MICROWAVE-ASSISTED ORGANIC REACTIONS
A COMPARATIVE ACCOUNT

THESIS

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AWARD OF THE DEGREE OF

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IN

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by

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CERTIFICATE

It is certified that the work presented in this thesis entitled

"MICROWAVE ASSISTED ORGANIC REACTIONS – A COMPARATIVE ACCOUNT"

is original and has been carried out by **Ms. Saima Qadir** under my supervision. This piece of work is suitable for submission for the award of Ph.D. degree in Chemistry. It is further certified that the work has not been submitted in part or full for award of any degree in this or any other university.

16th of March, 2009

(Prof. Khaliquz Zaman Khan)
Supervisor

Chapter 1

"Microwave-Assisted Organic Synthesis (MAOS)-Theoretical"

"Instead of preparing a cup of tea in the microwave while waiting for a conventional reaction to reach completion, why not put the reaction vessel in microwave instead!!!!"

1.1 Introduction

In recent years, the focal point in chemical research is the development of environmentally friendly processes in terms of sustainable chemistry. Of particular importance is a reduction in the amount of solvents and hazardous substances and more efficient use of energy, microwave-assisted synthesis being one of them.

In the electromagnetic spectrum, microwave radiation area is located between Infrared and Radio waves having a wave length in the range of 0.3mm to 0.5m corresponding to frequencies between 1×10^{12} - 6×10^{8} Hz. In the laboratory, microwave instruments generate the waves corresponding to a wavelength of 12.2 cm and energy of 2.45 GHz, as per the international convention so that any interference with telecommunications and radar equipments is minimized.

The electromagnetic radiation covers a wide range of frequencies or wavelengths.[1]

Spectral region	**Wavelength range(m)**	**Frequency range(Hz)**
γ-rays	1×10^{-12}	3×10^{19}
X-rays	10^{-12} - 10×10^{-9}	3×10^{19} - 3×10^{16}
Vacuum Ultraviolet	10^{-9} - 200×10^{-9}	3×10^{16} - 1.5×10^{15}
Ultraviolet	200 - 400×10^{-9}	1.5×10^{15} - 7.5×10^{14}
Visible	400 - 800×10^{-9}	7.5×10^{14} - 3.8×10^{14}
Near Infrared	0.8 - 2.5×10^{-6}	3.8×10^{14} - 1×10^{14}
Mid Infrared	2.5 - 50×10^{-6}	1×10^{-14} - 6×10^{-12}
Far Infrared	50 - 300×10^{-6}	6×10^{12} - 1×10^{12}
Microwaves	**0.3×10^{-3} - 0.5**	**1×10^{12} - 6×10^{8}**
Radio waves	0.5 - 300	6×10^{8} - 1×10^{6}

It may be mentioned here that the boundaries between any two adjacent regions of the spectrum are not strictly defined and radiation near a boundary between two regions can be accepted as belonging to either region.

Microwaves are reflected off metal surfaces but pass through paper, glass, china ware and plastic ware. Hence these materials find extensive use as reaction vessels or utensils since microwaves are absorbed directly by the chemical species or food

without affecting the container. Microwaves penetrate several centimeters deep into the material to be heated because of a high penetration power and the dissipation of energy results in a quick and even rise in temperature of the species.

1.2 Microwaves – "Out of Kitchen into the Chemical Laboratory"

Although the use of microwaves in the preparation of food dates back to around forty years, it is only since past two decades that they have found their way into the chemical laboratory.

"History of microwaves ovens"- An accidental discovery

In 1946, the real potential of microwaves came to lime light when Percy le Baron Spencer, an American Engineer working with radar equipments while testing a new type of vacuum tube – the magnetron, at Raytheon noticed that some candy he had in his pocket, melted when he accidentally leant against an open wave guide(a rectangular hollow tube of metal used to conduct microwaves). Spencer began conducting more experiments with uncooked kernels and raw eggs. He watched popcorn bounce around the room and raw egg placed near the magnetron, explode from the pressure built up inside. The potential of Spencer's discovery was soon realized at Raytheon who began to produce the first microwave ovens called the "Radaranges". Radaranges were large and expensive but it was not until 1967 when Amana, a subsidiary of Raytheon produced the first household microwave oven.[2]

Since then, upto the middle of 1980's, microwave ovens were used only for cooking and defrosting frozen food. However, in 1986, due to the independent work of Richard Gedye and co-workers at Laurentain University, Canada and Majetich[3] and Giguere[4] at the University of Georgia, USA, microwaves successfully made the transition from kitchen to the chemical laboratory as they could do much more than mere cooking. The researchers reported increase in the rates of a number of organic reactions using a commercially available microwave oven. These reports formed the basis of an ever increasing range of research publications over the next twenty years. Later considerations for the safety and the need to achieve controllable, reproducible and focused homogenous heating led to the development of specially designed microwave equipments. The new microwave ovens were fitted with temperature and pressure detection devices

making it possible to monitor a reaction while it is being irradiated under the oven.

1.3 Components and features

A schematic diagram of a microwave reactor is shown in figure 1.

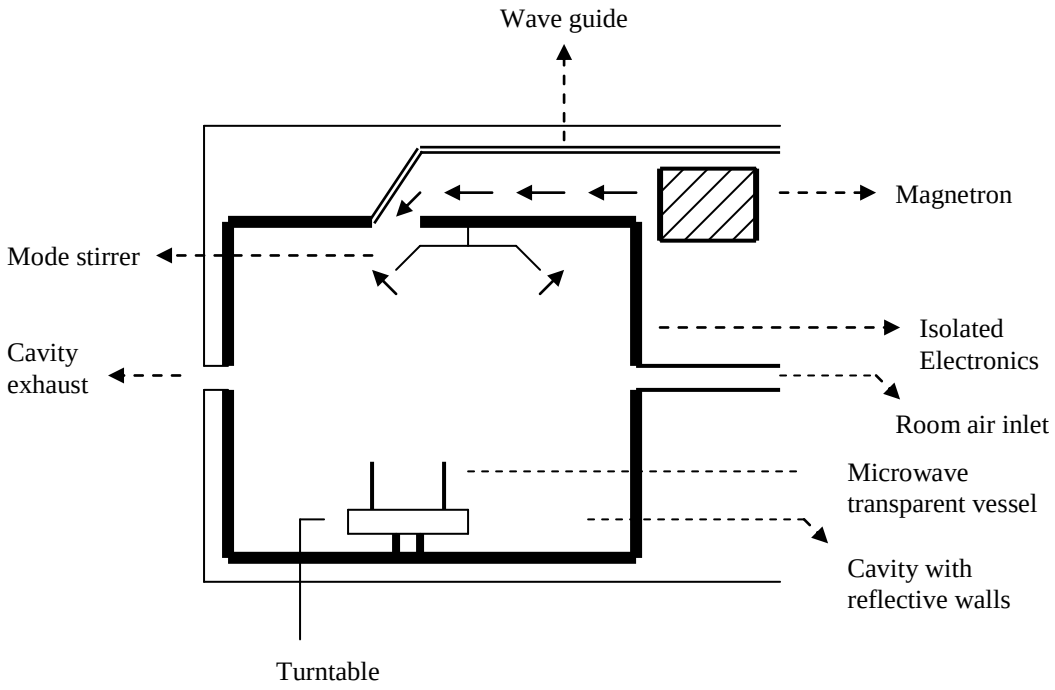


Fig.1. Cavity-type microwave reactor

The microwave oven consists of the following components:

- **Magnetron/Klystron** It is a thermionic diode possessing an anode and a directly heated cathode. It emits the radiation over a narrow frequency range.
- **Wave guide** It is a hollow tube of metal of rectangular cross-section with reflective walls to allow the transmission of microwaves from the magnetron to the microwave cavity.
- **Microwave cavity** It is the internal space of the oven where the samples are placed for irradation and usually contains a turn table to ensure that each sample experiences the same average heating. The cavity has reflective walls to

prevent the leakage of microwaves as well as to increase the efficiency of the oven.

- **Mode Stirrer** A reflective fan shaped paddle to ensure that the microwaves are evenly distributed throughout the cavity.
- **Door interlocks** These are safety devices in the door of the oven to prevent the door from being opened during microwave irradiation.
- **Exhaust fan** This isolates and ventilates the oven to prevent acid fumes from attacking the electronics of the unit.
- **Time control** This allows the time to be set for which the sample is to be irradiated
- **Power control** This allows the power level to be set before microwave irradiation of a sample is to be done.

Since the use of microwave ovens for cooking gained momentum during 1970's, manufacturers continued to improve the homogeneity of the field and other safety considerations. However, the design of the oven chamber or cavity which is crucial for the heating characteristics was not significantly changed until the end of 1980's. In 1986, the first focused microwave system was introduced.

Now a days, two types of microwave reactors are used - monomode and multimode.[5] The former gives focused rays using an optical fiber or IR detector into a cavity inside which the reaction vessel is kept and the bottom few centimeters of the vessel get exposed to microwaves whereas the upper region remains cool. In the latter, the distribution of electric field is not homogeneous creating temperature gradients in different zones called as "hot spots". In addition, the multimode oven doesn't have any provision for accurate temperature measurement. The microwave oven used for cooking purposes is a multimode reactor. Moreover, for the reaction vessel to withstand high pressures, teflon (polytetrafluoroethyene PTFE) has been employed in the manufacture of reaction vessels and tubes that can withstand pressures upto 1500 psi unlike glass vessels which cannot withstand such high pressures and lead to accidents. In spite of reproducible results obtained using monomode ovens, the use of multimode ovens

by chemists in research laboratories continues because of convenience and economical benefit.

1.4 Origin of microwave heating

Microwaves provide the only method of heating that does not involve thermal conduction. While as infra red or heat radiations get absorbed on the surface of a material, microwaves penetrate several centimeters deep into it carrying the electromagnetic energy to the core of the material. The heat generated in a sample on microwave exposure has mainly been attributed to the electric component of microwaves usually by two mechanisms - Dipolar polarization and ionic conduction or charge space transfer.[6]

1.4.1 Dipolar mechanism

Microwave heating of a solid or a liquid is related to the existence of an electric dipole in the molecule of the material. In water, for example, the dipole arises due to the different affinities of oxygen and hydrogen atoms for the available electron density and the angular shape of water molecule. As the electron density is concentrated more on the electronegative oxygen atom, the result is a net dipole moment for the water molecule.

Fig. 2. Dipolar molecules try to align with oscillating electric field of microwaves.

The heating effect generated in microwave-assisted organic transformations is mainly due to the dielectric polarization i.e. orientation of a dipole with that of the applied field (*figure 2*). If the field is alternating, the dipole tends to align and realign itself with the applied field leading to thermal agitation which in turn produces heat. This effect can be explained as follows:-

The polar molecules, in the absence of an electric field, will have a random arrangement. This chaotic order with greater entropy will be the natural,

lowest energy configuration for the assembly of molecules (*figure 3*). When placed in a strong electric field for sometime, these polar molecules will tend to align themselves parallel to this field (*figure 4*). This new arrangement of molecules will therefore be higher in energy because of decrease in entropy and can be thought of as storing potential energy due to the application of electric field. If the direction of the applied field is changed slowly, the polar molecules will also rotate and try to keep themselves aligned with the field (*figure 5*). If the direction of electric field is changed more quickly, some of the molecules may not be able to remain in alignment with the direction of applied field. The molecules may try hard to remain in parallel with the field but keep colliding with other molecules. The potential energy stored in the changing molecular alignment no longer matches the applied field. This excess energy is transformed into kinetic energy on collision between the molecules and this effect gives rise to microwave heating.[7]

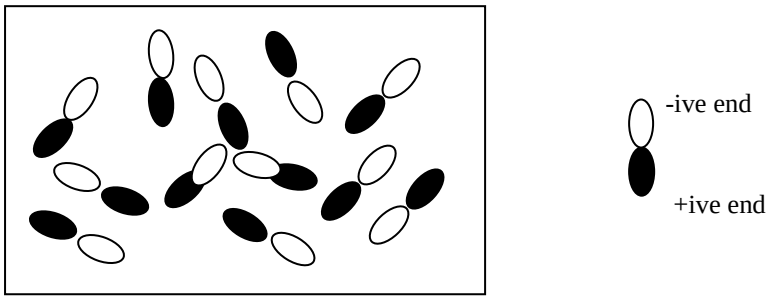


Fig 3. Dipoles in absence of an electric field

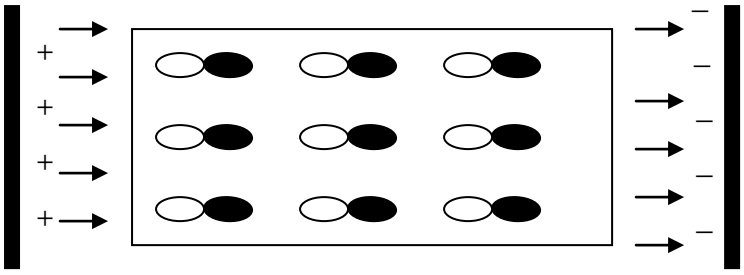


Fig.4. Dipoles in presence of an electric field

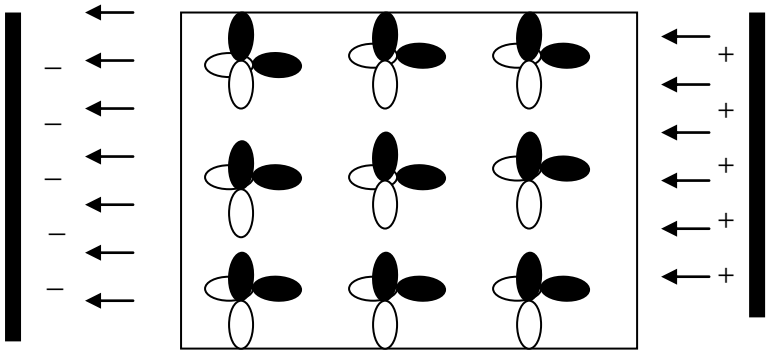


Fig. 5. Dipoles rotating in case of changing electric field

A variable power output is achieved by switching the magnetron on and off according to a duty cycle. The exposure of a molecule to this alternating current inverses the electric field at each alternation, with a subsequent tendency for dipoles to move together to follow the field. Such a characteristic changing field induces stirring and friction of molecules which appears as internal homogeneous heat.[8] In fact, the heating or cooking of food in microwave ovens is because of the dipolar polarization of water molecules present in the food. Other biological molecules in food are far too large to be able to rotate.

The ability of a material to convert electromagnetic energy into heat at a given frequency and temperature is expressed by the following equation

$$\tan \delta = \varepsilon / \acute{\varepsilon}$$

Where δ = dissipation factor

ε = dielectric loss

$\acute{\varepsilon}$ = dielectric constant

In addition to this, factors like interfacial polarization and Maxwell-Wagner effect may also contribute to the heating effect when the conducting particles are in contact with a non-conducting medium, for example, in heterogeneous reactions. Quantitatively, the larger the dielectric constants, the greater the interaction with microwaves.[7] Thus solvents like water, methanol, dimethyl formamide, dimethyl sulfoxide, chloroform, etc get heated up under microwave irradiation whereas

solvents such as hexane, benzene, carbon tetrachloride, etc do not couple and hence are microwave inactive.

The mechanism by which the rotating molecule can grab the energy from microwaves and thereby increase its rotational energy can be understood from the wave nature of the electromagnetic radiation. The radiation is an oscillating electric field which effect tends to move the charged particles one way or the other. If the rotating molecule possesses an electric dipole, the positive and negative ends will change their orientation periodically due to the interaction with electric field of microwaves.

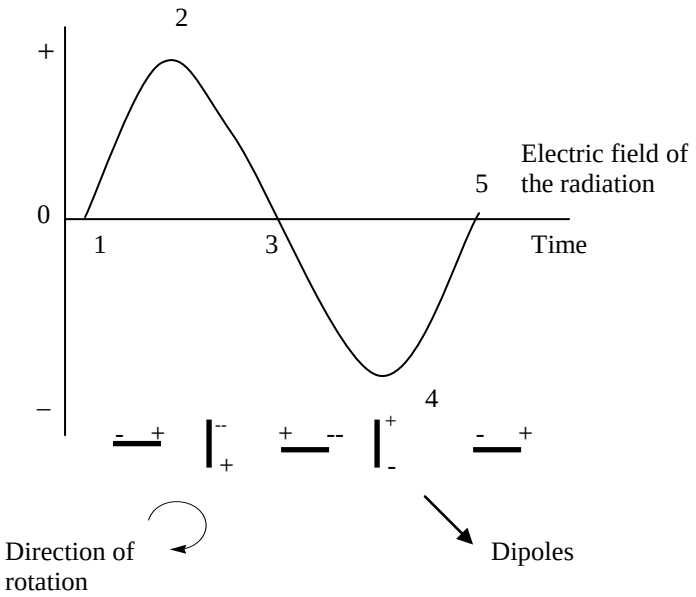


Fig.6. The interaction of the electric field of radiation with the dipole of molecule

When the molecule is in position 1, the electric field is such that it pushes the negative end up and therefore the positive end down making the molecule to rotate. When the molecule has rotated to position 5, the radiation has also moved along to its next cycle, but the interacting force will still make the molecule to rotate faster (*figure 6*). If the frequency of microwaves and that of the molecular rotation are equal, the electric field can interact with the molecular dipole and keep the molecule pushing to a higher rotational energy. It is this excess energy of the polar molecules that appears as heat. [8]

It is noteworthy that if the electric field changes direction very rapidly, the polar molecules will not have the time to react to the changing field and

will remain randomly oriented and consequently at these microwave frequencies, they will be unable to interact with the applied field and no heat will get generated.[8]

1.4.2 Ionic conduction mechanism

In a solution containing ions or even an isolated ion, ions will move in a solution under the influence of an electric field resulting in expenditure of energy due to an increased collision rate converting the kinetic energy to heat, for example, if two samples containing distilled water and tap water are heated in a single mode microwave cavity at the same time and power level, the final temperature will be higher in the tap water sample. It has been found that the conductivity mechanism is much stronger than the dipolar mechanism with regard to the heat generation capacity. [7]

1.5 Microwave penetration

In microwave heating, suitable frequencies for efficient heating and depth of penetration are in the frequency range between 500-5000MHz. Special frequencies are allocated for industry, laboratory and medical use. These frequencies are 433.92 MHz, 915 MHz and 5800 MHz, respectively. For most household microwave ovens, the frequency of 2450 MHz is used with respect to the penetration depth and cooking speed.

Figure 7 shows the relationship between the penetration depth, degree of heating and frequencies of microwave radiation. As evident from the graph, the lower the frequency, the deeper the penetration but a slower heating effect will result and the higher the frequency, the faster the heating speed but the smaller the penetration depth.

As the microwaves penetrate the material, power is lost in each successive layer of molecules as shown in figure 8. This is termed as "**Penetration degree of depth**" and is expressed as the point at which the microwaves are decreased to 37% of their original strength. It is an inverse ratio of frequency. So as the frequency is increased, the penetration depth decreases.[10]

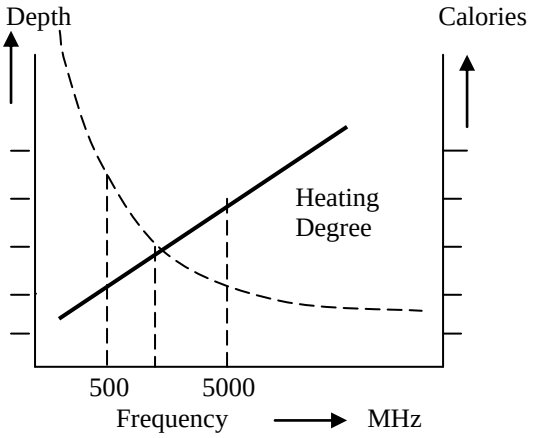


Fig. 7

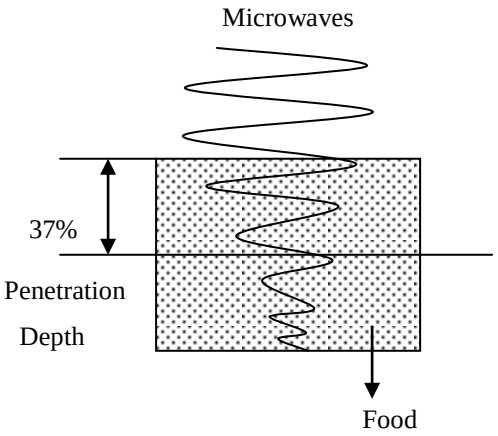


Fig. 8

1.6 Microwave versus the conventional effect

Microwaves provide the only method of heating that does not use thermal conduction. Unlike infra-red radiation absorbed on the surface of the material, microwaves penetrate several centimeters deep and dissipate the electromagnetic energy carried by them to the heart of the material. Microwave dielectric heating is dependent on the ability of a polar solvent or reaction mixture to absorb microwave energy and to convert it into heat.

Microwaves differ from conventional heat sources in that the solvents or reactants are directly heated without heating the reaction vessel i.e. there is an *insitu* generation of heat. The liquid or reaction mixture is often at a higher temperature than the vessel in which it is held and this in turn leads to an increase in the reaction rates and improvements in yield.

In conventional methods, the vessel gets heated first and heat gets transferred to the material by convection. As such the heat supplied is not homogeneously distributed. On the other hand, there is homogeneity of heat in case of microwave irradiation is more efficient in terms of the energy used and is consequently more rapid than conventional heat sources (*figure 9*)**.**

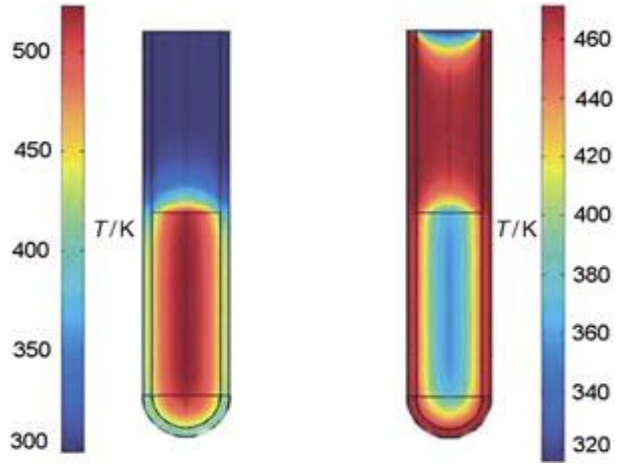


Figure 9. Inverted temperature gradients in microwave versus oil-bath heating: Difference in the temperature profiles (finite element modeling) after 1 min of microwave irradiation (left) and treatment in an oil bath (right). Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating) whereas in the oil-heated tube, the reaction mixture in contact with the vessel wall is heated first.

Not only are microwaves sometimes able to reduce chemical reaction times from hours to minutes, but they are also known to reduce side reactions, increase yields and improve reproducibility. Moreover, microwave-assisted synthesis is an excellent tool of green chemistry whereby environmentally friendly transformations have been carried out under solvent-less conditions. Hence microwave synthesis has an edge over conventional synthesis in terms of time, yield, and ease of workup making it a technique worth an implement in organic synthesis.[11,12] Microwave assisted synthesis is particularly important for industrial synthesis as it saves time, power and leads to improved yields (*figure 10*).

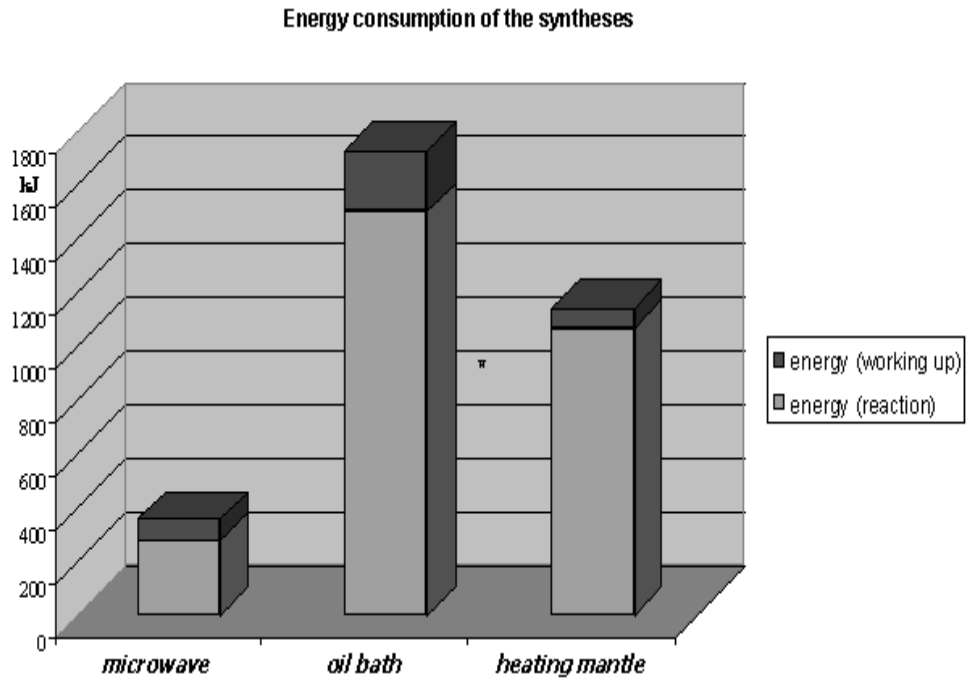


Figure 10. Three ways to get the reaction done, but different energy bills to pay.

1.7 Origin of microwave effects

The accelerations observed in microwave driven reactions have been presumed to be an outcome of the following contributions:-

1.7.1 Thermal effects

Thermal effect of microwaves is known to occur as a consequence of friction that the molecular dipoles undergo while aligning and realigning themselves with the rapidly reversing electric field of microwaves.[13] This can only be achieved using electromagnetic waves in the microwave region. Thermal effect or dielectric heating results from dipolar polarization as a consequence of dipole-dipole interactions between polar molecules and the electromagnetic field resulting in dissipation of energy as heat as an outcome of the agitation and intermolecular friction of molecules when the dipoles change their mutual orientation. This insitu generation of heat at the molecular level allows a much more homogeneity in temperature.

''Hot spots'' or inhomogeneities:-

Several authors have detected or postulated the presence of ''hot spots'' in samples irradiated with microwaves. This is a thermal effect that arises as a consequence of the non-homogeneity of the applied field, resulting in the

temperature, in certain zones within the sample, being much greater than the macroscopic temperature. These regions are not representative of the reaction conditions as a whole. It has been estimated that the temperature in hot spots is about 100–200^{0}C higher than the bulk temperature. This temperature difference was determined by calculations and on the basis of several transformations observed. Hot spots may be created by the difference in dielectric properties of materials by the uneven distribution of electromagnetic field strength.

1.7.2 Specific effects

Thermal effects associated with microwaves cannot completely account for the observed enhancements in reactivity and selectivity. Hence existence of specific effects associated with microwaves have been predicted.[13,14] This effect can be rationalized by consideration under the Arrhenius' law and can result from modifications in each term of this equation.

$$[\ k = A \exp -\Delta G^{\#} RT\ ]$$

(i) The increase in the pre-exponential factor A which represents the probability of molecular impacts. The collision frequency can be effectively influenced by mutual orientation of polar molecules involved in the reaction. As this factor is dependent on the vibration frequency of atoms at the reaction interface it could possibly be affected by microwaves.

(ii) The effect of microwaves on the activation parameters in the equation $\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$ is certainly a main specific effect. As a consequence of dipolar polarization, the magnitude of $-T\Delta S^{\#}$ term would increase in a microwave driven reaction.

1.7.3 Medium effects

Medium effects depend on the reaction medium under consideration or the solvent used (solvent effect).[14] If polar solvents are involved e.g. dimethyl formamide, dimethyl sulfoxide, methanol, chloroform, the main absorption may occur between the microwave and polar solvent molecules. Hence energy transfer will be from the solvent to the reactants. Consequently, results are expected to be the same as under conventional conditions. On the other hand, interesting results could be obtained using non-polar solvents like toluene, xylene or carbon tetrachloride, etc as these are microwave inactive. So there will be a direct

interaction between the microwaves and reactants, hence the results will be quite different. However due to the low boiling point of these solvents, the rapid increase in temperature in the reaction vessel upon microwave irradiation poses the difficulty of bumping or explosions. These difficulties are easily overcome by performing reactions on solid supports like silica gel, clays, etc. These solvent-free procedures are especially important aspects of green chemistry.[15]

1.7.4 Superheating effect

This effect has been observed in the organic solvents under microwave irradiation whereby solvents get superheated by 13-26°C above their conventional boiling points at atmospheric pressure.[16] This effect can be explained by the "inverted heat transfer" effect, that is, transfer of heat from the irradiated medium towards the exterior since boiling nuclei are formed at the surface of the liquid. This effect can often be observed using domestic multimode ovens in absence of any stirring.

Using quite simple apparatus like transparent plastics, Teflon or glass tubes, it is possible to increase the temperature of a reaction in common organic solvents upto 100°C above the conventional boiling point of solvents and the generation of 10-12 atmospheres higher pressure than normal atmospheric pressure in sealed tubes which in turn accelerates the reaction by multifold. This effect is expected to disappear when the experiments are carried out with well stirred mixtures using low microwave power.

