SECTION II

SYNTHESIS USING

MICROWAVE IRRADIATION
Chapter V

Synthesis of 3-phenyl and 3-Naphthylcoumarins
CHAPTER-V

3-Phenylcoumarins

Introduction

3-Phenylcoumarins (1) constitute a small but important group of naturally occurring coumarins. Owing to the diverse medicinal and photochemical use of these coumarins, they have strongly attracted the attention of chemists. Synthetic and natural analogues of variously substituted 3-phenylcoumarins have already been evaluated about their biological properties. For e.g. 3-phenylcoumarins are reported to possess anti-vitamin-k activity. Badhwar and Venkatraman have reported the coronary properties of these compounds. Fungicidal activities of 3-phenylcoumarin has also been reported. 3-phenylcoumarins have also been shown to play a vital role in electrophotographic and electroluminescent devices. A highly substituted 3-phenylcoumarin, i.e. 4-benzyl-3-(4-chlorophenyl)-7-methoxycoumarin (2) has been evaluated as a potent aromatase inhibitor. 6,7-Dihydroxy-3-phenylcoumarin (3) inhibits thromboplastin induced disseminated intravascular coagulation.

\[
\begin{align*}
1 & \quad R \quad R' \\
2 & \quad \text{H}_3\text{C} \quad \text{O} \\
3 & \quad \text{HO} \\
4 & \quad \text{OCH}_3 \\
5 & \quad \text{H}_3\text{CO}
\end{align*}
\]

Variously substituted 3-phenyl-4-hydroxycoumarins have been evaluated as HIV-I protease inhibitors. Fruitful and encouraging results are still coming as recently 3-phenylcoumarin derivatives have been reported to do inhibition of horse radish peroxidase catalytic activity.
For many years only two naturally occurring examples of 3-phenylcoumarins namely pachyrrhizin (4) and neofolin (5) were known, but later on large number of examples has been discovered in nature along with evaluation of their biological activity. For eg. 2',7-dihydroxy-4'-methoxy-3-phenylcoumarin (6) and 2',7-dihydroxy-4',5'-methylene dioxy-3-phenylcoumarin (7) have been isolated from the heart-wood of Dalbergia Oliveri\textsuperscript{11} and glycyrrin (8) from the roots of glycyrrhiza spp\textsuperscript{12}.

![Chemical structures of 3-phenylcoumarins](image)

Recently two more examples of naturally occurring 3-phenylcoumarins have been reported. Indicanine-A (9) has been isolated from the root bark of Erythrina indica and found to possess antimicrobial activity against staphylococcus aureus and mycobacterium smegmatics.\textsuperscript{13} Asphodelin-A (10), possessing antimicrobial activity has been isolated from Asphodelus microcarpus.\textsuperscript{14}

![Chemical structures of Indicanine-A and Asphodelin-A](image)

**Past work on the synthesis of 3-phenylcoumarin**

A large number of methods are known in the literature for the synthesis of 3-phenylcomarins. But among these methods Perkin’s method which involves the condensation of phenylacetic acid with appropriate 2-hydroxybenzaldehyde in acetic anhydride was the first method which was of practical use but later on some other methods were also developed for the synthesis of 3-phenylcoumarins. A brief account of these methods is given below.

**Perkin-Oglialoro reaction\textsuperscript{15-16}**

Perkin condensation\textsuperscript{15} (as modified by Oglialoro\textsuperscript{16}) involves the condensation of 2-hydroxy aryl aldehydes with a mixture of phenylacetic acid and acetic anhydride or...
sodium phenyl acetate with acetic anhydride (scheme 1). But this method suffers from drawback of using excess of acetic anhydride, high temperature for longer period, tedious work up, and unsatisfactory low yields.

\[
\begin{align*}
\text{R} & \quad \begin{array}{c}
\text{OH} \\
\text{CHO}
\end{array} \\
\text{CH}_2\text{COONa} \\
\text{Ac}_2\text{O}
\end{align*}
\text{170}-180\, ^\circ\text{C}
\]

**scheme 1**

**Modifications of Perkin reaction**

**Norland and Singer’s modification**

In this modification 2-hydroxybenzaldehyde was heated with phenylacetic acid and phenylacetic anhydride in presence of triethylamine to afford 3-phenylcoumarin (scheme 2).

\[
\begin{align*}
\text{OH} & \quad \text{PhCH}_2\text{COOH} \\
\text{CHO} & \quad (\text{PhCH}_2\text{CO})_2\text{O}, \text{Et}_3\text{N} \\
\end{align*}
\]

**scheme 2**

Another important modification involves the refluxing of 2-hydroxybenzaldehydes or 2-hydroxyacetophenones with phenylacetyl chloride in acetone medium in the presence of anhydrous \( \text{K}_2\text{CO}_3 \) to afford 3-phenylcoumarin in better yield (70-90%) but this required a large reaction period of 30 hours (scheme 3).

\[
\begin{align*}
\text{R} & \quad \text{OH} \\
\text{CHO} & \quad \text{PhCH}_2\text{COCl} \\
\text{R}_1 & \quad \text{acetone, 30 hrs.}
\end{align*}
\]

**scheme 3**

Later on Awasthi & Tiwari used N,N-dimethyl dichlorophosphoryl oxomethylene ammonium chloride for the activation of phenylacetic acid before its reaction with 2-hydroxybenzaldehyde to provide 3-phenylcoumarin in 75 to 95% yield (scheme 4).
In another modification 2-hydroxybenzaldehydes were reacted with phenylacetic anhydride in benzene-aqueous potassium carbonate biphasic medium using phase transfer catalyst to get 3-phenylcoumarin in better yields\(^\text{20}\) (scheme 5).

