Synthesis of benzofuranyl substituted Benzo[c]coumarins

The work incorporated in this chapter is on the synthesis of various 9-(benzofuran-2-yl)-7-hydroxy-6H-benzo[c]coumarins. The compounds have been synthesized by reacting various 3-coumarinoyl methyl pyridinium salts with appropriate an 2-acetyl benzofurans in the presence of sodium acetate in refluxing acetic acid. The structures of all the synthesized compounds have been supported by analytical and spectral evidences.

4.4 Introduction

The construction of benzene ring by fusion between 3rd and 4th position of coumarin nucleus results in a formation of benzo[c]coumarin (I).

Benzo[c]coumarin skeleton is prevalent in many synthetic and naturally occurring medicinal substances\textsuperscript{33,34}. They display a wide spectrum of biological\textsuperscript{35} and pharmacological activities such as anticoagulant, spasmylytic, diuretic and anticancer properties\textsuperscript{36}. Furthermore, this class of molecules can be used as valuable intermediates in the synthesis of more complex molecules such as cannabinoids, which are the active agents in pain relievers and drugs with antiemetic action\textsuperscript{37}. Initially, Caroll et al.\textsuperscript{38} have isolated cordiachromene A, a benzo[c]chromene derivative, which was named as tetrahydrocannabinol derivative, from Synoicum castellatum. Numerous graphislactones A, G and H were isolated from the endophytic fungus Cephalosporin acemonium IFB-E007\textsuperscript{39}. Graphislactone A has antioxidant and free radical scavenging properties, while G and H have been found active against the SW 1116 cell line\textsuperscript{39}. The resorcylic lactones alternariol
and alternariol 9-methyl ether are the main secondary metabolites of toxin producing *Alternaria* fungus \(^{40}\). Two new benzo[c]chromenes, *herpetolide A* and *herpetolide B* were isolated from the ethyl extract fraction, and their structures were elucidated on the basis of chemical and physicochemical evidence \(^{41}\). Some selected medicinally active benzo[c]coumarin derivatives are shown below. (**Chart 1**)

**Chart 1**

Various benzo[c]coumarin derivatives have been synthesized by different group of researchers utilizing different methods. Some selected reports on the synthesis of benzo[c]coumarin derivatives are documented below.
Gryko et al.\textsuperscript{1} have synthesized color-tunable fluorescent dye based on benzo[c]coumarin by reacting resorcinol and 2-bromobenzoic acid in the presence of CuSO\textsubscript{4} under alkaline condition (Hurtley condensation).

The three-component one-pot synthesis of 5-amino-6-cyano-3-hydroxybenzo[c]coumarin compounds derived from salicylaldehyde, malononitrile and ethyl acetoacetate was reported by A Fakhar\textsuperscript{12}. The reaction is conducted on grinding over MgO at room temperature resulting in good yields.

P Langer et al\textsuperscript{43} prepared 2,3-dihydro benzopyran derivatives (I) (prepared from benzopyran-4-one in three steps) and they were transformed into benzo[c]coumarins by the treatment of triethylamine and ethanol via biphenyl intermediate (Ia).

H Togo et al\textsuperscript{44} have synthesized benzo[c]coumarin by photocyclization of biphenyl 2-carboxylic acid using [bis(trifluoroacetoxy)iodo]benzene and free iodine as a radical generators.
Chapter 4, Section 2  
Benzimidazolyl substituted benzo[c]coumarins

\[ \text{HO-} \quad \text{Ph(O}_2\text{CCF}_3\text{)}_2 \quad \text{i) Ph(O}_2\text{CCF}_3\text{)}_2 \quad \text{ii) I}_2 \quad \text{hv} \]

Iaroshenko et al.\textsuperscript{45} have reported the synthesis of benzo[c]coumarin by base mediated cyclocondensation of 1,3-dicarbonyl compound with 4-chloro-3-formylcoumarin.

\[ \text{CHO} \quad \text{H}_3\text{C} \quad \text{CH}_3 \quad \text{K}_2\text{CO}_3 \quad \text{THF} \quad 50^\circ\text{C}, 4\text{hrs} \]

T H Harris and J V Hay\textsuperscript{46} have synthesized 1-methyl-3,7,9-trihydroxybenzo[c]coumarin (alternariol) from 3,5,7,9,11,13-hexaoxo tetradecanoic acid by the treatment of \text{NaOAc}/\text{AcOH}. The acid undergoes aldol cyclization at 8,13- and 2,7- positions and results in formation of biphenyl intermediate (III) which further cyclizes to alternariol.

\[ \text{NaOAc}/\text{AcOH} \quad (8,13 & 2,7-\text{Aldol cyclizations}) \]

M S Tremblay and D Sames\textsuperscript{47} have synthesized benzo[c]coumarins by lactonization of biphenyl derivative (II), which was prepared from aromatic boronic acid in three steps.
The inspection of above mentioned methods for the synthesis of benzo[c]coumarins disclose that, in most of the methods benzo[c]coumarin moiety has been built up by lactonization of appropriately substituted biphenyls.