1.7.5 Reaction mechanism effects

Such effects regard to how the polarity of the reactants gets altered during the progress of reaction. If the transition state (TS) is more polar than the ground state (GS), the former will be effectively stabilized than latter because of increased interaction with microwaves. The result is decrease in activation energy and enhanced rate of the reaction. [13,14]

The position of the TS along the reaction co-ordinate in view of the Hammond postulate has also to be considered. If the reaction has a small activation energy $\Delta G^{\#}$, the TS looks like the GS; only weak microwave specific effects can be foreseen (*figure 11*).

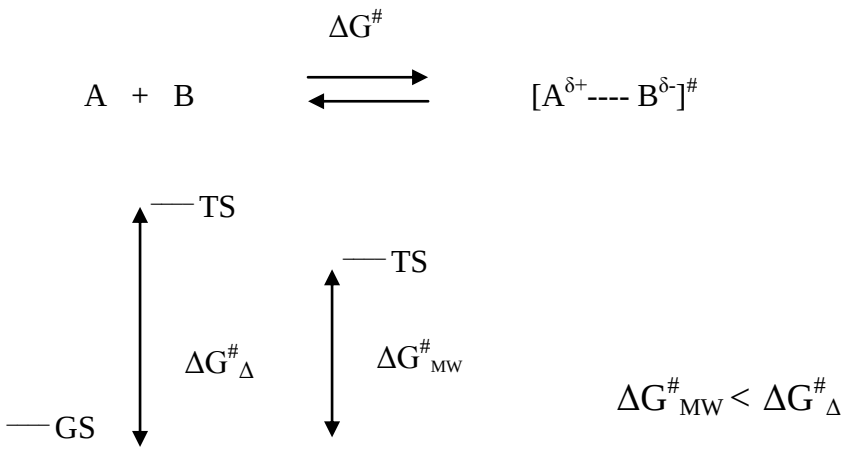


Fig.11. Relative stabilities of more polar transition state (TS) and less polar ground state (GS) in a microwave driven reaction.

1.8 Merits and Demerits of Microwave Heating

1.8.1 Merits/Advantages

- Microwave assisted synthesis reduces the time of reaction substantially. Microwave enhancement may take several forms like reaction rates get accelerated, yields get improved than the conventional counterparts and virtually no decomposition takes place during the drying of samples.
- Microwaves form an essential aspect of green chemistry because of the solvent-free technique. Reactants can be adsorbed on solid supports like clay, montmorillonite, silica gel, alumina, etc and then exposed to microwaves. This eco-friendly procedure minimized the use of solvents leading to cleaner reactions and improved yields in addition to being safer. Ability to control the desired chemo, regio or stereoselectivity is possible using microwave assisted synthesis.
- Microwave heating can be used with less operator intervention, improved safety and greater control over the reaction conditions as well as minimum sample contamination and loss.
- Use of continuous flow microwave systems allows the samples to be digested or extracted in an online system for direct analysis.
- Microwave reactions are ecofriendly and can be achieved under solvent-free conditions.[18-20]

- The advantages of microwaves are applicable to different disciplines of chemical research like drying of samples, melting of solid samples and a variety of organic and inorganic synthetic reactions.

1.8.2 Demerits/Limitations/Disadvantages

- Reaction requiring the use of dry nitrogen atmosphere, fuming, lachrymatory substances or substances which may corrode the interior of the oven cannot be conducted inside a microwave oven.
- There is a possibility that the higher temperatures/superheating of the solvent in sealed vessels may encourage the decomposition of the desired products or may lead to the formation of thermodynamically stable product in preference to the kinetically favoured product.
- Metals are reflective to microwaves and the radiation tends to bounce off them like the light from a mirror. Due to this, metal particles or metals have to be avoided inside the microwave oven because there is always a possibility of an electric spark in the oven.
- No closed vessels should be used except the ones specially designed for withstanding high pressures like teflon tubes.
- One of the draw backs of domestic microwave ovens is the power levels which significantly change from unit to unit.

1.9 Microwave-assisted organic synthesis (MAOS)

Microwave technology has been implemented in organic chemistry only since 1980's.[20-22] This slow uptake of the technology has mainly been attributed to the lack of controllability, reproducibility and safety aspects associated with domestic microwave ovens and generally a low understanding of the basics of microwave dielectric heating and other effects associated with it. However, since 1990's, due to the commercial availability of the microwave oven especially designed for organc synthesis, shorter reaction times and the solvent-free procedures coupled with the principles of green chemistry, the number of microwave based publications have increased multifold.[23-27] The use of microwaves on organic synthesis was first reported independently in 1986 by Giguere and Gedye et al. Since then, microwave assisted organic synthesis has blossomed into a useful technique and accelerations have been observed in a wide range of reactions.

Microwaves have been successfully applied to combinatorial chemistry whereby synthesis of large numbers of molecules is achieved by varying combinations of molecular building blocks and permutations of modular components.[28,29]

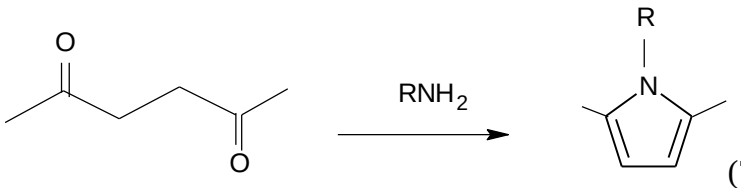
Control of the desired selectivity (chemo, regio, stereo and enantioselectivity) is the most important objective in organic synthesis.[30]The application of microwave irradiation involves the modifications of the reactivity as well as selectivity in relation to conventional heating.[31-33]

1.9.1 Microwave-assisted heterocyclic synthesis

Heterocyclic rings constitute the principle components in a vast number of biologically active compounds. As such, pharmaceutical companies and academic laboratories alike, value and encourage novel and efficient synthetic methodologies for the construction of heterocyclic rings. Five and six membered heterocyclic compounds like Pyrroles, Pyrazoles, Imidazoles, etc have been synthesized in improved yields under solvent-free microwave conditions and dramatic accelerations have been observed in contrast to their classical procedure.[34]

1.9.1.1 Pyrroles

Cyclisation of 1,4-diketones has been carried out under microwave conditions to yield the corresponding pyrrole derivative. The reaction requires only two minutes under microwave procedure in contrast to conventional conditions requiring 12 hours to achieve the conversion.[35]



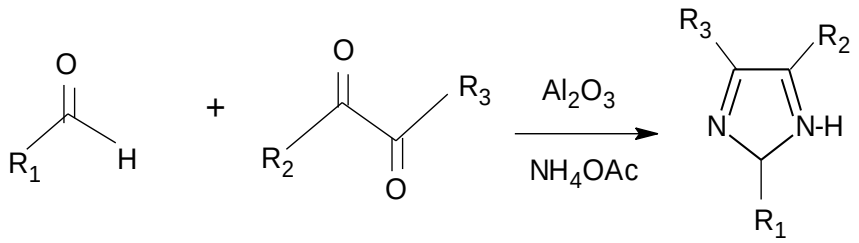
(75-90%)

R = $CH_2C_6H_5$, $4MeOC_6H_4$, $2ClC_6H_4$, etc

(MW, 100-200 W, 0.5-2.0 min., solvent-free)

1.9.1.2 Imidazoles

An important preparation of imidazoles is from an α-diketone, an aldehyde and ammonia. This microwave-assisted synthesis has been achieved in excellent yields in minimum time.[36]



75-85%

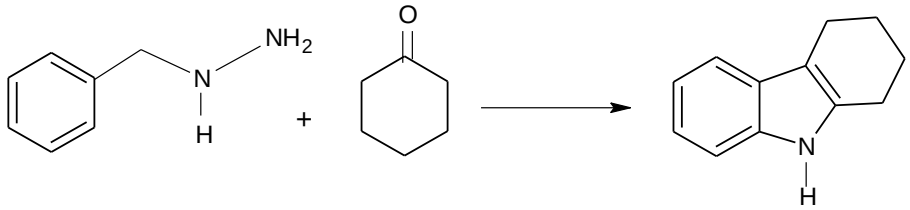
(MW, 130 W, 10 min, solvent-free)

$R_1 = C_6H_5$, $4ClC_6H_4$, 2-thiophenyl etc.
$R_2 = R_3 = C_6H_5$, $4MeC_6H_4$

The synthesis requires 10 minutes under microwave conditions in contrast to 4 hours of reflux in acetic acid.

1.9.1.3 Indoles

The classical Fischer-indole synthesis from an aryl hydrazine and a ketone is speeded-up by several 100-fold using microwave-assisted synthesis.

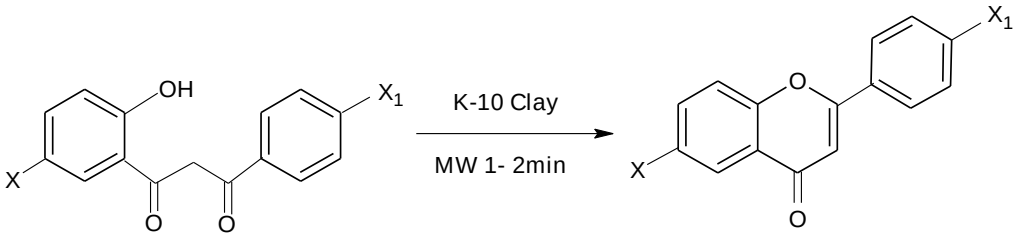


The synthesis is achieved in 30 seconds under microwave irradiation and in 2 hours under conventional conditions.[37]

1.9.3.4 Flavones

Flavonoids are a class of naturally occurring phenolic compounds widely distributed in the plant kingdom, the most abundant being the flavones. Members of this class display a wide variety of biological activities and have been useful in the treatment of various diseases. Flavones have been prepared by a variety of methods such as Allan–Robinson synthesis and synthesis from chalcones *via* an intramolecular Wittig strategy. The most prevalent approach, however, involves the Baker–Venkataraman rearrangement, wherein *o*-hydroxyacetophenone is benzoylated to form the benzoyl ester followed by treatment with base (pyridine/KOH) to

effect an acyl group migration, forming a 1,3-diketone.The diketone formed is then cyclized under strongly acidic conditions using sulfuric acid and acetic acid to deliver the flavone. Using benign and readily available starting materials, a solvent-free synthesis of flavones has been achieved which simply involves the microwave irradiation of *o*-hydroxydibenzoylmethanes adsorbed on montmorillonite K 10 clay for 1–2 minutes. Rapid and exclusive formation of cyclized flavones occurs in good yields.[38]



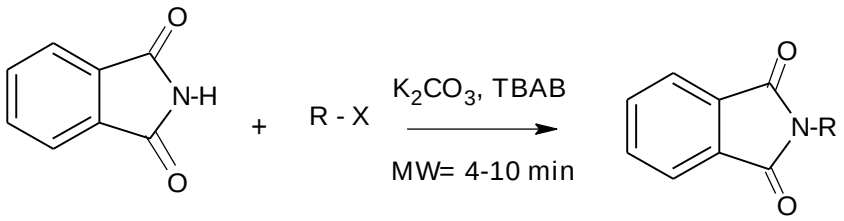
X = H, X_1 = H, Me, OMe, NO_2
R = OMe; X_1 = H, Me, OMe

1.9.2 Protection/deprotection reactions

The protection/deprotection reaction sequences form an integral part of organic manipulations such as the preparation of monomer building blocks, fine chemicals and precursors for pharmaceuticals and these reactions often involve the use of acidic, basic or hazardous and corrosive reagents and toxic metal salts. The microwave-accelerated protection/deprotection of functional groups that have been carried out under solvent-free conditions with improved yields.[39]

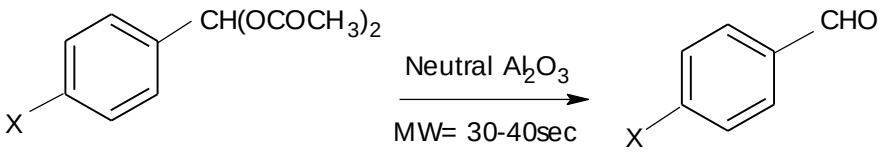
1.9.2.1 N-Alkylation reactions

A variety of solvent-free N-alkylation reactions have been reported which entail the use of phase transfer agents such as tetrabutylammonium bromide (TBAB) under microwave irradiation conditions. The important examples are N-alkylation of phthalimides in the presence of potassium carbonate and TBAB.[40]



1.9.2.2 Cleavage of aldehyde diacetates

The diacetate derivatives of aromatic aldehydes are rapidly cleaved on a neutral alumina surface upon brief exposure to microwave irradiation. The selectivity in these deprotection reactions is achievable by simply adjusting the duration of microwave exposure. As an example for molecules bearing an acetoxy functionality (R = $OCOCH_3$), the aldehyde diacetate is selectively removed in 30 seconds, whereas an extended period of 2 minutes is required to cleave both the diacetate and ester groups. The yields obtained are better than those possible by conventional methods and the protocol is applicable to compounds having olefinic moieties such as cinnamaldehyde diacetate present in them.[41]



X = H, Me, CN, NO_2, $OCOCH_3$

1.9.3 Oxidation reactions

1.9.3.1 Oxidation of alcohols and sulfides

The conventional oxidizing reagents employed for organic functionalities are peracids, peroxides, manganese dioxide (MnO_2), potassium permanganate ($KMnO_4$), chromium trioxide (CrO_3), potassium chromate (K_2CrO_4), and potassium dichromate

($K_2Cr_2O_7$), though these reagents have their own limitations in terms of toxicity, work-up and associated waste disposal problems.

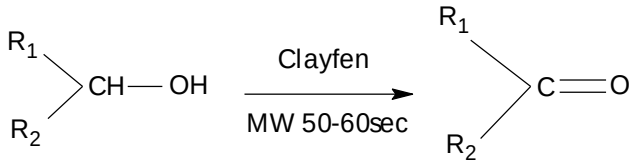
Metal-based reagents have been extensively used in organic synthesis. The utility of such reagents in the oxidative transformation is compromised due to their

inherent toxicity, cumbersome preparation, potential danger (ignition or explosion) in handling

of their complexes, difficulties in terms of product isolation and waste disposal. Introduction of metallic reagents on solid supports has circumvented some of these problems and provided an attractive alternative in organic synthesis because of the selectivity and associated ease of manipulation. Further, the immobilization of metals on the surface avoids their leaching into the environment.[42]

1.9.3.1.1 Selective and solvent-free oxidation with clayfen

A facile method for the oxidation of alcohols to carbonyl compounds has been reported using montmorillonite K-10 clay-supported [Iron(III) nitrate] (clayfen) under solvent-free conditions. The process is accelerated tremendously by exposure to microwave irradiation and the reaction presumably proceeds *via* the intermediacy of nitrosonium ions. Remarkably, no carboxylic acids are formed in the oxidation of primary alcohols. The experimental procedure simply involves mixing of neat alcohols with clayfen and a brief irradiation of the reaction mixtures in a microwave oven for 15–60 seconds in the absence of solvent. This extremely rapid, manipulatively simple, inexpensive and selective protocol avoids the use of excess solvents and toxic oxidants. Using clayfen [Iron(III) nitrate] in the solid state and in lesser amount, a rapid synthesis of carbonyl compounds in high yields has been achieved.[43]



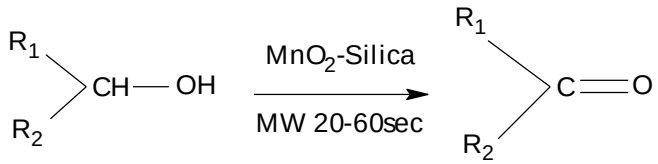
(87-96%)

R_1 = Ph, $4MeC_6H_4$, $4MeOC_6H_4$; R_2 = H

1.9.3.1.2 Activated manganese dioxide–silica

Using manganese dioxide–silica, an expeditious and high yield route to carbonyl compounds is developed. Benzyl alcohols are selectively

oxidized to carbonyl compounds using 35% MnO_2 'doped' silica under MW irradiation conditions.[44]

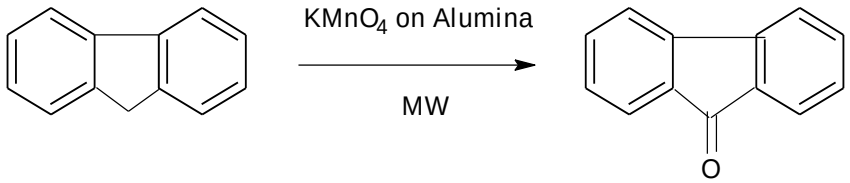


(67-96%)

R_1 = Ph, $4MeC_6H_4$, $4MeOC_6H_4$, Ph-CH=CH; R_2 = H

1.9.3.2 Oxidation of arenes with permanganate ($KMnO_4$)–alumina

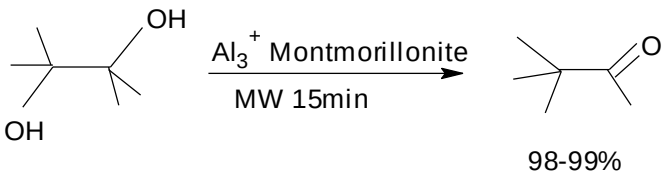
$KMnO_4$ impregnated alumina oxidises arenes to ketones within 10–30 minutes in solvent-free conditions using focused microwaves.[45]



1.9.4 Rearrangement reactions

1.9.4.1 Pinacol–pinacolone rearrangement

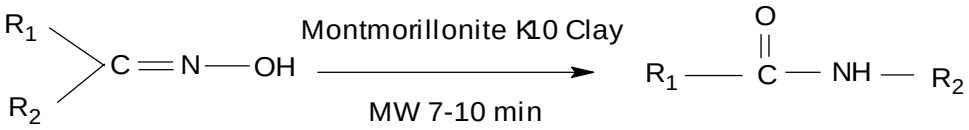
A solventless pinacol–pinacolone rearrangement using microwave irradiation has been achieved involving the irradiation of the *gem*-diols with Al^{3+}-montmorillonite K-10 clay for 15 minutes to afford the rearrangement product in excellent yields. These results are compared to conventional heating in an oil bath where the reaction times are too long (15 hours).[46]



98-99%

1.9.4.2 Beckmann rearrangement

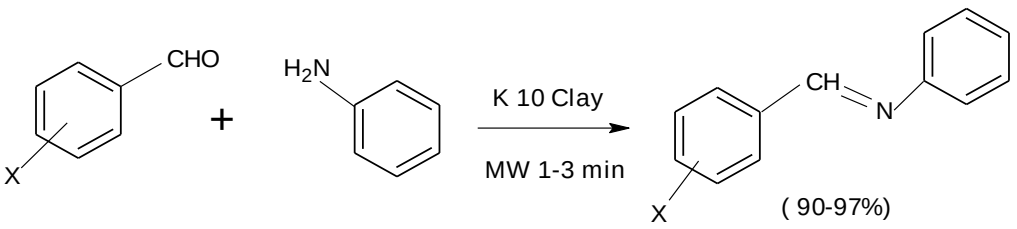
The Beckmann rearrangement of ketoximes with montmorillonite K-10 clay in 'dry' media in good yields has been reported.[47]



1.9.5 Condensation reactions

1.9.5.1 Synthesis of imines, enamines and nitroalkenes

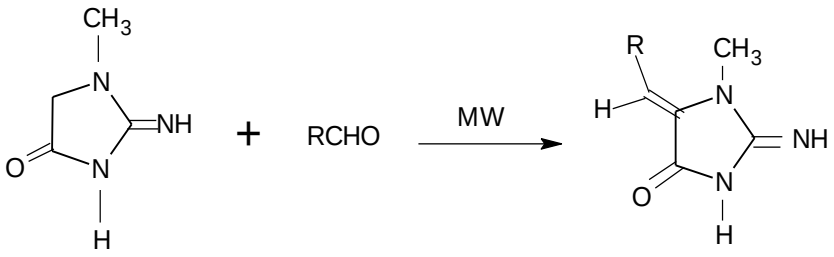
The driving force in the preparation of imines, enamines and nitroalkenes is the azeotropic removal of water from the intermediate, which is normally catalyzed by *p*-toluenesulfonic acid, titanium(IV) chloride, and montmorillonite K-10 clay. Conventionally, a Dean–Stark apparatus is used which requires a large excess of aromatic hydrocarbons such as benzene or toluene for azeotropic water elimination. Microwave-induced acceleration of such dehydration reactions using montmorillonite K-10 clay has been demonstrated in a facile preparation of imines and enamines *via* the reactions of primary and secondary amines with aldehydes and ketones, respectively.[48]



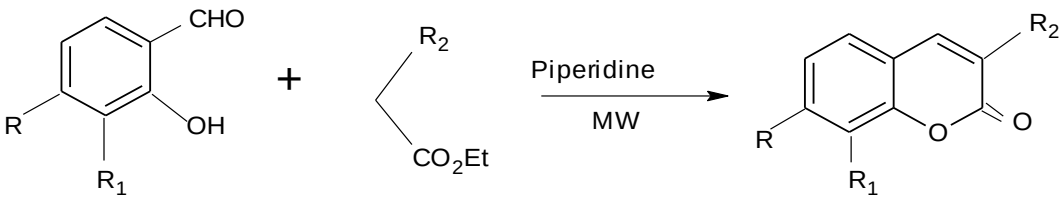
X = H, 2-OH, 4-OH, 4-Me, 4-OMe, 4-NMe_2

1.9.5.2 Knoevenagel condensation reactions—Coumarin synthesis

An expeditious Knoevenagel condensation of creatinine with aldehydes has been achieved using focused microwave irradiation (40–60 W) under solvent-free reaction conditions at 160–170 °C.[49]



The useful synthesis of coumarins *via* the microwave promoted Pechmann reaction has been extended to solventless systems wherein salicylaldehydes undergo Knoevenagel condensation with a variety of ethyl acetate derivatives under basic conditions (in piperidine) to afford coumarins.[50]

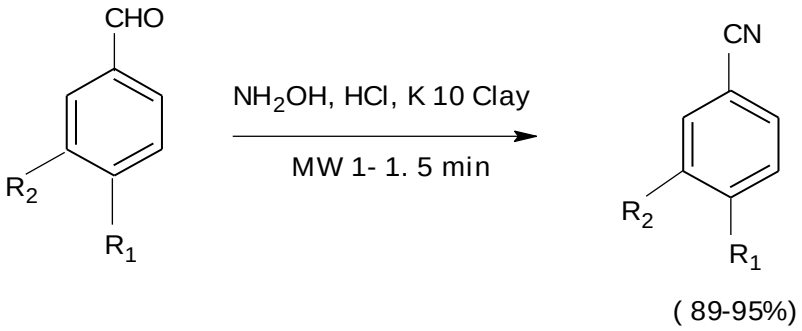


1.9.6 Miscellaneous reactions

1.9.6.1 Transformation of aromatic aldehydes to nitriles

The preparation of nitriles from aldehydes is an important chemical transformation.[51] The conventional methods entail the dehydration of aldoxime which is a time demanding process even for one-pot reactions. In the microwave-assisted method, hydroxylamine ‘doped’ on K-10 clay has been used to effect the above conversion in a one-pot synthesis using microwaves.[52] Arylaldehydes are rapidly converted into nitriles in good yields (89–95%) with hydroxylamine hydrochloride supported on montmorillonite K-10 clay in the absence of solvent. The reaction is a general one as exemplified by a variety of aldehydes that

undergo this facile conversion to afford high yields of the corresponding nitriles (89–95%) within a short microwave irradiation time (1–1.5 minutes). In the case of aliphatic aldehydes, however, only poor yields of nitriles (10–15%) are obtained with complex by-product formation.[53]



(89-95%)

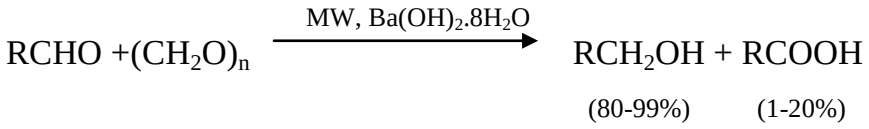
R_1 = H, R_2 = H, OMe, NO_2, OH, Br, Me

R_1 = R_2 = OMe

1.9.6.2 Conversion of aldehydes to alcohols—Solid state Cannizzaro reaction

The title reaction is the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt and is restricted to aldehydes that lack α-hydrogens and therefore can not undergo aldol condensation. Several investigations have been made on this oxidation–reduction reaction, which is usually carried out in homogeneous and strongly basic conditions.[54] The relative importance of the Cannizzaro reaction in synthetic organic chemistry decreased considerably after the discovery of lithium aluminium hydride, $LiAlH_4$, in 1946. The lower yields of the desired products have been another limitation of this reaction. However, the crossed Cannizzaro reaction,[55] using a scavenger and inexpensive paraformaldehyde to produce alcohol in higher yields, had been another choice prior to the introduction of hydride reducing agents. The reaction proceeds rapidly on a barium hydroxide, $Ba(OH)_2 \cdot 8H_2O$, surface which demonstrates the first application of this reagent in a solvent-free crossed Cannizzaro reaction.[56] In a typical experiment, a mixture of benzaldehyde (1mmol) and paraformaldehyde (2mmol) is mixed with barium hydroxide octahydrate (2mmol) and then irradiated in a microwave oven(100–110°C) or heated in an oil bath (100–110°C). In general, aldehydes bearing an electron

withdrawing substituent undergo reaction at a much faster rate than aldehydes with electron releasing groups appended.



Apart from this, a variety of organic reactions have been carried out under microwave irradiation with improved yields. These include the following reaction types - Alkylations,[57] Acetylations,[58] Asymmetric Reactions[59] Carbohydrates,[60] CO Insertions[61] Condensations,[62] Cyanations,[63] Cycloadditions,[64] Reactions Involving Ionic Liquids,[65] Michael Reactions,[66] Multicomponent Synthesis,[67] Photochemistry,[68] Polymerisation,[69] Solid-Phase Reactions,[70] and so on.[29]

1.10 Conclusions

Keeping in view the advantages of carrying out organic synthesis under microwave irradiation, the present work deals with the synthesis and synthetic conversion of an important class of organic compounds - Biscoumarins and their derivatives and a comparative account of the synthesis carried out under microwave and conventional conditions.

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Chapter 2

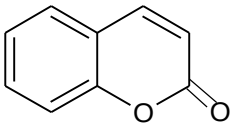
"Microwave-assisted biscoumarin Synthesis"

Abstract

"A convenient synthesis of various biscoumarins is described by condensing a series of aldehydes with 4-hydroxycoumarin under microwave conditions for the first time along with a comparative account of their syntheses under conventional conditions. The reactions have been carried out in solvent media as well as under solvent-free conditions. The reaction times have been shortened considerably with improvement in yield in comparison to classical methods and the adopted procedure provides an energy and time-saving protocol."

2.1 Introduction

Coumarins form an important group of naturally occurring organic compounds possessing enormous pharmacological,[1-4] industrial[5] and biological value[6]. The derivatives of coumarin usually occur as secondary metabolites present in seeds, roots and leaves of many plant species. Their functions though far from clear include plant growth regulators, fungistats and bacteriostats.[4] The parent coumarin bears the following structure.



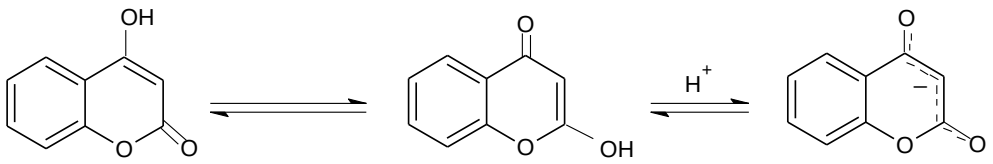
Coumarin nucleus

4-Hydroxycoumarin and its derivatives have long back been known for their anticoagulant,[7-9] antibacterial & antifungal[10-12] activities. In addition, certain derivatives are reported as antitumor[13,14] and anti-HIV agents.[15-17] Besides this, coumarins find diverse industrial applications as food additives and cosmetics,[6] laser dye media,[18,19] agrochemicals[6], dyes[20-23] as well as analytical reagents.[24-27] Biscoumarins, the bridge substituted dimers of 4-hydroxycoumarin have enormous potential as anticoagulants.[28-31]3,3'-Methylene-*bis*(4-hydroxycoumarin) commonly known as dicoumarol occurs naturally in Moldy clover.[8] It is the haemorrhagic agent responsible for the spoiled sweet clover disease of cattle[8]and has also been employed for the prevention and treatment of thrombosis.[32,33] Dicoumarol is also the starting material for the synthesis of various furocoumarins and benzopyrans.[34]

A number of biscoumarins have also been found to be urease inhibitors[35-37]. Urease is an enzyme that decomposes urea to ammonia and carbondioxide and is directly involved in the formation of renal stones causing various urological disorders. Additionally, bacterial ureases present in the soil devoid the agricultural area of nitrogenous nutrients and the toxicity of ammonia along with an increase in the level of CO_2 in the atmosphere poses a threat to both animal and plant kingdom.