In 1999 Bigot et al.\(^\text{21}\) reported the synthesis of 3-arylcoumarins by condensation of salicylaldehydes with various arylacetonitriles catalysed by anion exchange resin (scheme 6).

By Mukaiyama esterification conditions\(^\text{22,23}\)

Recently Mashraqui et al.\(^\text{22}\) reported a single step method for the synthesis of 3-phenylcoumarin using Mukaiyama esterification condition\(^\text{23}\). The reaction between salicylaldehyde and phenylacetic acid in the presence of 2 mole equivalents of freshly crystallised 2-chloromethylpyridinium iodide and triethylamine in dry acetonitrile under reflux in nitrogen atmosphere gave 3-phenylcoumarin in 81% yield (scheme 7).
By reduction of 4-hydroxy-3-phenylcoumarin$^{24}$

Ahluwalia and Mehta$^{24}$ reported synthesis of 3-phenylcoumarin from 4-hydroxy-3-phenyl coumarin, first tosylating 4-hydroxy group followed by reductive cleavage by Zn/HCl. Required 4-hydroxy-3-phenylcoumarin were obtained by the reaction of 2-hydroxyphenyl benzyl ketone with diethyl carbonate using sodium methoxide (scheme 8).

By Wittig reaction$^{25}$

2-Hydroxybenzaldehydes on reaction with ethoxycarbonyl phenylmethylene triphenylphosphoranes under Wittig reaction conditions afforded 2-hydroxyeinnamic esters which on heating at higher temperature were converted into 3-phenylcoumarins (scheme 9).
From Isoflavylium salts

Isoflavylium salts such as isoflav-3-enes on oxidation with chromic acid in presence of pyridine gave 3-phenylcoumarins (scheme 10).

\[ \text{R} \overset{\text{ClO}_4}{\text{O}} \overset{\text{CrO}_3 / \text{Pyridine}}{\text{O}} \text{R} \]

scheme 10

From 2-methoxychalcones

By reorganizing the central C_3 units variously substituted 2-methoxychalcones have been converted into 3-phenylcoumarins by a three step process (scheme 11).

\[ \text{R}_1 = \text{H}, \text{OMe}, \text{OH} \]
\[ \text{R}_2 = \text{H}, \text{Br} \]

scheme 11

Photochemical synthesis

A number of fluorescent 3-arylcoumarins have been synthesised by the photocoupling of 3-bromocoumarin with aromatic compounds (scheme 12)

\[ \text{ArH} \overset{\text{hv., r.t., 30-35 hrs. 0-87\%}}{\text{MeCN or MeCN - acetone}} \text{Ar} \]

scheme 12
Recently a new approach to the synthesis of 3-arylcoumarins has been reported using the reaction of 3-acyl and 3-ethoxycarbonyl coumarins with hydrazine of p-nitrophenyl acetic acid\textsuperscript{29} (scheme 13).

\begin{equation}
\text{R} = \text{H, OMe} \\
\text{X} = \text{COPh, COOEt, COMe}
\end{equation}

\textbf{scheme 13}

3-(1-Naphthyl)coumarin

Unlike 3-phenylcoumarins, 3-(1-naphthyl)coumarins are not of natural occurrence. As use of coumarins as anticoagulant drugs has been well established\textsuperscript{30}. Guminaska and Eckstein\textsuperscript{31} in 1960 found that coumarins substituted with 1-naphthyl group at 3-position show strong anticoagulant property and in some cases even stronger then 3-phenylcoumarin. Sook and Suek also synthesised some highly substituted 3-(1-naphthyl)coumarins showing anticoagulant property\textsuperscript{32}. Following these reports to expose the biological activities of 3-naphthylcoumarins, differently substituted 3-(1-naphthyl)coumarins were synthesised using different methods. Only few methods are available in the literature of the synthesis of this class of compounds, but these suffers one or more limitations of hazardous conditions, poor yields, multisteps, long reaction time etc. A brief account of the reported methods for the synthesis of these coumarins is given below.

\textbf{Past work on the synthesis of 3-(1-naphthyl)coumarins}

\textbf{By reaction of 2-methoxybenzaldehyde with naphthylacetonitrile\textsuperscript{33}}

2-Methoxybenzaldehyde on reaction with 1-naphthylacetonitrile in presence of alcoholic-KOH gave 2-(1-naphthyl)-3-(2-methoxyphenyl)acrylonitrile which on further reaction with pyridine hydrochloride gave 3-(1-naphthyl)coumarin (scheme 14).
By reaction of 2-hydroxybenzaldehyde with 1-naphthylacetic acid

2-Hydroxybenzaldehyde when condensed with 1-naphthylacetic acid initially gave 1-carboxystilbene which on cyclisation gave 3-(1-naphthyl)coumarin (scheme 15).

