4. THERMAL [1,3]-[1,3]-\textit{ PARA} REARRANGEMENT OF CHROMONE-3-YLMETHYL ARYL ETHERS - MECHANISTIC INVESTIGATION AND SYNTHESIS OF HYDROXYHOMOISOFLAVONES

4.1 INTRODUCTION

Molecules with a benzopyran ring are widely found in nature. They have drawn the attention of medicinal chemists as many of these compounds display varying pharmacological properties including antioxidant, anticancer, etc., [124-125]. The wide range of interesting activities and properties exhibited by benzopyran derivatives have prompted organic chemists to develop a convenient and efficient methodologies for the synthesis of polyheterocycles with a fused benzopyran moiety.

Rotenoids and isorotenoids are dimeric flavonoids, containing fused chromanone and chroman rings. Homoisoflavones and homopterocarpanes also possess the chromone ring system. Since the work described in this chapter deals with the development of new routes for homopterocarpanes and homoisoflavones, a brief introduction to the chemistry of these heterocyclic compounds is presented below.

Rotenoids [126] have drawn considerable attention as they exhibit various pharmacological properties like ichthyotoxical [127], insecticidal [128], antifeedant and antimicrobial [129] and are also commercially important [126]. Homoisoflavones, \textit{viz.}, 3-benzylchromene-4-ones (Figure 4.2) are naturally occurring flavonoids exhibiting potent pharmacological properties. These homoisoflavonoids can be cyclized to afford homopterocarpanes. Many homoisoflavonones possess anti-inflammatory [130], antioxidant [131],
antiproliferative [132], antifungal [133], antiviral [134] and antimutagenic activities [135].

Some of the homoisoflavonoids have been reported to be cytotoxic towards MCF-7 [136] and are good inhibitors of the enzyme COX-2 [137]. Homoisoflavonoids viz., 3-benzylidinechroman-4-ones and homoisoflavanones viz., 3-benzyl-4-chromanones are found naturally in plants [138]. Some of these isoflavonoids are also pharmacologically active [138].

4.1.1 Synthetic methods for homoisoflavonoids.

The construction of homoisoflavonoid skeleton is generally achieved using the two approaches. In one of the approaches, 4-chromanones are
condensed with arylaldehydes in methanol in the presence of HCl [139] or piperidine [140]. The resulting benzyldene derivatives are isomerized to isoflavones by using Pd/C. The other common approach is to subject the dihydrochalcone to an one carbon extension using ethoxymethylchloride [141], paraformaldehyde and diethylamine [142]. These methods suffer from the draw backs of tedious reaction conditions and low yields. Hence, there is continued interest in developing better methodologies. Few synthesis of homoisoflavones based on the above methodology are discussed below:

Dann and co-workers [143] synthesized benzylidinechroman-4-ones by aldol condensation of chroman-4-ones with benzaldehyde in methanol using HCl as catalyst (Scheme 4.1). The synthesis of benzylidinechromanones has been achieved in alkaline conditions too [144].

![Scheme 4.1 Synthesis of homoisoflavones from chromanones.](image)

Kirkiacharian *et al.*, [145] synthesized homoisoflavones via condensation of 2-hydroxyacetophenones with 3,4-dimethoxybenzaldehydes in methanol & aq. KOH, followed by hydrogenation over Pd/C to afford the 2'-hydroxydihydrochalcones in 80-90% yield. Subsequent treatment of the dihydrochalcones in ethylformate with sodium at 0°C afforded the homoisoflavones in good yield as outlined in Scheme 4.2.
Scheme 4.2 Synthesis of homoisoflavone from 2'-hydroxyacetophenone

Subbaraju and co-workers [146] have improved the dihydrochalcones methodology by the condensation of phenols and dihydrocinnamic acids using BF$_3$.Et$_2$O. Subsequent cyclisation of the dihydrochalcones to homoisoflavones has been achieved using DMF/PCl$_5$ in 70-80% yield (Scheme 4.3).

Scheme 4.3 BF$_3$ catalyzed synthesis of homoisoflavones.

Quite lately, Venkatarao et al., [147] have reported a similar strategy as above, but they have used HC(OEt)$_2$/HClO$_4$ instead of BF$_3$.Et$_2$O and DMF/POCl$_3$, to effect the cyclisation of 2'-hydroxydihydrochalcones to homoisoflavones.

4.2 OBJECTIVES

This chapter deals with the synthesis and thermal rearrangement of chromone-3-ylmethyl aryl ethers with the objective to devise a new & simple
route for the synthesis of isorotenoid 17, homopterocarpane 19 and homoisoflavone 21 skeleton as envisaged in Scheme 4.4:

Scheme 4.4 Retrosynthesis of isorotenoid, homoisoflavone and homopterocarpane

The chromon-3-ylmethyl aryl ether 1 upon thermal rearrangement can undergo either a [3,3]-sigmatropic shift (Claisen rearrangement) to afford the corresponding 3-exo-methylene-2-arylated chromone 18 (Path A) or a [1,3]-sigmatropic rearrangement which would lead to homoisoflavones 21; which in turn can be converted to homopterocarpane 19 (path B).

The exo-methylene chromone 18 upon simple cyclisation would lead the isorotenoid 17. Of particular interest in this unexplored approach is to find out if the 2,3-double bond of the chromone would behave like an allyl moiety of an allyl phenyl ether towards thermal rearrangement and undergo the Claisen rearrangement similar to allyl phenyl ether. If it does, it would lead to 2-phenyl-3-methylene-chromanone 18 which is suitably set for an intramolecular Michael reaction to furnish the isorotenoid skeleton 17. On the other hand, a [1,3]-migration of the chromone-3-ylmethyl moiety would result in homoisoflavone 21.

It is well established that when both the double bonds in the Claisen substrate are part of an aromatic system, such an ether does not undergo the
[3,3]-rearrangement. For example phenyl benzyl ether 22, where in both the double bonds are part of an aromatic ring, does not undergo Claisen rearrangement even when heated in high boiling solvents and only leads to a mixture of o-benzylphenol, p-benzylphenol and cleaved phenol as minor products, in addition to the starting material (Scheme 4.5) [148].

\[
\begin{align*}
\text{Scheme 4.5 Rearrangement of benzyl phenyl ether 22.}
\end{align*}
\]

In contrast, α-dimethylaminovinyl benzyl ether is smoothly converted to \(N,N\)-dimethyl-o-methylphenyl acetamide via Eschenmoscher rearrangement [39]. 4-Aryloxymethylcoumrins 26, wherein the double bond of the allyl moiety is part of heteroaromaticcoumarin ring, is stable under conditions of Claisen rearrangement, while the isomeric coumarin-3-ylmethyl aryl ethers 27 undergo [1,3]-rearrangement when refluxed in diphenyl ether (Scheme 4.6) [149]. Hence it is of interest to investigate the behaviour of chromone-3-ylmethyl aryl ethers 1 under the usual conditions of Claisen rearrangement.

\[
\begin{align*}
\text{Scheme 4.6 Thermal rearrangement of 3-aryloxymethylcoumarins 27.}
\end{align*}
\]
4.3 RESULTS AND DISCUSSION

4.3.1 Synthesis of chromone-3-ylmethyl aryl ethers 1a-k.

As discussed in the previous chapter (Section 3.3), the synthesis of key Claisen substrates, viz. Chromone-3-ylmethyl aryl ethers 1 could not be realized via Buchwald-Hartwig coupling reaction. Hence, it was decided to prepare these ethers by the conventional route i.e via the classical Williamson ether synthesis [108]. The chromonyl alcohols 2 were prepared according to the literature procedure [116]. Treatment of the alcohols 2a-c with PBr₃ in CH₂Cl₂ yielded the corresponding bromides 30a-c in about 80-85% yield; without any complication due to allylic rearrangement (Scheme 4.7).

![Scheme 4.7 Synthesis of bromomethylchromone 30.](image)

The bromides 30 are unknown compounds and were thoroughly characterized by NMR and mass spectral techniques. An upfield shift was observed in the resonance signal of OCH₂ protons of 2a (δ 4.59) upon conversion to the bromide 30a (δ 4.40). The crude bromide 30 obtained was used as such without purification for the subsequent nucleophilic displacement reaction.

3-Bromomethylchromone 30a underwent a facile reaction when reacted with phenol (1.0 equiv.) in DMF in the presence of K₂CO₃ and afforded the hitherto unknown chromonyl aryl ether 1a as a solid in about 82% yield after column chromatographic purification. A few other ethers 1b-k were also prepared following this procedure (Scheme 4.8).
Scheme 4.8 Synthesis of Chromone-3-ylmethyl aryl ethers 1a-k.