2.2 Theoretical

4-Hydroxycoumarin molecule, a member of the coumarin group has several interesting features. It is an acid of about the same strength as acetic acid and is not simply a β-ketolactone but also shows properties of a carboxylic acid and possesses both electrophillic and nucleophillic properties. This is because of the conjugated hydroxycarbonyl structure. It is this hydroxycarbonyl structure that accounts for the two strong absorption bands near 1700 cm^{-1} and the absence of an –OH band in IR spectrum. It undergoes a coumarin-chromone tautomerism represented as under. However, in solid state, it exists in the coumarin structure.[38.39]



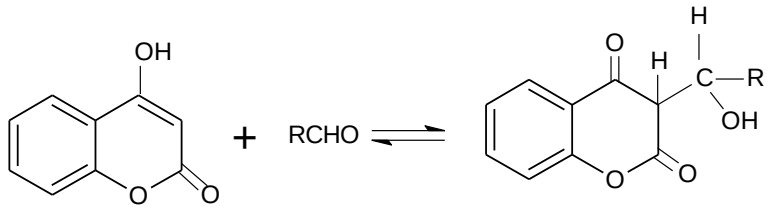
Coumarin structure **Chromone structure**

Coumarin –Chromone tautomerism of 4-hydroxycoumarin

The reaction of 4-hydroxycoumarin with aldehydes to yield biscoumarins is a Michael type reaction. In this reaction, two molecules of 4-hydroxycoumarin react with one molecule of the aldehyde to form bis(4-hydroxycoumarin). The mechanism has been proposed as under[40].

Step I.

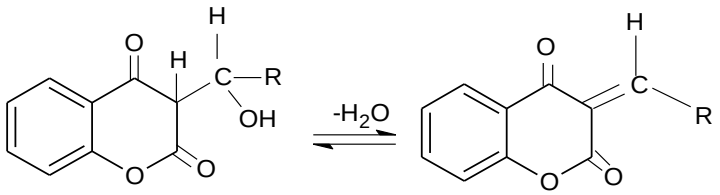
An aldol condensation between 4-hydroxycoumarin (I) and the aldehyde (II) to yield the aldol (III).



I II III

Step II.

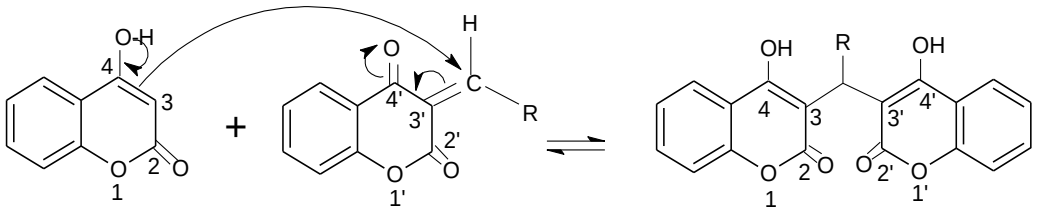
Dehydration of the aldol(III) to yield an α,β-unsaturated ketone(IV).



III IV

Step III.

Condensation of the ketone with another molecule of (I) by the Michael reaction to give the final product- the biscoumarin(V).



I IV V

Biscoumarins are colorless crystalline solids. Due to the presence of enolic hydroxyl groups[38], they dissolve in alkali to form dibasic salts and are readily methylated by diazomethane and form diesters. Heating with alkali opens the lactone rings and subsequent decarboxylation yields 1,5-diketones. Heating with aniline at 180^0C produces the aniline derivative of 4-hydroxycoumarin. They can also be dehydrated to form 4-substituted 1,4-pyrans, the loss of water occurring through the enolic hydroxyls at positions 4 and 4′.[34]

Biscoumarins have generally been synthesized by refluxing 4-hydroxycoumarin and aldehydes in ethanol for long hours[41-43]. Successful attempts have also been made to condense 4-hydroxycoumarin with various aromatic, heterocyclic and *α,β*-unsaturated aldehydes to get corresponding dicoumarols using different catalysts and media[44]. Sullivan et al[41] reported the synthesis of various biscoumarins by refluxing 4-hydroxycoumarin with various aldehydes in ethanol

requiring hours of reflux with average yields. Since then, biscoumarins are being synthesized using various aromatic and heterocyclic aldehydes by this method.[41] In the above reported procedures, the product appears as insoluble residue from the reaction mixture which is filtered, washed with alcohol and crystallized from the appropriate solvent. The condensation of 4-hydroxycoumarin with *α, β*-unsaturated aldehydes at room temperature to form biscoumarins in the presence of ethylene diammonium acetate in methanol has also been reported[44]. The synthesis requires hours of stirring at room temperature with a tedious workup in certain cases. Same authors have also reported the synthesis of various 3,3'-(arylidene)-*bis*(4-hydroxycoumarin) achieved through the above procedure.[43] Although yields ranged from 73-90% , the reaction requires days of stirring a room temperature. Piperidine has also been employed as a catalyst for the condensation of 4-hydroxycoumarin and various aldehydes to yield the corresponding biscoumarins[35-37]. This procedure involves stirring of reactants at room temperature for 4 hours followed by aqueous work up, and average to high yields have been reported. Glacial acetic acid has also been employed as a medium for the synthesis of various biscoumarins from 4-hydroxycoumarin and aldehydes[45]. The procedure reports varying yields and reaction times. Molecular iodine has recently been employed as a catalyst for synthesis of various biscoumarins in water while stirring the reaction mixture at 100^0 C for 20-30 minutes [46]. The aqueous work up has been followed by chromatographic purification of biscoumarins. In a recent report, synthesis of various biscoumarins has been achieved in good yields on KF-montmorillonite in dimethyl formamide under conventional conditions.[47]

2.3 Importance of present work

Since the concept of green chemistry is gaining momentum in the field of organic synthesis,[48-49] emphasis is being laid to devise new methods and procedures of synthesizing potentially important compounds in an eco-friendly environment. Keeping into consideration the enormous pharmacological potential of biscoumarins, it is of utmost importance that their synthesis should be achieved by a simple, effective and a time-saving method.

Although much work has been done on the synthesis of biscoumarins under

classical conditions, the use of microwave dielectric heating for their synthesis is novel. Since the first use of microwave ovens in organic synthesis,[50,51] this technique has blossomed as an eco-friendly procedure with the advantages of improved yields, easy work-ups and considerable shortening of reaction times. Several coumarins have been synthesized under microwave irradiation under solvent-free conditions and enhancements in yield and time reduction have been reported.[52-62]However, there is no report of synthesis of biscoumarins under these conditions.

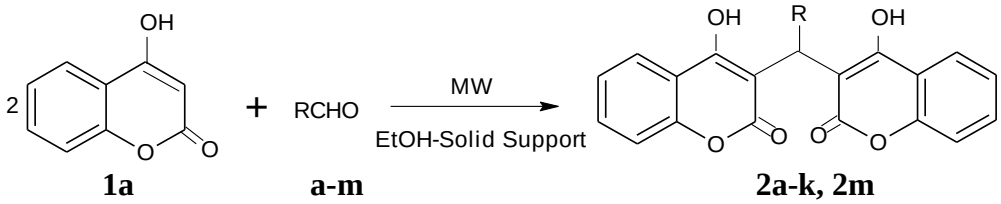
In this background, we report herein the first microwave assisted synthesis of biscoumarins with the advantages of minimum solvent usage, improved yields, and shortened reaction times without the usage of catalytic reagents employed in many conventional procedures. This efficient eco-friendly procedure provides a green chemistry approach for the synthesis of biscoumarins.

2.4 Results and discussion

2.4.1 General study

For the convenient synthesis of biscoumarins, formaldehyde and a range of aromatic aldehydes including an α, β-unsaturated and a heterocyclic aldehyde were condensed with 4-hydroxycoumarin. The reactions were carried out in solvent media (ethanol) as well as under solvent-free conditions (silica-gel supported) in the molar ratio of 1:2 taken an open vessel and irradiated in a multimode domestic microwave oven at the corresponding power and time as shown in *table* 1 and 2. Optimum irradiation times were precisely achieved but the reaction was carried out with intervals of 30 seconds in case of those involving liquid media to avoid solvent loss and bumps due to rapid rise in temperature. In case of solvent-free procedure, irradiation intervals were of one minute duration. Reactions were monitored periodically with the help of thin layer chromatography. The problems encountered while performing the reactions using solvent were easily overcome by solvent-free technique and the yields obtained were almost quantitative. However, in case of reactions in ethanol, yields get affected. This could be due to the solvent-microwave interaction in which heat transfer takes place from the solvent to the reactants confirming the observations made by various authors.[63,64] However, the general advantage of the procedure is

evident as considerably shorter time is required under microwave irradiation than reported so far for the synthesis of biscoumarins.

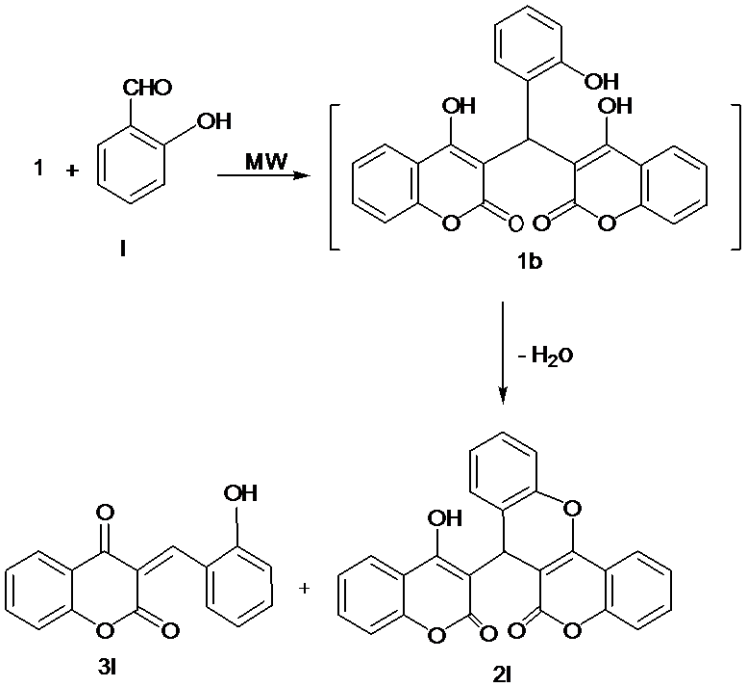


1a **a-m** **2a-k, 2m**

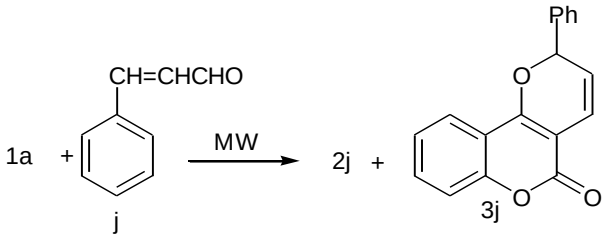
Scheme I. *Synthesis of biscoumarins from the condensation 4-hydroxycoumarin and various aldehydes under microwave-assisted conditions.*

a *Formaldehyde*
b *Benzaldehyde*
c *2-Chlorobenzaldehyde*
d *3-Chlorobenzaldehyde*
e *4-Chlorobenzaldehyde*
f *2-Nitrobenzaldehyde*
g *3-Nitrobenzaldehyde*
h *4-Nitrobenzaldehyde*
i *4-Methoxybenzaldehyde*
j *Vanillin*
k *Furfural*
l *salicyldehyde*
m *cinnamaldehyde*

The reaction of salicylaldehyde with 4-hydroxycoumarin deserves a special attention. The biscoumarin is never formed as reported in literature also.[41] Dehydration of the biscoumarin intermediate takes place because of the close vicinity of two hydroxyl groups to give the dehydration product along with a product resulting from 1:1 condensation of **1a** and **m** (*Scheme II*). Higher irradiation times lead to an increase in the yield of **2m** than **3m** whereas at lower irradiation times, **3m** predominates. This observation agrees well with the classical procedure.[41] Minor by-product(**3j**) was also formed through 1:1 condensation of **1a** and **j** [44]*(Scheme III)* . This clearly indicates that microwaves do not affect the mechanism of a reaction but the procedure is governed by the same laws as in classical chemistry. However enhanced effects result from the pattern of interaction between the reactants and the energy - a direct *insitu* generated heat in case of microwave irradiation and indirect conventional heat transfer in case of classical procedure.



Scheme II. *Dehydration of biscoumarin intermediate* ***(1b)*** *from salicyldehyde along with the formation of by-product.*



Scheme III. *By-product (**3j**) from cinnamaldehyde along with the corresponding biscoumarin.*

2.4.2 Comparative study

A comparison of microwave-assisted synthesis of biscoumarins from aromatic aldehydes with those carried out under conventional conditions has been drawn in *table* 4. The reactions were irradiated upto 5 minutes and a power level of 75% to monitor an exact comparison in terms of yields. The yields of biscoumarins for three different concentrations of 4-hydroxycoumarin and the corresponding aldehyde (1.5:0.77, 3:1.5,

6:3mmol) were hence obtained. For the same concentrations of 4-hydroxycoumarin and the corresponding aldehydes, more or less same yields were obtained under conventional and microwave conditions when the reactions were carried out in solvent media except that the reaction times were considerably shortened (*Fig. 1-6*). The reason as postulated by various authors is that ethanol being highly polar interacts more with microwave irradiation than the reactants[64] and consequently heat generated under microwave conditions gets transferred from the solvent to the reactants through convection as it happens in conventional heating. However, the exceptional result obtained in case of **2g** contradicts this argument (*table 4*). Getting high yield in solvent media in this case may be due to the heterogeneous field generated inside the multimode oven. Superheating effect in case of polar solvents under microwave irradiation may also contribute to this kind of results.[65] Such situations can be minimized using a monomode oven which produces a homogeneous field. Since the results obtained, when the reactions are carried out in liquid phase lack consistent reproducibility, efforts were made to carry them out under solvent-free conditions under which improved and consistent results were obtained (*table 2*). The direct interaction of microwaves with the reactants in solvent-free conditions gives better results as compared to the one in which the reactions have been carried out in solvent media. Exception being the case of **2g, 2i** and **2j** where the yields under solvent media were more than the yields obtained under solvent-free conditions. This may be as a result of uneven irradiation of the reaction mixture leading to temperature difference or "*hot spots*" in various parts of the reaction vessel [64]. Such temperature gradients may be minimized if a microwave oven with a provision for stirring the reaction mixture is used.

A study of the effect of concentration of reactants on the yields of the corresponding biscoumarins under solvent-free conditions has been shown in table 5. The increase in the concentration of reactants has a significant effect on the yield in general as indicated in the table. Two-thirds of the reactions show an increase in yield on increasing the amount of reactants and exceptionally high yields were obtained when 4-hydroxycoumarin and aldehydes **f, g and j** were used in 6:3mmol ratio. This indicates that the percent

conversion of reactants into products under solvent-free microwave conditions gets increased in most cases when the concentration of reactants is increased.

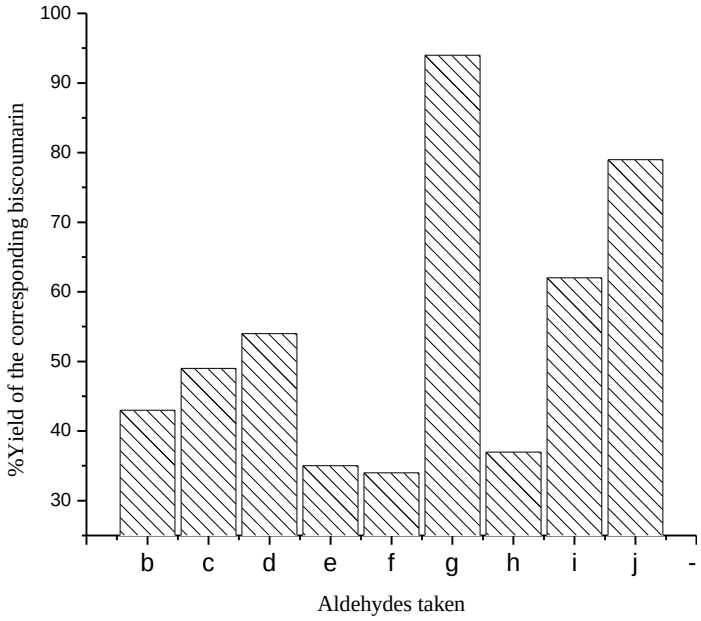


Fig. 1. Plot of percent yield of the corresponding biscoumarin vs the aldehyde with a 2:1 molar ratio of 4-hydroxycoumarin and aldehyde (3:1.5mmol) in ethanol under microwave irradiation.

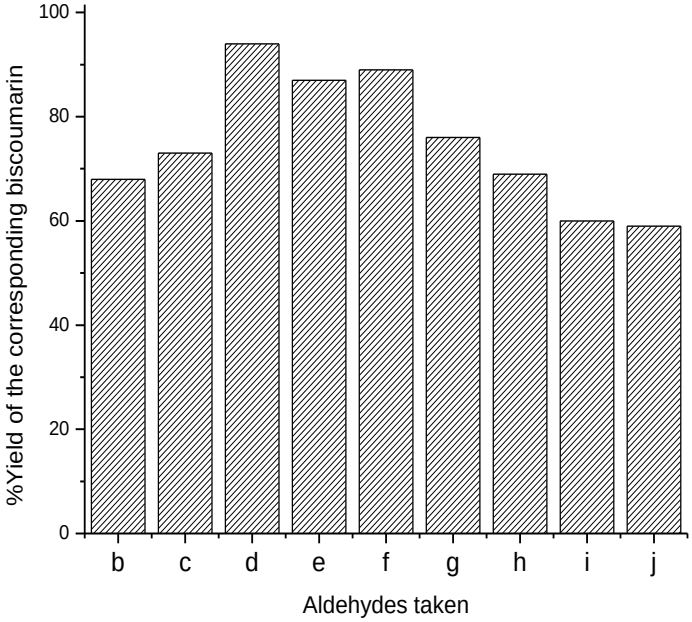


Fig. 2. Plot of percent yield of the corresponding biscoumarin vs the aldehyde with a 2:1 molar ratio of 4-hydroxycoumarin and aldehyde (3:1.5mmol) under solvent-free (silica) microwave irradiation.

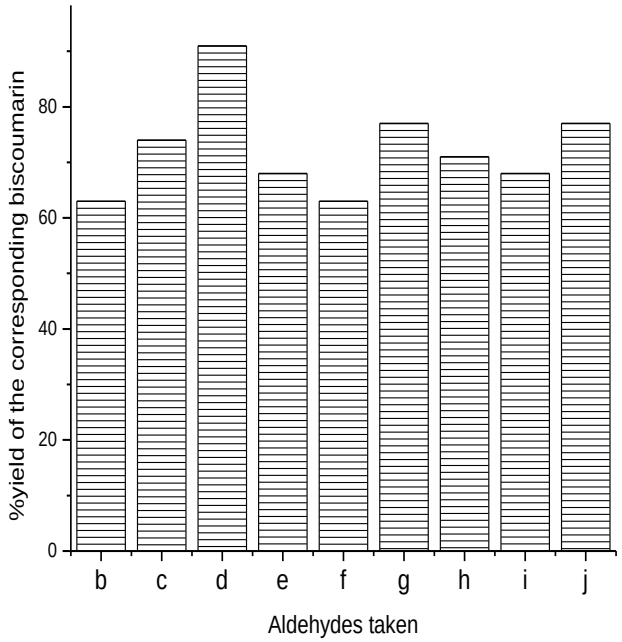


Fig. 3. Plot of percent yield of the corresponding biscoumarin vs the aldehyde with a 2:1 molar ratio of 4-hydroxycoumarin and aldehyde (1.54:0.77mmol) under solvent-free (silica) microwave irradiation.

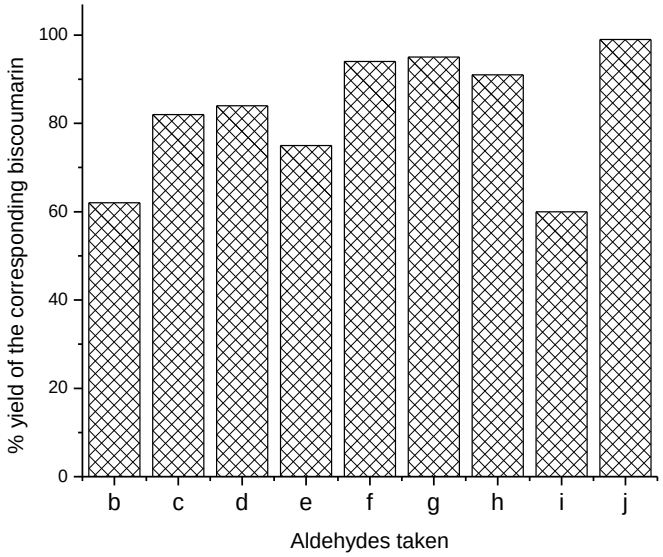


Fig. 4. Plot of percent yield of the corresponding biscoumarin vs the aldehyde with a 2:1 molar ratio of 4-hydroxycoumarin and aldehyde(6:3mmol) under solvent-free(silica) microwave irradiation.

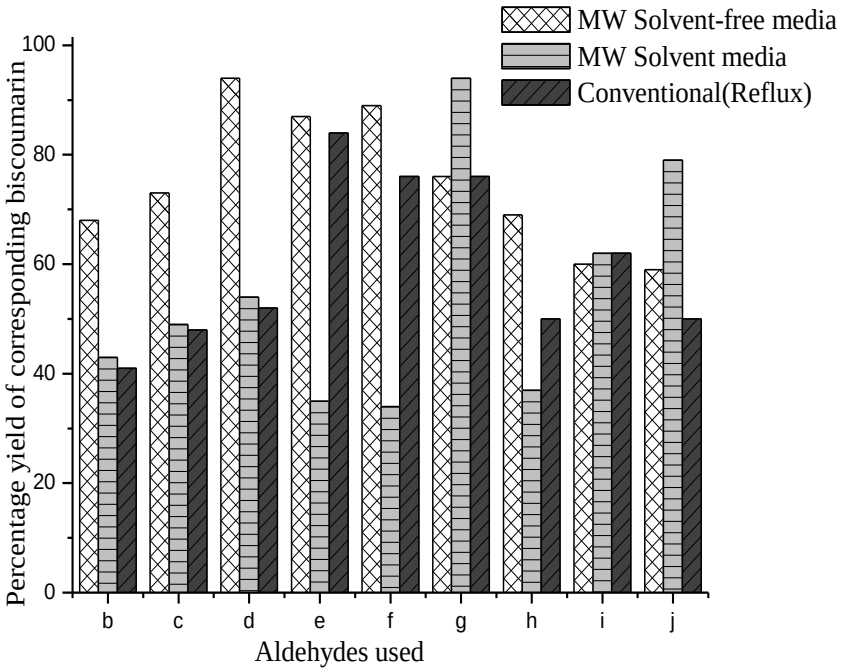


Fig.5. *Clubbed graph showing the comparative account of percentage yields of biscoumarins from 4-hydroxycoumarin and corresponding aldehydes taken in a 3:1.5 mmol ratio under three different conditions.*

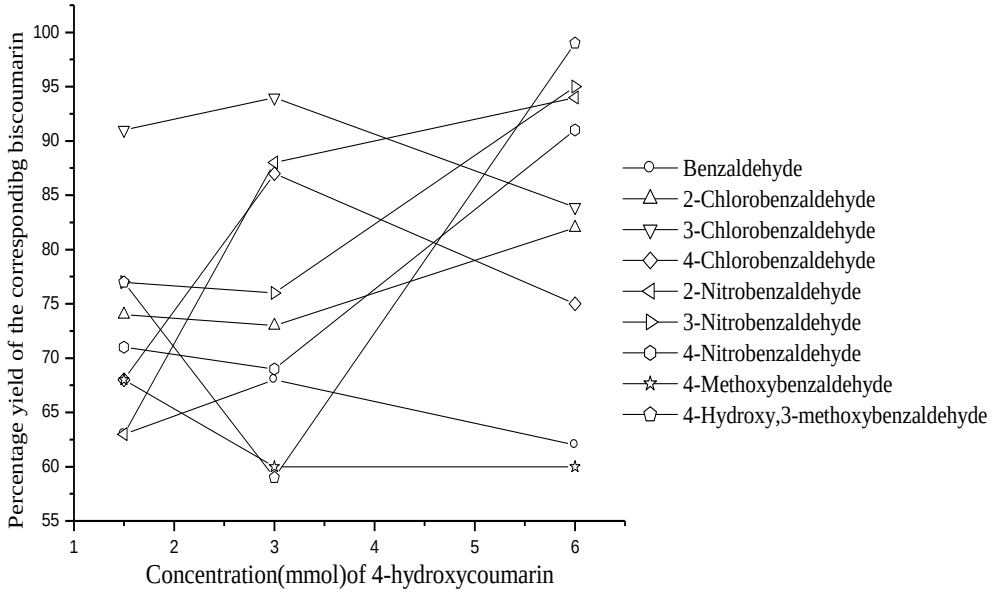


Fig. 6. Percent yield of the corresponding biscoumarin at three different concentrations of the coumarin (1.54,3.00,6.00mmol) and the corresponding aldehyde in 2:1 molar ratio under solvent-free microwave irradiation.

Table 1. *Synthesis of various biscoumarins under microwave irradiation.Error ±2*

1a mmol	2(a-k) mmol	R	Time Δ hrs	Time MW min	Product	Yield (%)Δ	Yield[a] (%)MW
3.10	2.30[2]	H	3	3	**2a**	77	83[b]
3.10	1.50[1]	C_6H_5	12	2	**2b**	78	86[b]
3.10	2.30[2]	$2ClC_6H_4$	3	4	**2c**	81	71[c]
3.10	2.30[2]	$3ClC_6H_4$	1	1	**2d**	90	99[c]
3.10	2.30[2]	$4ClC_6H_4$	12	3	**2e**	87	80[c]
3.10	1.50[1]	$2NO_2C_6H_4$	6	4*	**2f**	76	82[c]
3.10	1.50[1]	$3NO_2C_6H_4$	5	4*	**2g**	76	82[c]
3.10	1.50[1]	$4NO_2C_6H_4$	10	3*	**2h**	50	62[c]
3.10	1.80[3]	$4CH_3OC_6H_4$	12	4	**2i**	86	85[c]
3.10	1.50[1]	$4OH,3CH_3OC_6H_3$	6	8	**2j**	43	97[c]
3.10	1.50[1]	2-Furanyl	3	3	**2k**	27	38[c]

[*]Solvent-free; [a]combined isolated yield for 2-3 runs in case of reactions in ethanol; [b]50% power level; [c] 75% power level; [1]2:1 ratio of coumarin and aldehyde; [2]2:1.5 ratio of coumarin and aldehyde; [3]2:1.25 ratio of coumarin and aldehyde.

Table 2. *Condensation products of 4-hydroxycoumarin with salicylaldehyde and cinnamaldehyde.* Error ±2

1a (mmol)	2(l,m) (mmol)	R	Time Δ (hrs)	Time MW (min)	Product	Yield(%) Δ	Yield[a] (%)MW
3.10	1.50	$2\text{-}OHC_6H_4$	5	8*	**2l**	86	59[c]
					3l[d]	10	38
1.20	0.60		2	4	**2l**	20	30[c]
					3l	34	66
3.10	1.50	$CH{=}CH\text{-}C_6H_4$	3	4	**2m**	45	52[c]
					3m[d]	5	7[c]

[d]by-products from 1:1 ratio of reactants.

Table 3. *Percentage yield of biscoumarins* ***2b-j*** *under microwave conditions in both solvent as well as solvent-free media at a 3:1.5 mmol ratio of 4-hydroxycoumarin and the corresponding aldehydes.(Error ±2).*

Product	R	Solvent media			
		Time(min)	Yield (%)	Time(min)	Yield (%)
2b	C_6H_5	2	86	6	71
2c	$2ClC_6H_4$	4	49	6	88
2d	$3ClC_6H_4$	1	98	4	95
2e	$4ClC_6H_4$	3	90	5	85
2f	$2NO_2C_6H_4$	5	65	4	81
2g	$3NO_2C_6H_4$	6	86	6	87
2h	$4NO_2C_6H_4$	4	75	6	81
2i	$4CH_3OC_6H_4$	3	80	7	86
2j	$4OH,3OCH_3C_6H_3$	3	33	8	97

Table 4 . *Percentage yield of the corresponding biscoumarin under conventional and microwave irradiation at constant concentrations of 4-hydroxycoumarin and the aldehydes (3:1.5 mmol) in a 2:1 molar ratio(Error ±2).*

R	Conventional (Δ)		Microwave Yield(%)[1]	
	Time(hrs)	Yield(%)	Solvent[2]	Solvent-free[3]
C_6H_5	5	41	43	68
$2ClC_6H_4$	7	48	49	73
$3ClC_6H_4$	6	52	54	94
$4ClC_6H_4$	5	84	35	87
$2NO_2C_6H_4$	6	76	34	89
$3NO_2C_6H_4$	5	76	94	76
$4NO_2C_6H_4$	6	50	37	69
$4CH_3OC_6H_4$	7	62	62	60
$4OH,3OCH_3C_6H_3$	7	50	79	59

[1]Irradiation time:-5 min, Power:-75 %; [2]Ethanol; [3]Silica Gel.