By reaction of 2-hydroxybenzaldehyde with N,N-diethyl-1-naphthylacetamide

Variously substituted 3-(1-naphthyl) coumarins have also been synthesised in 25 to 30% by the reaction of 2-hydroxybenzaldehyde with N,N-diethyl-1-naphthylacetamide in presence of phosphorous oxychloride in chloroform solution under reflux for 10 hours by this method (scheme 16).

Using phase transfer catalyst

Recently phase transfer catalysed condition in biphase medium has been employed for the synthesis of 3-(1-naphthyl)coumarin. 2-Hydroxybenzaldehydes on reaction with 1-naphthylacetic anhydride in benzene, aq. potassium carbonate, biphase medium in the presence of tetra n-butyl ammonium hydrogen sulphate as phase transfer catalyst, gave 3-(1-naphthyl) coumarin, directly in one step 70% yield (scheme 17).
Microwaves in organic Synthesis

Microwave heating is very attractive tool for chemical application and has become a widely accepted non conventional energy source for performing organic synthesis. In the past few years heating and driving chemical reactions by microwave energy has been an increasingly popular theme in the scientific community as supported by increasing number of related publications in recent years particularly in 2003. Now this non classical heating technique is slowly moving from a laboratory curiosity to an established technique that is heavily used in both academia and industry. The efficiency of the 'microwave flash heating' in dramatically reducing reaction times (from days and hours to minutes and seconds) is just one of the many advantages. Other advantages of this technique include higher yields, milder reaction conditions, solid phase green synthesis under solvent free conditions, stereoselectivity etc.

A large number of examples of reactions involving the use of microwaves have been described in literature. Several reviews have appeared on the application of microwaves to reactions under solvent free conditions. The main fields of chemistry which have utilised the microwave heating are radio chemistry, polymer chemistry, heterocyclic chemistry, carbohydrate chemistry, medicinal chemistry and green chemistry.

Principle

Microwaves are electromagnetic radiations in the frequency range of 0.3 to 300 GHz. All domestic microwave ovens and all dedicated microwave reactors for chemical synthesis operate at a frequency of 2.45 GHz (corresponds to a wavelength of 12.24 cm.) to avoid interference with telecommunication and cellular phone frequencies. Microwave enhanced chemistry is based on the efficient heating of materials by 'microwave dielectric heating effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it in to heat. The electric component of an electromagnetic field causes heating by two main mechanisms-dipolar polarization and ionic conduction. Irradiation of the sample at the microwave frequency results in the dipoles or ions aligning in the applied electric field. As the applied field oscillate the dipole or ion field attempts to realign itself with the alternating electric field and in the process energy is lost in the form of heat through
molecular friction and dielectric loss. The amount of heat generated by the process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign or reorients too quickly with the applied field, no heating occurs. The allocated frequency of 2.45 Hz used in all commercial system lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely\textsuperscript{53-54}. The heating characteristics of a material (solvent or reagents) under microwave conditions depends on its dielectric properties. In general larger the dielectric constant, greater the coupling with microwaves. The solvents such as water, methanol, DMSO, DMF, ethyl acetate, acetone, chloroform, acetic acid, dichloromethane, are all heated when subjected to microwaves. Solvents such as hexane, toluene, diethyl ether, carbon tetrachloride do not couple with microwaves, therefore do not heat up.

**Experimental consideration**

In a microwave own radiation is generated by a magnetron, the microwaves are guided in to the cavity by a waveguide and reflected by the walls of the cavity. If the microwaves are not absorbed, they may be reflected back down the waveguide and damage the magnetron, therefore, the presence of a microwave active "dummy load" is essential which will absorb excess microwaves and avoid such damage.\textsuperscript{55}

**Modes of microwave assisted organic reactions**

There are generally two main way of carrying out the microwave assisted organic reactions using domestic microwave ovens.

1) **Microwave assisted organic reactions using solvent**

It is possible to carry out microwave assisted reactions under traditional conditions in which the reagents are dissolved in organic solvents. The experimental procedures are simple and can be carried out in open or sealed vessel and subjected to short period of reactions\textsuperscript{56}. This procedure can only be carried out if neither the solvent nor products are flammable, otherwise there is a risk of fire or explosion. If solvents are heated by microwaves irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent typically limits the temperature of the reaction mixture that can be achieved. In addition to practical simplicity of this type of procedure, it is some times found that volatile reaction by products evaporate rapidly thus avoiding methods for their
specific removal. But to carry out organic reactions under these conditions, one of the component of reaction mixture either reagent or solvent must be microwave active. If neither the solvent nor the reagent is microwave active then microactive additives are added to generate heat.

To achieve high reaction rate, high boiling microwaves active solvents such as DMSO, DMF, ethylene glycol, 1,2-dichlorobenzene(DCB) etc have been frequently used in open vessel microwave synthesis\textsuperscript{57}. This mode of microwave enhancement has been successfully applied for following type of chemical reactions.