The HRMS of 1a exhibited the molecular ion peak at M/z 253.0864 corresponding to the elemental composition C_{16}H_{13}O_{3} [M+H]^+. \textsuperscript{1}H NMR spectrum of the ether 1a (Figure 4.3) displayed the characteristic signals due to OCH\textsubscript{2} protons at \(\delta\) 5.07 as doublet. The signal due to olefinic H-2 appeared as a singlet at \(\delta\) 8.10. \textsuperscript{13}C NMR spectrum of 1a displayed 12 signals in accordance with its structure (Figure 4.4). COSY and HSQC spectra provided additional support. In the case of ethers where R2 = H, the signal due to the peri proton (\(\delta\) 8.26) near the carbonyl group was distinguishable from rest of the protons signals by its downfield chemical shift.
Figure 4.3 300 MHz $^1$HNMR spectrum of 1a in CDCl$_3$
Figure 4.4 75 MHz $^{13}$C NMR spectrum of 1a in CDCl$_3$
Figure 4.5  DEPT spectrum of 1a
Several substituted chromone-3-ylmethyl aryl ethers 1a-k were prepared in good yield following the optimized procedure (Table 4.1). In all the cases, we did not observe the products due to allylic rearrangement.

**Table 4.1** Synthesis of chromone-3ylmethyl aryl ethers 1a-k.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ether 1</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>R&lt;sup&gt;4&lt;/sup&gt;</th>
<th>R&lt;sup&gt;5&lt;/sup&gt;</th>
<th>R&lt;sup&gt;6&lt;/sup&gt;</th>
<th>R&lt;sup&gt;7&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>-CH=CH-</td>
<td>CH=CH-</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>-CH=CH-</td>
<td>CH=CH-</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>71</td>
</tr>
<tr>
<td>11</td>
<td>1k</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>68</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after column chromatography.

### 4.3.2 Synthesis of chromone-2-ylmethyl aryl ethers 33.

The isomeric chromone-2-ylmethyl aryl ethers 33a and 33b were prepared from 2-hydroxyacetophenones 5 as described in literature [150-151] involving two steps. 2-Hydroxyacetophenones 5 were reacted with phenoxyacetyl chloride 31 in pyridine to give the diketone intermediates 32, which were treated with KOH in pyridine followed by acid workup to furnish the chromone-2-ylmethyl aryl ethers 33 (Scheme 4.9).
Scheme 4.9 Synthesis of chromone-2-ylmethyl aryl ethers 33.

Though the ether 33a is already reported in literature [151], it was thoroughly characterized by NMR spectroscopy. The $^1$H NMR spectrum of the ether 33a showed the characteristic olefinic proton H$_3$ at $\delta$ 6.52 as a singlet. The $^{13}$C NMR spectrum of the ether 33a exhibited fourteen lines. The carbon of the –OCH$_2$ group resonated at $\delta$ 65.9. The spectral data were in accordance with the literature [151].

4.3.3 Thermal rearrangement of chromone-3-ylmethyl aryl ethers 1a-k.

The first thermal rearrangement of an allyl vinyl ether was reported in the year of 1912 by Claisen [30]. Among the several known organic solvents, for effecting Claisen rearrangement $N,N$-diethylaniline (N,N-DEA) is found to be best as it has not only the necessary high boiling point, but also it is a good free radical inhibitor [152]. Its basic nature renders the isolation of the product easy by simple extraction with an organic solvent and washing with dilute acid. Hence for the present rearrangement study it was chosen to start with $N,N$-DEA as the solvent.

In a typical reaction, a solution of the ether 1a in $N,N$-DEA was refluxed in inert atmosphere. The reaction was monitored by TLC. Although, TLC showed the formation of a single product, some amount of starting material 1a
was present even after 48 h. The reaction mixture was worked up using aqueous HCl and the crude product was purified by column chromatography over silica gel to afford a brown coloured solid 34a in 24% yield.

The HRMS of 34a exhibited the molecular ion peak at m/z 253.0867 corresponding to the elemental composition C$_{16}$H$_{13}$O$_3$ [M+1]$^+$ indicating that it is an isomer of the starting ether. The $^1$H NMR spectrum of 34a (Figure 4.6) exhibited a singlet at δ 3.74 integrating for 2 protons and a singlet at δ 7.62 due to the C-2 methine protons suggesting that the chromonylmethyl portion is intact and that the methylene group is probably linked to a phenyl ring. Also observed in the proton NMR spectrum was a signal at δ 4.82 which was exchangeable with D$_2$O, revealing it to be a OH proton. This was confirmed by the IR spectrum which showed a broad band at 3346 cm$^{-1}$. Apart from the above mentioned NMR signals, there were no other signals in the region around δ 4.8-5.3 in the NMR spectrum, signifying the absence of any exo-methylene protons. The $^{13}$C NMR spectrum of 34a (Figure 4.7) displayed totally 14 signals. The off resonance spectrum showed a characteristic triplet at δ 29.86 due to carbon attached to a benzylic group and a doublet at δ 153.83 due to the olefinic methine carbon. The $^{13}$C NMR spectrum displayed the signal due to the carbonyl carbon at δ 176.15. These data clearly reveal that the chromone-3-ylmethyl moiety is intact accounting for 9 carbons. Taking this into consideration and the fact that the $^{13}$C NMR spectrum exhibited only 14 signals, one could surmise that the phenyl ring moiety should have been transformed to a 1,4-disubstituted benzene ring rather than to a 1,2-substituted benzene ring. Based on this analysis, the structure of this product 34a was assigned as 4'-hydroxyhomoisoflavone (Scheme 4.10), resulting from a para-rearrangement [153]. However, there was no evidence for the formation of product 18 due to ortho Claisen rearrangement or the exo-methylene product 35 due to allylic transposition.
Scheme 4.10 *Para*-rearrangement of chromone-3-ylmethyl aryl ethers 1a.

The structure of 34a was also confirmed by converting it to the acetate derivative 36 by treatment with Ac₂O. The hitherto unknown acetate 36 too was characterised by NMR and HRMS spectra (Scheme 4.11).

Scheme 4.11 Synthesis of acetyl derivative of 4'-hydroxyhomoisoflavones.
Figure 4.6 300 MHz $^1$HNMR spectrum of 34a in CDCl$_3$
Figure 4.7 75 MHz $^3$CNMR spectrum of 34a in CDCl$_3$
Figure 4.8 DEPT spectrum of 34a
Since this rearrangement of 1a to 34a could not be pushed to completion despite refluxing in diethylaniline for long hours, this rearrangement was studied with several high boiling solvents, polar protic, dipolar aprotic and non polar as listed in Table 4.2. Diphenyl ether (Ph₂O) was found to be the best solvent for this rearrangement (bp: 258°C) whose boiling point is much higher than that of diethylaniline (bp: 216°C). This solvent was used by Majumdar et al., for a similar rearrangement of coumarin-3ylmethyl aryl ethers. In refluxing diphenyl ether, the rearrangement of 1a to 34a proceeded to completion in 5 h. The reaction was also quite clean, as indicated by TLC and HPLC monitoring and the isolated yield of 34a was good (74%).

Table 4.2 Thermal rearrangement of ethers 1a in different solvents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>B.Pt</th>
<th>Temp. (°C)</th>
<th>Rxn Time (h)</th>
<th>Observation</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dimethylformamide</td>
<td>153°C</td>
<td>150-155</td>
<td>36</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>O-Dichlorobenzene</td>
<td>180°C</td>
<td>175-180</td>
<td>48</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Dimethyl sulphoxide</td>
<td>189°C</td>
<td>185-190</td>
<td>36</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>Ethylene glycol</td>
<td>197°C</td>
<td>190-195</td>
<td>12</td>
<td>Decomposition</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>N-Methyl 2-pyrrolidone</td>
<td>202°C</td>
<td>200-205</td>
<td>20</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>N,N-diethylaniline</td>
<td>216°C</td>
<td>215-220</td>
<td>48</td>
<td>Para-rearrangement</td>
<td>24%</td>
</tr>
<tr>
<td>7</td>
<td>p-chlorophenol</td>
<td>220°C</td>
<td>200-210</td>
<td>10</td>
<td>No reaction</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>Diphenylether</td>
<td>258°C</td>
<td>240-245</td>
<td>4</td>
<td>Para-rearrangement</td>
<td>74%</td>
</tr>
<tr>
<td>9</td>
<td>Quinoline</td>
<td>238°C</td>
<td>230-240</td>
<td>8</td>
<td>Decomposition</td>
<td>--</td>
</tr>
</tbody>
</table>

This transformation was found to be a general one. A few other chromonyl ethers viz., 1b-g were also smoothly converted to the corresponding 4'-hydroxyisoflavones in moderate to good yields when refluxed in diphenyl ether for 5 h (Scheme 4.12). The reaction time and yields are summarized in (Table 4.3). In none of the cases was there any evidence for the formation of products due to ortho migration 18 or allylic transposition 35 (Scheme 4.10).
\[
\begin{align*}
\text{Scheme 4.12} & \quad \text{Para-rearrangement of chromones 1a-g.}
\end{align*}
\]

Table 4.3 Thermal rearrangement of chromone-3-ylmethyl aryl ethers 1a-g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ether 1</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>(R^3)</th>
<th>(R^4)</th>
<th>(R^5)</th>
<th>(R^6)</th>
<th>(R^7)</th>
<th>Product</th>
<th>Yield(^a) (%)</th>
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<tbody>
<tr>
<td>1</td>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>34a</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>-CH=CH-</td>
<td>-CH=CH-</td>
<td>H</td>
<td>H</td>
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<td>H</td>
<td>H</td>
<td>34b</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>34c</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>34d</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>34e</td>
<td>66</td>
</tr>
<tr>
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<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>34g</td>
<td>68</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield after column chromatography.

