzal acetophenone (4.8)} \]

**4.3. Conclusion**

The mass spectral fragmentations of chalcone and its methoxy and hydroxy substituted analogues were investigated by using both CI and ESI ionization. The results indicate that Nazarov type cyclisation occurs in protonated chalcone to yield 3-phenyl indanone and the substituted analogues yield 3-arylindanones. Extend of cyclisation is greater in the ESI produced ions. The OCH\(_3\) or OH group at the \textit{ortho} position can act as a catalyst, by decreasing activation energy, for the H-shift which is a key step for the cyclisation. The ketene elimination occurs due the H-shift catalyzed by the oxygen atom of the OCH\(_3\) or OH group. But when the OCH\(_3\) or OH groups are absent in the \textit{ortho} position the cyclisation takes place to a lesser extend and competitive expulsions of CO, H\(_2\)O and benzene (or substituted benzene) takes place instead of ketene. The elimination of CO, H\(_2\)O and benzene are characteristic of protonated 3-phenylindanone. The structures of the [M+H-
ketene$^+$ and [M+H-CO]$^+$ were identified by comparison of their CAD mass spectra with those of the authentic standards. The proposed mechanisms are based on molecular orbital calculations and are supported by high-resolution data, tandem mass spectrometric experiments and d-labeling. This study revealed that protonated chalcone undergoes Nazarov cyclisation in the gas-phase analogous to the reported cyclisation in solution phase. Extend of cyclisation depends on the ionization method and position of substituent. In addition, we demonstrate that the cyclisation and fragmentation of 2-methoxy and 2-hydroxychalcone are examples of intramolecular proton transport catalysis.

4.4. Experimental

4.4.1. Preparation of Benzal acetophenone (chalcone) (4.1) [36, 37]

Benzaldehyde - 5.5 ml
Acetophenone - 6.0 ml
Sodium hydroxide - 2.5 gm in 25 ml distilled water

2.5 gm of NaOH was dissolved in 25 ml of distilled water and 6.0 ml of acetophenone was slowly added followed by the drop wise addition of 5.5 ml of benzaldehyde with stirring. The mixture was kept in a water bath and stirred for five hours. The mixture was added to crush ice, acidified with dilute HCl, extracted with ether, washed with water and the solvent was removed by distillation to get the product, 4.1. Yield 8 gm. It was purified by recrystallisation from ethanol. M.P = 53˚C (Reported [36] 54-57˚C).

IR (KBr) cm$^{-1}$: 3051 (aromatic CH stretch), 1664(α, β-unsaturated C=O stretch), 1448-1607 (C=C stretch), 1214(C-O stretch)

$^1$H NMR (CDCl$_3$): δ 7.3-8 (m, 11H), 8.2 (d, 1H).
4.4.2. Preparation of 2-Methoxybenzal acetophenone (4.2) [36, 37]

2-Methoxybenzaldehyde - 5.0 ml (5.6gm)
Acetophenone - 5.0 ml (5.0gm)
Sodium hydroxide - 2.5 gm in 25 ml distilled water

2-Methoxychalcone was prepared by adopting the procedure used for the preparation of compound 4.1. The product was purified by recrystallisation from ethanol. Yield 3.5 gm. M.P. = 60˚ C (Reported [37] 61˚ C).

IR (KBr) cm⁻¹: 3062 (aromatic CH stretch), 2939(methyl CH stretch), 1660(α, β-unsaturated C=O stretch), 1598 (alkene C=C stretch), 1465-1574(aromatic C=C stretch), 1248(C-O stretch)

¹H NMR (CDCl₃): δ 3.9 (s, 3 H), 6.9 (d, 1 H), 7.3-8 (m, 9 H), 8.2 (d, 1 H).

4.4.3. Preparation of 2-Methoxybenzal propiophenone (4.3) [36, 39]

2-Methoxybenzaldehyde - 5.0 ml (5.6gm)
Propiophenone - 5.5 ml (5.5gm)
Sodium hydroxide - 2.5 gm in 25 ml distilled water

The title compound was prepared by employing the procedure used for the preparation of 2-methoxybenzal acetophenone (4.1). Yield 5ml, purified by column chromatography.