With a view to developing a new method for the synthesis of benzo[c]coumarin, the present work was carried out. In the present work a new method for the synthesis of benzo[c]coumarin has been developed in which a benzene ring has been built up between 3rd and 4th position of a preformed coumarin moiety.

Benzofurans are the important group of heterocyclic compounds, which are known to possess important biological properties. Benzofurans occur in a large number of natural products. Many of the natural benzofurans have physiological, pharmacological and toxic properties. The most recognized benzofurans are *Ailanthoidol*, *Bufuralol* and *Amiodarone*. *Ailanthoidol*, is a neolignan derivative, which has been reported to have antiviral, antioxidant and antifungal activities. *Amiodarone*, a benzofuran derivative, is widely used in the treatment of ventricular tachyarrhythmia and atrial fibrillation. Benzofuran derivatives derived from 2-acetyl benzofurans have antimicrobial, antitumor, anti-inflammatory, fungicidal, weed killing activity and used for treatment of cardiac arrhythmias.

Considering the significance of benzofuran, it was thought worthwhile to incorporate this moiety in benzo[c]coumarin as a substituent group and therefore in the present work synthesis of various 9-(benzofuran-2-yl)-7-hydroxybenzo[c]coumarins has been carried out.

### 4.5 Present work

It is reported that the sodium acetate catalyzed reaction of \(\alpha,\beta\)-unsaturated ketones (chalcons) with chloroacetone pyridinium salt gives
1,3,5-trisubstituted benzene derivatives\textsuperscript{58}. The detail mechanism is shown in Scheme 1.

The mechanism involves Michael addition of the active methylene functionality of chloroacetone pyridinium salt on \(a,\beta\)-unsaturated ketone system which results a 1,5-dicarbonyl system with methyl group at one of the ends. This 1,5-dicarbonyl intermediate upon further internal cyclization involving carbonyl and methyl group followed by aromatization gives 1,3,5-trisubstituted benzene derivative. This methodology has been utilized in our present work for designing a benzene ring between 3\textsuperscript{rd} and 4\textsuperscript{th} position of coumarin.

\begin{center}
\textbf{Scheme 1}
\end{center}

In the methodology given above (Scheme 1) the benzene ring has been built up by sodium acetate/methanol catalyzed cyclization of the 1,5-dione intermediate having methyl group at one end. This methodology has been utilized in the present work and various 9-(benzofuran-2-yl)-7-hydroxy-6\(H\)-benzo[c]coumarins \textbf{3a-l} have been synthesized. However in the preparation of compounds \textbf{3a-l} AcONa/AcOH was used instead of AcONa/MeOH.
4.5.1 Synthesis of 9-(benzofuran-2-yl)-7-hydroxy-6H-benzo[c]coumarins (3a-l).

Various 9-(benzofuran-2-yl)-7-hydroxy-6H-benzo[c]coumarins 3a-l have been synthesized by reacting various 3-coumarinoyl methyl pyridinium salts 1a-d with an appropriate 2-acetyl benzofuran 2a-c in the presence of sodium acetate and acetic acid (Scheme 2).

![Scheme 2](image)

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<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>Br</td>
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</tr>
</tbody>
</table>

Scheme 2

The starting material 3-coumarinoyl methyl pyridinium salts 1a-d were prepared by the reaction of appropriate 3-(ω-bromoacetyl)coumarins with pyridine in refluxing toluene. The 3-(ω-bromoacetyl)coumarins were in turn prepared by reacting 3-acetylcoumarins with bromine in acetic acid.
The required starting material 2-acetyl benzofurans 2a-c were prepared by the reaction of an appropriately substituted salicyldehydrs with chloroacetone in the presence of $K_2CO_3$ in dry acetone at 60°C.

The reaction proceeded smoothly and gave the title compounds 3a-1 in good yield (60-72%).