Since only the product due to \textit{para}-rearrangement and not the one product due to \textit{ortho} Claisen rearrangement was observed in all the above cases, despite the fact that one or both the \textit{ortho} positions were unsubstituted, it was of interest to investigate the behaviour of ethers where in the \textit{para} position was blocked. When the \textit{para}-substituted ether 1h was refluxed in \(\text{Ph}_2\text{O}\) for 5 h, it was smoothly transformed to the 2’-hydroxyhomoisoflavones 21h in 83% yield. The structure of 21h was established based on its analytical and spectral data (Scheme 4.13). Analysis of the NMR spectrum of the crude product did not indicate the presence of product due to normal Claisen rearrangement, 18 or 35 due to allylic transposition (Scheme 4.13).
Scheme 4.13 Synthesis of 2'-hydroxyhomoisoflavones 21.

The HRMS of 21h displayed peak due to the molecular ion at 266.0942 [M+H]+ corresponding to a molecular formula C_{17}H_{15}O_{3}. The IR spectrum of 21h showed a fairly intense band at 3131 cm\(^{-1}\) corresponding to the hydroxyl group and a strong band at 1642 cm\(^{-1}\) due to the chromone carbonyl group. The \(^1\)H NMR spectrum of 21h clearly revealed the absence of the signal due to the O-CH\(_2\) proton. Instead it showed a new signal at \(\delta\) 3.70 due to Ar–CH\(_2\) proton (Figure 4.9). The signal due to OH proton was observed at \(\delta\) 9.22 (exchangeable with D\(_2\)O). The signals due to the H-2 and peri proton were seen at \(\delta\) 8.09 and \(\delta\) 8.23 respectively. The \(^{13}\)C NMR spectrum of 21h showed seventeen signals (Figure 4.10) in accordance with the assigned structure.
Figure 4.9 300 MHz $^1$HNMR spectrum of $21h$ in CDCl$_3$
Figure 4.10 75 MHz $^{13}$CNMR spectrum of 21h in CDCl$_3$
It is clear that this ether, unlike a typical allyl phenyl ether, does not undergo normal Claisen rearrangement involving a [3,3]-sigmatropic shift, but showed preference to undergo a formal [1,3]-ortho rearrangement.

The generality of this formal [1,3]-ortho migration transformation was established by extending it to a few more para-substituted chromonyl aryl ethers 1i-k. The reaction time and yields of 2'-hydroxyisoflavones 21h-k are summarized in Table 4.4.

Table 4.4 Synthesis of 2'-hydroxyhomoisoflavones 21.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ether 1</th>
<th>Rxn time (hrs)</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
<th>R7</th>
<th>Product 21</th>
<th>Yield (\text{a})) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1h</td>
<td>5</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>21h</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>1i</td>
<td>6</td>
<td>H</td>
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<td>21i</td>
<td>73</td>
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<td>Et</td>
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<td>21j</td>
<td>69</td>
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<tr>
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<td>H</td>
<td>21k</td>
<td>65</td>
</tr>
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</table>

\(\text{a})\) Isolated yield after column chromatography.

4.3.4 Mechanistic study of the thermal rearrangement of chromone-3-ylmethyl aryl ethers.

Intervention of O→C [1,3]-rearrangement in the uncatalysed thermal rearrangement of aryl allyl ethers is rare though it is commonly observed under Lewis acid, Bronsted acid and metal complexes catalysis conditions [154-155]. Way back Behagel et al., had reported that attempted Claisen rearrangement of benzyl phenyl ether for 7 days at 250°C furnished orthobenzylphenol (4%) and para benzyl phenol (8%) as minor products, in addition to the cleaved phenol (2%) and unrearranged starting material (Scheme 4.5) [148]. The authors had also studied the rearrangement of optically active \(\alpha\)-phenylethyl phenyl ether of known configuration and based on the results concluded that this rearrangement proceeded with retention of stereochemistry [148, 156]. This reaction was a very poor yielding one and hence of little synthetic utility.
Majumadar et al., observed that thermal rearrangement of coumarin-3-ylmethyl aryl ethers leads to *para*-migration products when the *para* position is free and [1,3]-products when the *para* position is blocked \(^{[149]}\) (Scheme 4.6). The authors suggested without any supporting evidence that the *para*-rearrangements might proceed through a \([1s,5s]\)-shift which is geometrically not feasible (Scheme 4.14) and the *ortho*-rearrangement by a \([1s,3a]\)-shift.

![Scheme 4.14 Direct \([1s, 5s]\)-*para* rearrangement.](image)

The intervention of [1,3]-rearrangement involving the allylic shift of phenoxy group from \(\alpha\)-position to the \(\gamma\)-position, *viz.*, allylic transposition during the course of aromatic Claisen rearrangement has not been witnessed in any of the earlier studies. Recently Hou et al., \(^{[157]}\) revisited the Claisen rearrangement of aryl butenyl ethers and observed that the thermal rearrangement of aryl cinnamyl ethers gave rise to a mixture of products due to normal [3,3]-shift and formal [1,3]-shift.

![Scheme 4.15 Domino \(O\)-[1,3]-shift and [3,3]-shift.](image)

These authors had shown by a detailed experimental investigation, supported by DFT calculations, that the formal [1,3]-shift product actually stems from a domino process due to migration of the aryloxy moiety from \(\alpha\)- to \(\gamma\)-position of the allyl group, *viz.*, allylic transposition of the phenoxy group, a(C- to C-[1,3]-shift) followed by a [3,3]-shift (Scheme 4.15).
The authors had also observed that the extent of formation of the allylic transposed product was found to be dependent upon the nature of the solvent. In polar protic solvent, this product was formed to a greater extent. In the case of rearrangement in o-dichlorobenzene 23% of [1,3]-product was formed, while in aqueous ethylene glycol, the percentage of [1,3]-product increased to 41%. It is interesting to note that they had not reported the formation of para-rearrangement product in their study.

As there are no reports on Claisen rearrangement involving the double bond of the chromone ring as part of the allyl moiety, it triggered us to take up of this formal [1,3]-rearrangement for mechanistic investigation.

In the light of Hou’s work, the rearrangement of 1a in Ph$_2$O was monitored by HPLC, TLC and NMR data to ascertain whether any similar allylic transposed intermediate was formed, as a transient or isolable species in the transformation of 1a to 34a. These monitoring studies did not indicate the intervention of any such intermediates. In the case of the rearrangement of para-substituted ether 1h too, HPLC and NMR reaction monitoring did not reveal the formation of any intermediates. In both the cases, the NMR spectrum of the samples taken in the early stages was devoid of the signals due to the exomethylene protons and acetal proton characteristic of 35 (Scheme 4.15) which is a crucial intermediate in the mechanistic pathway based on Hou’s et al., work. Thus on the basis of the obtained data from the HPLC and NMR reaction monitoring of this rearrangement one could tentatively rule out a domino (C$_o$ to C$_o$)-[1,3] and O- to C-[3,3]-pathway for the ortho-rearrangement leading to product 34. It is probable that the products 34 were formed directly by a domino transformation involving two [3,3]-shift as envisaged in Scheme 4.18 concerted [1,3]-sigmatropic shifts from ethers 1. The possibility of a breakage of the ether 1 into its ion pairs and recombination of the ion pairs within the solvent cage is ruled out as there was no change in the course of the reaction in going from non-polar Ph$_2$O to a mixture of Ph$_2$O and dipolar aprotic N-methyl-2-pyrrolidone, as monitored by HPLC. And there was also no evidence for the formation of bis-alkylated
products 37 and 38 (Figure 4.11) [158] which rules out the mechanism based on breakage and ion pair recombination outside the solvent cage.

![Figure 4.11 Bis-alkylated phenols.](image)

The findings from a crossover experiment conducted with ethers 1b and 1d ruled out the possibility of breakage and recombination mechanism. When an equimolar mixture of the ethers 1b and 1d was refluxed in Ph₂O and the crude products analysed by HPLC, only the phenols 34b and 34d could be detected and no evidence could be found for the presence of the crossover products 34f and 34a (Scheme 4.16).