Table 5. *Yield of the corresponding biscoumarin at three different concentrations of 4-hydroxycoumarin and the corresponding aldehyde in a 2:1 molar ratio under solvent-free microwave irradiation at constant time(5 min) and power(75%).*[#] Error ±2

1(mmol)	b-j(mmol)	R	Product	Yield(%)[#]
1.5	0.77	C_6H_5	**2b**	63
3	1.5			68
6	3			62
1.5	0.77	$2ClC_6H_4$	**2c**	74
3	1.5			73
6	3			82
1.5	0.77	$3ClC_6H_4$	**2d**	91
3	1.5			94
6	3			84
1.5	0.77	$4ClC_6H_4$	**2e**	68
3	1.5			87
6	3			75
1.5	0.77	$2NO_2C_6H_4$	**2f**	63
3	1.5			88
6	3			94
1.5	0.77	$3NO_2C_6H_4$	**2g**	77
3	1.5			76
6	3			95
1.5	0.77	$4NO_2C_6H_4$	**2h**	71
3	1.5			69
6	3			91
1.5	0.77	$4CH_3OC_6H_4$	**2i**	68
3	1.5			60
6	3			60
1.5	0.77	$4OH,3OCH_3C_6H_3$	**2j**	77
3	1.5			59
6	3			99

2.5 General procedure for the synthesis of 3,3′-arylidene-*bis*(4-hydroxy-1-benzopyran-2-one)

2. 5. 1 Under microwave irradiation

2.5.1.1 *Solvent media.*

4-Hydroxycoumarin and the corresponding aldehyde in 2:1 molar ratio were dissolved in minimum amount of ethanol. The reaction mixture was taken in a glass beaker covered with a glass lid and irradiated under the microwave oven at the corresponding times shown in table 1. The product appearing as an insoluble residue was filtered and washed with ethanol, dried and crystallized from the appropriate solvent to afford the desired products. Further workup of the mother liquor afforded more of the products.

In case of the condensation of **1a** with **m**, the green yellow crystals of **3m** formed after microwave exposure were filtered and washed with alcohol and the mother liquor upon concentration gave the white crystals of **2m**. Further concentration of the mother liquor gave more of **2m** and **3m**. When the irradiation times were increased, **2m** crystallized out first from the reaction mixture and work up of mother liquor yielded **3m**.

2.5.1.2 Solvent-free media

4-Hydroxycoumarin and the corresponding aldehyde in 2:1 molar ratio were adsorbed on silica-gel (60-120 mesh) and irradiated under the microwave oven for the time indicated in table 1. The mixture was eluted with acetone and concentrated when the product precipitated out. This was filtered and washed with alcohol to remove any unreacted **1a**, dried and crystallized from the appropriate solvent.

2.5.2 Under reflux

A mixture of 4-hydroxycoumarin and the corresponding aldehyde were dissolved in 20ml ethanol in the molar ratios shown in table and were refluxed on a water bath for the corresponding time. The insoluble residue formed was filtered, washed with ethanol and dried and crystallized from the appropriate solvent.

2.6 Experimental

General study

The melting points were taken in open capillaries using the electrothermal method on a *Labotech/Perfit* instrument and are uncorrected. Infrared spectra were recorded on a *Perkin Elmer* 2000-FT spectrometer. Ultravoilet spectra were measured in chloroform (spectral grade) as the solvent on a *Schimadzu* UV-1650PC UV/Visible

Spectrophotometer. ^{1}H-NMR spectra were recorded on a 200MHz instrument using $CDCl_3$ as the solvent and TMS as the internal standard. All the solvents and chemicals used were of AR grade and 4-hydroxycoumarin in particular was of spectrochemical grade. All the reactions were irradiated in a multimode *Sharp Carousel*^{TM} microwave oven.

Reaction of 4-hydroxycoumarin(1a) with formaldehyde(a) to yield 3,3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2a)

Under microwave conditions

A mixture of 4-hydroxycoumarin (0.5gms) and formaldehyde (0.043ml) dissolved in 5ml ethanol was taken in a 50ml beaker and irradiated in the microwave oven for 3 minutes at medium power (50% power level). The insoluble residue formed was filtered, washed with ethanol, dried and crystallized from benzene/chloroform:methanol as white star-shaped crystals of 3,3'-methylene-*bis*(4-hydroxy-1H-benzopyran-2-one) or dicoumarol. Yield = 0.43gms

Under conventional conditions

A mixture of 4-hydroxycoumarin (0.5gms) and formaldehyde (0.043ml) in 20ml ethanol was refluxed on a water bath for 3 hours. The insoluble residue formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystals. Yield = 0.40gms

Spectral data of 3,3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2a

^{1}H-NMR(200 MHz, $CDCl_3$): δ2.7, 2H, s, (H-11); 7.3-8.1, m, 8H(8×Ar-CH)

IR(KBr,cm^{-1}): 1649.6, 1601.5, 1569.2, 1348.2, 1311.5, 1111.1, 773.3

MS(m/z): 336(ESI); **UV(λ_{max}), $CHCl_3$:** 312 nm; **M.Pt.** 275-77 ^{o}C

Reaction of 4-hydroxycoumarin(1a) with benzaldehyde (b) to yield 3,3'-phenylmethylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2b)

Under microwave conditions.

A mixture of 4-hydroxycoumarin(0.5gms) and benzaldehyde(0.17ml) dissolved in 5ml ethanol was taken in a 50ml beaker and irradiated in the microwave oven for 2 minutes at medium power(50% power level). The insoluble residue formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. Yield = 0.56gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and benzaldehyde(0.17ml) in 20ml ethanol was refluxed on a water bath for 12 hours. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from from chloroform:methanol. Yield = 0.51gms

Spectral data of 3,3'-phenylmethylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2b

^{1}H-NMR(200 MHz, $CDCl_3$): δ6.2 IH,s,(H-11); 7.2-8.3,13H,m,(13×Ar-CH);

IR(KBr,cm^{-1}): 1661.1, 1618,1604.7, 1569.5, 762.2l;

MS(m/z): 412(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 215 ^oC

Reaction of 4-hydroxycoumarin(1a) with 2-chlorobenzaldehyde(c) to yield 3,3'-(2-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 2-chlorobenzaldehyde(0.25ml) dissolved in 5ml ethanol was taken in a 50ml beaker and irradiated in the microwave oven for 4 minutes at medium-high power(75% power level). The insoluble residue formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. Yield = 0.55 gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 2-chlorobenzaldehyde(0.25ml) in 20ml ethanol was refluxed on a water bath for 3 hours

. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.63gms

Spectral data of 3,3'-(2-chlorobenzylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2c

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.2, IH, s,(H-11); 7.3-8.2,12H,m,(12×Ar-CH);
IR(KBr,cm^{-1}): 1648.3, 1618.4, 1601.7, 1565.7, 767.9
MS(m/z): 445.9(ESI); **UV(λ_{max}) , $CHCl_3$:** 312 nm; **M.Pt.** 198-199 ^oC

Reaction of 4-hydroxycoumarin(1a) with 3-chlorobenzaldehyde(d) to yield 3,3'-(3-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2d)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 3-chlorobenzaldehyde(0.25ml) dissolved in 5ml ethanol was taken in a 50ml beaker and irradiated in the microwave oven for 4 minutes at medium-high power(75% power level). The insoluble residue formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. Yield = 0.77 gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 3-chlorobenzaldehyde(0.25ml) in 20ml ethanol was refluxed on a water bath for 3 hours. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.70 gms

Spectral data of 3,3'-(3-chlorobenzylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2d

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.1, IH, s,(H-11); 7.2-8.1,12H,m,(12×Ar-CH);
IR(KBr,cm^{-1}): 1663.9, 1617.7, 1568.5, 762.;
MS(m/z): 445.9(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 222-224 ^oC

Reaction of 4-hydroxycoumarin(1a) with 4-chlorobenzaldehyde(e) to yield 3,3'-(4-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2e)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 4-chlorobenzaldehyde(0.32gms) dissolved in 5ml ethanol was taken in a 50ml beaker and irradiated in the microwave oven for 4 minutes at medium-high power(75% power level). The insoluble residue formed was filtered, washed with ethanol, dried and crystalline from chloroform:methanol as white crystalline product. Yield = 0.62gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 4-chlorobenzaldehyde(0.32gms) in 20ml ethanol was refluxed on a water bath for 3 hours. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.68 gms

Spectral data of 3,3'-(4-chlorobenzylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2e

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.1, IH, s,(H-11); 7.2-8.1,12H, m,(12×Ar-CH);
IR(KBr,cm^{-1}): 1663.9, 1617.7, 1568.5, 762.;
MS(m/z): 445.9(ESI); **UV(λ_{max}), $CHCl_3$:** 312 nm; **M.Pt.** 222-224 ^oC

Reaction of 4-hydroxycoumarin(1a) with 2-nitrobenzaldehyde(f) to yield 3,3'-(2-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2f)

Under microwave conditions

A mixture of 4-hydroxycoumarin (0.5gms) and 2-nitrobenzaldehyde (0.23gms) dissolved in ethanol was adsorbed on silica-gel and irradiated in the microwave oven for 4 minutes at medium-high power(75% power level). The insoluble residue formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. Yield = 0.57gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 2-nitrobenzaldehyde(0.23gms) in 20ml ethanol was refluxed on a water bath for 6 hours. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.53 gms

Spectral data of 3,3'-(2-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2f

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.7, IH, s,(H-11); 7.2-8.1,12H,m,(12×Ar-CH)

IR(KBr,cm^{-1}): 1653.87, 1616.2, 1567.9, 762.6

MS(m/z): 456.9(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 200-202 ^oC

Reaction of 4-hydroxycoumarin(1a) with 3-nitrobenzaldehyde(g) to yield 3,3'-(3-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2g)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 3-nitrobenzaldehyde(0.23gms) dissolved in ethanol was adsorbed on silica gel and irradiated in the microwave oven for 4 minutes at medium-high power(75% power level). The insoluble residue formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. Yield = 0.57gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 3-nitrobenzaldehyde(0.23gms) in 20ml ethanol was refluxed on a water bath for 5 hours. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.53 gms

Spectral data of 3,3'-(3-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2g

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.2, IH, s,(H-11); 7.2-8.2,12H,m,(12×Ar-CH)

IR(KBr,cm^{-1}): 1657.8, 1617.6, 1567.6, 762.9

MS(m/z): 457(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 212-215 ^oC

Reaction of 4-hydroxycoumarin(1a) with 4-nitrobenzaldehyde(h) to yield 3,3'-(4-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2h)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 4-nitrobenzaldehyde(0.23gms) dissolved in ethanol was adsorbed on silica-gel and irradiated in the microwave oven for 3 minutes at medium-high power(75% power level). The insoluble orange residue formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. Yield = 0.43gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 4-nitrobenzaldehyde(0.25ml) in 20ml ethanol was refluxed on a water bath for 10 hours. The insoluble orange residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.35 gms

Spectral data of 3,3'-(4-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2h

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.2, IH, s,(H-11); 7.2-8.2,12H,m,(12×Ar-CH)

IR(KBr,cm^{-1}): 1654.5, 1617.8, 1563.7, 782.9

MS(m/z): 457(ESI); **UV(λ_{max}), $CHCl_3$:**312nm; **M.Pt.** 242-245 ^oC

Reaction of 4-hydroxycoumarin(1a) with 4-methoxybenzaldehyde(i) to yield 3,3′-(4-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2i)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 4-methoxybenzaldehyde(0.23ml) dissolved in 5ml ethanol was taken in a 50ml beaker and irradiated in the microwave oven for 4 minutes at medium-high power(75% power level). The insoluble residue

formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. Yield = 0.62gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 4-methoxybenzaldehyde(0.23ml) in 20ml ethanol was refluxed on a water bath for 12 hours. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.63 gms

Spectral data of 3,3'-(4-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2i

^{1}H-NMR(200 MHz, $CDCl_3$): δ 3.9, 3H, s,(OCH_3); 6.2,IH,s,(H-11);6.9-8.2, 12H,m,(12×Ar-CH)

IR(KBr,cm^{-1}): 1654.3, 1636.3, 1560.4, 781.8

MS(m/z): 442(ESI); **UV(λ_{max}), $CHCl_3$:** 312 nm ; **M.Pt.** 238-240 ^oC

Reaction of 4-hydroxycoumarin(1a) with 4-hydroxy,3-methoxybenzaldehyde (vanillin)(j) to yield 3,3'-(4-hydroxy,3-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2j)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and vanillin(0.23gms) dissolved in 5ml ethanol was taken in a 50ml beaker and irradiated in the microwave oven for 8 minutes at medium-high power(75% power level). The insoluble residue formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. Yield = 0.68gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and vanillin(0.23gms) in 8-10ml ethanol was refluxed on a water bath for 6 hours. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.30 gms

Spectral data of 3,3'-(4-hydroxy,3-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2j

^{1}H-NMR(200 MHz, $CDCl_3$): δ6.8-7.9, m, 11H(11×Ar-CH), 8.1, 4-OH; 6.1,s,2(OH), 3.98, s, OCH_3; 5.6,s, CH.

IR(KBr,cm^{-1}): 1669.6, 1617.6, 1560.4, 1514.8, 768.1

MS(m/z): 458(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 212-15^oC

Reaction of 4-hydroxycoumarin(1a) with 2-furfural(k) to yield 3,3'-(2-Furanyl)-bis(4-hydroxy-1H-benzopyran-2-one)-(2k)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 2-furfural (0.13ml) dissolved in 5ml ethanol was taken in a 50ml beaker and irradiated in the microwave oven for 3 minutes at medium-high power(75% power level). The insoluble residue formed initially after one and a half minute of irradiation was filtered, washed with ethanol, dried and the mother liquor was irradiated further till three minutes when more of the product was obtained. This was crystallized from chloroform:methanol as white crystalline product. Yield = 0.24gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and 2-furfural (0.13ml) in 15ml ethanol was refluxed on a water bath for 3 hours. The insoluble residue formed was filtered, washed with ethanol and dried. It was obtained as a white crystalline product from chloroform:methanol. Yield = 0.17 gms

Spectral data of 3,3'-(2-furanyl)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-2k

^{1}H-NMR(200 MHz, $CDCl_3$): δ); 3.6,IH,s,(H-11);6.5-6.8, m, 3H(3×Ar-CH); 7.2-8.1(8H, M, 8×Ar-CH).

IR(KBr,cm^{-1}): 1654.1, 1617.1, 1566.5, 767.1.

MS(m/z): (ESI); **M.Pt.** 188-190^oC

Reaction of 4-hydroxycoumarin(1a) with 2-hydroxybenzaldehyde (salicyladehyde) (l) to yield 3-[6-oxo(1)benzopyrano(4,3-*b*)-(1)benzopyran-7-yl]-4-hydroxy-*1H*-benzopyran-2-one)-(2l) and 3-(o-hydroxybenzal)-2,4-diketochroman-(3l)

Under microwave conditions

a) *Solvent-free conditions.*

A mixture of 4-hydroxycoumarin(0.5gms) and salicyladeyhde(0.16ml) dissolved in ethanol was adsorbed on silica-gel and irradiated in the microwave oven for 8 minutes at medium-high power(75% power level). The mixture was eluted with acetone and upon concentration, the insoluble white residue of **2m** formed was filtered, washed with ethanol, dried and crystallized from chloroform:methanol as white crystalline product. The filtrate upon concentration and workup yielded greenish yellow crystals of **3m.**

Yield:- **2m** = 0.37gms; **3m** = 0.15 gms

b) Solvent media.

4-hydroxycoumarin (0.2gms) was dissolved in 4-5ml ethanol in a 50 ml beaker and to it was added 0.06ml of salicyladeyhde. The mixture was irradiated in the microwave oven for 4 minutes at medium-high power(75% power level). On cooling the reaction mixture, greenish yellow feathery crystals of **3l** separated first. These were filtered and washed with alcohol and after workup of the mother liquor, white feathery crystals of **2m** separated out which were washed with ethanol, dried and recrystallized from chloroform for further purification.

Yield:- **2m** = 0.10 gms; **3m** = 0.08 gms

Under conventional conditions

a) A mixture of 4-hydroxycoumarin(0.5gms) and salicylaldehyde (0.16ml) in 8-10 ml ethanol was refluxed on a water bath for 5 hours. The insoluble white residue of **2m** formed was filtered, washed with ethanol and dried. Workup of the mother liquor yielded further of the product. It was obtained as a white crystalline solid from chloroform:methanol. The filtrate upon concentration yielded greenish yellow feathery crystals of **3m**.

Yield:- **2m** = 0.54gms; **3m** = 0.04 gms

b) A mixture of 4-hydroxycoumarin(0.2gms) and salicylaldehyde (0.06ml) in 5ml ethanol was refluxed on a water bath for 2 hours. The greenish yellow cryatals of **3m** formed were filtered, washed with ethanol and dried. Further workup of the mother liquor gave the white product **2m.** It was crystallized from chloroform:ethyl acetate as white feathery crystals.

Yield:- **2m** = 0.05gms; **3m** = 0.05 gms

Spectral data of 3-[6-oxo(1)benzopyrano(4,3-*b*)-(1)benzopyran-7-yl]-4-hydroxy-*1H*-benzopyran-2-one) - 2l

^{1}H-NMR(200 MHz, $CDCl_3$): δ 7.3-8.2, m,12H, (12×Ar-CH); 4.6, IH, s ,(CH).

IR(KBr,cm^{-1}): 1700, 1669.9, 1640.7, 1618, 1570.1, 1395.2, 763.6, 756.5

MS(m/z): 410(ESI); **M.Pt.** 232-34^{0}C

Spectral data of 3-(o-hydroxybenzal)-2,4-diketochroman – 3l

^{1}H-NMR(200 MHz, $CDCl_3$): δ 7.5-8.3, m,8H, (8× Ar-CH); 6.18, IH, s,(=CH).

IR(KBr,cm^{-1}): 1719.8, 1629.0, 1606.8, 1590.0, 1566.1, 1242.6, 1214.2

MS(m/z): 266(ESI); **M.Pt.** 170^{0}C

Reaction of 4-hydroxycoumarin(1a) with 3-phenylprop-2-enal (cinnamaldehyde) (m) to yield *(E)*-3,3'-(3-phenylprop-2-enylidene)-b*is*(4-hydroxy-*1H*-benzopyran-2-one)- (2m) and 2-phenyl-*2H, 5H*-pyrano[3,2-c][1]benzopyran-5-one-(3m)

Under microwave conditions

A mixture of 4-hydroxycoumarin(0.5gms) and cinnamaldehyde (0.2ml) dissolved in 5ml ethanol were taken in a 50ml beaker and irradiated in the microwave oven for 4 minutes at medium-high power(75% power level). The insoluble orange residue formed was filtered, washed with ethanol, dried and upon fractional crystallization crystallized from chloroform:methanol yielded **2l** as white crystalline product and **3l** as orange yellow crystals.

Yield:- **2l** = 0.35gms; **3l** = 0.03gms

Under conventional conditions

A mixture of 4-hydroxycoumarin(0.5gms) and cinnamaldehyde (0.2ml) in 10ml ethanol were refluxed on a water bath for 3 hours. The insoluble orange residue formed was filtered, washed with ethanol and dried. Tlc plates showed two spots corresponding to **2l** and **3l**. Upon fractional crystallization form chloroform:methanol, **2l** was obtained as a white crystallized product and orange yellow crystals of **3l** separated after workup of mother liqour.

Yield:- **2l** = 0.31gms; **3l** = 0.02gms

Spectral data of *(E)*-3,3'-(3-phenylprop-2-enylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one) – 2m

^{1}H-NMR(200 MHz, $CDCl_3$): δ 7.1-7.8, m, 13H(13×Ar-CH); 6.9, d, 1H, H-11; 6.26.7,m, -CH=CH-

IR(KBr,cm^{-1}): 1671.9, 1618.2, 1604.1, 1567.7, 1353.0, 1108.1, 767.2.

MS(m/z): 438(ESI); **M.Pt.** 190^{0}C

Spectral data of 2-phenyl-*2H*, *5H*-pyrano[3,2-c][1]benzopyran-5-one -3m

^{1}H-NMR(200 MHz, $CDCl_3$): δ 7.8-7.3, m, 9H(9×Ar-CH), 6.9, d, IH; 6.1, d, 1H, 5.74,D, IH.

IR(KBr,cm^{-1}): 1718.3, 1620, 1675.7, 1632.6, 1400.1, 764.8, 755.9.

MS(m/z): 276(ESI); **M.Pt.** 204-206^{0}C

Comparative study

1. In solvent media.

4-Hydroxycoumarin and the corresponding aldehydes were taken in a 2:1 molar ratio at three different concentrations as shown in table 5 and dissolved in minimum amount of ethanol. The reaction mixture was irradiated under the microwave oven at the corresponding times. The product which precipitated out as an insoluble residue was filtered, washed with ethanol, dried and crystallised from the appropriate solvent.

2. In solvent-free media.

4-Hydroxycoumarin and the corresponding aldehydes taken in a 2:1 molar ratio were adsorbed on silica-gel (60-120 mesh) and irradiated under the microwave oven. The reaction mixture was eluted with acetone which upon concentration yielded the product as a precipitate. It was filtered and washed with alcohol to remove any unreacted **1**, dried and crystallised from the appropriate solvent.

2.8 Conclusions

Biscoumarins have been conveniently prepared with improved yields under solvent-free microwave conditions in minimum time than reported so far in literature. This novel procedure is simple, efficient and the usage of solvent-free conditions makes it an eco-friendly procedure. Moreover, the use of domestic microwave oven makes the procedure more convenient and easily accessible.

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Chapter 3

"Ultraviolet study of microwave-assisted reactions"

Abstract

Ultraviolet/Visible *spectrophotometry has been employed to monitor the progress of microwave-assisted synthesis of biscoumarins. The kinetics of the reactions have been studied by calculating percentage conversions with time and a comparison has been made from the data with that observed for the same reactions during the study carried out in previous chapter.*

3.1 Introduction

Spectrometry is one of the most widely used methods of analysis, particularly in the visible region. Its applications find wide use in clinical chemistry and environmental laboratories because of the conversion of many substances to their colored derivatives.

Of the various spectroscopic techniques available, **Ultraviolet/Visible** spectrophotometry is an interesting and easy method for observing the progress of a chemical reaction. It has been employed as an excellent analytical tool to monitor the progress of a reaction. It is also one of the spectroscopic techniques used to detect the presence of conjugation and other functional groups present in a sample. The kinetics of a reaction can be studied accurately to arrive at the rate and order of a reaction as well as to study the effect of solvent, temperature and concentration on the progress of reaction. [1-5] Owing to the accuracy and reliability of the method, we decided to monitor the progress of microwave-assisted synthesis of biscoumarins using this technique.

Microwave-assisted organic synthesis (MAOS) is now a days the leading trend in synthetic organic chemistry owing to shorter reaction times, solvent-free procedures and easy workups in addition to increased yields. A huge number of syntheses have been reported in view of the above advantages.[6] However, the kinetic studies of a very few of them have been carried out.[5] In order to gain further insight into the reaction mechanism of a microwave assisted organic reaction, a kinetic study of a microwave assisted reaction was undertaken using UV spectrophotometry. The rates of product formation have been monitored as a function of time. Since we have been working on the microwave assisted synthesis of biscoumarins, we decided to monitor the changes in chemical composition under microwave irradiation for observing how the particular reaction develops as a function of time. The UV/Visible spectra of the reactants and products were characterized by relatively sharp peaks, which were easily identifiable. Product peaks did not overlap with those of the reactants and the peak positions did not significantly vary with temperature.

3.2 Theory of UV/Visible Spectroscopy

UV/Visible spectra are a result of electronic excitations in a molecule and are characteristic for the molecules having similar functional groups. It is for this reason that this technique is also known as **electronic spectroscopy** since it involves the promotion of sigma (*σ), pi (π)* or nonbonding(*n)* electrons from the ground electronic state to higher energy electronic state. [6] This spectral technique is very useful for detecting conjugated double bonds as well as aromatic conjugation in molecules. It also distinguishes between conjugated and non-conjugated systems. e.g. *α, β*-unsaturated carbonyl compounds from *β,γ*-analogues; homoannular and heteroannular conjugated dienes, etc.

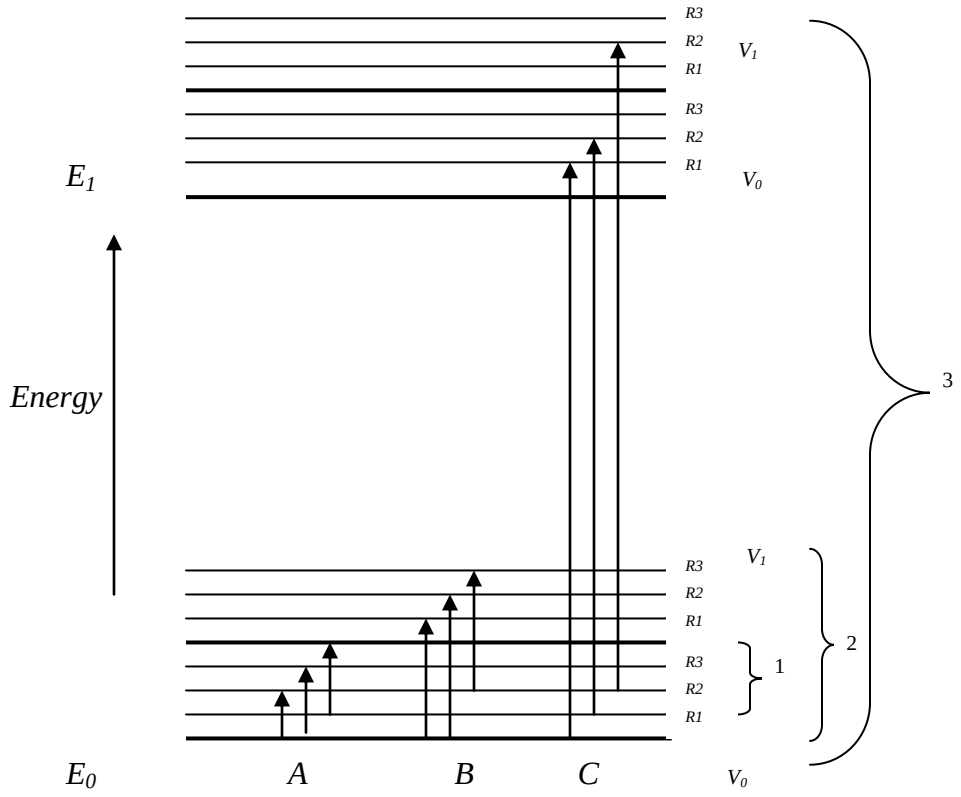


Figure 1. *Energy level diagram showing the energy changes associated with absorption of electromagnetic radiation.* ***A****- (Pure rotational transition);* ***B****- (Rotational-vibrational changes);* ***C****- (rotational- vibrational-electronic changes);* E_{0}*- Ground electronic state;* E_{1}*- First excited electronic state;* ***1****- Rotational energy levels;* ***2****- Vibrational energy levels;* ***3****- Electronic energy levels*

The ultraviolet region of electromagnetic radiation ranges from 200-400 nm and the visible region from 400-800 nm. The electronic transitions that take place in the ultraviolet and visible regions of the spectrum are due to the absorption of radiation by specific types of groups, bonds and functional groups within the molecule. When a molecule absorbs UV/Visible radiation, its σ, π or *n* electrons get promoted from the ground state to the respective excited states (σ*and π*). Since in a particular electronic level, there are various vibrational levels which further contain various rotational levels, an electron in a particular energy level on absorption of UV/Visible radiation gets excited from one electronic level into a particular rotational cum vibrational level of an excited electronic level. Hence the absorption spectra appear as broad bands. In other words, an electronic transition is accompanied by a rotational and vibrational transition. (*figure 1*)
The absorption of radiant energy by matter can be described quantitatively through the general principle known as Beer's law which states that,

> "*The rate of decrease of the intensity of a beam of monochromatic radiation with the thickness of an absorbing medium while passing through its solution, is directly proportional to the intensity of incident radiation as well as to the concentration of solution."*

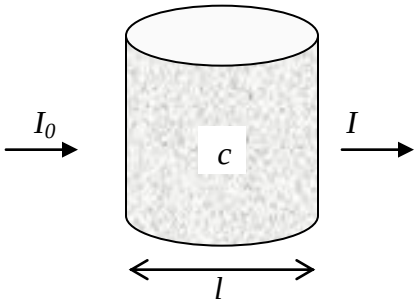


Figure 2. *Absorption of incident radiation of intensity I_0 while passing through a solution of concentration c and path length l leads to a decrease in its intensity to I.*

Mathematically,

$$-\frac{dI}{dl} = kIc$$

Where, I = intensity of monochromatic radiation after passing through thickness *l* of the medium,

dI = infinitesimally small decrease in the intensity of incident radiation on passing through infinitesimally small thickness dl of the absorbing solution,

l = thickness of the absorbing medium in centimeters,

k = molar absorption coefficient,

and c = concentration of the solution in grams per litre,

If I_0 be the intensity of the radiation before entering the absorbing solution (when *l*=0), then the intensity of the radiation I after passing through the thickness *l* of the medium can be calculated as,

$$\int_{I_0}^{I} dI/I = -\int_{l=0}^{l=l} kcdl$$

$$\ln I/I_0 = -kcl$$

Or $$I = I_0 e^{-kcl}$$

Replacing k by a new constant *a*,

$$\log I_o / I = acl$$

Or $$A = acl$$

Where A is called the *absorbance*

The above equation can also be written by changing natural logarithm to the logarithm of base 10,

$$I = I_0 10^{-acl}$$

If the path length *l* is expressed in centimeters and concentration c in grams per litre, the constant *a* is called the absorptivity and is dependent on the wavelength and the nature of the absorbing material. *a* has the units of cm^{-1} mol^{-1} L. If the concentration is expressed in moles per litre, *a* is replaced by ε known as the *molar absorptivity*.