The detailed mechanism for the formation of 3a-1 is shown in scheme 3.

Scheme 3
Here, the anion generated from the acetyl benzofuran adds to the 3,4-double bond of coumarin and results in the formation of intermediate (A) having 1,5-dione functionality. The active methylene group then gets cyclized with carbonyl group of benzofuran moiety resulting in the formation of intermediate (B) which finally gets converted into the product by loss of water molecule and subsequent aromatization.

The structures of all the compounds 3a-l were confirmed by analytical and spectral data.

Thus, the condensation of 3-coumarinoyl methyl pyridinium salt 1a with 2-acetyl benzofuran 2a in the presence of sodium acetate and acetic acid proceeded smoothly and gave the product 3a as an off white colored solid in 60% yield.

The IR spectrum of compound 3a (Fig 1) showed a strong band at 1672 cm\(^{-1}\), which is due to carbonyl stretching of \(\delta\)-lactone ring present in coumarin moiety. The decrease in C=O stretching frequency from the normal value (~1710 cm\(^{-1}\)) is due to hydrogen bonding with C\(_7\)-OH. The bands observed at 1609 cm\(^{-1}\) is due to aromatic C=C stretching vibration. The band observed at 3104 cm\(^{-1}\) is due to aromatic C-H stretching vibrations. A broad band observed around 3436 cm\(^{-1}\) is due to phenolic -OH stretching.

In the \(^1\)H-NMR spectrum, compound 3a (in CDCl\(_3\)) (Fig 2), all the eleven aromatic protons were observed between 6.91-7.93 \(\delta\) as a multiplet. The –OH signal was observed at 11.42 \(\delta\) as a singlet, which was confirmed by recording D\(_2\)O exchange.

The \(^{13}\)C-APT spectrum of compound 3a (in CDCl\(_3\)) (Fig 3) showed signals at 95.66, 105.07, 105.36, 108.22, 111.29, 112.40, 112.89, 114.67, 119.00, 121.80, 121.94, 124.81, 135.83, 138.57, 140.55, 148.05, 152.85, 156.50, 159.15, 162.50 and 164.52 \(\delta\) corresponding to twenty one different types of carbon atoms present in the compound. The most downfield signal appeared at 164.52 \(\delta\) is assigned to the carbonyl carbon of the \(\delta\)-lactone ring of coumarin. The \(^{13}\)C-APT spectrum showed inverted signals at 95.66, 105.07, 108.22, 111.29, 112.43, 112.89,
114.67, 119.00, 121.80, 124.8 and 135.87 δ which are due to eleven tertiary carbons present in the compound.

The mass spectrum of compound **3a (Fig 4)** showed M+ peak at 328(35%) (m/z %) along with some other fragment peaks at 44(100%), 77 (20%), 128(9%), 57(6%), etc. The appearance of molecular ion peak at 328 mass unit supports the structure of compound **3a**.

The IR and NMR data for the other compounds **3b-1** are given below.

**Compound 3b**

**IR** (cm⁻¹) \( \nu_{\text{max}} \) 1687 (C=O stretching of δ-lactone of coumarin), 1614 (aromatic C=C stretching), 3069 (aromatic C-H stretching), 2939 (aliphatic C-H stretching), 3403 (O-H stretching).

**\(^1\)H-NMR** (δ, ppm) (CDCl₃) (Fig 5) 3.89 (3H, s, OCH₃), 6.87-8.01 (10H, m, Ar-H), 11.38 (1H, s, -OH proton) (D₂O exchangeable).

**\(^{13}\)C-APT** (δ, ppm) (CDCl₃) (Fig 6) 55.74 (OCH₃), 101.41(CH), 104.53(C), 105.15(CH), 107.51(CH), 110.65(CH), 111.14(C), 111.45(CH), 113.18(CH), 121.61(CH), 123.42(CH), 124.50(CH), 125.70(CH), 128.61(C), 136.19(C), 138.36(C), 152.04(C), 153.75(C), 155.26(C), 161.80(C), 162.64(C), 165.22(CO).

**Compound 3c**

**IR** (cm⁻¹) \( \nu_{\text{max}} \) 1686 (C=O stretching of δ-lactone of coumarin), 1617 (aromatic C=C stretching), 3063 (aromatic C-H stretching), 3409 (O-H stretching).