IR (CHCl₃) cm⁻¹: 3074 (aromatic CH stretch), 2941(methyl CH stretch) 1665(α, β-unsaturated C=O stretch), 1484-1598 (C=C stretch), 1241(C-O stretch)

¹H NMR (CDCl₃): δ 1.1 (s, 3 H), 3.9 (s, 3 H), 6.9 (d, 1 H), 7.0 (m, 3H), 7.5 (m, 4 H), 7.8 (d, 1 H), 8.0 (d, 1 H).
4.4.4. Preparation of Benzal-2-methoxy acetophenone (4.4)[36,38]

(a). Preparation of 2-methoxyacetophenone

- 2-Hydroxyacetophenone - 8 ml
- Dimethylsulphate - 15 ml
- Potassium carbonate - 15 gm

8 ml of 2-hydroxyacetophenone was taken in a 100 ml R.B. flask, 15 ml of dimethyl sulphate was added with stirring followed by 15 gm of K₂CO₃. Excess of cold water was added. The content was extracted with ether, washed with water, dried by adding anh. Na₂SO₄ and ether was distilled out. 5 ml of 2-methoxy acetophenone was obtained.

(b). Preparation of Benzal-2-methoxyacetophenone

- 2-Methoxy acetophenone - 5 ml
- Benzaldehyde - 3.5 ml
- Diethyl ether - 20 ml
- Sodium hydroxide - 3.5 gm

Benzal-2-methoxyacetophenone was prepared by adopting the procedure used for the preparation of compound 4.1. The product was purified by column chromatography. Yield 7.5 ml. B.P = 224° C (Reported [38] 226° C).

**IR** (CHCl₃) cm⁻¹: 3060 (aromatic CH stretch), 2942(methyl CH stretch), 1657(α, β-unsaturated C=O stretch), 1449-1657(C=C stretch), 1241(C-O stretch).

**¹H NMR** (in CDCl₃): δ 3.9 (s, 3 H), 7.0 (m, 2 H), 7.3-7.8 (m, 9 H)

4.4.5. Preparation of 2-Hydroxybenzal acetophenone (4.5) [36, 40]

- Salicylaldehyde - 5.5 ml
- Acetophenone - 6.0 ml
Sodium hydroxide - 2.5 gm in 25 ml distilled water

2.5 gm of NaOH was dissolved in 25 ml of distilled water; 6.0 ml of acetophenone was slowly added followed by the drop wise addition of 5.5 ml of salicylaldehyde with stirring. The mixture was kept in a water bath for acquiring the room temperature and stirred for four hours. The mixture was added to crush ice and acidified with dilute HCl. The precipitated 2-hydroxybenzal acetophenone was filtered, washed with water and dried. The product was purified by recrystallisation from ethanol. Yield 8.5 gm. M.P = 156˚ C (Reported [40, 41] 154-155˚ C).

**IR** (KBr) cm\(^{-1}\): 3210( aromatic O-H stretch), 3084 ( aromatic CH stretch), 1640(\(\alpha, \beta\)-unsaturated C=O stretch), 1562-1600 (alkene C=C stretch), 1457( aromatic C=C stretch), 1231(C-O stretch).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.3 (s, 1H), 6.9 (d, 1H), 7.0-8.0 (m, 9H), 8.2 (d, 1H).

**4.4.6. Preparation of Benzal-2-hydroxy acetophenone (4.6)** [36, 42]

Benzaldehyde - 5.5 ml

2-Hydroxy acetophenone - 6.3ml

Sodium hydroxide - 2.5 gm in 25 ml distilled water

Benzal-2-hydroxyacetophenone was prepared adopting the procedure used for the preparation of 4.5. Yield 8 gm. The product was purified by recrystallisation from ethanol.

**IR** (KBr) cm\(^{-1}\): 3480( aromatic O-H stretch), 3058 ( aromatic CH stretch), 1639(\(\alpha, \beta\)-unsaturated C=O stretch), 1437-1630(C=C stretch), 1229(C-O stretch).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.9 7.1 (m, 2H), 7.3-8.0 (m, 9H), 8.2 (d, 1H).

**4.4.7. Preparation of 4-Methoxybenzal acetophenone (4.7)** [36, 43]

4-Methoxybenzaldehyde - 5.0 ml (5.6gm)
Acetophenone - 5.0 ml (5.0gm)
Sodium hydroxide - 2.5 gm in 25 ml distilled water

The title compound was prepared by employing the procedure used for the preparation of 2-methoxybenzal acetophenone (4.2). Yield 2.5 gm, purified by recrystallisation from ethanol. M.P = 130° C (Reported [43] 132-34° C).

**IR (KBr) cm⁻¹:** 3062 (*aromatic CH stretch*), 2935 (*methyl CH stretch*), 1659(*α, β-unsaturated C=O stretch*), 1600 (*alkene C=C stretch*), 1551-1573 (*aromatic C=C stretch*), 1253 (*C-O stretch*).