![Scheme 4.16 Crossover experiment of ethers 1b and 1d.](image)

Based on all these findings, the following mechanism depicted in scheme, has been proposed for the ortho-rearrangement (Scheme 4.17).
Mechanism of para-rearrangement of ethers 1 to 34: The rearrangement of chromone-3-ylmethyl aryl ethers unsubstituted at the para position of the phenyl ring resulted in the formation of 3-(4-hydroxy-benzyl)-chromen-4-ones (4'-hydroxyhomoisoflavones) due to para-rearrangement and not due to the products of ortho-rearrangement even in those cases where the ortho positions are free. A free radical mechanism is ruled out since the reaction is facile when carried out with N,N-DEA as solvent, which itself is a free-radical inhibitor [159]. Further, this thermal transformation was not inhibited when the reaction was performed in the presence of other free radical inhibitors like TEMPO or BHT.

This para-rearrangement necessarily has to be a domino transformation as a concerted [1,5]-migration of the chromonylmethyl moiety from oxygen to para position of the phenyl ring is geometrically not feasible. It has to proceed by an initial ortho-Claisen migration (a [3,3]-shift), followed by a Cope
rearrangement (a [3,3]-shift) or by the alternate pathway involving an initial [1,3]-*ortho* migration of the chromonylmethyl moiety followed again by one more [1,3]-migration as outlined in scheme 4.18.

In the case of *para*-Claisen rearrangement of aryl allyl ethers, only the former pathway operates, *viz.*, two consecutive [3,3]-shifts (Scheme 4.18). But, in the case of chromone-3-ylmethyl aryl ethers, the available evidence points out to the alternative pathway, involving a domino [1,3]-[1,3]-migrations (Scheme 4.18).

It is known that CaCO$_3$ can stop the Claisen rearrangement at the *ortho* stage by bringing out rapid enolisation of the *ortho*-dienone [160]. When the ether 1a was refluxed in diphenyl ether with CaCO$_3$, there was no change in the course of the reaction and only the *para*-migration product 34a was isolated. Interestingly, when the base was changed to Cs$_2$CO$_3$, the rearrangement of ether 1a stopped at the *ortho* migration stage and furnished the product of [1,3]-*ortho* migration 21a (Scheme 4.19). Importantly, it did not lead to the product of [3,3]-sigmatropic shift. Further, in a control experiment, it was observed that the phenolic product of *ortho* [1,3]-rearrangement 1a was stable under the thermal conditions and did not get converted to the *para*-rearrangement product 34a. These findings reveal that the first intermediate in the *para*-rearrangement arises out of a [1,3]-migration of the chromenylmethyl moiety from *O-* to *ortho* carbon, *viz.*, *O* to *C*-[1,3]-shift. The usual pathway involving successive [3,3]-shifts would involve loss of aromaticity of both the rings (aryl and the heteroaromatic pyrone ring) in the transition state for the first rearrangement and as such this would be energetically less feasible compared to the alternative pathway involving a [1,3]-shift which involves loss of aromaticity of only the aryl ring.

![Scheme 4.19 Ortho-rearrangement of 1a in the presence of Cs$_2$CO$_3$](image-url)
In this context, it may be noted that the behavior of coumarin-4-ylmethyl aryl ethers 26 under conditions of thermal Claisen rearrangement is in remarkable contrast to that of 4H-chromene-3-ylmethyl aryl ethers 44 [161], 2H-chromene-4-ylmethyl aryl ethers 42 [162], and 2H-chromene-3-ylmethyl aryl ethers 43 [161], all lacking the carbonyl functionality. The chromene-4-ylmethyl aryl ether 42 undergoes a clean Claisen rearrangement when heated in a high boiling solvent leading to [3,2-b]benzofuran or [2,3-b]benzofuran derivative 45 [162], while analogous coumarin-4-ylmethyl aryl ethers 26 are stable towards thermal Claisen rearrangement. On the other hand, the chromene-3-ylmethyl aryl ether 43 undergoes the Claisen rearrangement only very sluggishly and afforded 46 [161]. In contrast, 4H-chromene-3-ylmethyl aryl ethers 44 is known to exhibit a totally different behavior when heated in N,N-DEA to furnish products of oxidative rearrangement and afforded 47 [161] (Scheme 4.20).

Scheme 4.20  Thermal behaviour of chromonyl and chromenyl ethers.
It is interesting to note that the thermal rearrangement of 3-(2,6-dimethylphenyloxy)-methylchromone 1g resulted in the formation of the 3',5'-dimethyl-4'-hydroxyhomoisoflavone 34g in 76% yield (Entry 7, Table 4.3). The formation of 34g can be rationalised as depicted in Scheme 4.21 based on the mechanism proposed in the case of ethers 1a-1f discussed above. In the case of \textit{para}-rearrangement of chromone-3-ylmethyl 2,6-dimethylphenyl ethers, the bulkier chromone-3-ylmethyl group preferentially migrates rather than the smaller methyl group.

\begin{center}
\includegraphics[width=\textwidth]{scheme_4.21.png}
\end{center}

\textbf{Scheme 4.21} Thermal rearrangement of 2,6-disubstituted chromone-3-ylmethyl aryl ethers 1g.

\subsection*{4.3.5 Thermal rearrangement study of chromone-2-ylmethyl aryl ethers 33.}

The unusual course of the thermal rearrangement of the chromone-3-ylmethyl aryl ethers 1 prompted us to examine the behavior of the isomeric chromone-2-ylmethyl aryl ethers 33a and 33b. In remarkable contrast to the efficient [1,3] sigmatropic shift undergone by the ethers 1, the ethers 33a and 33b were found to be inert when refluxed in diethylaniline for 40 h or in diphenyl ether for 10 h (Scheme 4.22). The contrasting behavior of the ethers 1 and 44 reveals the significant effect of the carbonyl functionality placed in conjugation with the allylic double bond in ethers 1 and also the effect of the ring oxygen in facilitating the rearrangement in the case of ether 1 as compared to that of 44.
4.4 CONCLUSION

Chromone-3-ylmethyl aryl ethers do not behave like simple allyl aryl ethers under thermal conditions of rearrangement. Chromone-3-ylmethyl aryl ethers with unsubstituted para-position and at least one vacant ortho-positions have been found to undergo a novel domino [1,3]-[1,3]-para rearrangement to give 4’-hydroxyhomoisoflavones under thermal conditions. In the case of para-substituted ethers, the thermal rearrangement lead to 2’-hydroxyhomoisoflavones involving a O- to C-[1,3]-migration, instead of the expected Claisen rearrangement. Interestingly, the isomeric chromone-2-ylmethyl aryl ethers are inert under thermal Claisen rearrangement condition.

The obtained product of para-rearrangement was in divergent to the anticipations and hence the TFA mediated rearrangement of chromon-3-ylmethyl aryl ethers and chromone-2-ylmethyl aryl ethers has been deliberated in the subsequent chapter.

4.5 EXPERIMENTAL

4.5.1 General procedure for the preparation of 3-(phenoxyethyl)-4H-chromen-4-one (1a-k).

Step 1: To a solution of 3-hydroxymethylchromone (1.0 g, 0.5 mmol) in CH₂Cl₂ (10 mL) at 0°C is added very slowly PBr₃ (2.7 g, 0.1 mmol) with vigorous stirring. After the reaction has reached completion, as monitored by TLC, the reaction mixture was poured over crushed ice and extracted into ether. The solvent was removed under vacuo to yield 3-bromomethylchromones 30.
Step 2: A mixture of phenol (4.3 g, 0.46 mmol), anhydr. K$_2$CO$_3$ (8.7 g, 0.6 mmol) and 3-(bromomethyl)-4H-chromen-4-one 30 (1.0 g, 0.42 mmol) was stirred in DMF (10 mL) at RT for 2-3 h. The reaction mixture was then poured into water (30 ml) and filtered. The crude was purified by column chromatography using ethyl acetate/hexane as eluant to yield chromone-3-ylmethyl aryl ethers 1.

3-(phenoxy methyl)-4H-chromen-4-one 1a.