**\(^1\)H-NMR** (δ, ppm) (CDCl₃) (Fig 7) 7.19-8.20 (10H, m, Ar-H), 11.54 (1H, s, -OH proton) (D₂O exchangeable).

**\(^{13}\)C-APT** (δ, ppm) (CDCl₃) (Fig 8) 105.61(CH), 107.73(CH), 108.87(CH), 112.13(CH), 112.57(CH), 113.82(CH), 114.91(CH), 119.00(CH), 124.19(CH), 124.85(CH), 130.31 136.00(C), 138.34(C), 144.79(C), 148.09(C), 150.49(C), 152.60(C), 153.20(C), 155.45(C), 156.31(C), 162.57(C).
**Compound 3d**

IR (cm\(^{-1}\)) \(\nu_{\text{max}}\) 1671 (C=O stretching of \(\delta\)-lactone of coumarin), 1615 (aromatic C=C stretching), 2920 (aliphatic C-H stretching), 3061 (aromatic C-H stretching), 3429 (O-H stretching).

\(^1\)H-NMR (\(\delta, \text{ ppm}\)) (CDCl\(_3\)) (Fig 9)

4.00 (3H, s, OCH\(_3\)), 7.07-8.03 (10H, m, Ar-H), 11.44 (1H, s, -OH proton) (D\(_2\)O exchangeable).

\(^{13}\)C-APT (\(\delta, \text{ ppm}\)) (CDCl\(_3\)) (Fig 10)

56.30 (OCH\(_3\)), 105.38(CH), 108.76(CH), 111.56(CH), 112.08(CH), 112.53(CH), 114.87(CH), 118.97(C), 121.63(CH), 123.46(CH), 124.95(CH), 125.86(CH), 128.66(C), 136.07(C), 137.76(C), 138.54(C), 148.16(C), 152.42(C), 155.31(C), 156.81(C), 158.21(C), 162.61(CO).

**Compound 3e**

IR (cm\(^{-1}\)) \(\nu_{\text{max}}\) 1680 (C=O stretching of \(\delta\)-lactone of coumarin), 1609 (aromatic C=C stretching), 3064 (aromatic C-H stretching), 2922 (aliphatic C-H stretching), 3430 (O-H stretching).

\(^1\)H-NMR (\(\delta, \text{ ppm}\)) (CDCl\(_3\)) (Fig 11)

3.91 (6H, s, 2XOCH\(_3\)), 6.85-8.04 (9H, m, Ar-H), 11.35 (1H, s, -OH proton) (D\(_2\)O exchangeable).

\(^{13}\)C-APT (\(\delta, \text{ ppm}\)) (CDCl\(_3\)) (Fig 12)

55.94(OCH\(_3\)), 56.01(OCH\(_3\)), 95.79(CH), 101.56(CH), 105.26(CH), 107.11(CH), 110.17(CH), 111.26(CH), 112.85(CH), 113.22(C), 121.72(CH), 122.14(C), 124.45(CH), 136.37(C), 138.91(C), 150.60(C), 151.49(C), 152.15(C), 153.14(C), 156.56(C), 159.21(C), 161.86(C), 162.74(CO).

**Compound 3f**

IR (cm\(^{-1}\)) \(\nu_{\text{max}}\) 1683 (C=O stretching of \(\delta\)-lactone of coumarin), 1624 (aromatic C=C stretching), 3090 (aromatic C-H stretching), 2920 (aliphatic C-H stretching), 3417 (O-H stretching).
<table>
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<th>Compounds</th>
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<th>13C-NMR (δ, ppm) (CDCl₃)</th>
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<td><strong>Compound 3g</strong></td>
<td>4.00 (3H, s, OCH₃), 6.91-7.93 (9H, m, Ar-H), 11.43 (1H, s, -OH proton) (D₂O exchangeable)</td>
<td>56.25 (OCH₃), 95.72 (CH), 105.35(CH), 108.23(CH), 111.32(CH), 112.47(CH), 112.89(CH), 114.70(CH), 119.03(C), 121.80(C), 121.97(CH), 124.80(CH), 127.22(C), 135.90(C), 138.60(C), 140.40(C), 142.28(C), 145.72(C), 150.80(C), 159.18(C), 162.54(C), 164.52(CO).</td>
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<tr>
<td><strong>Compound 3h</strong></td>
<td>3.92 (3H, s, OCH₃), 4.09 (3H, s, OCH₃), 6.89-8.11 (9H, m, Ar-H), 11.37 (1H, s, -OH proton) (D₂O exchangeable)</td>
<td>55.79 (OCH₃), 56.14(OCH₃), 98.99(CH), 101.63(CH), 105.51(CH), 107.84(CH), 109.09(C), 111.10(CH), 113.28(CH), 113.90(CH), 122.83(C), 124.23(CH), 124.85(CH), 132.38(C).</td>
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</table>
137.66(C), 139.60(C), 140.76(C), 142.08(C), 144.68(C), 150.50(C), 152.47(C), 156.62(C), 162.77(CO).