- Pericyclic reactions\textsuperscript{58}
- Cyclisation reactions\textsuperscript{59}
- Oxidations\textsuperscript{60}
- Alkenes synthesis\textsuperscript{61}
- Decarboxylation\textsuperscript{62}
- Synthesis of oximes\textsuperscript{63}
- Condensation reaction\textsuperscript{64}

2) Microwave assisted organic reactions in the absence of solvents (i.e. in dry media)

Microwave assisted organic reactions under solvent free conditions are generally of two types. In one type, the reagents are preadsorbed on to either a more or less microwave transparent solid support (silica, alumina or clay).\textsuperscript{65-67} In this type at least one of the reagent must be microwave active. In second type a microwave active solid support such as graphite\textsuperscript{68} is used and thus the reactants need not to be microwave active.

In this procedure the reagents and solid support are efficiently mixed in an appropriate solvent which is then evaporated. The types of chemical reactions involving this mode of microwave enhancement are briefly listed below.

- Heterocyclic synthesis\textsuperscript{57,69}
- Peptide synthesis\textsuperscript{70}
- Condensation and rearrangement reactions\textsuperscript{71}
- Pericyclic reactions\textsuperscript{72}
- Oxidation reactions\textsuperscript{73}
- Aromatic substitution reaction\textsuperscript{74}
- Protection and deprotection of functional groups\textsuperscript{75-76}
PRESENT WORK

Among the various methods discussed for the synthesis of 3-phenylcoumarins, the Perkin's method is one of the most important from practical point of view. Though number of modification have been made on this method but still it suffers from one or other limitations of the longer reaction period or the lower yields.

As barium hydroxide has been found to act as an excellent condensing base in number of reactions. Thus it was proposed to make an attempt for the condensation of 2-hydroxy benzaldehyde with phenylacetic anhydride in the presence of anhydrous barium hydroxide. 2-Hydroxybenzaldehyde and phenylacetic anhydride were thus ground together under solvent free conditions using anhydrous barium hydroxide, but no reaction was found to take place. 2-Hydroxybenzaldehyde and phenylacetic anhydride were then refluxed with anhydrous barium hydroxide in ethanol and no appreciable reaction was found to take place when checked on TLC even after a period of 8 hours. Similarly not much improvement was observed when the reaction was carried out in dry dioxane medium. Dimethylsulphoxide (DMSO), an aprotic polar solvent has been known to act as an excellent medium for the condensation reaction. Thus this condensation reaction was next taken up in dimethylsulphoxide medium and reaction was found to be completed after heating for 1 hour at 140\textdegree{}C-145\textdegree{}C. The colourless compound obtained in 85\% yield, after diluting the reaction mixture with ice cold water, acidifying with conc. HCl and crystallization from ethanol (m.p. 140-141\textdegree{}C), was identified as 3-phenylcoumarin based on its IR and \textsuperscript{1}H-NMR spectral data.

As the organic reactions are known to get improved in terms of their reaction times and yields, when are carried out under microwave conditions, it was thus proposed to carry out the above reaction under microwave conditions. Solution of 2-hydroxybenzaldehyde and phenylacetic anhydride in dimethylsulphoxide and anhydrous barium hydroxide was subjected to microwave irradiations in a loosely stoppered round bottom flask using 40\% power (360W) of microwave oven for 10 seconds (2 \times 5 sec.). The completion of the reaction was checked on TLC and reaction mixture was worked up by acidifying with conc. HCl under ice cold conditions and the compound obtained after crystallization from ethanol (m.p. 140-141\textdegree{}C ) was identified to be 3-phenylcoumarin (96\% yield) by direct comparison (Co-TLC and IR) with the sample prepared above under thermal
conditions. This appeared to be a highly efficient procedure for the synthesis of 3-phenylcoumarins in high yield. Thus the condensation between 2-hydroxy benzaldehyde and phenylacetic anhydride or 4-methoxy phenylacetic anhydride was carried out using microwave irradiations, as it require much shorter time period for the completion of reaction along with appreciate enhancement in yield. This method was used for the synthesis of various substituted 3-phenyl and 3-(4-methoxy) phenylcoumarins.

Encouraged by the results obtained, it was proposed to extend the present method for the synthesis of 3-(1-naphthyl)coumarins. 2-Hydroxybenzaldehyde was thus reacted with 1-naphthylacetic anhydride in the presence of anhydrous barium hydroxide in DMSO medium using microwave irradiations and 3-(1-naphthyl)coumarin was obtained in 94% yield. Success of this method was shown by synthesis of 6-methyl, 6-bromo and 6-chloro-3-(1-naphthyl)coumarins. Detailed description of the work is given below.