Thus the shortest statement of Beer's law is,

$$A = \varepsilon cl \qquad \text{--- } \textit{Equation I}$$

Molar absorptivity ε is characteristic for a particular combination of solute and solvent for a given wavelength and has the units of L cm^{-1} mol^{-1}. Molar absorptivity ε is an intensive property of a substance representing the relative intensity of an absorption band. ε is a measure of the probability of the electronic transition taking place whereas A is an extensive property of a particular sample and therefore varies with the concentration of the sample and the path length of the cell unlike ε. [7,8]

3.3 Types of Electronic transitions

Electrons in a molecule can be classified into four different types – (1) closed shell electrons that are not involved in bonding and consequently have too high excitation energies to contribute to the absorption in the UV/Visible region, (2) covalent single bonded or σ (sigma) electrons. These electrons also possess a very high excitation energy to contribute to excitation in the UV/Visible region e.g. in saturated hydrocarbons, (3) paired non-bonding outer shell electrons (*n* electrons), for example, in compounds containing N, O, S and halogens. These electrons are loosely held and get excited on absorption of UV/Visible radiation, and (4) electrons in π-orbitals (pi-electrons) in unsaturated compounds. These are most readily excited electrons under UV/visible radiation.[6-8]

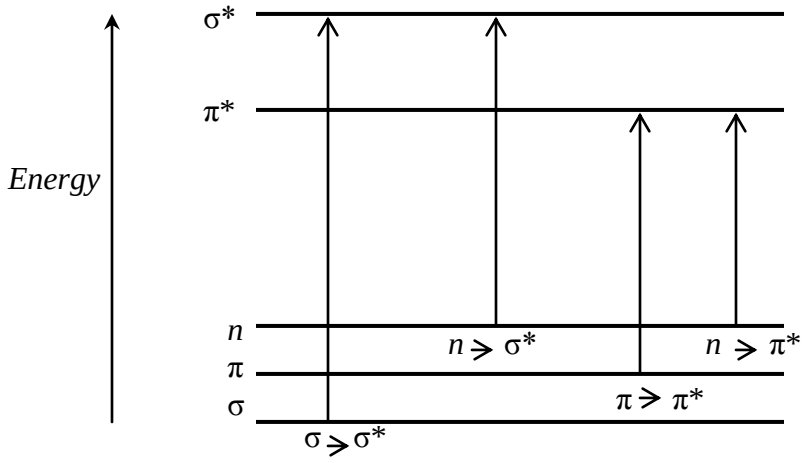


Figure 3 *. Types of electronic transitions*

Since a molecule possesses unoccupied orbitals or anti-bonding orbitals, these constitute the excited energy levels and are either *sigma*-antibonding or *pi*-antibonding denoted as σ* and π* respectively. Hence absorption of radiation results in electronic transition from a bonding (σ or π) or non-bonding orbital to antibonding orbitals (*figure 3*). The most electronic common transitions are:-

1. *σ → σ* transition.* It is a very high energy transition because the σ-bonds in general are very strong and consequently the distance between the σ-bonding and the corresponding antibonding orbital is very large to allow for an electronic transition in the UV/Visible region. For saturated compounds like methane, propane, etc, absorption occurs near 150 nm. The usual spectroscopic technique cannot be used below 200 nm because of strong absorption by the oxygen present in air. To study such a transition, the whole path length needs to be evacuated and hence this region is also named as **vacuum ultraviolet** region.
2. *n → σ* transition.* This type of electronic transition requires comparatively lesser energy than *σ → σ* transition* but also takes place at wavelengths less than 200 nm that is in the vacuum ultraviolet region. e.g. in saturated compounds containing one heteroatom with unshared pair of electrons like amines, ethers,

aldehydes, ketones, alcohols, etc. For example, water absorbs at 167 nm and methanol at 174 nm.

3. $\pi \rightarrow \pi^*$ *transition.* This type of transition is one of the most common type of transition in the UV/Visible region and takes place in unsaturated compounds i.e. in compounds containing double or triple bonds. This type of transition requires small energy and hence occurs at longer wavelengths. Conjugation in organic molecules can be readily detected using this type of transition as more the number of conjugated double bonds, longer the wavelength of absorption and the compound appears colored if absorption takes place in the visible region. ε_{max} (1000-100,000).e.g. *lycopene,* a red colored pigment in tomatoes, consists of eleven double bonds in conjugation and absorbs at 476 nm in hexane as solvent. Similarly, *β*-carotene, having eleven double bonds in conjugation, absorbs at 453nm.
4. $n \rightarrow \pi^*$ *transition.* This type of transition takes place in compounds containing a heteroatom involved in double bond formation and having an unshared electron pair. e.g. in carbonyl compounds. This type of transition requires least amount of energy out of all transitions. However, it is symmetry forbidden and hence the probability of such a transition is very low as evident from the value of ε_{max} (less than 1000). Acetone, for example, exhibits a high intensity $\pi \rightarrow \pi^*$ transition at 190 nm (ε_{max} -10,000) and a low intensity $n \rightarrow \pi^*$ transition at 270 nm (ε_{max}- 15).

3.4 Instrumentation

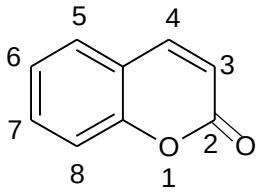
A UV/Visible spectrophotometer consists of a light source, monochromator, detector, amplifier and the recording device. The sources of light are – A tungsten filament incandescent lamp and hydrogen deuterium discharge lamp which covers the whole of the UV/Visible region. The tungsten filament lamp is rich in red radiation while as the hydrogen deuterium discharge lamp covers the region below it. The region below 200 nm is not suitable for study because of strong absorption by oxygen present in the air.

Therefore to study absorptions below 200nm, the whole path length is to be evacuated and hence such a region is called vacuum ultraviolet region.

Most of the UV/Visible spectrophotometers are double beam instruments. The primary source of radiation is dispersed with the help of rotating prism and the various wavelengths of a light source are hence separated and then selected by slits such that the rotation of the prism causes a series of continuously increasing wavelengths to pass through the slits for recording purposes. The selected beam becomes monochromatic and is then divided into two beams of equal intensity. One of the selected monochromatic beams is passed through sample solution and the other beam of equal intensity is passed through reference solvent. The reference as well as the solution of the sample may be contained in cells made of quartz which is transparent throughout the region under study. Glass is not used since it absorbs strongly in the ultraviolet region.[6-8]

3.5 Ultraviolet/Visible Spectra of Coumarins

Coumarins are a class of organic compounds called *β*-lactones having a benzopyran nucleus containing a keto group at the *β*-position as in 4-hydoxycoumarins and are also termed as *β*-ketolactones. Therefore they show mostly >C=O and >C=C< transitions, that is, n- π' and π- π'. UV/Visible spectra are useful for distinguishing coumarin from chromones. Chromones normally show a strong absorption of 240-250 nm (log ε 3.8) whereas coumarins usually show a minimum at this wavelength. Coumarins show absorption bands at 274 and 322 nm (log ε 4.03 & 3.72) which have been attributed to the benzene and pyrone rings, respectively.



Coumarin nucleus

Coumarins are labile at pH ≥12 and consequently even neutral coumarins like 5,7- and 6,7- dimethoxy coumarins show base induces shifts in their UV/Visible spectra due to hydrolysis and isomerisation. The prominent band, due to electronic transitions in coumarins, is the B-band due to π- π* transitions in aromatic and heteroaromatic part of the molecule. [9]

In the present work, UV/Visible Spectroscopy has been used to study the kinetics of the synthesis of biscoumarins from the condensation of 4-hydroxycoumarin with various aldehydes under microwave irradiation. The progress of the reaction has been monitored as a function of time and the percentage yield has been estimated using UV/Visible spectrometry. The calculated percentage conversion of the reactants into products agrees well with the observed percentage yields done in our work for the same time of study. [10]

3.6 Materials and methods

All the reactions studied under UV/Visible spectrophotometry were carried out in a Sharp Carousel domestic microwave oven at a power level of 75% kept constant throughout all the reactions. 4-Hydroxycoumarin (1mmol) and the corresponding aldehyde (0.5mmol) in a 2:1 molar ratio were dissolved in minimum amount of ethanol and adsorbed on silica-gel (60-120 mesh). Five such reactions in each case were irradiated at different times of 1, 2, 3, 4 and 5 minutes respectively. The reaction mixture was eluted with acetone and after the removal of eluant, the mixture was dissolved in 20 ml chloroform. From the stocks thus prepared, aliquots of equal concentration were prepared in chloroform by dilution from the respective reaction mixtures. The entire study in the work was carried out in a Schimadzu UV-1650 spectrophotometer in a 1cm quartz cell at room temperature in chloroform as the solvent. Aliquots from each solution were subjected to study under UV the spectra over a wavelength range of 200-400 nm.

For this study, solutions of the reactants and the product prepared in chloroform were subjected to UV study to look for the wavelength where minimum interference or overlapping of the moieties takes place (*Figure 4*). Once the wavelength of study was set, different concentrations of the sample were prepared and a calibration curve was plotted

at the required wavelength. This was used to find out the concentration of the sample in the five reactions subjected to microwave irradiation at different times. Since the reactions were carried out under solvent-free conditions, it was not suitable to irradiate the same reaction mixture at intervals and study the percentage conversion into product under UV because this would have led to a change in concentration of the reactants as well as the product every time the reaction mixture would be eluted. So, in order to maintain the concentrations considerably accurate, we took five reaction mixtures bearing an equal concentration of reactants which were adsorbed on the same amount of solid support and irradiated at different times.

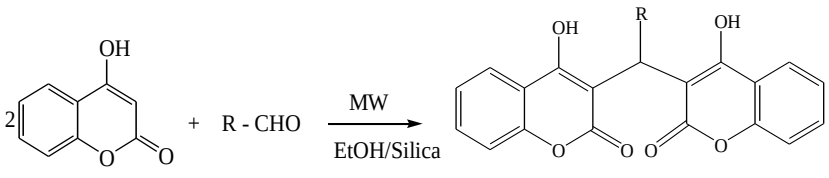
From Beer's law, $\boldsymbol{A = \varepsilon c l}$

Where $\boldsymbol{A}$ is the absorbance, $\boldsymbol{\varepsilon}$ is the molar absorptivity in cm^{-1} mol^{-1} L and $\boldsymbol{l}$ is the path length of the cell (=1 cm). Percentage conversion was then calculated from either the decrease in concentration of the reactant or increase in the concentration of the product as the case may be.

Since,

$$\text{Percentage yield} = \frac{\text{Concentration of reactant}_{t=0} - \text{concentration of reactant}_{t=t}}{\text{Concentration of reactant}_{t=0}} \times 100$$

Synthesis of biscoumarins, has been carried out under microwave solvent-free conditions, from 4-hydroxycoumarin and aromatic aldehydes.(*Scheme 1*)



1a 4-hydroxycoumarin | **2(a-g)** Aldehyde | **3(a-g)** Biscoumarin

Scheme 1. Reaction of 4-hydroxycoumarin with different aromatic aldehydes to yield biscoumarins.

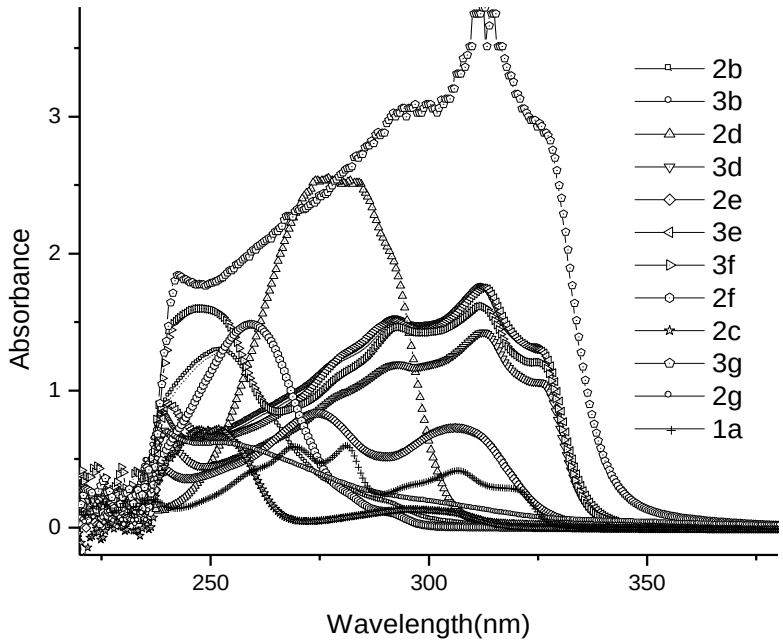


Fig. 4. *UV spectra showing the absorption maxima of reactants and products.*

3.7 Results and discussion

The calculated percentage conversion of the reactants into products agrees well with the isolated percent yields done in our work for the same time of study.[10] Seven reactions have been studied and in each case, either the decrease in concentration of one of the reactants or increase in concentration of the product has been used as the parameter for calculation of percentage yield. For this study, solutions of the reactants and product prepared in chloroform were subjected to UV study to look for the wavelength where minimum interference or overlapping of the moieties takes place. Once the wavelength of study was set, different concentrations of the sample were prepared and a calibration curve was plotted at the required wavelength. From the linear-fit data, the value of ε was obtained from the slope of the curve using the equation,

$$\varepsilon = A/C, \quad \text{since, } l = 1\text{cm}$$

Once ε was set, the concentration of the sample in the five reactions, subjected to microwave irradiation at different times was calculated. Since the reactions were carried out under solvent-free conditions, it was not suitable to irradiate the same reaction

mixture at intervals and study the percentage conversion into product under UV because this would have led to a change in concentration of the reactants as well as the product every time the reaction mixture would be eluted. So in order to maintain the concentrations considerably accurate, we took five reaction mixtures bearing an equal concentration of reactants which were adsorbed on the same amount of solid support and irradiated at different times. Percentage conversion was hence calculated from either the decrease in concentration of the reactant or increase in the concentration of the product as the case may be.

3.7.1 Reaction between 4-hydroxycoumarin (*1a*) and 3-chlorobenzaldehyde (*2a*) to yield 3,3'-(3-chlorobenzylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one); (*3a*)

An extensive study of the reaction of **1a** with **2a** was undertaken under UV spectrophotometry. Solutions of **1a**, **2a** and **3a** (1.5×10^{-5}M) were prepared in chloroform and analyzed under UV to establish the wavelength of study where one of the three moieties interfered least with the other two. The plots obtained are shown in *figure 5*. The wavelength optimum for the study of biscoumarin formation from **1a** and **2a** was taken as 246 nm for **2a**. Since this wavelength had no interference from either **1a** or the product **3a**. The decrease in the intensity of this wavelength was taken as the parameter to study the percent conversion of reactants into products. ε_{max} for **2a** 246nm was calculated to be 23395.65 from its calibration curve.(*Figures 6 & 7*).

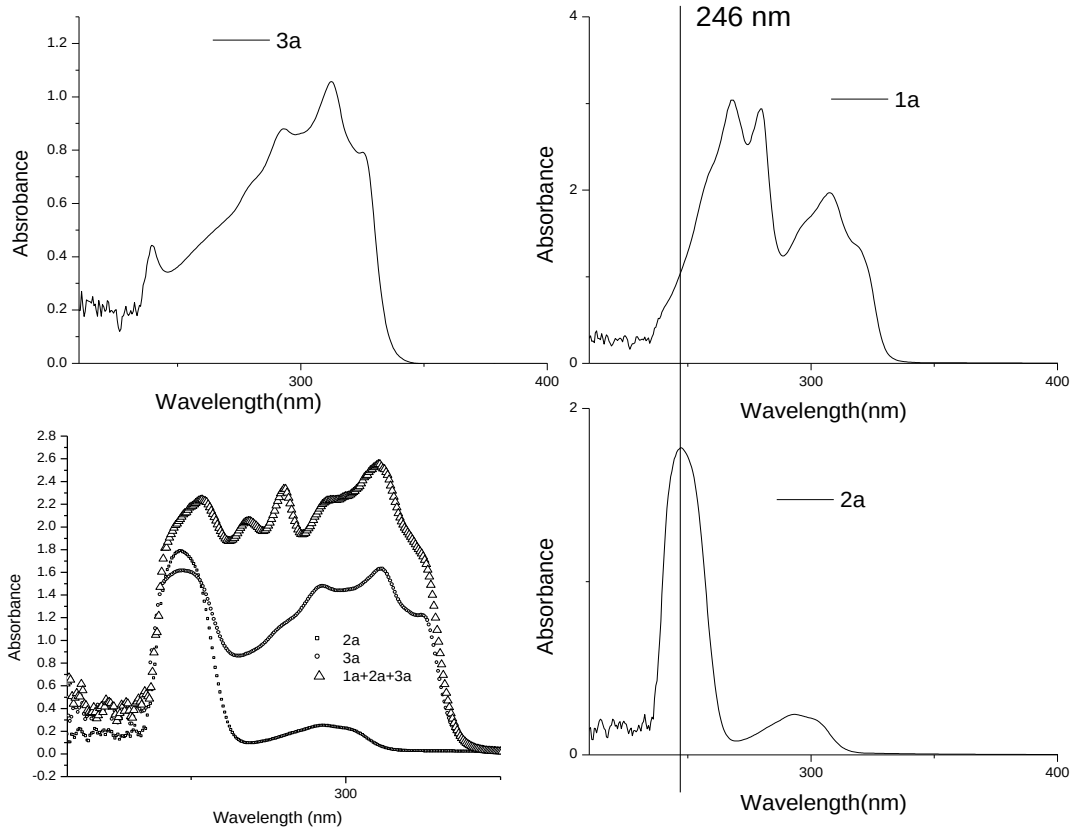


Fig. 5. Plot of absorbance vs wavelength for 1a, 2c and 3c to study the wavelength of minimum interaction

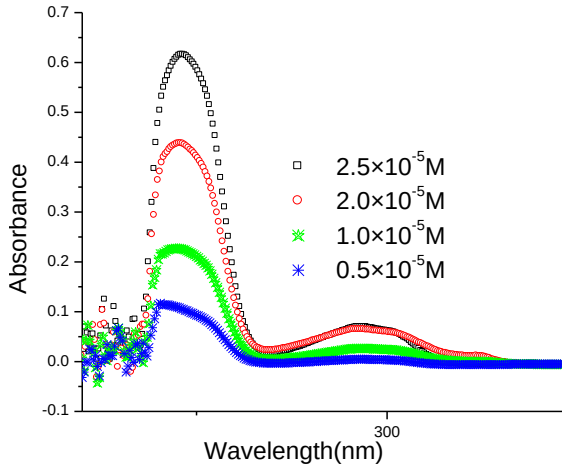


Fig.6. Plot of absorbance vs wavelength for different concentrations of 2a

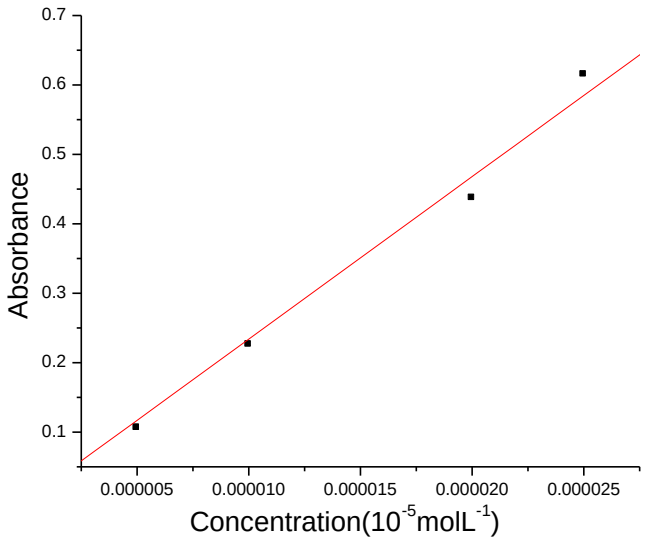


Fig. 7.Linear fit plot of 2a at 246nm.

All the reactions were repeated three to four times for an exact comparison and the final data obtained is shown in *table 1*. It is indicated from *figure 6* that the intensity of the peak at 246 nm of **2a** gets decreased as the reaction progresses and is almost absent in the reaction mixture irradiated for five minutes. The average time of 5 minutes was observed as the optimum time for reaction completion for all the aldehydes used in the present work.

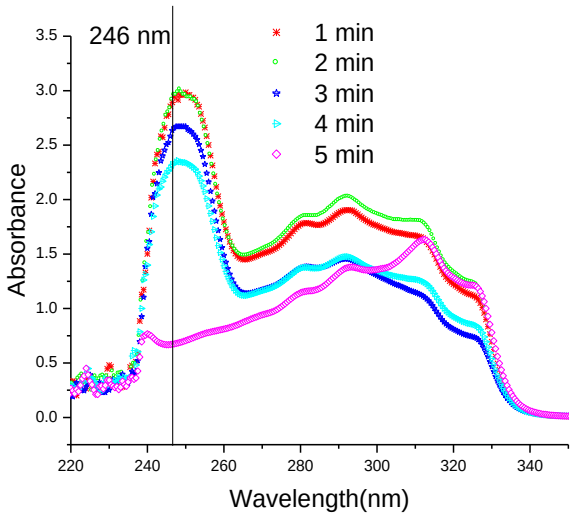


Fig. 8. UV spectra of the reaction between 1a and 2a at different times.

The five reaction mixtures bearing an equal concentration of reactants were subjected to microwave irradiation at five different times to study the progress of reaction with time (*Figure 8*). Initial concentration of the aldehyde (t=0) after dilution from the reaction mixture was 2.5×10^{-5}M in the aliquots subjected to UV spectra in all the reactions. The progress of the reaction follows a sigmoid type of curve. (*Figure 9*).

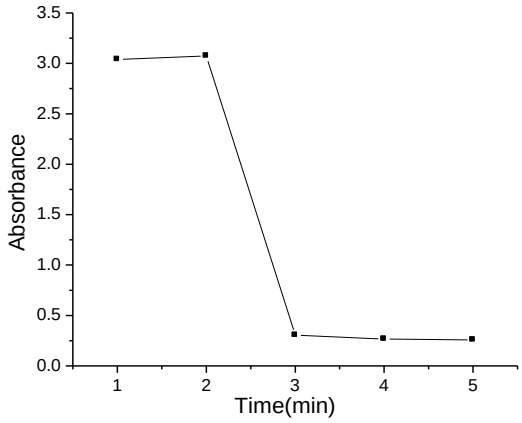


Fig. 9. Graph showing the progress of reaction from the decrease in concentration of 2a with time.

3.7.2 Reaction between 4-hydroxycoumarin (1a) and benzaldehyde (*2b*) to yield 3,3'-phenylmethylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one); (*3b*)

In this case, the wavelength of the product **3b** at 327 nm was taken for study as this wavelength had little interference from the reactants (*Figure 10*). ε_{max} was calculated to be 26316.44 from the linear fit data of the product at 327 nm (*Figures 11 & 12*). Percent yield was hence calculated for all the five reactions irradiated at different times (*Figure 13*) under microwave irradiation as shown in table1. Expected concentration of the product in the reaction mixture was calculated to be 5×10^{-5}M in the aliquots subjected to UV spectra in all the reactions. The progress of the reaction follows a sigmoid type of curve (*Figure 14*).

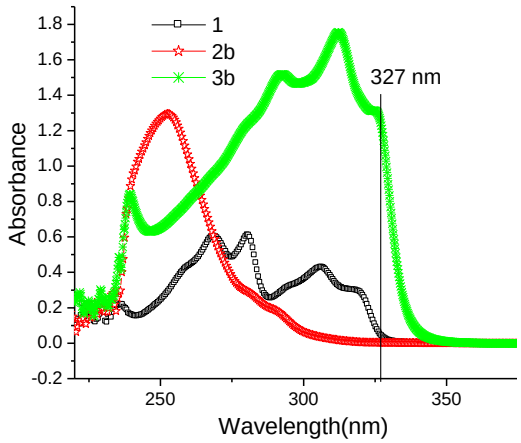


Fig. 10. Plot of absorbance vs wavelength for 1a, 2b and 3b (4.90×10^{-5}M).

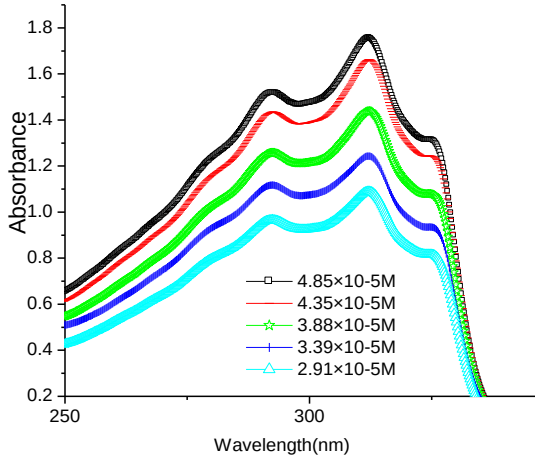


Fig. 11. Plot of absorbance vs wavelength for different concentrations of 3b.

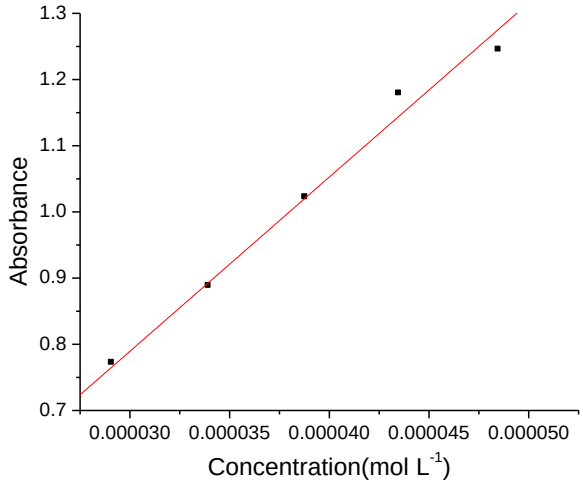


Fig.12. Linear fit plot of 3b at 327 nm.

As indicated from *figure 12*, the reaction shows a gradual progress with time which is more prominent initially and contrary to observed yield, an average percent conversion is indicated but the effect of irradiation is evident as an increase in the conversion of reactants into product is taking place.

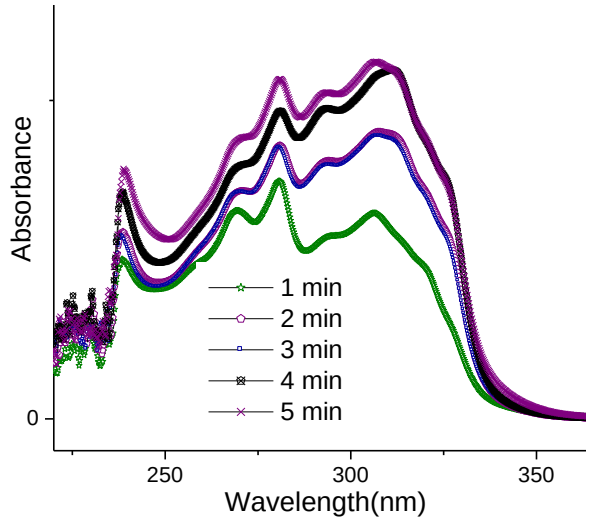


Fig. 13. UV spectra of the reaction between 1a and 2b at different times.

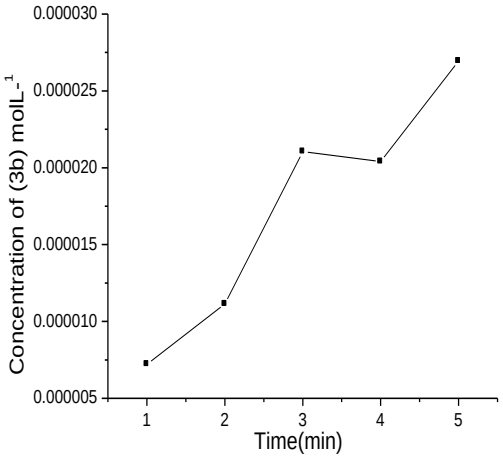


Fig. 14. Graph showing the progress of reaction with time.

3.7.3. Reaction between 4-hydroxycoumarin (1a) and 2-chlorobenzaldehyde (*2c*) to yield 3,3′ -(2-chlorobenzylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one); (*3c*)

In this case, the wavelength of the aldehyde (**2c**) at 248 nm was taken for study and ε_{max} was calculated to be 16046.02 from the linear fit data of the aldehyde at 248 nm (*Figures 15 & 16*). Percentage yield was hence calculated for all the five reactions irradiated at different times (*Figure 17*) under the microwave as shown in table 1. Initial concentration of the aldehyde (t=0) in the aliquots subjected to UV spectra after dilution from the reaction mixture was 2.5×10^{-5}M.