**1H NMR** (CDCl₃): δ 3.9 (s, 3 H), 6.9 (d, 1 H), 7.3-8 (m, 9 H), 8.2 (d, 1 H).

**4.4.8. Preparation of 4-Hydroxybenzal acetophenone (4.8) [36, 40]**

4-hydroxybenzaldehyde - 5.5 ml
Acetophenone - 6.0 ml
Sodium hydroxide - 2.5 gm in 25 ml distilled water

4-Hydroxybenzal acetophenone was prepared by employing the procedure used for the preparation of 2-hydroxybenzal acetophenone (4.4). Yield 8.0gm. The product was purified by recrystallisation from ethanol. M.P. = 182° C (Reported [36, 44] 182.5-184° C).

**IR (KBr) cm⁻¹:** 3235 (*aromatic O-H stretch*), 3060 (*aromatic CH stretch*), 1650(*α, β-unsaturated C=O stretch*), 1600 (*alkene C=C stretch*), 1512-1561 (*aromatic C=C stretch*), 1219 (*C-O stretch*).

**1H NMR** (CDCl₃): δ 6.9(d, 1H), 7.2 (s, 1 H), 7.4-8 (m, 10H).

**4.4.9. Preparation of 2-Methoxy benzhydrol (4.9) [45, 33, 46]**

2-Methoxybenzaldehyde - 3.5 ml (3.9 gm)
Bromobenzene - 3.0 ml (4.5 gm)
Magnesium metal - 0.75 gm
Dry ether - 35 ml

3.3 ml of bromobenzene in 20 ml of dry ether and 0.6 gm of magnesium pieces was added. The mixture was stirred for 4 hrs after adding a crystal of iodine to initiate the reaction. 3.5 ml of 2-Methoxybenzaldehyde in 15 ml of dry ether was added drop wise. The mixture was stirred for half an hour more and acidified by adding 5 ml of diluted HCl. The content was extracted with ether. Ether layer was washed with water, dried by adding anhydrous Na₂SO₄ and the solvent distilled off. The content was further purified by column chromatography. Yield 2.5 ml, B.P. = 180˚ C (Reported [33] 181-2˚ C).

**IR** (CHCl₃) cm⁻¹: 3450(O-H stretch), 3063 (aromatic CH stretch), 2943(methyl CH stretch), 1597-1663(aromatic C=C stretch), 1241(C-O stretch).

**¹H NMR** (CDCl₃): δ 3.9 (s, 3H), 7.0 (m, 3H), 7.2-7.6 (m, 5 H), 7.8 (d, 1 H).

4.4.10. Preparation of 2-Hydroxybenzhydrol (4.10) [45, 33]

<table>
<thead>
<tr>
<th>Material</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Hydroxybenzaldehyde</td>
<td>3.0 ml (3.5 gm)</td>
</tr>
<tr>
<td>Bromobenzene</td>
<td>6.0 ml (9.0 gm)</td>
</tr>
<tr>
<td>Magnesium metal</td>
<td>1.4 gm</td>
</tr>
<tr>
<td>Dry ether</td>
<td>35 ml</td>
</tr>
</tbody>
</table>

The title compound as prepared by employing the procedure used for the preparation of 2-methoxybenzhydrol (4.9). Yield 2.5 gm, purified by recrystallisation from ethanol. M.P. = 87˚ C (Reported [43] 87-89˚ C)

**IR** (KBr) cm⁻¹: 3356(O-H stretch), 3061 (aromatic CH stretch), 1582-1663(aromatic C=C stretch), 1227(C-O stretch).

**¹H NMR** (CDCl₃) : δ 5.7 (s, 1H), 6.8-7.6 (m, 9H), 9.9 (s, 1H), 11 (s, 1H).
4.4.13. Preparation of 1,1-Diphenyl ethanol\[(4.13)\] \([45, 47, 48]\]

- Acetophenone: 6.0 ml (6 gm)
- Bromobenzene: 5.0 ml (7.5 gm)
- Magnesium metal: 1.4 gm
- Dry ether: 30 ml

The title compound is prepared by employing the procedure used for the preparation of 2-methoxybenzhydrol \((4.9)\). Yield 3.0 gm, purified by recrystallisation from ethanol.

M.P. = 77 °C (Reported \([47, 48]\) 77-80° C)

\textbf{IR (KBr) cm}^{-1}: 3404(O-H stretch), 3054 (aromatic CH stretch), 2976(methyl CH stretch), 1593 (C=C stretch), 1371(C-O stretch)

\textbf{\textsuperscript{1}H NMR (CDCl\textsubscript{3})}: \delta 2.0(s, 3H), 7.2-7.4(m, 10H)
4.5. References


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