**Compound 3i**

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<td>IR (cm⁻¹)</td>
<td>( \nu_{\text{max}} 1688 ) (C=O stretching of ( \delta )-lactone of coumarin), 1611 (aromatic C=C stretching), 2952 (aliphatic C-H stretching), 3060 (aromatic C-H stretching), 3401 (O-H stretching) (D₂O exchangeable).</td>
</tr>
<tr>
<td>(^1\text{H-NMR} (\delta, ppm) (CDCl}_3) (Fig 19)</td>
<td>3.92 (3H, s, OCH₃), 6.87-8.08 (9H, m, Ar-H), 11.37 (1H, s, -OH proton) (D₂O exchangeable).</td>
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<td>(^{13}\text{C-APT} (\delta, ppm) (CDCl}_3) (Fig 20)</td>
<td>55.94 (OCH₃), 108.11(CH), 110.13(CH), 111.21(CH), 112.94(CH), 115.80(C), 116.97(CH), 117.79(CH), 118.64(CH), 122.04(CH), 123.49(CH), 125.65(CH), 128.18(C), 135.99(C), 139.15(C), 150.33(C), 151.95(C), 152.62(C), 155.19(C), 156.46(C), 161.00(C), 162.01(C).</td>
</tr>
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**Compound 3j**

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<td>(^1\text{H-NMR} (\delta, ppm) (CDCl}_3) (Fig 21)</td>
<td>7.31-9.10 (13H, multiplet, aromatic protons), 11.52 (1H, singlet, -OH proton) (D₂O exchangeable).</td>
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<td>(^{13}\text{C-APT} (\delta, ppm) (CDCl}_3) (Fig 22)</td>
<td>105.92(CH), 109.96(C), 111.47(CH), 111.62(CH), 112.79(C), 113.06(C), 113.86(CH), 115.62(C), 116.96(CH), 118.45(C), 121.74(CH), 123.59(CH), 125.03(CH), 126.01(CH), 126.10(CH), 128.34(CH), 128.58(C), 129.52(CH), 132.15(C), 132.49(CH), 136.71(C), 139.09(C), 150.52(C), 153.40(C), 160.76(CO).</td>
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</table>
Chapter 4, Section 2  
Benzimidazolyl substituted benzo[c]coumarins

stir stretching).

\( ^{1}H\)-NMR  
(\( \delta \), ppm)  
(CDCl\(_{3}\))  
(Fig 23)  
4.17 (3H, s, OCH\(_{3}\)), 6.91-8.86 (12H, m, Ar-H), 11.60 (1H, s, -OH proton) (D\(_{2}\)O exchangeable).

\( ^{13}C\)-APT  
(\( \delta \), ppm)  
(CDCl\(_{3}\))  
(Fig 24)  
56.53 (OCH\(_{3}\)), 106.09(CH), 108.76(CH), 109.99(C), 111.50(CH), 112.81(C), 112.94(C), 113.80(CH), 114.47(CH), 115.64(C), 116.88(CH), 118.47(C), 124.30(CH), 124.96(CH), 126.08(CH), 128.25(CH), 129.47(CH), 130.38(C), 132.10(CH), 132.46(C), 136.58(C), 138.77(C), 144.81(C), 149.57(C), 153.64(C), 160.70(CO).

**Compound 3l**

IR (cm\(^{-1}\))  
\( \nu_{\text{max}} \) 1699 (C=O stretching of \( \delta \)-lactone of coumarin), 1614 (aromatic C=C stretching), 3056 (aromatic C-H stretching), 3425 (O-H stretching).

\( ^{1}H\)-NMR  
(\( \delta \), ppm)  
(CDCl\(_{3}\))  
(Fig 25)  
6.92-8.77 (12H, m, Ar-H), 11.63 (1H, s, -OH proton) (D\(_{2}\)O exchangeable).