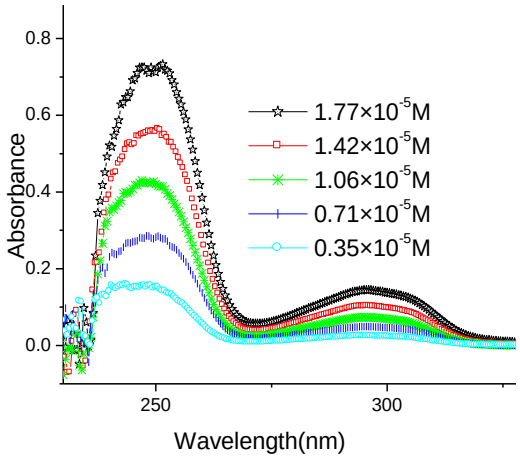


Fig. 15. Plot of absorbance vs wavelength for different concentrations of 2c.

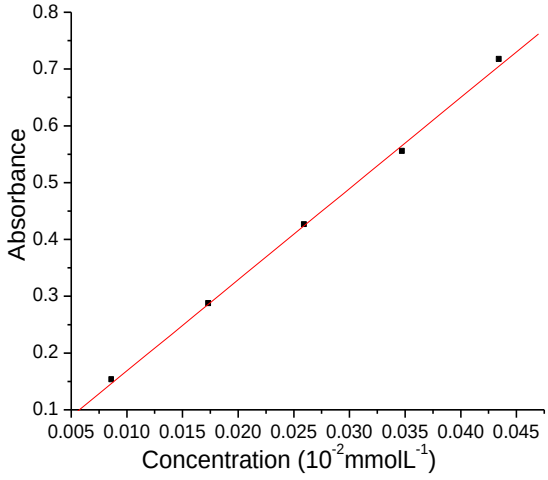


Fig. 16. Linear fit plot of 2c at 248 nm for different concentrations.

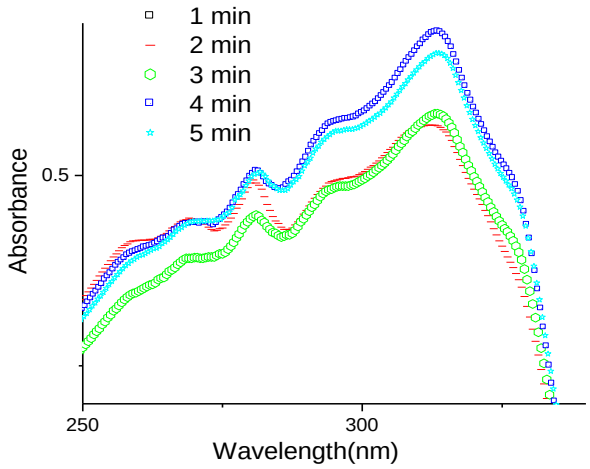


Fig.17. UV spectra of the reaction between 1a and 2c.

As indicated from *figure 18*, there is an abrupt increase in the progress of reaction just within a minute of irradiation indicating the requirement of a very short induction period for the conversion of reactants into the product. The progress of the reaction follows a sigmoid type of curve (*Figure 18*).

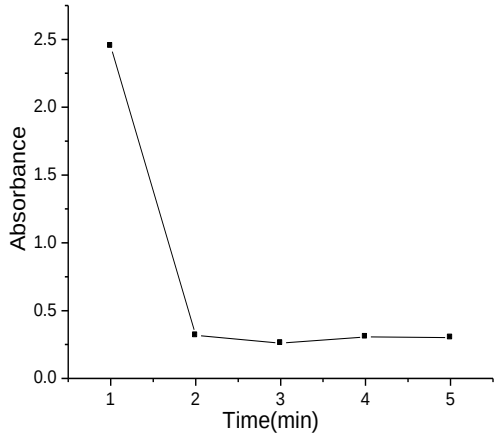


Fig. 18 .Graph showing the progress of reaction with time.

3.7.4 Reaction between 4-hydroxycoumarin (1a) and 4-methoxybenzaldehyde (*2d*) to yield 3,3′-(4-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one (*3d*)

In this case, the wavelength of the product at 327 nm was taken for study as this wavelength had little interference from the reactants (*Figure 19*) and ε_{max} was calculated

to be 13600 from the linear fit data of the product at 327 nm (*Figure 20 & 21*). Percent yield was hence calculated for all the five reactions irradiated at different times (*Figure 22*) under the microwave as shown in table 1. Expected concentration of product in the reaction mixture was 5×10^{-5}M in the aliquots subjected to UV spectra in all the reactions at t=5 min. The progress of the reaction follows a sigmoid type of curve (*Figure 23*). The reaction also requires a very short induction period of less than a minute as indicated from the figure.

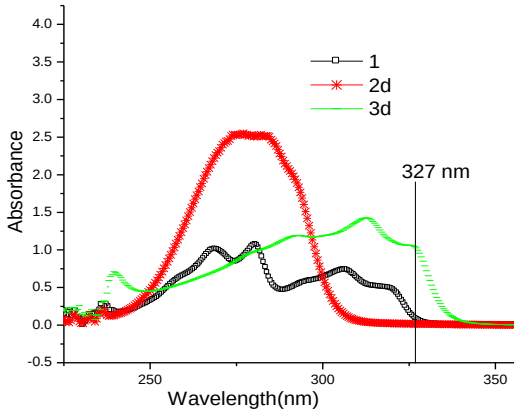


Fig. 19. Plot of absorbance vs wavelength for 1a, 2d and 3d (4.10×10^{-5}M).

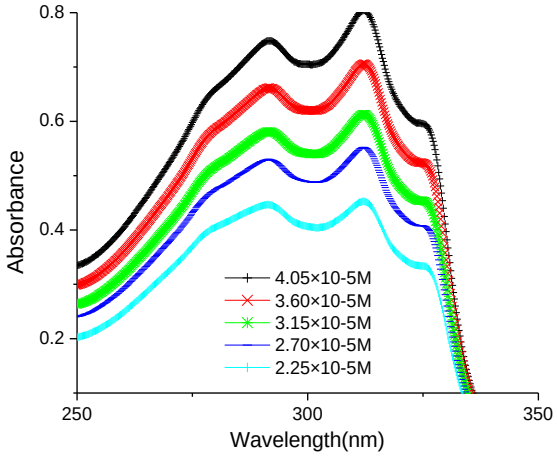


Fig. 20. Plot of absorbance vs wavelength for different concentrations of 3d.

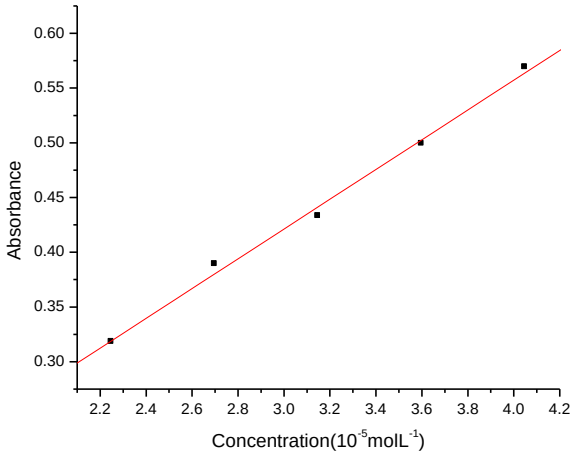


Fig. 21. Linear-fit plot of 3d at 327 nm.

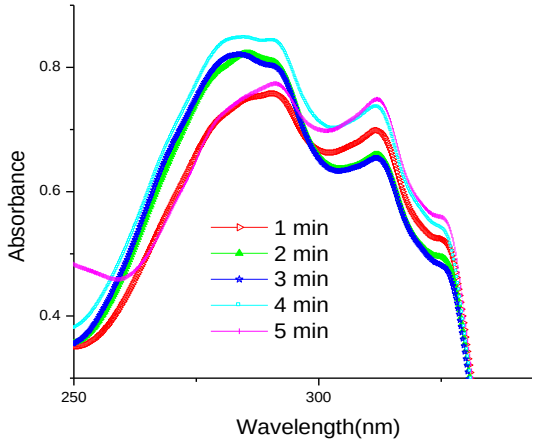


Fig. 22. UV plot of the reaction of 1a with 2d at different times.

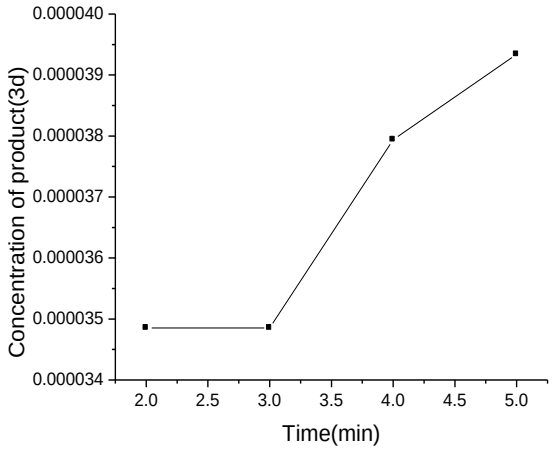


Fig. 23. Graph showing the progress of reaction with time.

3.7.5 Reaction between 4-hydroxycoumarin (1a) and 4-hydroxy, 3-methoxybenzaldehyde (vanillin) (*2e*) to yield 3,3'-(4-hydroxy,3-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one); (*3e*)

In this case, wavelength of **3e** at 327 nm was taken for study because of little interference with the reactants (*Figure 24*) and ε_{max} was calculated to be 34771.98 from the linear fit data of product at 327 nm (*Figures 25 & 26*). Percent yield was hence calculated for all the five reactions irradiated at different times (*Figure 27*) under microwaves as shown in the table. Expected concentration of product in the reaction mixture was calculated to be 6.57×10^{-5}M in the aliquots subjected to UV spectra in all reactions at t=5 min. The progress of the reaction follows a sigmoid type of curve (*Figure28*). There is almost 50 percent progress in the reaction initially and continues to be so upto four minutes of irradiation and a further minute of irradiation leads abruptly to almost cent percent completion of reaction. The calculated yield also agrees very well with the observed yield.

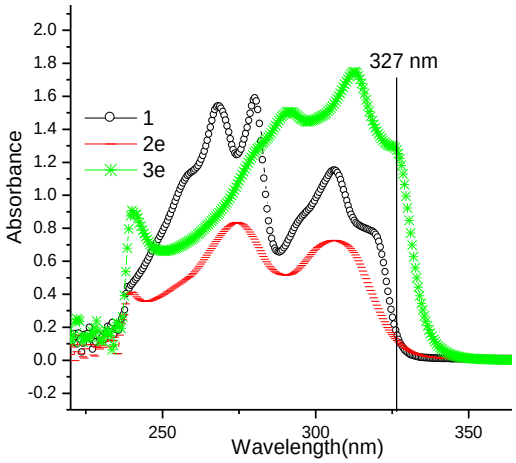


Fig. 24. Plot of absorbance vs wavelength for 1a, 2e and 3e (6.50×10^{-5}M).

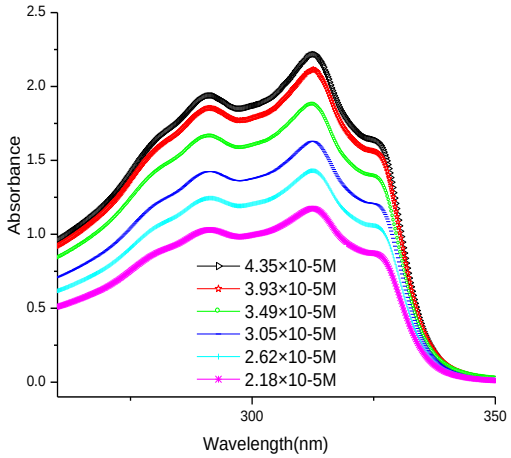


Fig. 25. Plot of absorbance vs wavelength for different concentrations of 3e.

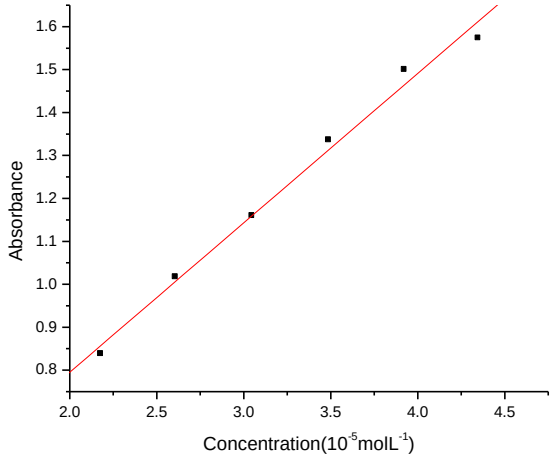


Fig. 26. Linear fit plot of 3e at 327 nm.

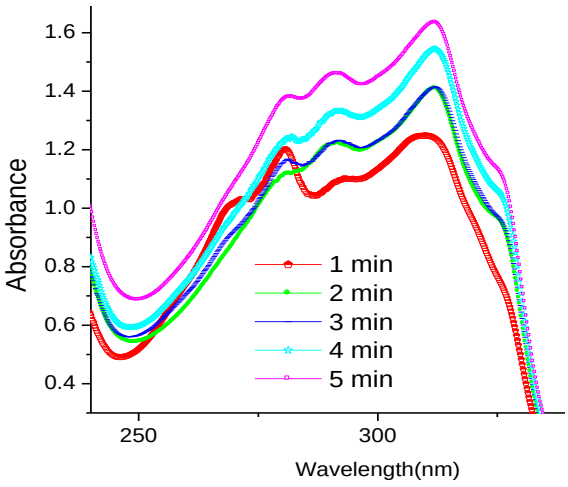


Fig. 27. Reaction of 1a with 2e at different times

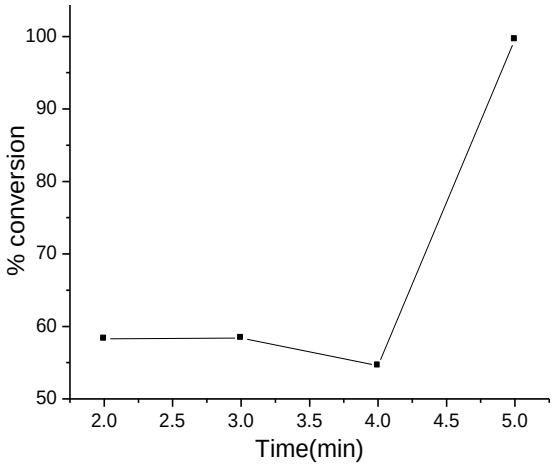


Fig. 28 . Graph showing the percent conversion with time.

3.7.6. Reaction between 4-hydroxycoumarin (1a) and 4-chlorobenzaldehyde (2f) to yield 3, 3'- (4 -chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one); (3f)

In this case, wavelength of **3f** at 327 nm was taken for study because of little interference with the reactants (*Figure 29*) and ε_{max} was calculated to be 18697.50 from the linear fit data of product at 327 nm (*Figure 30*). Percent yield was hence calculated for all the five reactions irradiated at different times (*Figure 31*) under microwaves as shown in the table. Expected concentration of product in the reaction mixture was calculated to be 2.70×10^{-5}M in the aliquots subjected to UV spectra. The progress of the reaction follows a sigmoid type of curve and excellent conversion is indicated (*Figure 32*).

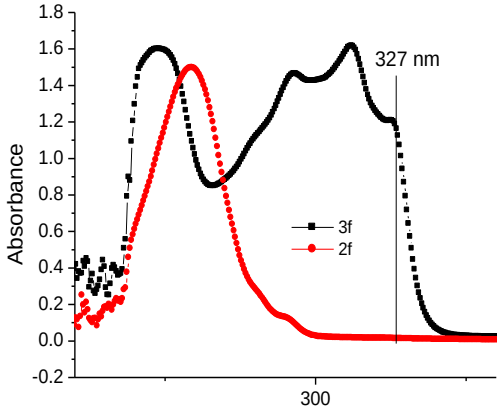


Fig. 29 . Plot of absorbance vs wavelength of 2f and 3f.

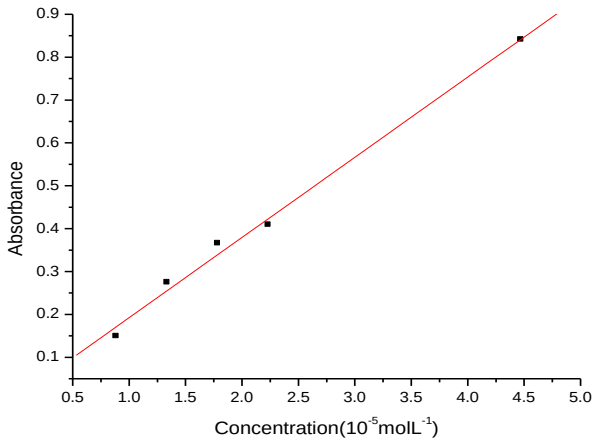


Fig. 30. Linear fit data of 3f at 327 nm.

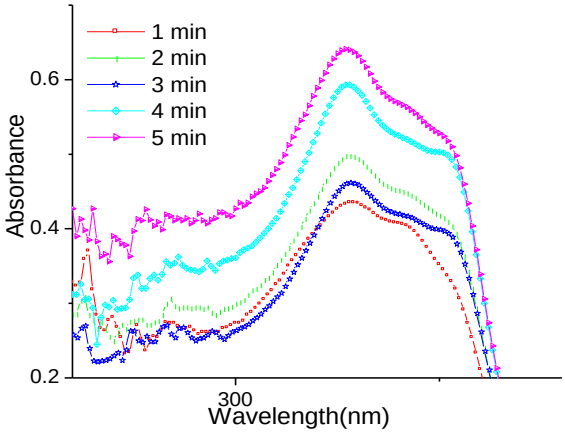


Fig. 31.UV spectra of reaction between 1a and 2f at different times.

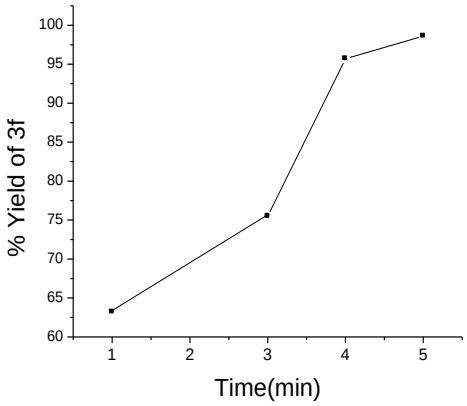


Fig. 32. Graph showing the progress of reaction with time at different times.

3.7.7 Reaction between 4-hydroxycoumarin (1a) and 2-nitrobenzaldehyde (2g) to yield 3, 3'-(2 -nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one) (3g)

In this case, wavelength of **3g** at 327 nm was taken for study because of little interference with the reactants and ε_{max} was calculated to be 44144.2665 from the linear fit data of product at 327 nm (*Figures 33 & 34*). Percentage yield was hence calculated for all the five reactions irradiated at different times (*Figure 35*) under the microwave as shown in the table. Expected concentration of product in the reaction mixture was calculated to be equal to 1.6×10^{-4}M in the aliquots subjected to UV spectra. There is an average progress in the reaction but a sigmoid type of curve is followed (*Figure 36*).

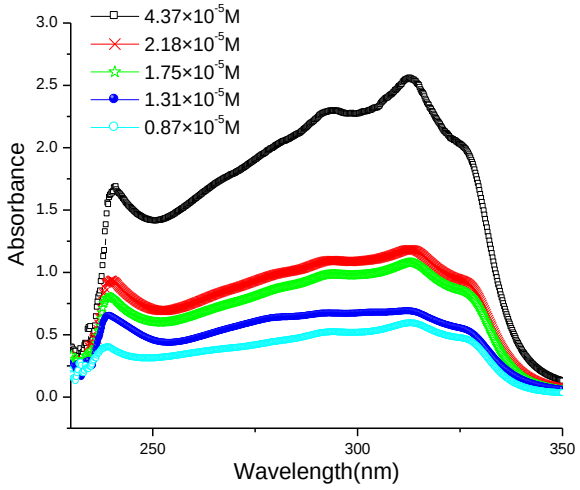


Fig. 33. Plot of absorbance vs wavelength for different concentrations of 3g.

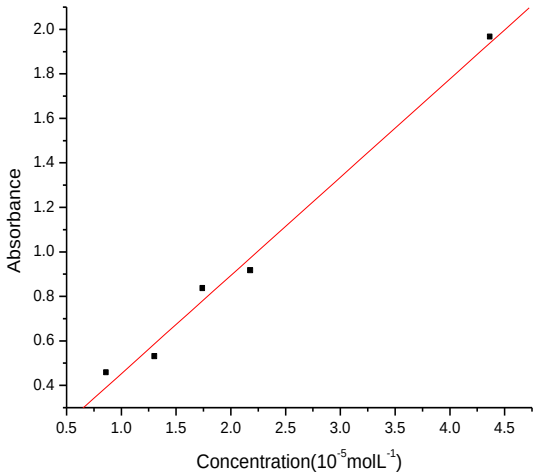


Fig. 34. Linear fit data of 3g at 327 nm.

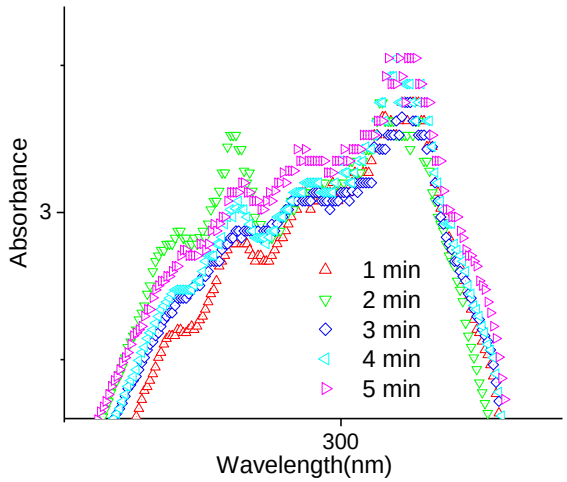


Fig. 35. UV spectra of reaction between 1a and 2g at different times.

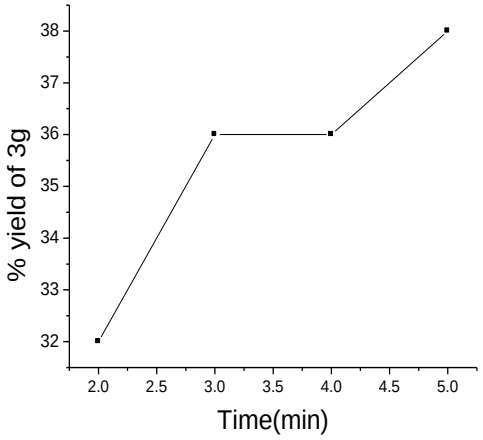


Fig. 36. Graph showing the progress of reaction with time.

In almost all the reactions studied, the progress follows a sigmoid type of curve (*Figure 37*). Initially as indicated from their respective graphs, the reaction requires some induction period after a minute of irradiation where after the reactants get almost abruptly converted into products. A few exceptions may arise because of improper heating in the oven. However, the percentage yield differences observed in products **3b** and **3g** are evident and contrary to observed yields although microwave conditions have been used in either case.

Table 1. *UV monitoring of the progress of biscoumarin formation under microwave irradiation as a function of time.(Error ±2)*

Aldehyde	R	Product	ε ($Lmol^{-1}cm^{-1}$)	Time (min)	Percentage Conversion	Isolated yield%
2a	**$3ClC_6H_4$**	**3a**	2a at 246 nm ε_{246} (23395.656)	1	42	-
				2	42	-
				3	94	-
				4	95	-
				5	95	84-94
2b	**C_6H_5**	**3b**	3b at 327nm ε_{327} (26316.44386)	1	14	-
				2	22	-
				3	42	-
				4	41	-
				5	54	62-68
2c	**$2ClC_6H_4$**	**3c**	2c at 248 nm. ε_{248} (16046.02)	1	4	-
				2	88	-
				3	90	-
				4	88	-
				5	88	73-82
2d	**$4CH_3OC_6H_4$**	**3d**	3d at 327 nm ε_{327}(13600)	1	-	-
				2	86	-
				3	86	-
				4	85	-
				5	84	60-68
2e	**4-OH,3-$CH_3C_6H_3$**	**3e**	3e at 327 nm ε_{327}(34771.9828)	1	-	-
				2	58	-
				3	58	-
				4	56	-
				5	99	78-99
2f	**$4ClC_6H_4$**	**3f**	3f at 327 nm ε_{327}(18697.50)	1	63	
				2	78	
				3	76	
				4	96	
				5	98	68-87
2g	**$2NO_2C_6H_4$**	**3g**	3g at 327 nm ε_{327}(44144.2665)	1	-	
				2	32	
				3	36	
				4	36	
				5	38	63-94

This can be attributed to the differences in microwave exposure even if the same equipment is used. In a domestic microwave oven, the high and low field strengths commonly referred to as “hot and cold” spots leads to a variations in temperature between different parts of the reaction mixture. Microwaves, no doubt, lead to increased reaction rates but the field of exposure and the time interval of irradiation, if not taken

care of, may spoil a reaction at the same time. Evidently, more research is required to investigate the underlying principles of this heating method. So, in order to achieve a microwave assisted organic synthesis in which factors like superheating effects,[7] dipolar mechanism, ionic conduction mechanism,[8] penetration effect, thermal effects,[9] etc do contribute to increased yields and shorter reaction times, but lack of reproducibility, because of inhomogenieties in microwave exposure and the heterogeneous field generated inside a domestic microwave oven does contribute to the exceptional results.

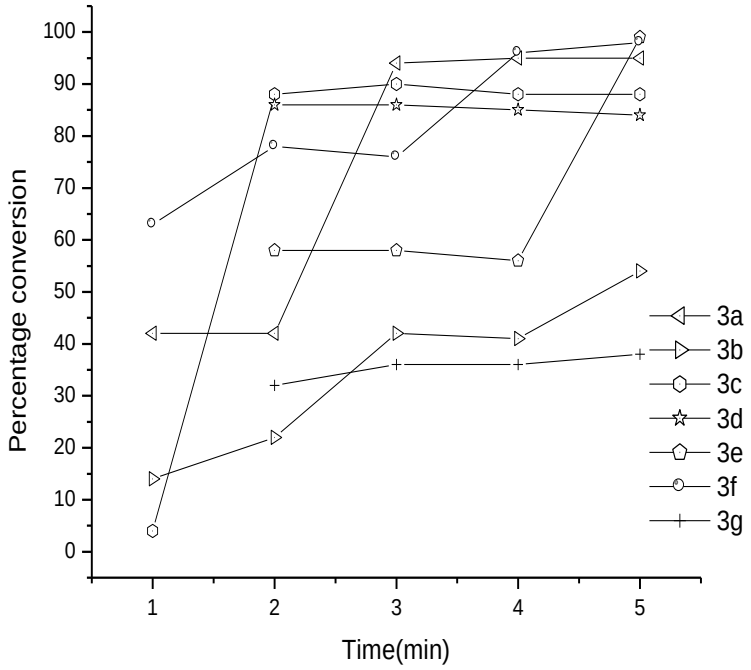


Fig. 37 UV spectra showing the progress of the reactions with time.

3.8 Experimental

All the reactions studied under UV analysis were carried out in a Sharp Carousel domestic microwave oven at a power level of 75% kept constant throughout all reactions. 4-Hydroxycoumarin (1mmol) and the corresponding aldehyde (0.5mmol) in a

2:1 molar ratio were dissolved in minimum amount of ethanol and adsorbed on silica-gel (60-120 mesh). Five such reactions in each case were irradiated at different times of 1, 2, 3, 4 and 5 minutes, respectively. The reaction mixture was eluted with acetone and after the removal of eluant, the mixture was dissolved in 20 ml chloroform. From the stocks thus prepared, aliquots of equal concentration were prepared in chloroform by dilution from the respective reaction mixtures. All the UV study in the work was carried out in a Schimadzu UV spectrophotometer in a 1cm quartz cell at room temperature in chloroform as the solvent.

Aliquots from each solution were subjected to the spectra over a wavelength range of 200-400 nm. Improved yields observed from the UV data when compared to their isolated yields amounts to losses during isolation and crystallization. Exceptions being when the aldehydes **2b** and **2g** were used, the isolated yield were better than as obtained from the UV data. This may be as a result of improper microwave exposure in the multimode oven.