**Reaction of 2-hydroxybenzaldehyde and phenylacetic anhydride using anhydrous barium hydroxide in dimethylsulphoxide medium under thermal conditions and microwave irradiations: synthesis of 3-phenylcoumarin (13)**

**Method A: Thermal conditions**

In an attempt to find out the new approach for the synthesis of 3-phenylcoumarins, a solution of 2-hydroxybenzaldehyde (11; 4.09 mmol), phenylacetic anhydride (12; 4.50 mmol) in dimethylsulphoxide and anhydrous barium hydroxide was heated in a round bottom flask on an oil bath maintained at 140-150°C under anhydrous conditions. The progress and completion of the reaction was checked on TLC, which showed a blue fluorescent spot in ultraviolet light whereas starting material exhibited themselves as purple non fluorescent spots. The starting aldehyde was found to have reacted completely in 1 hour. The reaction mixture was worked up by diluting the reaction mixture with ice cold water and acidifying with conc. HCl. Solid product was obtained which on crystallization from diethyl ether-petroleum ether gave a product in 85% yield. In IR it showed absorption at 1721 cm\(^{-1}\), showing formation of a coumarin unit. Whereas in \(^1\)H-NMR it showed a signal for one proton at \(\delta 7.66\) due to H-4 of coumarin along with the multiplet for nine protons at \(\delta 7.02\) to 7.60. Based on this data
compound was identified as 3-phenylcoumarin (13), which was further confirmed by comparison of m.p. with literature value.\textsuperscript{17}

**Method B: Microwave irradiations**

A mixture of 2-hydroxybenzaldehyde (11; 4.09 mmol), phenylacetic anhydride (12; 4.50 mmol) in dimethylsulphoxide and anhydrous barium hydroxide was irradiated in microwave oven for 5 seconds using 40\% power (360W) of the oven. The progress and completion of the reaction was checked on TLC. For complete conversion the reaction mixture was further irradiated for 5 seconds, when starting aldehyde was found to have reacted completely. The reaction mixture was worked up to give 3-phenylcoumarin (13) in 96\% yield, whose structure was confirmed by comparison (Co-IR, m.m.p.) with the sample prepared above.

\[
\begin{align*}
&\text{OH} \\
&\text{CHO}
\end{align*}
\]

**Synthesis of 6-methyl-3-phenylcoumarin (15)**

A solution of 2-hydroxy-5-methylbenzaldehyde (14), phenylacetic anhydride (12) in dimethylsulphoxide and anhydrous barium hydroxide in 20 ml loosely stoppered round bottom flask was irradiated with microwaves for 10 seconds, when 6-methyl-3-phenylcoumarin (15) was obtained as colourless crystal in 92\% yield, whose structure was confirmed by its IR, \textsuperscript{1}H-NMR spectral data, and comparison of m.p. with literature value.\textsuperscript{78}

\[
\begin{align*}
&\text{OH} \\
&\text{CHO}
\end{align*}
\]

**Synthesis of 6-chloro-3-phenylcoumarin (17)**

A solution of 2-hydroxy-5-chlorobenzaldehyde (16) and phenylacetic anhydride (12) in dimethylsulphoxide and anhydrous barium hydroxide on irradiation with microwaves (40\% power) for (2 x 5) seconds gave 6-chloro-3-phenylcoumarin (17) in 95\% yield, whose structure was confirmed by IR and \textsuperscript{1}H-NMR data.
Synthesis of 6-bromo-3-phenylcoumarin (19)

A solution of 2-hydroxy-5-bromobenzaldehyde (18) and phenylacetic anhydride (12) in dimethylsulphoxide and anhydrous barium hydroxide was taken in 20 ml loosely stoppered round bottom flask and irradiated with microwaves in microwave oven using 40% power for (2 x 5) seconds to give 6-bromo-3-phenylcoumarin (19) in 96% yield, whose structure was confirmed by its IR, $^1$H-NMR spectral data, and by comparison of m.p. with literature value.\(^{27}\)

Synthesis of 3-(4-methoxyphenyl) coumarin (21)

A solution of 2-hydroxybenzaldehyde (11), 4-methoxyphenylacetic anhydride (20) in dimethylsulphoxide and anhydrous barium hydroxide was irradiated with microwaves for (2 x 5) seconds using 40% power of the oven. The progress of the reaction was checked on TLC. The reaction mixture on working up as described earlier gave pale yellow solid in 90% yield. The compound was identified as 3-(4-methoxyphenyl)coumarin (21) from IR (1718 cm\(^{-1}\)), $^1$H-NMR data ($\delta$ 3.80 (s, 3H, OCH\(_3\)), 6.85-7.70 (m, 8H, Aromatic), 7.75 (s, 1H, H-4) and by comparison of m.p. with literature value.\(^{20}\)
Synthesis of 3-(4-methoxyphenyl)-6-methylcoumarin (22)

A solution of 2-hydroxy-5-methylbenzaldehyde (14), 4-methoxyphenylacetic anhydride (20) in dimethylsulphoxide and anhydrous barium hydroxide on irradiation with microwaves (40% power) for (2 x 5) seconds gave 3-(4-methoxyphenyl)-6-methylcoumarin (22) in 95% yield, whose structure was confirmed by its IR, $^1$H-NMR, and by comparison of m.p. with literature value.\(^\text{20}\)

$$
\text{14} + \text{H}_2\text{CO} + \text{anhyd. Ba(OH)$_2$/ DMSO } \xrightarrow{\text{MW (2 x 5) sec.}} \text{22}
$$