\( ^{13}C\)-APT  
(\( \delta \), ppm)  
(CDCl\(_{3}\))  
(Fig 26)  
96.00(CH), 105.84(CH), 110.70(CH), 112.88(C), 113.06(CH), 113.11(CH), 115.72(CH), 116.92(C), 121.96(CH), 122.26(CH), 124.90(CH), 125.96(CH), 128.18(C), 129.45(CH), 132.02(C), 132.28(C), 136.40(C), 138.87(C), 146.64(C), 149.55(C), 152.79(C), 156.50(C), 158.77(C), 162.02(CO).

In case of compound 3l the number of signals in \( ^{13}C\)-APT spectrum is one less than expected. The lack of one signal may be due to overlapping of two carbon signals, which may have identical chemical shifts.
Chapter 4, Section 2                                Benzimidazolyl substituted benzo[c]coumarins

Department of Chemistry, Sardar Patel University

Fig 1. IR spectrum of compound 3a

Fig 2. $^1$H-NMR spectrum of compound 3a
Fig 3. $^{13}$C-APT spectrum of compound 3a

Fig 4. Mass spectrum of compound 3a
Fig 5. $^1$H-NMR spectrum of compound 3b

Fig 6. $^{13}$C-APT spectrum of compound 3b
Fig 7. $^1$H-NMR spectrum of compound 3c

Fig 8. $^{13}$C-APT spectrum of compound 3c
Fig 9. $^1$H-NMR spectrum of compound 3d

Fig 10. $^{13}$C-APT spectrum of compound 3d
Fig 11. $^1$H-NMR spectrum of compound 3e

Fig 12. $^{13}$C-APT spectrum of compound 3e
Fig 13. $^1$H-NMR spectrum of compound 3f

Fig 14. $^{13}$C-APT spectrum of compound 3f
Fig 15. $^1$H-NMR spectrum of compound 3g

Fig 16. $^{13}$C-APT spectrum of compound 3g
Fig 17. $^1$H-NMR spectrum of compound 3h

Fig 18. $^{13}$C-APT spectrum of compound 3h
Figure 19. $^1$H-NMR spectrum of compound 3i

Figure 20. $^{13}$C-APT spectrum of compound 3i
Fig 21. $^1$H-NMR spectrum of compound 3j

Fig 22. $^{13}$C-APT spectrum of compound 3j
Chapter 4, Section 2  
Benzimidazolyl substituted benzo[c]coumarins

Fig 23. $^1$H-NMR spectrum of compound 3k

Fig 24. $^{13}$C-APT spectrum of compound 3k
Fig 25. $^1$H-NMR spectrum of compound 3l

Fig 26. $^{13}$C-APT spectrum of compound 3l
4.6 Experimental

The following starting materials were used.

- 3-acetyl coumarin
- 7-methoxy-3-acetyl coumarin
- 8-methoxy-3-acetyl coumarin
- 5,6-benzo-3-acetyl coumarin

The preparation of 3-acetyl coumarin, 8-methoxy-3-acetyl coumarin and 5,6-benzo-3-acetyl coumarin is described in chapter 2 and 3 respectively. The preparation of 7-methoxy-3-acetyl coumarin is given below.

4.6.1 Preparation of 7-methoxy-3-acetyl coumarin.

In a 100 mL round bottom flask, a mixture of 4-methoxy salicylaldehyde (0.01 mol), ethyl acetoacetate (0.01 mol) and 3-4 drops of piperidine was stirred for 10 minutes at room temperature. It was then heated for 30 minutes in boiling water bath. On cooling, a yellow solid product was obtained, which was filtered out and washed with cold ether. It was recrystallized from chloroform-hexane.

**7-Methoxy-3-acetyl coumarin:** Yield: 96% mp 172-173°C (lit. mp 173-179°C)

4.6.2 Preparation of 3-bromoacetyl coumarins.

In a 100 mL three necked flask, a solution of appropriate 3-acetyl coumarin (0.01 mol) in glacial acetic acid (20 mL) was taken. To this, bromine (0.01 mol) in glacial acetic acid (10 mL) was added with stirring during 30 minutes at room temperature. The reaction mixture was stirred at room temperature for 3 hours. It was then poured into ice cold
water and the solid obtained was filtered out. It was washed with water and dried. The product was recrystallized from chloroform.