![Structural formula of 3-(phenoxy methyl)-4H-chromen-4-one 1a.](image)

White solid; Mp. 113-115°C; IR (KBr, cm$^{-1}$): 3099, 1639, 1614, 1599, 1467, 1420, 1352, 1244, 1163, 1056, 934, 857, 754, 688; $^1$H NMR (300MHz, CDCl$_3$): δ 5.07 (d, J = 1.2 Hz, 2H, -OCH$_2$), 6.96-7.03 (m, 3H, Ar-H), 7.28-7.34 (m, 2H, Ar-H), 7.40-7.49 (m, 2H, Ar-H), 7.69 (br. dt, J = 1.5, 7.2 Hz, 1H, Ar-H), 8.10 (s, 1H, H2), 8.26 (br. dd, J = 1.5,6.6 Hz, 1H, H-5); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 62.0(-OCH$_2$), 114.7, 118.2, 120.5, 121.3, 123.7, 125.2, 125.7, 129.6, 133.8, 153.5, 156.5, 158.1, 176.6(C-4); HRMS (EIMS): M/z calculated for C$_{16}$H$_{13}$O$_3$ [M+H]$^+$: 253.0865, found: 253.0864.

2-(phenoxy methyl)-1H-benzo[f]chromen-1-one 1b.

![Structural formula of 2-(phenoxy methyl)-1H-benzo[f]chromen-1-one 1b.](image)

Off-white solid; Mp. 142-144°C; IR (KBr, cm$^{-1}$): 2921, 1654, 1626, 1497, 1441, 1340, 1247, 1041, 819, 751, 689, 515; $^1$H NMR (300MHz, CDCl$_3$): δ 5.16 (d, J = 1.2 Hz, 2H, -OCH$_2$), 6.99 (t, J=7.5 Hz, 1H, Ar-H), 7.05 (d, J=7.8 Hz, 2H, Ar-H), 7.30-7.35 (m, 2H, Ar-H), 7.52 (d, J=9.3 Hz, 1H, Ar-H), 7.77 (br. td, J=1.5 Hz, 1H, Ar-H), 7.91 (d, J=8.1 Hz, 1H, Ar-H), 8.09 (d, J=9.0 Hz, 1H, Ar-H), 8.14 (t, J=1.2 Hz, 1H, H-2), 10.06 (d, J=8.7 Hz, 1H, H-4). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 62.3(-OCH$_2$), 114.7, 116.9, 117.6, 121.3, 123.1, 126.7, 127.0, 128.2, 129.3, 129.6, 130.5, 130.6, 135.6, 150.9, 157.7, 158.2, 178.3(C-4); HRMS (EIMS): M/z calculated for C$_{20}$H$_{15}$O$_3$ [M+H]$^+$: 303.1021, found. 303.1014.
3-[(2-chlorophenoxy) methyl]-4H-chromen-4-one 1c.

White solid; Mp. 174-178°C; IR (KBr, cm\(^{-1}\)): 2338, 1744, 1566, 1466, 1358, 1211, 1119, 995, 918, 756, 725, 663; \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 5.13 (s, 2H, -OCH\(_2\)), 6.94 (t, J = 7.5 Hz, 1H), 7.10 (d, J=8.1 Hz, 1H, Ar-H), 7.25-7.26 (m, 1H, Ar-H), 7.38-7.46 (m, 1H, Ar-H), 7.50-7.51 (d, J=8.45 Hz, 1H, Ar-H), 7.70 (t, J=8.1 Hz, 1H, Ar-H), 8.26 (s, 2H, H-2 & H-5);
\(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 63.0(-OCH\(_2\)), 113.7, 118.2, 120.1, 122.0, 123.0, 123.6, 125.2, 125.6, 127.9, 130.3, 133.8, 153.5, 153.6, 156.4, 176.5(C-4); HRMS (EIMS): M/z calculated for C\(_{16}\)H\(_{11}\)ClO\(_3\) [M]^+: 286.0397, found. 286.0397.

3-[(2-Methylphenoxy)methyl]-4H-chromen-4-one 1d.

White solid; Mp. 144-146°C; IR (KBr, cm\(^{-1}\)): 2361, 1744, 1628, 1358, 1211, 1149, 1119, 1088, 995, 818, 617; \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 2.30 (s, 3H, Ar-CH\(_3\)), 5.07 (s, 2H, -OCH\(_2\)), 6.90 (t, J=7.5 Hz, 1H, Ar-H), 7.15-7.25 (m, 2H, Ar-H), 7.40-7.50 (m, 2H, Ar-H), 7.66-7.72 (m, 1H, Ar-H), 8.11 (s, 1H, H-2), 8.26 (d, J=8.1 Hz, 1H, H-5); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 16.3(Ar-CH\(_3\)), 62.1(-OCH\(_2\)), 111.3, 118.2, 120.8, 121.0, 123.7, 125.2, 125.7, 126.7, 127.0, 130.8, 133.7, 153.1, 156.2, 156.5, 176.6(C-4); HRMS (EIMS): M/z calculated for C\(_{17}\)H\(_{14}\)O\(_3\) [M]^+: 266.0943, found. 266.0942.

3-[(3, 5-dimethylphenoxy)methyl]-4H-chromen-4-one 1e.

White solid; Mp. 161-164°C; IR (KBr, cm\(^{-1}\)): 2338, 1728, 1628, 1597, 1466, 1342, 1196, 1088, 1049, 918, 849, 764, 609; \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 2.29 (s, 6H, 2 x Ar-CH\(_3\)), 5.03 (d, J=0.9 Hz, 2H, -OCH\(_2\)), 6.63-6.65 (m, 2H, Ar-H), 7.40-7.49 (m, 2H, Ar-H), 7.68 (br. td, J = 1.8, 6.9 Hz, 1H, Ar-H), 8.09 (s, 1H, H-2), 8.26 (dd, J = 1.2, 6.6 Hz, 1H, H-5); \(^13\)C NMR (75
MHz, CDCl$_3$: $\delta$ 21.4(Ar-CH$_3$), 61.9(-OCH$_2$), 112.4, 118.2, 120.6, 123.1, 123.7, 125.2, 125.7, 133.7, 139.3, 153.3, 156.4, 158.2, 176.6 (C-4); HRMS (EIMS): $M/z$ calculated for C$_{18}$H$_{17}$O$_3$ [M]$^+$: 280.1099, found. 280.1098.

2-((o-tolyloxy)methyl)-1H-benzo[f]chromen-1-one 1f.

Off-white solid; Mp. 184-187°C; $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 3.78 (s, 3H, Ar-CH$_3$), 5.01 (s, 2H, -OCH$_2$), 6.85 (d, $J=6.0$ Hz, 2H, Ar-H), 6.96 (d, $J=6.3$ Hz, 2H, Ar-H), 7.41-7.49 (m, 1H, Ar-H), 7.69 (t, $J=6.0$ Hz, 1H, Ar-H), 8.10 (s, 1H, H-2), 8.26 (d, $J=6.0$ Hz, 1H, H-5); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 55.7, 62.7(-OCH$_2$), 114.7, 115.7, 118.2, 120.6, 123.7, 125.2, 125.7, 133.8, 152.3, 153.5, 154.2, 156.5, 176.7(C-4); HRMS (EIMS): $M/z$ calculated for C$_{21}$H$_{16}$O$_3$ [M]$^+$: 316.1099, found. 316.1099.

3-[(2, 6-dimethylphenoxy)methyl]-4H-chromen-4-one 1g.

Off-white solid; Mp. 177-179°C; $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 2.32 (s, 6H, 2 x Ar-CH$_3$), 4.80 (d, $J=1.2$ Hz, 2H, -OCH$_2$), 6.96 (dd, $J=6.1$Hz, 1H, Ar-H), 7.03-7.05 (m, 2H, Ar-H), 7.40-7.45 (m, 1H, Ar-H), 7.45-7.51 (m, 1H, Ar-H), 7.67-7.72 (m, 1H, Ar-H), 8.22-8.27 (m, 2H, H2 & H-5); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 16.2 (Ar-CH$_3$), 65.7(-OCH$_2$), 118.2, 121.3, 123.8, 124.2, 125.2, 128.9, 131.0, 135.7, 153.4, 155.3, 156.5, 176.7(C-4); HRMS (EIMS): $M/z$ calculated for C$_{21}$H$_{16}$O$_3$ [M]$^+$: 280.1099, found. 280.1095.

3-[(4-methylphenoxy)methyl]-4H-chromen-4-one 1h.

White solid; Mp. 143-146°C; IR (KBr, cm$^{-1}$): 2867, 1639, 1614, 1467, 1352, 1244, 1163, 1055, 934, 835, 753, 688; $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 2.29 (s, 3H, Ar-CH$_3$), 5.04 (s, 2H, -OCH$_2$), 6.91 (d, $J=8.4$ Hz, 2H, Ar-H), 7.10 (d, $J=8.1$ Hz, 2H, Ar-H), 7.44 (m, 2H, Ar-H), 7.68 (t,
J=7.2 Hz, 1H, Ar-H), 8.09 (s, 1H, H-2), 8.25 (d, J=8.1 Hz, 1H, H-5); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 20.4(Ar-CH$_3$), 62.1(-OCH$_2$), 114.6, 118.2, 120.6, 123.7, 125.2, 125.7, 130.0, 130.6, 133.7, 153.5, 156.0, 156.4, 176.74(C-4); HRMS (EIMS): M/z calculated for C$_{17}$H$_{15}$O$_3$ [M+H]$^+$: 267.1021, found. 267.0943.