3.9 Spectral data of biscoumarins 3a-g.

Spectral data of 3,3'-(3-chlorobenzylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-3a

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.1, IH, s,(H-11); 7.2-8.1,12H,m,(12×Ar-CH);

IR(KBr,cm^{-1}): 1663.9, 1617.7, 1568.5, 762.;

MS(m/z): 445.9(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 222-224 ^oC

Spectral data of 3,3'-phenylmethylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-3b

^{1}H-NMR(200 MHz, $CDCl_3$): δ6.2 IH,s,(H-11); 7.2-8.3,13H,m,(13× Ar-CH);

IR(KBr,cm^{-1}): 1661.1, 1618,1604.7, 1569.5, 762.2;

MS(m/z): 412(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 215 ^oC

Spectral data of 3,3'-(2-chlorobenzylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-3c

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.2, IH, s,(H-11); 7.3-8.2,12H,m,(12× Ar-CH);

IR(KBr,cm^{-1}): 1648.3, 1618.4, 1601.7, 1565.7, 767.9

MS(m/z): 445.9(ESI); **UV(λ_{max}) , $CHCl_3$:** 312 nm; **M.Pt.** 198-199 ^oC

Spectral data of 3,3'-(4-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-3d

^{1}H-NMR(200 MHz, $CDCl_3$): δ 3.9, 3H, s,(OCH_3); 6.2,IH,s,(H-11);6.9-8.2, 12H,m,(12×Ar-CH)

IR(KBr,cm^{-1}): 1654.3, 1636.3, 1560.4, 781.8

MS(m/z): 442(ESI); **UV(λ_{max}), $CHCl_3$:** 312 nm ; **M.Pt.** 238-240 ^oC

Spectral data of 3,3'-(4-hydroxy,3-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-3e

^{1}H-NMR(200 MHz, $CDCl_3$): δ6.8-7.9, m, 11H(11×Ar-CH), 8.1, 4-OH; 6.1,s,2(OH), 3.98, s, OCH_3, 5.6,s, CH.

IR(KBr,cm^{-1}): 1669.6, 1617.6, 1560.4, 1514.8, 768.1

MS(m/z): 458(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 212-15^oC

Spectral data of 3,3'-(4-chlorobenzylidene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-3f

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.1, IH, s,(H-11); 7.2-8.1,12H, m,(12× Ar-CH);

IR(KBr,cm^{-1}): 1663.9, 1617.7, 1568.5, 762.;

MS(m/z): 445.9(ESI); **UV(λ_{max}), $CHCl_3$:** 312 nm; **M.Pt.** 222-224 ^oC

Spectral data of 3,3'-(2-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-3g

^{1}H-NMR(200 MHz, $CDCl_3$): δ 6.7, IH, s,(H-11); 7.2-8.1,12H,m,(12×Ar-CH)

IR(KBr,cm^{-1}): 1653.87, 1616.2, 1567.9, 762.6

MS(m/z): 456.9(ESI); **UV(λ_{max}), $CHCl_3$:**312 nm; **M.Pt.** 200-202 ^oC

3.10 Conclusions

Ultraviolet spectroscopy has been successfully employed to study the kinetics of biscoumarin formation in the reaction of 4-hydroxycoumarin with various aldehydes under microwave irradiation. The calculated yields agree well with the isolated yields within experimental errors.

3.11 References

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Chapter 4

Part I

"Microwave-assisted reaction of dicoumarols with dimethylsulfoxide-acetic anhydride"

Abstract

4-Hydroxycoumarin and various biscoumarins synthesized under microwave conditions were treated with DMSO-Ac_2O reagent under same conditions to yield different products including some novel ones. A comparative account of the reactions with conventional procedure, as reported in literature, has been drawn and improved yields have been obtained in much lesser time under microwave conditions.

4.1 Introduction

Dimethyl sulfoxide (DMSO), initially used as a dipolar aprotic solvent especially in kinetic studies, has found extensive use in synthetic organic chemistry. Kornblum first used it to bring about oxidation of allylic halides and alcohols.[1] Subsequent use of sulfoxonium ylide as a source of methylene in the preparation of oxiranes and cyclopropanes by Corey and co-workers[2,3] opened a new area of DMSO chemistry.[4]

4.1.1 Physical properties

DMSO is a highly polar, high boiling, aprotic, water miscible, hygroscopic organic liquid. It is essentially odorless, water white and has a low order of toxicity. It is a versatile and powerful solvent that dissolves most aromatic and unsaturated hydrocarbons, organo-nitrogen compounds, organo-sulfur compounds and many inorganic salts. It is miscible with most of the common organic solvents such as alcohols, esters, ketones, lower ethers, chlorinated and aromatic solvents. However, saturated aliphatic hydrocarbons are virtually insoluble in DMSO.

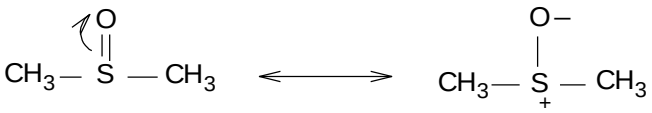
As a reaction solvent, DMSO is valuable for displacement, elimination, and condensation reactions involving anions. In DMSO, the rates of these reactions are often increased by several orders of magnitude. The most dominant characteristics of DMSO in its usefulness as a reaction solvent are its high polarity, essentially aprotic nature, and solvating ability toward cations. The high dipole moment of the sulfur-oxygen bond (4.3) and high dielectric constant (approx. 48) suggest its solvating properties and its ability to disperse charged solutes.

DMSO is not a hydrogen donor in hydrogen bonding and solvates anions poorly except by dipolar association to polarizable anions. The hydrogen atoms of DMSO are quite inert, although they are replaceable under sufficiently severe conditions (at pKa = 35.1). The oxygen of DMSO is somewhat basic and participates strongly as a hydrogen bond acceptor.[5]

4.1.2 Chemical properties

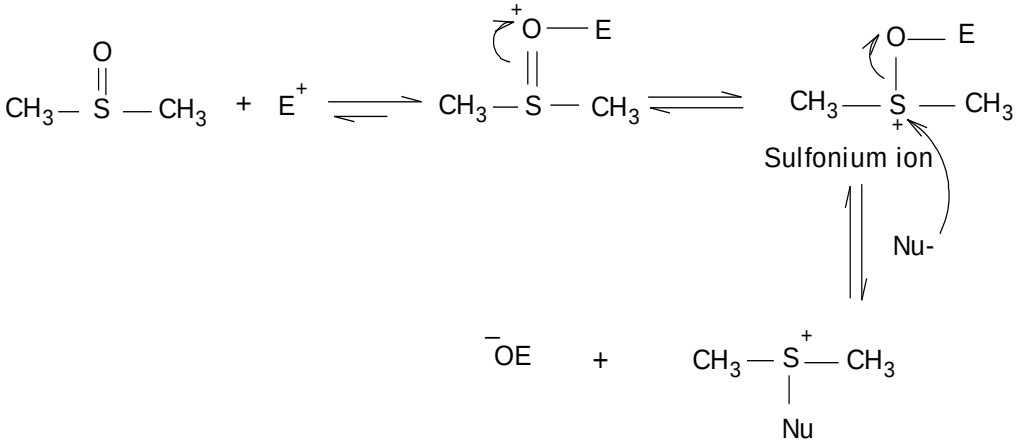
DMSO as a reagent

The reactivity of DMSO is mainly because of the presence of vacant 3d orbitals on sulfur atom like that of other compounds of sulfur. It exists as the mesomeric structures (i) and (ii).



(i) **(ii)**

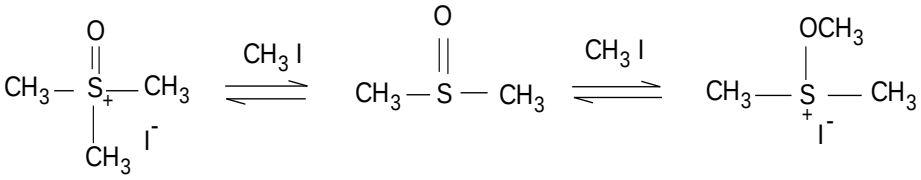
Reaction of dimethyl sulfoxide involves a nucleophilic attack on sulfur because of partial positive charge and vacant d-orbitals which, however, is not favored because of lone pair of electrons on sulfur. Therefore, an initial electrophilic attack on oxygen is necessary to facilitate attack by a nucleophile on sulfur to give sulfonium species, formation of which is followed by further reactions (*scheme 1*). [1]



Scheme 1. Initial electrophilic attack on dimethyl sulfoxide to form the sulfonium species followed by the nucleophilic attack.

Nucleophilicity of the sulfur atom in dimethyl sulfoxide has been observed only in a reaction when it is exposed to methyl iodide.[6] Of the two O- and S- alkylated products

formed, the latter is more stable and is the eventual product of prolonged methylation (*scheme 2*).



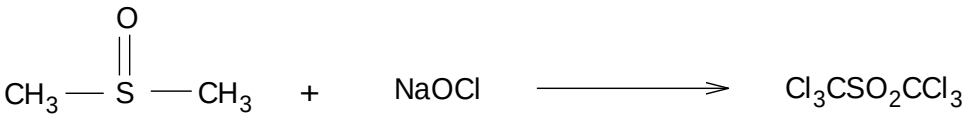
Scheme 2. Methylation of dimethyl sulfoxide with methyl iodide to give O-and S-alkylated products.

4.2 Some reactions of DMSO

4.2.1 Oxidation of DMSO

DMSO reacts with strong oxidizing agents to give dimethyl sulfone ($CH_3SO_2CH_3$). Oxidation with ozone gives a good yield of the sulfone. Both dichromate and permanganate oxidation have been used for quantitative determination of DMSO.

Aqueous chlorine under acidic conditions gives dimethyl sulfone and methanesulfonylchloride but under alkaline conditions, the oxidation is accompanied by chlorination to give hexachlorodimethylsulfone (*scheme 3*). [5]

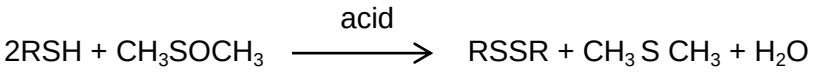


Scheme 3

DMSO also undergoes oxidation with hydrogen peroxide, organic peroxides or hydroperoxides, particularly, in presence of catalysts, to give the sulfone.[5]

4.2.2 Reduction of DMSO

DMSO is reduced to dimethyl sulfide (CH_3SCH_3) by a number of strong reducing agents, including aluminium hydrides and boranes. Mercaptans reduce acidified DMSO and themselves get oxidized to disulfides (*scheme 4*). [5]

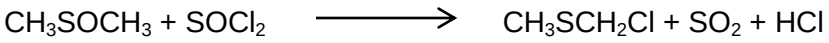


Scheme 4

4.2.3 Reaction with Acid Halides

DMSO has long been known to react with chlorine or acid chlorides, such as sulfur monochloride S_2Cl_2, to give chloromethyl methyl sulfide, whereas with sulfuryl chloride SO_2Cl_2, only 13% of the chloromethyl methyl sulfide is obtained. Aromatic sulfonyl chlorides, thionyl chloride and organic acid chlorides also give chloromethyl methyl sulfide.

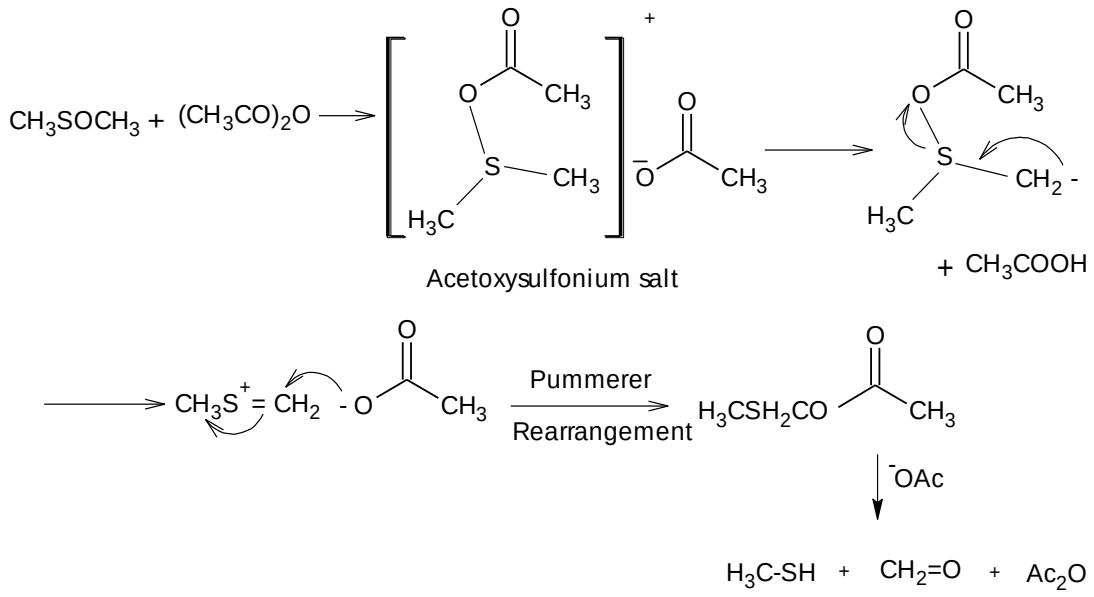
With thionyl chloride, the reaction can be represented as in *scheme 5*. [5]



Scheme 5

4.2.4 Reaction with Acid Anhydrides

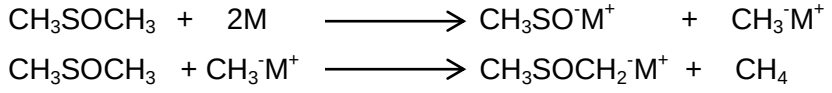
Carboxylic acid anhydrides react with DMSO in a manner similar to that of acid halides. With acetic anhydride, the final product is acetoxymethyl methyl sulfide ($CH_3CO_2CH_2SCH_3$) resulting through the Pummerer rearrangement. This product upon prolonged standing suffers $^{-}$OAc catalysed decomposition to give acetic anhydride, formaldehyde and thiomethanol. The first step in the reaction of DMSO with acetic anhydride is, however, the formation of the acetoxysulfonium salt (*Scheme 6*). [5]



Scheme 6

4.2.5 Reaction with Metals

The reaction of DMSO with sodium and potassium metals does not lead to simple removal of hydrogen, but leads to cleavage of carbon-sulfur bond. [5]

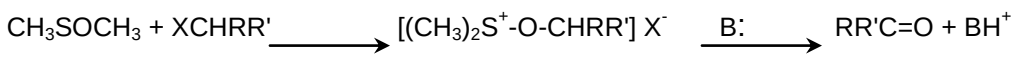


Scheme 7

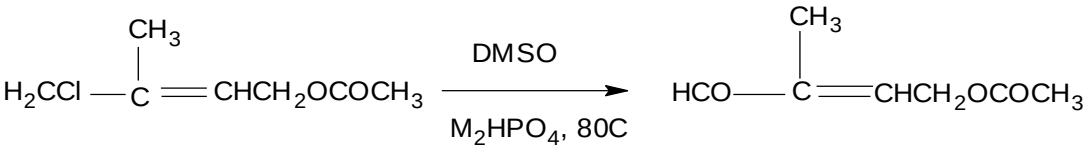
The electrolytic reduction of sodium chloride or sodium iodide in DMSO similarly leads to a mixture of hydrogen and methane gases at the cathode (*Scheme 7*). [5]

4.2.6 Kornblum Reaction

Kornblum and co-workers have demonstrated that in DMSO, α-bromoketones at room temperature and primary alkyl tosylates on heating afford the corresponding carbonyl compounds, presumably through an oxysulfonium intermediate. Some reactive alkyl halides, such as methyl iodide, also react with DMSO to form the oxosulfonium intermediate (the O-alkyl derivative). However, this intermediate rearranges readily to the more stable oxosulfonium salt, i.e. $(CH_3)_3S^+O^-$, and no oxidation takes place. [5]

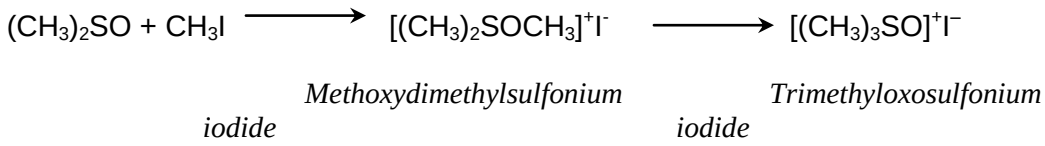


Some reactive halides, such as benzyl, can also be oxidized to the corresponding carbonyl compounds but higher reaction temperatures are necessary. An acid acceptor, e.g. sodium hydrogen carbonate, is frequently used. The relatively unreactive alkyl halides, such as 1-chloroheptane, can be oxidized by DMSO if the chloride is first converted to the tosylate. The DMSO oxidation of the primary allylic chloride, 4-chloro-3-methyl-2-buten-1-ol acetate, does not proceed well when sodium hydrogen carbonate is used as the acid acceptor. However, this reaction runs well when a dibasic metal phosphate, Na_2HPO_4 or K_2HPO_4, is used. [1,5]

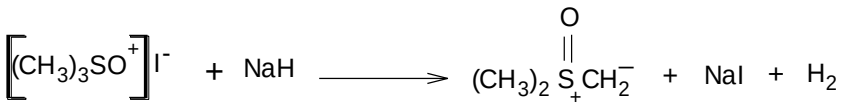


4.2.7 Methoxydimethylsulfonium Salts and Trimethyloxosulfonium Salts

Alkylating agents, such as methyl iodide, react initially with DMSO at the oxygen to give methoxydimethylsulfonium iodide (see the previous section, Kornblum reaction). These alkoxysulfonium salts are quite reactive and with continued heating either decompose to give the carbonyl compounds or rearrange to the more stable trimethyloxosulfonium salts. In case of methyl iodide, trimethylsoxosulfonium iodide is produced.



Trimethyloxosulfonium iodide is of interest because treatment with sodium hydride or dimethyl sodium produces dimethyloxosulfoniummethylide which is an excellent reagent for introducing a methylene group into a variety of structures. [5]



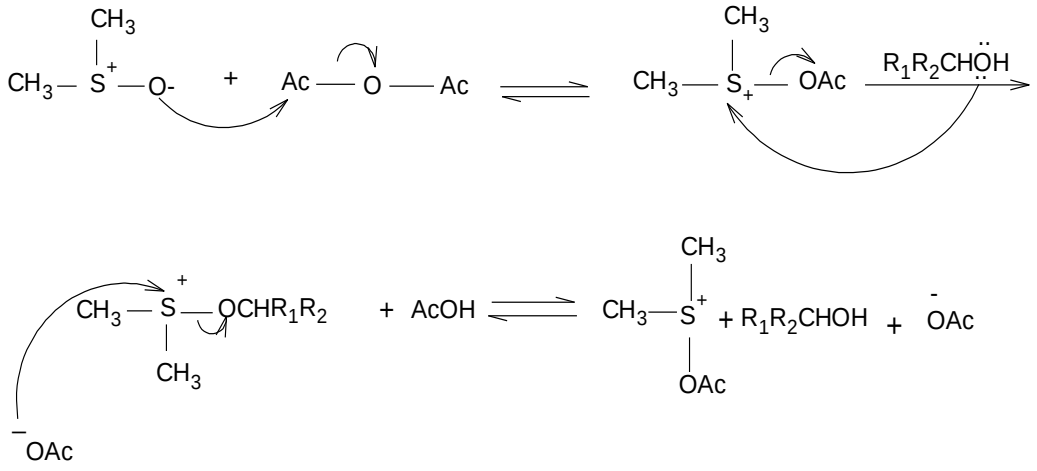
dimethyloxosulfonium methylide

4.3 Activating reagents

Dimethyl sulfoxide has been used as an oxidizing agent over the years and in combination with electrophilic activators like acetic anhydride,[8] TFAA,[15] oxalyl chloride,[17] etc., a variety of reactions have been reported.[7] Phenols, in general, undergo various oxidative reactions with DMSO activated by acetic anhydride or dicyclohexylcarbodiimide (DCC)[8].

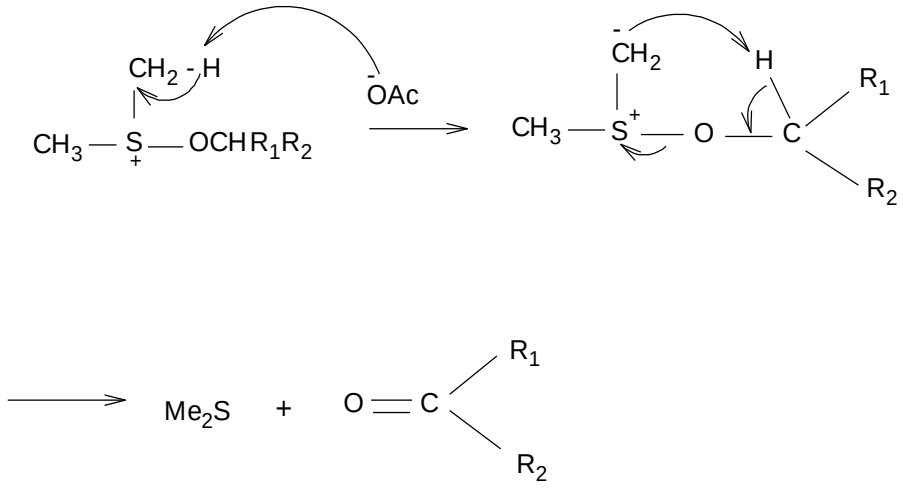
4.3.1 Acetic anhydride

The DMSO/Ac_2O oxidation is most generally applied to alcohols which are hindered and, therefore, are not acylated before establishment of oxygen-sulfur bond which is crucial to the oxidation reaction.[9] Acetic anhydride supplies both the electrophilic activator Ac^+ and base ^-OAc needed for abstraction of proton in the oxidation step. At low temperature, the initial steps of the reaction are reversible and may be written as depicted in scheme 8.[8]



Scheme 8. Reversible interaction of alcohols using dimethylsulfoxide-acetic anhydride mixture.

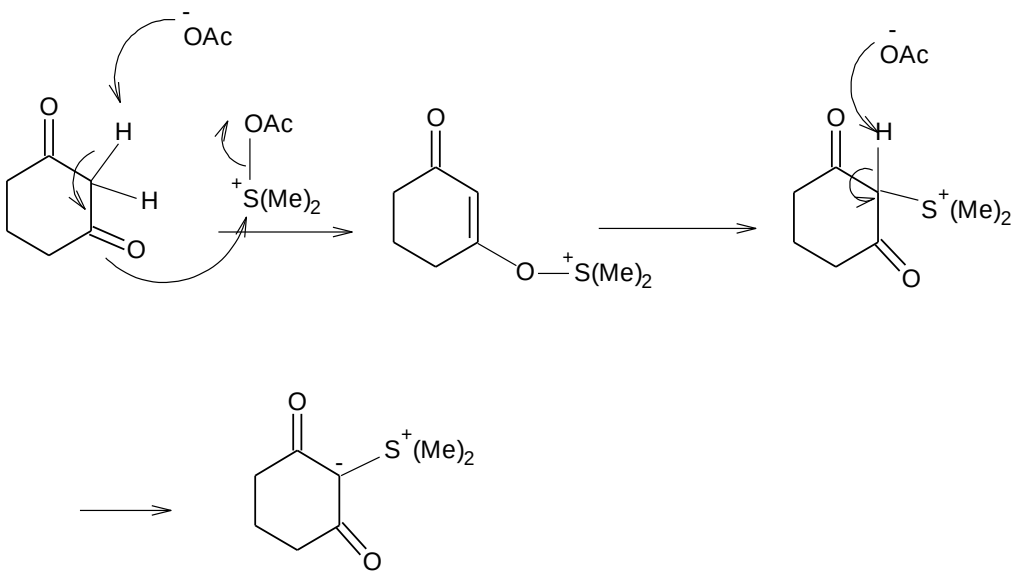
However, if the sulphonium salt of the alcohol does not undergo Pummerer rearrangement at the reaction temperature, ylide is formed which disintegrates to yield the carbonyl compound and dimethyl sulfide (*scheme 9*).[10]



Scheme 9. Ylide formation of the sulphonium salt followed by oxidation to carbonyl compound.

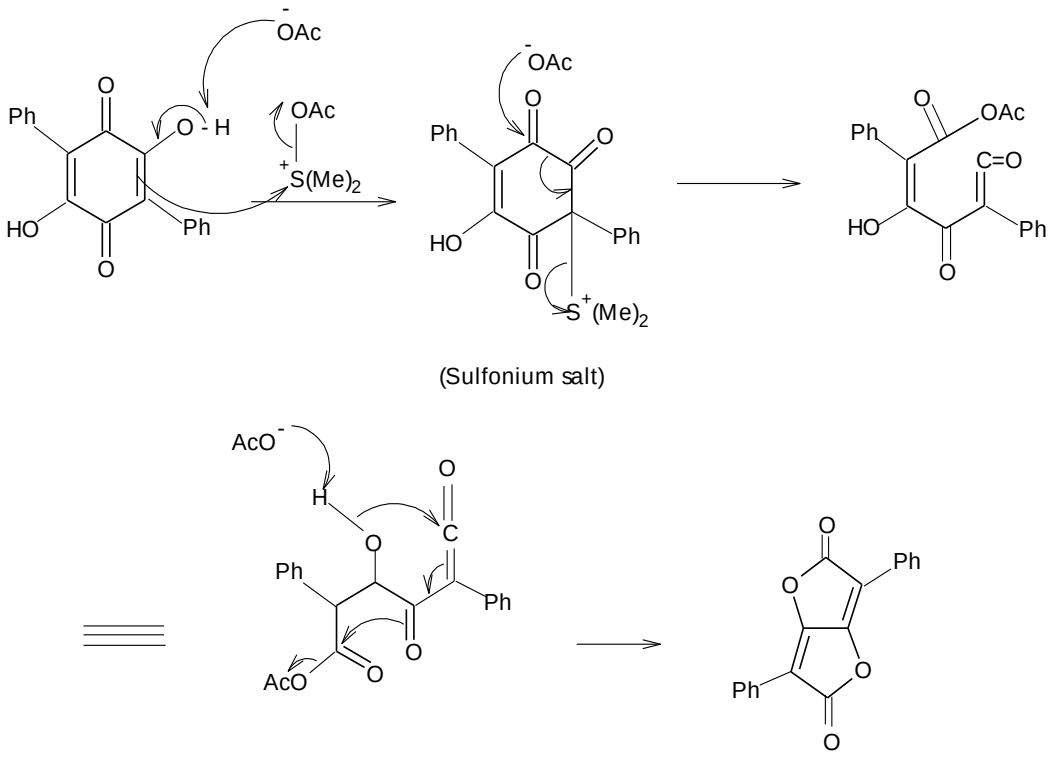
A number of side reactions take place when DMSO-acetic anhydride procedure is employed. The usual side products are acetates and methylthiomethyl ethers ($RR'CHOCH_2SCH_3$). The advantage of the acetic anhydride-DMSO mixture is the fact that highly hindered alcohols, which would be inert to other DMSO-activator systems, are oxidized.[7,8]

β-Dicarbonyl compounds are, however, different in that they react with this reagent to give stable sulfur ylides (*scheme 10*). [11]



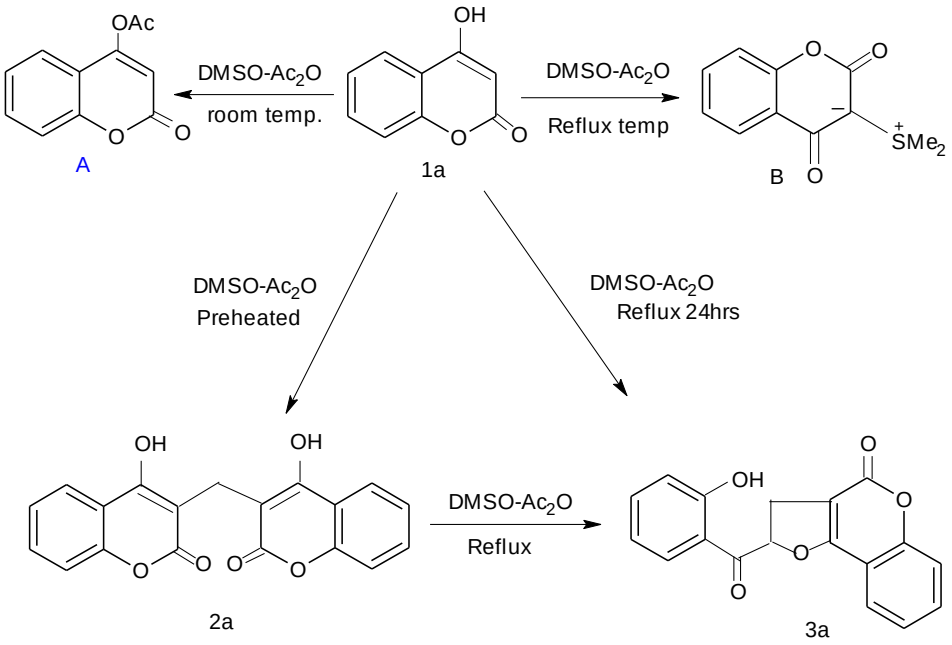
Scheme 10. Reaction of β-dicarbonyl compounds with DMSO/Ac_2O to give stable sulfur ylides.

DMSO activated by acetic anhydride induces oxidative rearrangements in 2, 5-dihydroxy-3, 6-diphenyl-1,4-benzoquinone to give pulvinic acid lactone (*scheme 11*).[7] The sulfonium intermediate stabilizes itself through fission of the quinone ring followed by cyclisation because ylide formation is not possible.



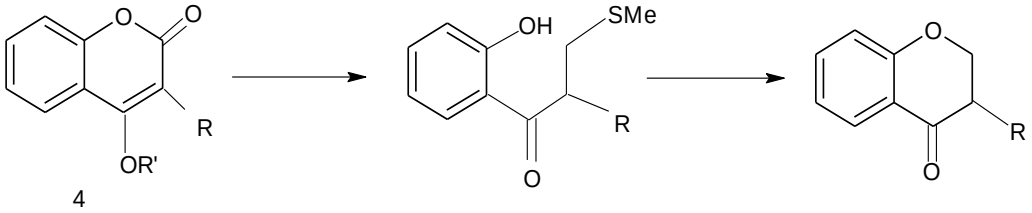
Scheme 11. Oxidative rearrangement in benzoquinone derivative using DMSO/Ac_2O.