3-(ω-Bromoacetyl)coumarin: \( R = R_1 = R_2 = R_3 = H \); Yield: 83%, mp 162°C (lit.\(^{60}\) mp 165°C)

8-Methoxy-3-(ω-bromoacetyl)coumarin: \( R = R_1 = R_2 = H, R_3 = OCH_3 \); Yield: 80%, mp 201°C (lit.\(^{61}\) mp 206°C)

7-Methoxy-3-(ω-bromoacetyl)coumarin: \( R = R_1 = R_3 = H, R_2 = OCH_3 \); Yield: 70%, mp 201°C (lit.\(^{59}\) mp 202°C)

5,6-Benzo-3-(ω-bromoacetyl)coumarin: \( R + R_1 = \text{benzo, } R_2 = R_3 = H \); Yield: 84%, mp 199-201°C (lit.\(^{59}\) mp 198-200°C)

4.6.3 Preparation of 3-coumarinoyl methyl pyridinium salt (1a-d).

In a 100 mL round bottom flask fitted with a reflux condenser, a solution of appropriate 3-(ω-bromoacetyl)coumarin (0.01 mol) in dry toluene (30 mL) was taken and pyridine (0.01 mol) was added. The reaction mixture was refluxed in an oil bath for 2 hours. It was then allowed to come to room temperature and was left for 4 to 5 hours. The pyridinium salt was separated out which was filtered out and washed with hot toluene and dried. It was recrystallized from acetic acid.

3-Coumarinoyl methyl pyridinium salt (1a): \( R = R_1 = R_2 = R_3 = H \); Yield: 93%, mp 218°C (dec.) (lit.\(^{60}\) mp 220°C(dec.))

8-Methoxy-3-coumarinoyl methyl pyridinium salt (1c): \( R = R_1 = R_2 = H, R_3 = OCH_3 \); Yield: 91%, mp 250°C (dec.) (lit.\(^{61}\) mp 250°C (dec.))

7-Methoxy-3-coumarinoyl methyl pyridinium salt (1b): \( R = R_1 = R_3 = H, R_2 = OCH_3 \); Yield: 80%, mp 238-239°C (dec.) (lit.\(^{59}\) mp 235-240°C (dec.))

5,6-Benzo-3-coumarinoyl methyl pyridinium salt (1d): \( R + R_1 = \text{benzo, } R_2 = R_3 = H \); Yield: 84%, mp 179-180°C (dec.) (lit.\(^{59}\) mp 180°C (dec.))
4.6.4 Preparation of 2-acetyl benzofuran (2a-c).

\[
\begin{align*}
\text{Cl} & \quad \text{CHO} \\
\text{R}_4 & \quad \text{OH} \\
\text{K}_2\text{CO}_3 & \quad \text{Dry acetone} \\
\text{R}_5 & \quad \text{CH}_3 \\
\text{R}_4 & \quad \text{R}_5 \\
& \quad \text{2a-c}
\end{align*}
\]

In a 250 mL round bottom flask equipped with a condenser, a mixture of appropriate salicylaldehyde (0.1 mol), chloroacetone (0.1 mol), dry acetone (150 mL) and anhydrous potassium carbonate (0.2 mol) was refluxed for 8 hours. Acetone was removed by distillation and cold water (200 mL) was added to residue to dissolve potassium carbonate. It was kept at room temperature 2–3 hours. The solid obtained was filtered out and washed with cold water. It was recrystallized from chloroform-hexane to white crystals.

2-Acetyl benzofuran (2a): Yield: 76%, mp 73°C (lit. mp 74-76°C)

7-Methoxy-2-acetyl benzofuran (2b): Yield: 82%, mp 90°C (lit. mp 87-89°C)

5-Bromo-2-acetyl benzofuran (2c): Yield: 70%, mp 120°C (lit. mp 118-119°C)

4.6.5 Preparation of 9-[benzofuran-2-yl]-7-hydroxy-6H-benzo[c]coumarins (3a-l).

The following general procedure was used.

In a 100 mL three necked round bottom flask equipped with a dropping funnel, condenser, guard tube and magnetic needle, a solution of an appropriate 3-coumarinoyl methyl pyridinium salt 1a-d (0.004 mol)
was taken in a glacial acetic acid (15 mL). To this, sodium acetate (0.012 mol) was added with stirring. Then, appropriate 2-acetyl benzofuran 2a-c in glacial acetic acid (10 mL) was added with stirring at room temperature during 10 minutes. The reaction mixture was further stirred for 20 minutes at room temperature and then refluxed for 8 hours. It was then allowed to cool to room temperature and poured into cold water (75 mL). The crude solid obtained was then extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with water (3 x 20 mL). It was dried over anhydrous sodium sulfate. The removal of chloroform under reduced pressure gave a solid product. This was purified by column chromatography using silica gel and chloroform-petroleum ether (60-80) (6:4) as an eluent. Thus, 9-(benzofuran-2-yl)-7-hydroxy-6H-benzo[c]coumarins 3a-1 were obtained as yellow colored solid, which were recrystallized from chloroform-hexane.