3-[(4-Chlorophenoxy)methyl]-4H-chromen-4-one $^{1i}$. White solid; Mp. 153-156°C; IR (KBr, cm$^{-1}$): 2913, 1640, 1625, 1613, 1494, 1464, 1253, 1160, 1049, 822, 754; $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 5.02 (d, J=0.6 Hz, 2H, -OCH$_2$), 6.93-6.96 (m, 2H, Ar-H), 7.23-7.27 (m, 2H, Ar-H), 7.416-7.503 (m, 2H, Ar-H), 8.09 (s, 1H, H-2), 8.25 (dd, J=1.5, 6.3 Hz, 1H, H-5); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 62.3(-OCH$_2$), 116.0, 118.2, 120.1, 123.7, 125.3, 125.7, 126.2, 129.4, 133.9, 153.7, 156.4, 156.7, 176.6(C-4); HRMS (EIMS): M/z for C$_{16}$H$_{11}$ClO$_3$ [M]$^+$: Calc. 286.0397, found. 286.0395.

3-[(4-Ethylphenoxy)methyl]-4H-chromen-4-one $^{1j}$. Off-white solid; Mp. 107-109°C; IR (KBr, cm$^{-1}$): 2957, 1649, 1610, 1513, 1467, 1417, 1244, 1159, 1056, 823, 760, 690; $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.21 (t, J=7.5 Hz, 3H, Ar-CH$_2$CH$_3$), 2.60 (q, J=7.5 Hz, 2H, Ar-CH$_2$CH$_3$), 5.04 (d, J=0.9 Hz, 2H, -OCH$_2$), 6.94 (d, J=8.7 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 7.39-7.48 (m, 2H), 7.68 (td, J=1.5, 6.9 Hz, 2H), 8.09 (s, 1H, H-2), 8.25 (dd, J=1.5, 6.3 Hz, 1H, H-5); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 15.8(Ar-CH$_2$CH$_3$), 27.9(Ar-CH$_2$CH$_3$), 62.1(-OCH$_2$), 114.6, 118.2, 120.6, 123.7, 125.2, 125.7, 128.8, 133.7, 137.1, 153.5, 156.2, 156.4, 176.7 (C-4); HRMS (EIMS): M/z calculated for C$_{18}$H$_{16}$O$_3$ [M]$^+$: 280.1099, found. 280.1099.
3-[(4-methoxyphenoxy)methyl]-4H-chromen-4-one 1k.

White solid; Mp. 151-155°C; \(^1H\) NMR (300MHz, CDCl\(_3\)): \(\delta 3.78 \, (s, \, 3H, \, Ar\text{-}OCH_3), \, 5.01 \, (s, \, 2H, \, -OCH_2), \, 6.85 \, (d, \, J=8.0 \, Hz, \, 2H, \, Ar\text{-}H), \, 6.96 \, (d, \, J=8.4 \, Hz, \, 2H, \, Ar\text{-}H), \, 7.41-7.49 \, (m, \, 1H, \, Ar\text{-}H), \, 7.69 \, (br. t, \, J≈7.2 \, Hz, \, 1H, \, Ar\text{-}H), \, 8.10 \, (s, \, 1H, \, H-2), \, 8.26 \, (d, \, J≈8.0 \, Hz, \, 1H, \, H-5)\); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): \(\delta 55.7(Ar\text{-}OCH_3), \, 62.7(-OCH_2), \, 114.7, \, 115.7, \, 118.2, \, 120.6, \, 123.7, \, 125.2, \, 125.7, \, 133.8, \, 152.3, \, 153.5, \, 154.2, \, 156.5, \, 176.7\) (C-4); HRMS (EIMS): M/z calculated for C\(_{18}\)H\(_{16}\)O\(_3\) [M\(^+\)]: 282.0892, found. 282.0894.

4.5.2 General Procedure for the preparation of 3-(4-hydroxybenzyl)-4H-chromen-4-one (34a-g/21h-k).

A solution of 3-(phenoxy)methyl)-4H-chromen-4-one 1a-g/1h-k (500 mg) in Ph\(_2\)O (10 ml) was heated at reflux for 5-7 h. After reaction completion, as monitored by TLC, the crude product was chromatographed over silica-gel to yield rearranged chromones 34a-g/21h-k.

3-(4-hydroxybenzyl)-4H-chromen-4-one 34a.

Pale yellow solid; Mp. 210-212°C; IR (KBr, cm\(^{-1}\): 2921, 1635, 1467, 1355, 1142, 767, 569; \(^1H\) NMR (300MHz, CDCl\(_3\)): \(\delta 3.75 \, (s, \, 2H, \, Ar\text{-}CH_2), \, 4.82 \, (s, \, 1H, \, Ar\text{-}OH), \, 6.77 \, (d, \, J=8.4 \, Hz, \, 2H, \, Ar\text{-}H), \, 7.17 \, (d, \, J=8.4 \, Hz, \, 2H, \, Ar\text{-}H), \, 7.36-7.43 \, (m, \, 2H, \, Ar\text{-}H), \, 7.61 \, (s, \, 1H, \, H-2), \, 7.64-7.67 \, (m, \, 1H, \, Ar\text{-}H), \, 8.23 \, (dd, \, J=7.8 \, Hz, \, 1H, \, H-5)\); \(^{13}C\) NMR (75 MHz, DMSO-d\(_6\)): \(\delta 30.9(Ar\text{-}CH_2), \, 115.5, \, 118.0, \, 124.9, \, 125.9, \, 127.8, \, 130.2, \, 130.5, \, 133.4, \, 133.7, \, 144.8, \, 153.0(C-2), \, 154.3, \, 156.49, \, 176.1(C-4)\).
2-(4-hydroxybenzyl)-1H-benzo[f]chromen-1-one 34b.

Off-white solid; **Mp.** 210-212°C; **IR** (KBr, cm⁻¹): 2361, 1744, 1599, 1512, 1358, 1211, 849, 633, 579; **¹H NMR** (300MHz, DMSO-d₆): δ 3.68 (s, 2H, Ar-CH₂), 6.67 (d, J=6.9 Hz, 2H, Ar-H), 7.14 (d, J=6.9 Hz, 2H, Ar-H), 7.67-7.76 (m, 3H, Ar-H), 8.08 (d, J=7.5 Hz, 2H, Ar-H), 8.28-8.34 (m, 2H, Ar-H), 9.23 (s, 1H, H-2), 9.93 (d, J=7.5 Hz, 1H, H-5); **¹³C NMR** (75 MHz, DMSO-d₆): δ 30.0 (Ar-CH₂), 114.9, 115.9, 117.9, 125.9, 126.4, 126.5, 128.5, 128.9, 129.3, 129.5, 129.7, 130.1, 135.5, 151.5 (C-2), 155.5, 157.2, 177.9 (C-4); **HRMS** (EIMS): *M/z* calculated for C₂₀H₁₅O₃ [M+H]⁺: 303.1021, found. 303.1029.

3-(3-chloro-4-hydroxybenzyl)-4H-chromen-4-one 34c.

Off-white solid; **Mp.** 140-142°C; **IR** (KBr, cm⁻¹): 2338, 1728, 1628, 1512, 1358, 1211, 1165, 818, 748, 633, 586; **¹H NMR** (300MHz, DMSO-d₆): δ 3.61 (s, 2H, Ar-CH₂), 6.87 (d, J=8.4 Hz, 2H, Ar-H), 7.08 (d, J=8.1 Hz, 2H, Ar-H), 7.28 (s, 1H, Ar-H), 7.47 (br. t, J=7.2 Hz, 1H, Ar-H), 7.62 (d, J=9.0 Hz, 1H, Ar-H), 7.78 (br. t, J=4.5 Hz, 1H, Ar-H), 8.04 (d, J=7.8 Hz, 1H, Ar-H), 8.36 (s, 1H, H-2), 9.99 (s, 1H, H-5); **¹³C NMR** (75 MHz, DMSO-d₆): δ 30.0 ((Ar-CH₂)), 116.7, 118.7, 119.5, 123.6, 123.8, 125.3, 125.6, 128.5, 130.0, 131.5, 134.3, 151.6, 154.5 (C-2), 156.3, 176.5 (C-4); **HRMS** (EIMS): *M/z* calculated for C₁₆H₁₂ClO₃ [M+H]⁺: 287.0475, found. 287.0480.

3-(4-hydroxy-3-methylbenzyl)-4H-chromen-4-one 34d.