Synthesis of 6-chloro-3-(4-methoxyphenyl)coumarin (23)

A solution of 5-chloro-2-hydroxybenzaldehyde (16), 4-methoxyphenylacetic anhydride (20) in dimethylsulphoxide and anhydrous barium hydroxide on irradiation with microwaves (40% power) for (2 x 5) seconds and working up as described earlier gave 6-chloro-3-(4-methoxyphenyl)coumarin (23) in 92% yield, whose structure was confirmed by its IR and $^1$H-NMR data.

$$
\text{16} + \text{H}_2\text{CO} + \text{anhyd. Ba(OH)$_2$/ DMSO } \xrightarrow{\text{MW (2 x 5) sec.}} \text{23}
$$

Synthesis of 6-bromo-3-(4-methoxyphenyl)coumarin (24)

A solution of 5-bromo-2-hydroxybenzaldehyde (18), 4-methoxyphenylacetic anhydride (20) in dimethylsulphoxide and anhydrous barium hydroxide on irradiation with microwaves (40% power) for (2 x 5) seconds and working up as described earlier gave 6-chloro-3-(4-methoxyphenyl)coumarin (24) in 92% yield, whose structure was confirmed by its IR and $^1$H-NMR data.

$$
\text{18} + \text{H}_2\text{CO} + \text{anhyd. Ba(OH)$_2$/ DMSO } \xrightarrow{\text{MW (2 x 5) sec.}} \text{24}
$$
Synthesis of 3-(1-naphthyl)coumarin (26)

A solution of 2-hydroxybenzaldehyde (11), 1-naphthylacetic anhydride (25) in dimethylsulphoxide was irradiated in microwave oven with anhydrous Ba(OH)$_2$ for (3 × 5) seconds. Completion of the reaction was checked on TLC. The reaction mixture was worked up as described earlier to give a colourless solid in 94% yield (m.p. 154-55°C). The product was confirmed as 3-(1-naphthyl) coumarin (26) from its IR (C=O, 1718 cm$^{-1}$), $^1$H-NMR (multiplet at $\delta$ 7.25-7.93 for twelve protons, eleven aromatic protons and one H-4 proton) and by comparison of m.p. with literature value.\textsuperscript{35}

\[
\text{C}_9\text{H}_7\text{O}_2 + \text{C}_9\text{H}_8\text{O}_4 \xrightarrow{\text{MW} \ (3 \times 5) \ \text{sec.}} \text{C}_{13}\text{H}_{10}\text{O}_3
\]

Synthesis of 6-methyl-3-(1-naphthyl)coumarin (27)

A solution of 2-hydroxy-5-methylbenzaldehyde (14), 1-naphthylacetic anhydride (25) in dimethylsulphoxide and anhydrous Ba(OH)$_2$ on irradiation with microwaves and working up as described earlier gave 6-methyl-3-(1-naphthyl)coumarin (27) in 91% yield, whose structure was confirmed by IR, $^1$H-NMR data and by comparison of m.p. with literature value.\textsuperscript{35}

\[
\text{C}_9\text{H}_{12}\text{O}_2 + \text{C}_9\text{H}_8\text{O}_4 \xrightarrow{\text{MW} \ (3 \times 5) \ \text{sec.}} \text{C}_{14}\text{H}_{14}\text{O}_3
\]

Synthesis of 6-chloro-3-(1-naphthyl)coumarin (28)

A solution of 5-chloro-2-hydroxybenzaldehyde (16) and 1-naphthylacetic anhydride (25) in dimethylsulphoxide and anhydrous barium hydroxide on irradiation with microwaves and working up as described earlier gave 6-chloro-3-(1-naphthyl)coumarin (28) in 92% yield, whose structure was confirmed by IR, $^1$H-NMR data and by comparison of m.p. with literature value.\textsuperscript{35}
Synthesis of 6-bromo-3-(1-naphthyl)coumarin (29)

A solution of 5-bromo-2-hydroxybenzaldehyde (18) and 1-naphthylacetic anhydride (25) in dimethylsulphoxide and anhydrous barium hydroxide in a 20 ml loosely stoppered round bottom flask on irradiation with microwaves (40% power) for (2× 5 sec.) and working up as described earlier gave 6-bromo-3-(1-naphthyl)coumarin (29) in 94% yield, whose structure was confirmed by IR, 1H-NMR data and by comparison of m.p. with literature value.36
Experimental

Note: The reactions were carried out in Samsung microwave oven with output energy 900W, frequency 2450 MHz and temperature control arrangement model no. CE118KF.

Phenylacetic anhydride

To an ice cold solution of phenylacetic acid (10 g) in dry ether (30 ml) and pyridine (5.2 ml) was added a mixture of thionyl chloride (3.7 ml) in dry ether (30 ml) gradually with shaking. The reaction mixture was kept at room temperature for overnight and then acidified with ice cold dilute HCl (1: 3, 20 ml). Colourless solid that separated out, was filtered and washed well with ice cold water and then titurated with 5% dilute sodium bicarbonate solution to remove any unreacted phenylacetic acid. It was filtered and washed well with cold water to get phenylacetic anhydride (12) as colourless crystals (7.2 g), m.p. 73°C (lit. m.p. 72.5°C).