**Compound 3a:** \( R = R_1 = R_2 = R_3 = R_4 = R_5 = H; \)

Yield = 60%  
mp 218°C  
Molecular Formula: \( \text{C}_{21}\text{H}_{12}\text{O}_4 \)

Analysis  
% C  
% H  
Found  
76.77  
3.73  
Calculated  
76.82  
3.68

**Compound 3b:** \( R = R_1 = R_2 = R_3 = R_5 = H, R_4 = \text{OCH}_3; \)

Yield = 67%  
mp 250°C  
Molecular Formula: \( \text{C}_{22}\text{H}_{14}\text{O}_5 \)

Analysis  
% C  
% H  
Found  
73.67  
3.88  
Calculated  
73.74  
3.94

**Compound 3c:** \( R = R_1 = R_2 = R_3 = R_4 = \text{H}, R_5 = \text{Br}; \)

Yield = 62%  
mp 256°C  
Molecular Formula: \( \text{C}_{21}\text{H}_{11}\text{BrO}_4 \)

Analysis  
% C  
% H  
Found  
61.78  
2.20  
Calculated  
61.94  
2.27

**Compound 3d:** \( R = R_1 = R_2 = R_4 = R_5 = \text{H}, R_3 = \text{OCH}_3; \)

Yield = 70%  
mp 215-216°C  
Molecular Formula: \( \text{C}_{22}\text{H}_{14}\text{O}_5 \)

Analysis  
% C  
% H  
Found  
73.60  
3.89


Calculated 73.74  3.94

**Compound 3e**: $R = R_1 = R_2 = R_5 = H, R_3 = R_4 = OCH_3$;

Yield = 64\%  

\[ \text{mp} \ 248^\circ\text{C} \]

Molecular Formula: $C_{23}H_{16}O_6$

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<td>% H</td>
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<td>60.48</td>
<td>60.43</td>
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<td>% H</td>
<td>2.94</td>
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**Compound 3f**: $R = R_1 = R_2 = R_4 = H, R_3 = OCH_3, R_5 = Br$;

Yield = 72\%  

\[ \text{mp} \ 192-193^\circ\text{C} \]

Molecular Formula: $C_{22}H_{13}BrO_5$

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<td>60.48</td>
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<tr>
<td>% H</td>
<td>3.00</td>
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**Compound 3g**: $R = R_1 = R_3 = R_4 = Br, R_2 = H$;

Yield = 68\%  

\[ \text{mp} \ 253-254^\circ\text{C} \]

Molecular Formula: $C_{22}H_{14}O_5$

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<td>% H</td>
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**Compound 3h**: $R = R_1 = R_3 = R_5 = H, R_4 = R_2 = OCH_3$;

Yield = 60\%  

\[ \text{mp} \ 226^\circ\text{C} \]

Molecular Formula: $C_{23}H_{16}O_6$

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<td>% H</td>
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**Compound 3i**: $R = R_1 = R_3 = R_5 = H, R_2 = OCH_3, R_4 = Br$;

Yield = 62\%  

\[ \text{mp} \ 240-241^\circ\text{C} \]

Molecular Formula: $C_{22}H_{13}BrO_5$

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<tr>
<td>% H</td>
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<td>3.00</td>
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**Compound 3j**: $R + R_1 = Benzo, R_2 = R_3 = R_4 = R_5 = H$;

Yield = 70\%  

\[ \text{mp} \ 224-225^\circ\text{C} \]

Molecular Formula: $C_{25}H_{14}O_4$

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<tr>
<td>% H</td>
<td>3.68</td>
<td>3.73</td>
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**Compound 3k**: $R + R_1 = Benzo, R_2 = R_3 = R_5 = H, R_4 = OCH_3$;

Yield = 65\%  

\[ \text{mp} \ 244^\circ\text{C} \]

Molecular Formula: $C_{26}H_{16}O_5$
### Compound 3l

**R + R<sub>1</sub> = Benzo,  R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Br;**

**Yield = 68%**

**MP:** 230-231°C

**Molecular Formula:** C<sub>25</sub>H<sub>13</sub>BrO<sub>4</sub>

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<td>65.66</td>
<td>2.87</td>
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