Off-white solid; **Mp.** 118-120°C; **IR** (KBr, cm⁻¹): 3393, 1636, 1464, 1354, 1268, 1142, 757, 650, 485; **¹H NMR** (300MHz, CDCl₃): δ 2.22 (s, 3H, Ar-CH₃), 3.72 (s, 2H, Ar-CH₂), 4.85 (s, 1H, Ar-OH), 6.69 (s, 1H, Ar-H), 6.98-7.03 (m, 2H, Ar-H), 7.35-7.42 (m, 2H, Ar-H),
7.60-7.66 (m, 2H, H-2 & Ar-H), 8.23 (d, J=8.1 Hz, 1H, H-5); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)): \(\delta\) 16.0 (Ar-CH\(_3\)), 30.7(Ar-CH\(_2\)), 115.1, 118.0, 120.2, 123.8, 124.5, 124.8, 125.2, 125.9, 127.2, 129.1, 131.4, 133.3, 153.2, 153.6, 156.4, 177.6(C-4); HRMS (EIMS): \(M/2\) calculated for C\(_{17}\)H\(_{15}\)O\(_3\) [M+H]: 267.1021, found. 267.1026.

3-(4-hydroxy-2,6-dimethylbenzyl)-4H-chromen-4-one 34e.

![Diagram of 3-(4-hydroxy-2,6-dimethylbenzyl)-4H-chromen-4-one 34e.](image-url)

Off-white solid; \(\text{Mp.}\) 122-124°C; IR (KBr, cm\(^{-1}\)): 2361, 1744, 1597, 1520, 1350, 1165, 1088, 1018, 918, 849, 756, 663; \(^{1}\text{H}\) NMR (300MHz, DMSO-d\(_6\)): \(\delta\) 2.12 (s, 6H, 2 X Ar-CH\(_3\)), 3.62 (s, 2H, Ar-CH\(_2\)), 6.50 (s, 2H, Ar-H), 7.21 (s, 1H, Ar-H), 7.49 (t, J=7.5 Hz, 1H, Ar-H), 7.58 (d, J=8.4 Hz, 1H, Ar-H), 7.79 (t, J=7.5 Hz, 1H, Ar-H), 8.11 (d, J=7.5 Hz, 1H, H-2), 9.10 (s, 1H, H-5); \(^{13}\text{C}\) NMR (75 MHz, DMSO-d\(_6\)): \(\delta\) 19.5(Ar-CH\(_3\)), 24.1(Ar-CH\(_2\)), 114.9, 118.2, 122.1, 122.6, 123.9, 124.9, 125.1, 133.9, 137.5, 152.2(C-2), 155.4, 155.7, 176.5(C-4); HRMS (EIMS): \(M/2\) calculated for C\(_{18}\)H\(_{17}\)O\(_3\) [M+H]: 281.1178, found. 281.1187.

2-(4-hydroxy-3-methylbenzyl)-1H-benzo[f]chromen-1-one 34f.

![Diagram of 2-(4-hydroxy-3-methylbenzyl)-1H-benzo[f]chromen-1-one 34f.](image-url)

Off-white solid; \(\text{Mp.}\) 133-135°C; \(^{1}\text{H}\) NMR (300MHz, DMSO-d\(_6\)): \(\delta\) 2.06 (s, 3H, Ar-CH\(_3\)), 3.64 (s, 2H, Ar-CH\(_2\)), 6.67 (d, J= 6.0 Hz, 1H, Ar-H), 6.94 (t, J= 1.2, 6.0 Hz, 1H, Ar-H), 7.02 (s, 1H, Ar-H), 7.65-7.71 (m, 2H, Ar-H), 7.74-7.78 (m, 1H, Ar-H), 8.08 (d, J= 5.7 Hz, 1H, Ar-H), 8.31 (d, J= 6.9 Hz, 1H, Ar-H), 8.34 (s, 1H, H-2), 9.07 (s, 1H, Ar-H), 9.94 (d, J= 6.4 Hz, 1H, H-5); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)+DMSO-d\(_6\)): \(\delta\) 20.3(Ar-CH\(_3\)), 26.3(Ar-CH\(_2\)), 116.1, 117.6, 124.9, 126.3, 126.4, 126.7, 128.2, 128.4, 128.9, 130.2, 130.3, 130.4, 131.1, 135.5, 151.4, 152.8, 157.6, 176.5(C-4); HRMS (EIMS): \(M/2\) calculated for C\(_{18}\)H\(_{17}\)O\(_3\) [M]: 316.1099, found. 316.1096.
3-(4-hydroxy-3,5-dimethylbenzyl)-4H-chromen-4-one 34g.

Off-white solid; **Mp.** 168-170°C; **¹H NMR** (300MHz, CDCl₃): δ 2.21 (s, 6H, 2 X Ar-CH₃), 3.68 (s, 2H, Ar-CH₂), 4.65 (s, 1H, Ar-OH), 6.89 (s, 2H, Ar-H), 7.34-7.42 (m, 2H, Ar-H), 7.60 (s, 1H, H-2), 7.62-7.66 (m, 2H, Ar-H), 8.23 (dd, J=1.8 Hz, 1.5Hz, 1H, H-5); **¹³C NMR** (75 MHz, CDCl₃): δ 15.9(Ar-CH₃), 30.8(Ar-CH₂), 118.0, 123.2, 123.9, 124.8, 125.1, 126.0, 129.1, 130.0, 133.3, 150.8, 153.1(C-2), 156.1, 156.4, 177.5(C-4); **HRMS** (EIMS): M/z calculated for C₁₈H₁₇O₃ [M⁺]: 280.1099, found. 280.1097.

3-(2-hydroxy-5-methylbenzyl)-4H-chromen-4-one 21h.

White solid; **Mp.** 182-184°C, (lit: 182°C); **IR** (KBr, cm⁻¹): 509, 760, 819, 1245, 1466, 1499, 1593, 1624, 3131; **¹H NMR** (300MHz, CDCl₃): δ 2.23 (s, 3H, Ar-CH₃), 3.70 (s, 2H, Ar-CH₂), 6.84-6.94 (m, 3H, Ar-H), 7.38-7.47 (m, 2H, Ar-H), 7.67 (td, J=1.8, 5.4 Hz, 1H, Ar-H), 8.09 (s, 1H, H-2), 8.23 (dd, J=1.5, 6.6 Hz, 1H, H-5), 9.22 (s, 1H, Ar-OH); **¹³C NMR** (75 MHz, CDCl₃): δ 20.4(Ar-CH₃), 27.5(Ar-CH₂), 118.0, 118.4, 123.0, 124.7, 125.4, 125.5, 126.0, 129.1, 129.7, 130.5, 134.2, 152.6, 153.4(C-2), 156.7, 179.67(C-4); **HRMS** (EIMS): M/z calculated for C₁₇H₁₄O₃ [M⁺]: 266.0943, found. 266.0942.

3-(5-chloro-2-hydroxybenzyl)-4H-chromen-4-one 21i.

White solid; **Mp.** 197-199°C; **IR** (KBr, cm⁻¹): 510, 652, 762, 776, 827, 1145, 1246, 1358, 1480, 1624, 3085; **¹H NMR** (300MHz, CDCl₃): δ 3.69 (s, 2H, Ar-CH₂), 6.90 (d, J=8.1 Hz, 1H, Ar-H), 7.06-7.09 (m, 2H, Ar-H), 7.41-7.50 (m, 2H, Ar-H), 7.71 (t, J=7.2 Hz, 1H, Ar-H), 8.11 (s, 1H, H-2), 8.23 (d, J=7.8 Hz, 2H, H-5), 9.62 (s, 1H, Ar-OH); **¹³C NMR** (75 MHz, CDCl₃): δ 27.5(Ar-CH₂), 118.1, 120.0, 122.8, 124.0, 124.9, 125.6, 126.0, 127.4,
128.4, 129.7, 134.5, 153.6(C-2), 153.8, 156.7, 179.7(C-4); HRMS (EIMS): M/z calculated for C_{16}H_{11}ClO_3 [M]^+: 286.0397, found. 286.0395.

3-(5-Ethyl-2-hydroxybenzyl)-4H-chromen-4-one 21j.

White solid; Mp. 162-164°C; IR (KBr, cm^{-1}): 3234, 1629, 1607, 1466, 1413, 1353, 1269, 1161, 933, 767, 753; \(^1H\) NMR (300MHz, CDCl_3): \(\delta\) 1.18 (t, \(J=7.5\) Hz, 3H, Ar-CH\(_2\)CH\(_3\)), 2.53 (q, \(J=7.5\) Hz, 2H, Ar-CH\(_2\)CH\(_3\)), 3.71 (s, 2H, Ar-CH\(_2\)-), 6.87-6.97 (m, 3H, Ar-H), 7.36-7.46 (m, 2H, Ar-H), 7.67 (td, \(J=1.5\), 6.9 Hz, 1H, Ar-H), 8.09 (s, 1H, H-2), 8.21 (dd, \(J=1.5\), 6.6 Hz, 1H, Ar-H), 9.28 (s, 1H, H-5); \(^{13}C\) NMR (75 MHz, CDCl_3): \(\delta\) 15.8 (Ar-CH\(_2\)CH\(_3\)), 27.6(Ar-CH\(_2\)CH\(_3\)), 27.9(-OCH\(_3\)), 118.0, 118.4, 123.0, 124.7, 125.4, 125.5, 126.0, 127.9, 129.4, 134.2, 136.3, 152.8, 153.4(C-2), 156.7, 179.6(C-4); HRMS (EIMS): M/z calculated for C\(_{18}\)H\(_{16}\)O\(_3\) [M]^+: 280.1099, found. 280.1098.