3-Phenylcoumarin (13)

Thermal conditions

A solution of 2-hydroxybenzaldehyde (11; 0.5 g), phenylacetic anhydride (12; 1.15 g) in dimethylsulphoxide (10 ml) and anhydrous barium hydroxide in a round bottom flask fitted with an air condenser and calcium chloride guard tube were heated in an oil bath maintained at 140-150°C. The progress of the reaction was checked on TLC and reaction was found to be completed in 1 hour. The reaction mixture was diluted with ice cold water (30 ml) and acidified with conc. HCl, when a colourless solid separated out, which was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 3-phenylcoumarin (13) as colourless crystals (0.77 g), m.p.139-40°C (lit. m.p. 141°C).

IR (KBr): 1721 cm⁻¹ (C=O).

¹H-NMR (CDCl₃): δ 7.02-7.60 (m, 9H, Ar-H), 7.66 (s, 1H, H-4).

Microwave irradiations

A solution of 2-hydroxybenzaldehyde (11; 0.5 g), phenylacetic anhydride (12; 1.15 g) in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) taken in a loosely stoppered round bottom flask was subjected to microwave irradiations, using 40% power (360W) of the oven for 10 seconds (2 x 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and
acidified with conc. HCl. Solid product thus obtained was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 3-phenylcoumarin (13; 0.87 g), m.p. 140-41°C (lit. m.p. 141°C). IR (KBr): 1721 cm\(^{-1}\) (C=O).

### 6-Methyl-3-phenylcoumarin (15)

A solution of 2-hydroxy-5-methylbenzaldehyde (14; 0.5 g), phenylacetic anhydride (12; 1.0 g) and dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 x 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product thus obtained was filtered washed with water recrystallised from diethyl ether-petroleum ether to give 6-methyl-3-phenylcoumarin (15; 0.8 g) m.p. 146-47°C (lit. m.p. 146-47°C). IR (KBr): 1720 cm\(^{-1}\) (C=O).

\(^1\)H-NMR (CDCl\(_3\)): δ 2.28 (s, 3H, CH\(_3\)), 7.20-7.60 (m, 8H, Ar-H), 7.68 (s, 1H, H-4).

### 6-Chloro-3-phenylcoumarin (17)

A solution of 5-chloro-2-hydroxybenzaldehyde (16; 0.5 g), phenylacetic anhydride (12; 0.90 g) in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 x 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 6-chloro-3-phenylcoumarin (17; 0.78 g), m.p. 195-196°C (lit. m.p. 194°C). IR (KBr): 1719 cm\(^{-1}\) (C=O).

\(^1\)H-NMR (CDCl\(_3\)): δ 7.26-7.68 (m, 8H, Ar-H), 7.72 (s, 1H, H-4).

### 6-Bromo-3-phenylcoumarin (19)

A solution of 5-bromo-2-hydroxybenzaldehyde (18; 0.5 g), phenylacetic anhydride (12; 0.7 g) in DMSO (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 x 5 sec.). Completion of the reaction was checked on
TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether mixture to give 6-bromo-3-phenylcoumarin (19; 0.72 g), m.p. 187–88\(^{0}\)C (lit. m.p. 188–90\(^{0}\)C).\(^{27}\)
IR (KBr): 1726 cm\(^{-1}\) (C=O).
\(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 7.20–7.64 (m, 8H, Ar-H), 7.70 (s, 1H, H-4).

4-Methoxyphenylacetic anhydride (20)
To an ice cold solution of 4-methoxyphenyl acetic acid (10 g) in dry ether (30 ml) and pyridine (5 ml) was added a mixture of thionyl chloride (2.2 ml) in dry ether (30 ml) drop wise with continuous shaking and maintaining the ice cold conditions. The reaction mixture was kept overnight and then acidified by adding crushed ice and dilute HCl (1: 3, 20 ml). The solid that separated out, was filtered and titurated well with 5% aq. sodium bicarbonate solution (20 ml) to remove any unreacted acid. It was filtered, washed well with cold water when 4-methoxyphenylacetic anhydride (20) was obtained as colourless solid (8.0 g), m.p. 68–69\(^{0}\)C (lit. m.p. 69\(^{0}\)C).\(^{79}\)

3-(4-Methoxyphenyl)coumarin (21)
A solution of 2-hydroxybenzaldehyde (11; 0.5 g), 4-methoxyphenylacetic anhydride (20; 1.41 g) dissolved in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 x 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 3-(4-methoxyphenyl)coumarin (21; 0.93 g), m.p. 140–41\(^{0}\)C (lit m.p. 140\(^{0}\)C).\(^{20}\)
IR (KBr): 1720 cm\(^{-1}\) (C=O).
\(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 3.80 (s, 3H, OCH\(_3\)), 6.85–7.70 (m, 8H, Ar-H), 7.75 (s, 1H, H-4).

3-(4-Methoxyphenyl)-6-methylcoumarin (22)
A solution of 2-hydroxy-5-methylbenzaldehyde (14; 0.5 g), 4-methoxy phenylacetic anhydride (20; 1.28 g) dissolved in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 x 5 sec.).
Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 3-(4-methoxyphenyl)-6-methylcoumarin (22; 0.90 g), m.p. 140-41°C (lit. m.p. 143°C). IR (KBr): 1720 cm⁻¹ (C=O).

H-NMR (CDCl₃): δ 2.31 (s, 3H, CH₃), 3.80 (s, 3H, OCH₃), 6.92-7.65 (m, 7H, Ar-H), 7.73 (s, 1H, H-4).

6-Chloro-3-(4-methoxyphenyl) coumarin (23)

A solution of 5-chloro-2-hydroxybenzaldehyde (16; 0.5 g), 4-methoxyphenylacetic anhydride (20; 1.1 g) in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 x 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 6-chloro-3-(4-methoxyphenyl)coumarin (23; 0.84 g) m.p. 190°C.

IR (KBr): 1718 cm⁻¹ (C=O).

H-NMR (CDCl₃): δ 3.86 (s, 3H, OCH₃), 6.97-7.68 (m, 8H, 7Ar-H & 1H, H-4).

6-Bromo-3-(4-methoxyphenyl) coumarin (24)

A solution of 5-bromo-2-hydroxybenzaldehyde (18; 0.5 g), phenylacetic anhydride (20; 0.86 g) in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 x 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 6-bromo-3-(4-methoxyphenyl)coumarin (24; 0.75 g) m.p. 201-02°C.

IR (KBr): 1720 cm⁻¹ (C=O).

H-NMR (CDCl₃): δ 3.86 (s, 3H, OCH₃), 6.97-7.68 (m, 8H, 7Ar-H & 1H, H-4).
1-Naphthalacetic anhydride (25)

To an ice cold solution of 1-naphthalacetic acid (10 g) and pyridine (5.3 ml) in dry ether (16 ml) was added a solution of thionyl chloride (3.7 ml) in dry ether (16 ml) gradually with stirring. After keeping the solution at room temperature overnight, it was neutralized with ice cold dilute HCl (1 : 3, 20 ml) when a colourless solid separated out which was filtered, washed with ice cold water and treated with cold solution of sodium bicarbonate to remove any unreacted acid left. The solid thus obtained was filtered, washed with water and dried in vacuum over calcium chloride to give 1-naphthalacetic anhydride (25; 5.8 g), m.p. 115-16°C (lit. m.p. 117-19°C).80

3-(1-Naphthyl)coumarin (26)

A solution of 2-hydroxybenzaldehyde (11; 0.5 g), 1-naphthalacetic anhydride (25; 1.59 g) in DMSO (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 15 seconds (3 x 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 3-(1-naphthyl) coumarin (26; 1.05 g) m.p. 154-55°C (lit. m.p 155-56°C).35

IR (KBr): 1718 cm⁻¹ (C = O).

¹H-NMR (CDCl₃): δ 7.25-7.93 (m, 12H, Ar-H & H-4).

6-Methyl-3-(1-naphthyl)coumarin (27)

A solution of 2-hydroxy-5-methylbenzaldehyde (14; 0.5 g), and 1-napthylacetic anhydride (25; 1.43 g) in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 15 seconds (3 x 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 6-methyl-3-(1-naphthyl) coumarin (27; 0.95 g), m.p. 134-135°C (lit. m.p 133-134°C).35

IR (KBr): 1720 cm⁻¹ (C = O).

¹H-NMR (CDCl₃): δ 2.32 (s, 3H, CH₃), 7.30-7.92 (m, 11H, Ar-H and H-4).
6-Chloro-3-(1-naphthyl)coumarin (28)

5-Chloro-2-hydroxybenzaldehyde (16; 0.50 g), 1-naphthylacetic anhydride (1.25 g) dissolved in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 × 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 6-chloro-3-(1-naphthyl)coumarin (28; 0.90 g), m.p. 155-156°C (lit. m.p. 154-55°C).35

IR (KBr): 1720 cm\(^{-1}\) (C = O).

\(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 7.25-7.94 (m, 11H, Ar-H & H-4).

6-Bromo-3-(1-naphthyl)coumarin (29)

A solution of 5-bromo-2-hydroxybenzaldehyde (18; 0.50 g), 1-naphthylacetic anhydride (0.97 g) in dimethylsulphoxide (5 ml) and anhydrous barium hydroxide (0.5 g) in a loosely stoppered round bottom flask was subjected to microwave irradiations using 40% power (360W) for 10 seconds (2 × 5 sec.). Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised from diethyl ether-petroleum ether to give 6-bromo-3-(1-naphthyl)coumarin (29; 0.82 g), m.p. 126-27°C (lit. m.p. 126-27°C).36

IR (KBr): 1721 cm\(^{-1}\) (C = O).

\(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 7.13-7.92 (m, 11H, Ar-H & H-4).
References