3-(2-hydroxy-5-methoxybenzyl)-4H-chromen-4-one 21k.

White solid; \(^1H\) NMR (300MHz, CDCl_3): \(\delta\) 3.71 (s, 2H, Ar-CH\(_2\)-), 3.73 (s, 3H, Ar-OCH\(_3\)), 6.70 (d, \(J=8.1Hz\), 2H, Ar-H), 6.91 (d, \(J=6.3Hz\), 1H, Ar-H), 7.40-7.48 (m, 2H, Ar-H), 7.70 (t, \(J=5.1Hz\), 1H, Ar-H), 8.09 (s, 1H, H-2), 8.24 (d, 1H, Ar-H), 9.09 (s, 1H, H-5); \(^{13}C\) NMR (75 MHz, CDCl_3): \(\delta\) 27.7(Ar-CH\(_2\)-), 55.7(Ar-OCH\(_3\)), 113.4, 115.5, 118.1, 119.3, 123.0, 124.5, 125.5, 126.0, 126.7, 134.3, 148.9, 153.3, 153.5, 156.7, 179.6(C-4); HRMS (EIMS): M/z calculated for C\(_{18}\)H\(_{16}\)O\(_3\) [M]^+: 282.0892, found. 282.0890.

3-(2-hydroxybenzyl)-4H-chromen-4-one 21a

White solid; Mp. 175-178°C (lit: 179-182°C); IR (KBr, cm^{-1}): 2961, 1627, 1601, 1570, 1458, 1466, 1102, 758, 590.69; \(^1H\) NMR (300MHz, CDCl_3): \(\delta\) 3.74 (s, 2H, Ar-CH\(_2\)-), 6.84 (t, \(J=7.2Hz\), 1H, Ar-H),
6.96 (d, J=8.1 Hz, 1H, Ar-H), 7.12-7.16 (m, 2H, Ar-H), 7.39-7.48 (m, 2H, Ar-H), 7.70 (td, J=1.2, 7.2 Hz, 1H, Ar-H), 8.10 (s, 1H, H-2), 8.24 (d, J=8.1 Hz, 1H, Ar-H), 9.46 (s, 1H, H-5) (Fig. 4.12); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 27.5 (Ar-CH$_2$), 118.0, 118.6, 120.5, 123.0, 124.6, 125.5, 125.8, 126.0, 128.6, 130.1, 134.3, 153.5 (C-2), 155.0, 156.7, 179.7 (C-4) (Fig. 4.13).

4.5.3 General Procedure for the synthesis of 4-((4-oxo-4H-chromen-3-yl)methyl)phenyl acetate 36.

A solution of 3-(4-hydroxybenzyl)-4H-chromen-4-one 34a (100 mg, 0.39 mmol) and NaOAc (100 mg, 1.2 mmol) in Ac$_2$O (2 ml) was heated to 60-65°C for 1-2 h. The reaction mixture was poured into ice-water, extracted with chloroform, and the extract was washed successively with 5% aq. NaHCO$_3$, sat. brine and dried. The crude product was chromatographed over silica-gel.

4-((4-oxo-4H-chromen-3-yl)methyl)phenyl acetate 36.

Off White solid; $^1$H NMR (500MHz, CDCl$_3$): δ 2.20 (s, 3H, (OCOCH$_3$)), 3.73 (s, 2H, Ar-CH$_2$), 6.94 (td, J = 8.5 Hz, 2.5 Hz, 2H, Ar-H), 7.23 (d, J = 8.5 Hz, 2H, Ar-H), 7.29-7.35 (m, 2H, Ar-H), 7.55-7.58 (m, 2H, H-2 & Ar-H), 8.15 (dd, J = 1.5 Hz, 1H, H-5); $^{13}$C NMR (125MHz, CDCl$_3$): δ 21.2 (OCOCH$_3$), 31.2 (Ar-CH$_2$), 118.1, 121.7, 121.7, 123.9, 124.5, 125.1, 126.0, 130.0, 133.6, 136.5, 149.4, 153.2, 156.6, 169.6, 177.5 (C-4); HRMS (EI): M/z calculated for C$_{18}$H$_{14}$O$_4$ [M]+: 294.0892, found. 294.0894.

4.5.4 General procedure for the preparation of chromone-2-ylmethyl aryl ether (33a-b).

Step-1: A mixture of POCl$_3$ (5.6 g, 3.5 mmol) and aryloxyacetic acid (2.4 g, 1.5 mmol) was added slowly into a solution of 2-hydroxyacetophenone (2.0 g, 1.4 mmol) in dry pyridine (20.0 mL). The mixture was refluxed for 2 h and
quenched with aq. HCl. The product was extracted with EtOAc. The organic layer washed with 10% NaOH solution. The solution was distilled and crystallized with ethanol yielded 2-(O-aryloxyacetyl)acetophenone 32.

Step-2: To a solution of 32 (1.0 g, 0.37 mmol) in dry pyridine (4.0 mL), KOH (0.31 g, 0.55 mmol) was added and the mixture stirred for 1 h at 65°C. The reaction mixture was quenched with aq. HCl and extracted with EtOAc. The EtOAc layer was distilled, crystallized and yielded chromone-2-ylmethyl aryl ether 33.

2-(phenoxymethyl)-4H-chromen-4-one 33a.

![Structure of 2-(phenoxymethyl)-4H-chromen-4-one 33a](image)

Off-White solid; **Mp.100-102°C; IR (KBr, cm⁻¹):** 2278, 1650, 1629, 1467, 1357, 1246, 1070, 753, 694, 584; **¹H NMR** (300MHz, CDCl₃): δ 4.95 (s, 2H, -OCH₂), 6.52 (s, 1H, H-3), 6.96-7.03 (m, 3H, Ar-H), 7.28-7.34 (m, 2H, Ar-H), 7.36-7.46 (m, 2H, Ar-H), 7.65 (dt, J=1.8, 6.9 Hz, 1H, Ar-H), 8.19 (dd, J=1.8, 6.3 Hz, 1H, H-5) (Fig. 4.15); **¹³C NMR** (75 MHz, CDCl₃): δ 65.9(-OCH₂), 109.8, 114.7, 117.9, 122.0, 124.0, 125.3, 125.8, 129.7, 133.8, 156.2, 157.5, 163.7, 177.86(C-4) (Fig. 4.16).

3-(phenoxymethyl)-1H-benzo[f]chromen-1-one 33b.

![Structure of 3-(phenoxymethyl)-1H-benzo[f]chromen-1-one 33b](image)

White solid; **Mp.158-160°C; IR (KBr, cm⁻¹):** 3062, 1662, 1596, 1437, 1240, 956, 825, 758, 582, 506; **¹H NMR** (300MHz, CDCl₃): δ 5.02 (s, 2H, -OCH₂), 6.67 (s, 1H, H-3), 6.99-7.05 (m, 3H, Ar-H), 7.30-7.36 (m, 2H, Ar-H), 7.50 (d, J=9.0 Hz, 1H, Ar-H), 7.61 (td, J=0.9, 13.8 Hz, 1H, Ar-H), 7.72-7.78 (m, 1H, Ar-H), 7.90 (d, J=8.1 Hz, 1H, Ar-H), 8.09 (d, J=9.0 Hz, 1H, Ar-H), 10.02 (d, J=8.7 Hz, 1H, H-5); **¹³C NMR** (75 MHz, CDCl₃): δ 65.7 (-OCH₂), 113.0, 114.8, 117.3, 117.4, 122.0, 126.6, 127.0, 128.1, 129.3, 129.7, 130.4, 130.6, 135.5, 157.4, 157.6, 160.8, 179.7(C-4).
Figure 4.12 300 MHz $^1$HNMR spectrum of 21a in CDCl$_3$
Figure 4.13 75 MHz $^1$C-NMR spectrum of 21a in CDCl$_3$
Figure 4.14 DEPT spectrum of 21a
Figure 4.15 300 MHz $^1$HNMR spectrum of 33a in CDCl$_3$
Figure 4.16 75 MHz $^{13}$CNMR spectrum of 33a in CDCl$_3$