Since 4-hydroxycoumarin and biscoumarins possess nucleophilic groups due to coumarin-chromone tautomerism, their interaction with DMSO/Ac_2O reagent, as expected, was fruitful. 4-Hydroxycoumarin (**1a**) and its derivatives have been reported to react with DMSO/Ac_2O under varying conditions of temperature to yield a range of products (*scheme 12*). [12] However, 4-Hydroxycoumarin derivatives give mixtures of methylthiomethyl derivatives, in addition, to dimeric product when the activator is P_4O_{10}.[12]Prior heating of the reagent has been reported to modify the property of the reagent to yield different products with 4-hydroxycoumarin derivatives. In some cases, either an oxidative rearrangement takes place or the formation of sulfonium ylids. [12]



Scheme 12. Reaction of 4-hydroxycoumarin with DMSO/Ac_2O to yield different products.

With 3-phenyl and 3-allyl-4-hydroxycoumarins (**4**), the reagent forms acetate (**4a**) at room temperature and undergoes extensive decomposition at reflux temperature but under controlled conditions, sulphides **(5)** are the main products which are easily converted to chromanones **(6)** (*scheme 13*). [13]



4

(R = Ph or Allyl; R'=H)

4a: (R'=Ac)

5

6

Scheme 13. Reaction of 3-phenyl and 3-allyl-4-hydroxycoumarin with DMSO/Ac_2O.

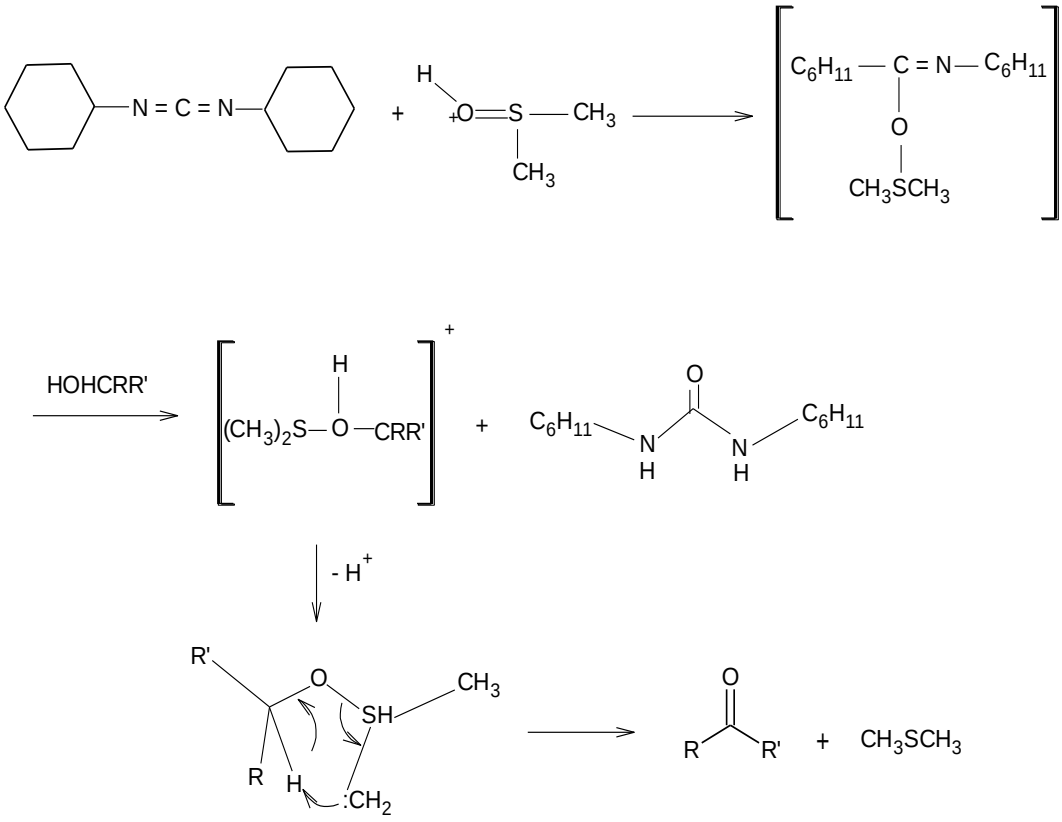
4.3.2 Trifluoroacetic anhydride

Trifluoroacetic anhydride and DMSO react exothermally at -60°C in methylene chloride to produce a white precipitate, presumably an ion pair, trifluoroacetoxy dimethylsulfonium trifluoroacetate $[(CH_3)_2S^+\text{-}O\text{-}COCF_3]^- OCOCF_3$. This reacts rapidly with

alcohols, even sterically hindered ones (e.g. 2-adamantol and neopentyl-type alcohols) to give the corresponding carbonyls. Trifluoroacetic anhydride is an excellent activator for DMSO because of short reaction times and high yields of carbonyl compounds with minimal by-product formation. The major drawback is the need to work at very low temperatures (-30 to -60° C). [5,14]

4.3.3 Dicyclohexylcarbodiimide

This method of oxidation is generally referred to as the "*Pfitzner-Moffatt*" technique. The reaction involves addition of an alcohol substrate to a solution of dicyclohexylcarbodiimide (DCC) in DMSO with an acid, such as phosphoric acid or pyridinium trifluoroacetate, present as a proton source. This results in reaction conditions near neutrality at room temperature. The oxidation technique is applicable to primary or secondary alcohol groups in an almost unlimited variety of compounds, including alkaloids, steroids and carbohydrates. Steric effects are not important except in highly hindered systems. In this reaction, DMSO molecule is first converted to a labile intermediate which is susceptible to attack at the sulfur by an alcohol group to produce an alkoxysulfonium salt which undergoes base-catalyzed decomposition to the carbonyl compound (*scheme 14*). Protecting groups such as isopropylidene, benzylidene, acetate, benzoate, and sulfonate esters and ethers are stable in the conditions used for oxidation. [5]



Scheme 14

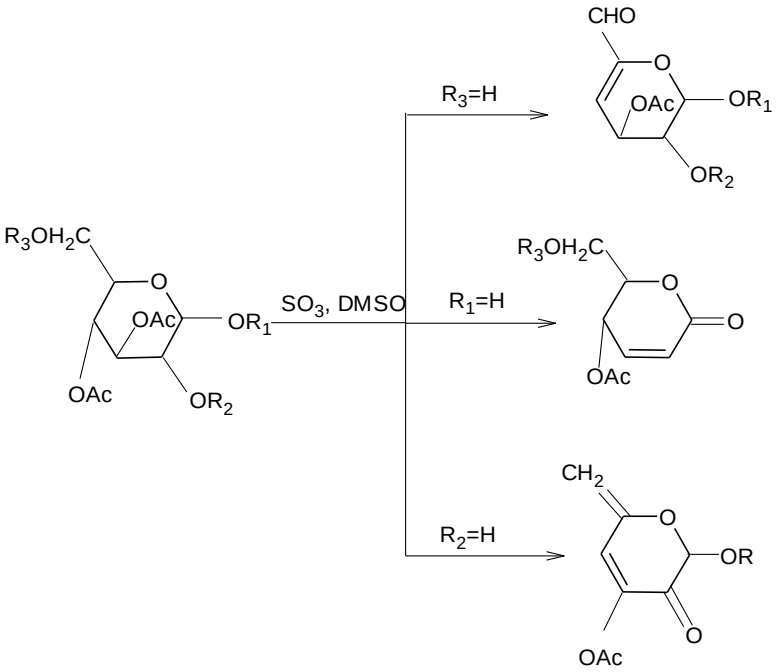
4.3.4 Phosphorus pentoxide

It has been found that DMSO containing phosphorus pentoxide rapidly oxidizes the alcoholic groups of carbohydrates and other compounds at room temperature or elevated temperatures to the corresponding aldehydes or ketones. In general, oxidations proceed most efficiently in the presence of 3-4 molar equivalents of DMSO and 1.2-2.0 molar equivalents of phosphorus pentoxide. The carbohydrate oxidation with DMSO-P_4O_{10} should be run at about 60-65°C. This system catalyzes carbohydrate polymerization at temperatures below 35° C. DMSO, DMF and pyridine seem to be the best solvents for this reaction. [15]

4.3.5 Sulfur trioxide-pyridine

The combination of DMSO with SO_3-pyridine complex in presence of triethylamine yields a reagent that rapidly oxidizes primary and secondary alcohols in good yield at room temperature to aldehydes and ketones, respectively. An attractive feature of this reagent is its property of affecting oxidation of allylic alcohols to the corresponding *α, β*-unsaturated carbonyl compounds. The SO_3-pyridine complex in DMSO can be used to

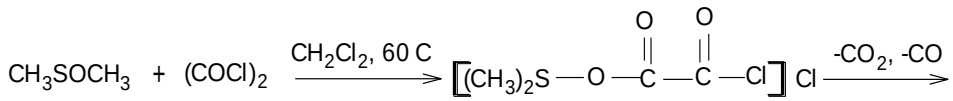
oxidize acid-labile trans-diols or cis-diols to quinones. This reagent has also been used to oxidize alkaloid hydroxyls to ketone groups. Application of the DMSO-SO_3-pyridine reagent to partially acetylated carbohydrates leads to oxidation as well as elimination of the elements of acetic acid, thus providing a high yield to novel unsaturated carbohydrates (*scheme 15*). [16]



Scheme 15

4.3.6 Oxalyl chloride

Oxalyl chloride is an efficient and useful activator, superior to trifluoroacetic anhydride, for the conversion of alcohols to their alkoxysulfonium salts which, upon basification, result in generally higher and frequently quantitative yields of the corresponding carbonyl compounds. The unstable intermediate formed at low temperatures (usually-60°C) instantaneously loses carbon dioxide and carbon monoxide. The new intermediate is the same as that proposed for dimethyl sulfide-chlorine reagent. This product has been reacted with a wide variety of alcohols to convert them to carbonyl compounds (*scheme 16*). [5,17]



Scheme 16

Apart from acetic anhydride, other electrophilic reagents that activate DMSO include chlorine[2], sulfonic anhydride[15], pyridine[16], oxalyl chloride[17], triflouroacetic acid[18], thionyl chloride[19], t-butylhypochlorite[20], triflouromethane[21], bromine[22], iodine[19], hypobromic acid and many other nucleophiles.[5]

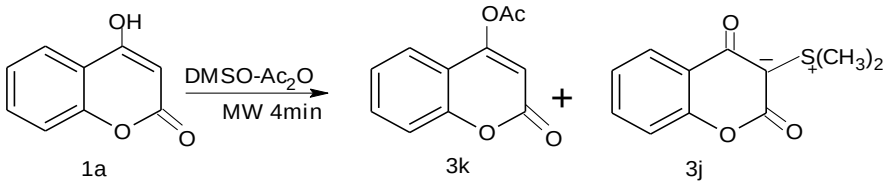
4.4 Results and Discussion

4-Hydroxycoumarins and dicoumarols both being enols and heterocyclic phenols, also having elements of structure in common with hydroxyquinone, react with DMSO-Ac_2O reagent under different conditions to yield a wide range of products (*scheme 7*). The outcome of the reaction depends upon the temperature at which it is carried out as well as whether DMSO-Ac_2O is used as such or as a preheated mixture; the products being different under different conditions. However, the reaction conditions are time consuming and tedious either requiring days at room temperature or hours of reflux at higher temperatures. [23-25]

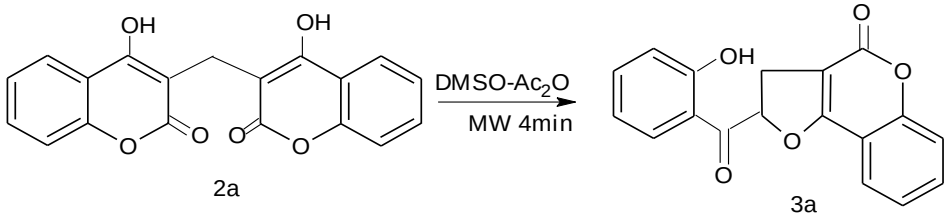
Since, this work deals with microwave-assisted synthesis of known temperature dependent reactions that have been carried out in a conventional way, various dicoumarols synthesized under microwave conditions were treated with the DMSO-Ac_2O reagent under same conditions and improved yields of the products were obtained in contrast to the classical procedure (*scheme 17, 18 and 19*).

The advantage of the synthesis is that reaction time has also considerably shortened from hours to a few minutes (*Table 1a,b*). The product in all the cases crystallized out of reaction mixture and residue on ether-aqueous workup followed by chromatographic purification yielded further of the product. This transformation of dicoumarols to their various derivatives under microwave conditions is much more efficient, time saving and

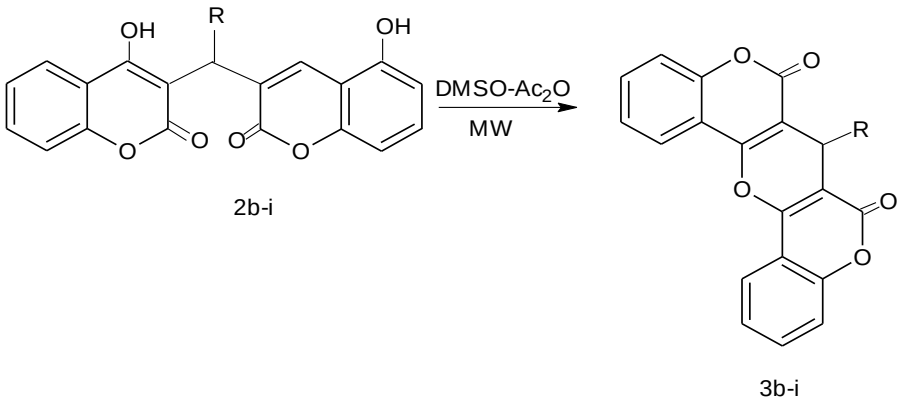
high yielding than conventional procedure. The mechanism of product formation has been shown in *schemes 20-22*. Dimethylsulfoxide being a polar solvent may contradict the increased rate of reaction because of its interaction with microwaves. But the same interaction may have led to a rapid increase in the temperature of reaction mixture on microwave exposure. Additionally, factors like superheating effect[26] along with other predicted microwave effects,[27,28] may also contribute to increase in reaction rates.



Scheme17. Microwave-assisted reaction of 4-hydroxycoumarin with dimethyl sulfoxide-acetic anhydride to yield the acetate(A) and ylide(B)



Scheme 18. Microwave-assisted transformation of dicoumarol into dihydrofurocoumarin using dimethyl sulfoxide-acetic anhydride mixture.

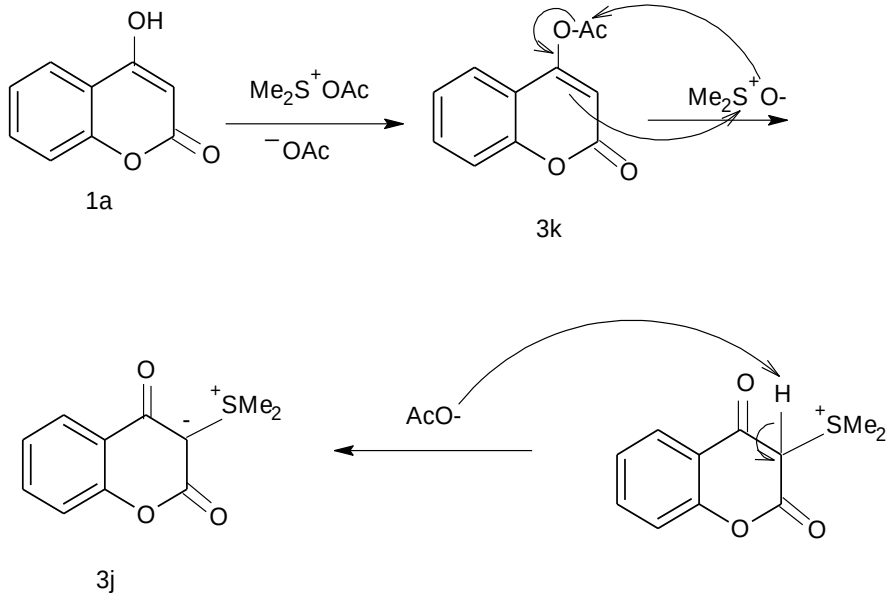


Scheme19. Microwave-assisted reaction of substituted biscoumarins with dimethylsulfoxide-acetic anhydride mixture to give products arising out of oxidative rearrangement and cyclisation.

In order to achieve the microwave-assisted transformation, 4-hydroxycoumarin (**1a**) and DMSO-Ac_2O were subjected to microwave irradiation in the corresponding amounts as shown in *table 1b*. 4-Hydroxycoumarin yields a variety of products with the reagent under different temperatures (*scheme 12*). At room temperature, its acetate (**3k**) is obtained (*scheme 20*). The same was obtained when performed under microwave irradiation at medium power. But when power level was increased, its ylide (**3j**) was the major product along with very minor amounts of the acetate. The mechanism of the formation of these products has been shown in *scheme 20*. Same products have been obtained when 4-hydoxycoumarin reacts with DMSO-Ac_2O at 120^0C. [12]

It is observed that majority of the products have very high melting points as compared with biscoumarins. This may be due to greater magnitude of Vander Waals forces due to high molecular weights. Moreover, decrease in yield in spite of the microwave conditions may be attributed to losses during isolation, chromatographic separation and crystallization.

Table 1a,b shows the relative amounts of the reactants and DMSO/Ac_2O mixture taken in each case. The relative amounts of DMSO/Ac_2O vary with the biscoumarin taken because of different nature of reactants as well as to their solubility to some extent in the reagent.



Scheme 20. Mechanism of ylide formation from 4-hydroxycoumarin using dimethyl sulfoxide-acetic anhydride as the reagent.

Table 1a. Synthesis of derivatives from various dicoumarols and 4-hydroxycoumarin microwave irradiation.

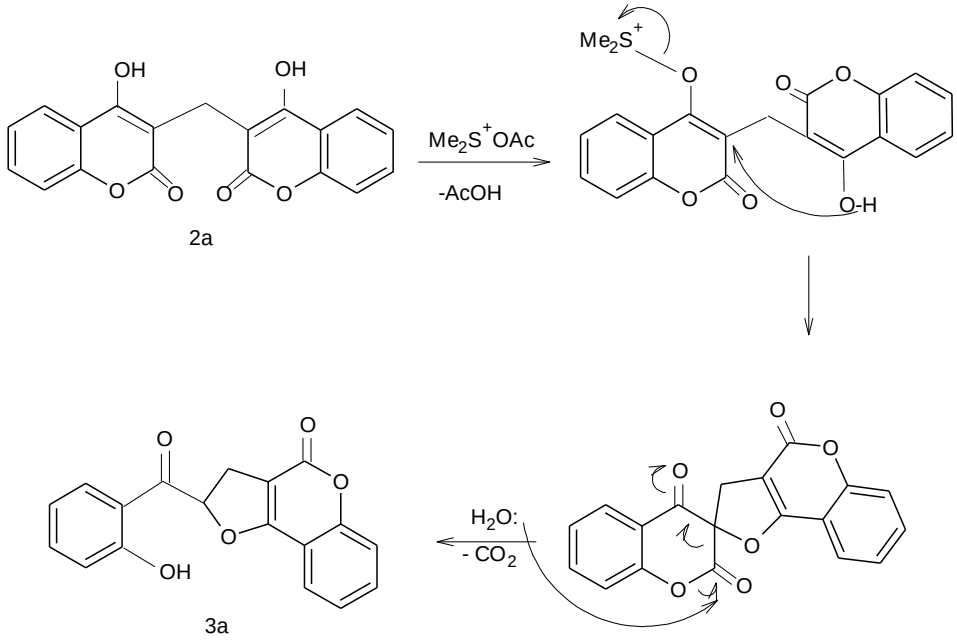
Dicoumarol (mmol)	DMSO/Ac_2O mixture (ml) 2:1 v/v ratio	$Time_{MW}$ (min)	R	Product	M.pt. (^0C)	Yld(%)	Lit. data*
2a - 6.0	18	4	H	**3a**	210	66	
2b - 7.3	15	2	C_6H_5	**3b**	320	66	13%-6hrs
2c - 6.7	9	1	$2ClC_6H_4$	**3c**	274-77	81	
2d - 6.7	6	5	$3ClC_6H_4$	**3d**	246-48	65	
2e - 6.7	9	1	$4ClC_6H_4$	**3e**	330	69	58%-20min
2f - 4.4	15	4	$2NO_2C_6H_4$	**3f**	302	62	10%-5.5hrs
2g - 4.4	9	2	$3NO_2C_6H_4$	**3g**	218	64	
2h - 2.2	12	6	$4NO_2C_6H_4$	**3h**	314	63	
2i - 6.8	6	3	$4CH_3OC_6H_4$	**3i**	287-88	64	28%-1.5hrs

*[23-25]

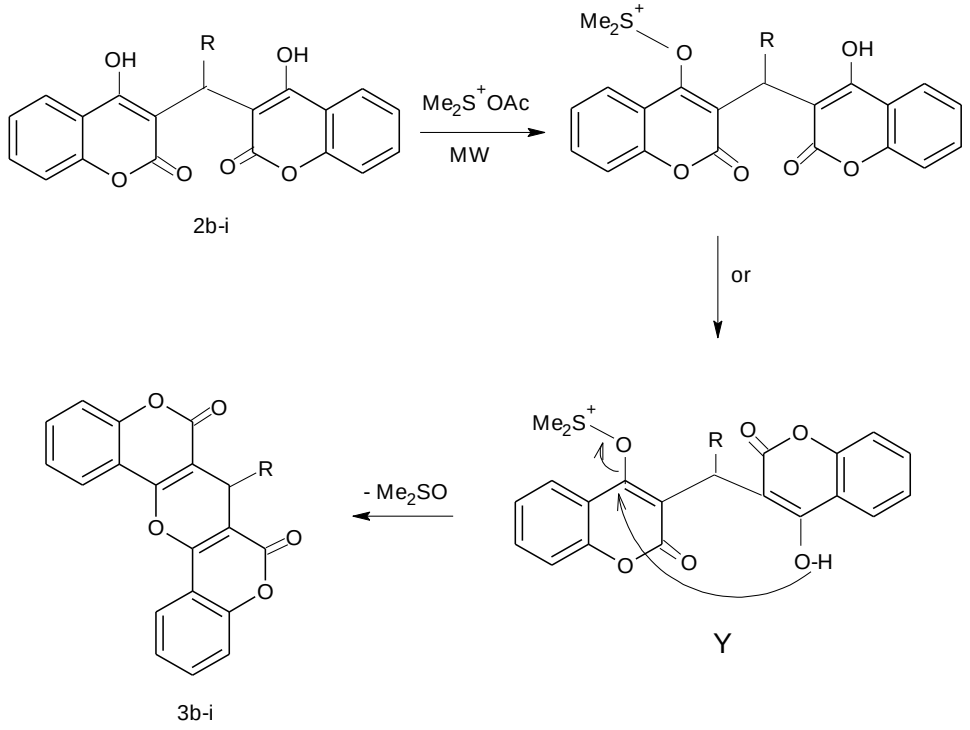
Table 1b. Microwave-assisted reaction of 4-hydroxycoumarin with DMSO-Ac_2O mixture.

4-Hydroxycoumarin (mmol)	DMSO/Ac_2O mixture (ml) 2:1 v/v ratio	$Time_{MW}$ (min)	Product	M.pt. (^0C)	Yld(%)	Lit. data*
1a - 6.2	3	4	**3j**	190	63	120^0C, 5hrs,75%
			3k	110-12	2	

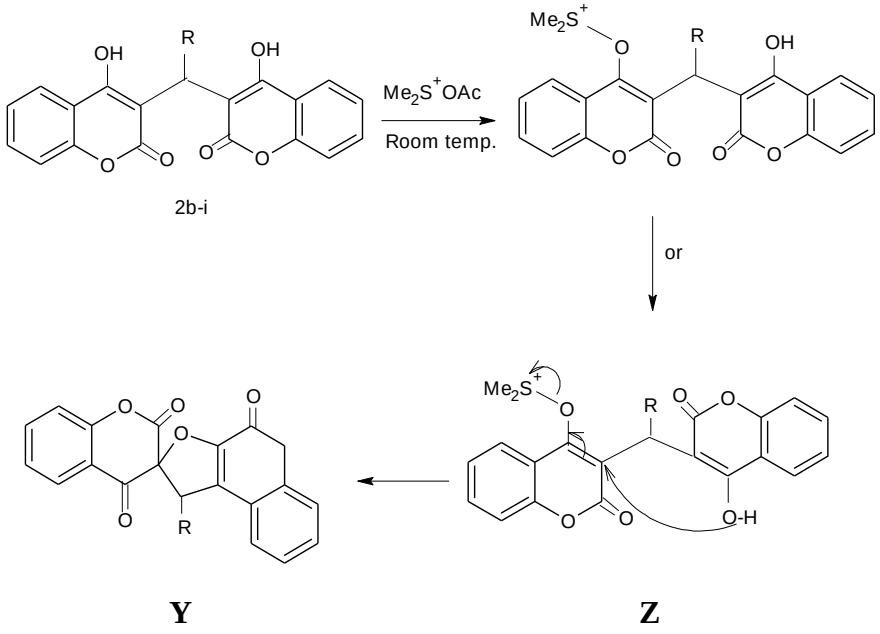
*[23-25]



Scheme 21. Mechanism of dihydrofurocoumarin formation from the reaction of dicoumarol with dimethylsulfoxide-acetic anhydride.



Scheme 22. Mechanism of formation of different benzopyranopyrans from the microwave-assisted reaction of dimethylsulfoxide-acetic anhydride mixture with substituted dicoumarols



*Scheme 23. Mechanism of formation of spiran derivative(**Y**) from the reaction of substituted biscoumarin with dimethylsulfoxide at room temperature.*

The coumarin hydroxyl is converted to oxosulphonium salt (**Y**) on treatment with DMSO/Ac_2O. At higher temperature, it cyclises with the elimination of dimethyl sulfoxide. At room temperature, though, only the spiran (**Z**) is reported to have been formed (*scheme 23*).[25] Since the reaction was carried out under microwave conditions, no spiran was formed in this case.

4.5 Experimental

Melting points were taken in open capillaries using the electrothermal method on a *Labotech/Perfit* instrument and are uncorrected. Infrared spectra were recorded on a *Perkin Elmer* 2000-FT spectrometer. Ultraviolet spectra were measured in chloroform (spectral grade) on a *Schimadzu* UV-1650PC UV/Visible Spectrophotometer. ^{1}H-NMR spectra were recorded on a 200MHz instrument using $CDCl_3$ as the solvent and TMS as the internal standard. All the solvents and chemicals used were of AR grade and 4-hydroxycoumarin, in particular, was of Spectrochemical grade. All reactions were carried out in a multimode *Sharp Carousel*^{TM} microwave oven. The products formed have been identified by a comparison of their spectra with those reported in literature. Physical properties also agree well in accordance with the data reported in literature. [12, 23-25]

Dimethyl sulfoxide was dried according to the standard procedure. In all the reactions, a 2:1 v/v ratio of DMSO-Ac_2O was used. Irradiations were carried out at intervals of one minute duration. Reaction mixtures were taken in 50 ml Erlenmeyer flasks covered with cotton plug to avoid moisture contact. TLC monitoring of the reactions established the completion of reaction or the point of no further progress. The products which precipitated out from the reaction mixture were filtered and washed thoroughly with distilled water to remove any DMSO/Ac_2O, dried and crystallized from appropriate solvent. The mother liquor was extracted with diethyl ether and chromatographed over silica gel and eluted with appropriate solvent system usually Chloroform: Petroleum ether mixture with increasing polarity.

4.5.1 Reaction between 3, 3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one) (2a) and DMSO/Ac_2O under microwave conditions to yield 2, 3- dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2-c][1]benzopyran-4-one (3a)

To 2 gms of 3, 3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one) (2a) was added 18 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug containing $CaCO_3$ to avoid moisture contact. The reaction mixture was subjected to microwave irradiation for 4 minutes- medium-hi power (75%) at intervals of 30 second duration to prevent uncontrolled heat generation. TLC monitoring indicated the progress of reaction. The white product which precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform.

Aqueous workup of the filtrate using extraction from ether yielded a mixture of compounds. The mixture was subjected to column chromatography but only 3a was obtained using petroleum ether-chloroform 50/50 v/v mixture as the eluant. Yield: 1.20 gms

Spectral data of 2, 3- dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2 c][1]benzopyran-4-one – (3a)

^{I}H-NMR (200MHz, $CDCl_3$): δ 6.35, IH, *q*, (O = C — C<u>H</u> — O —); δ 6.9-7.8, 8H, *m*, (8× Ar-CH); δ 3.6, 2H, *m*, (— CH — C<u>H_2</u> —); δ 11.7, 1H, *s*, (O<u>H</u>)

IR, ν_{max}(KBr, cm^{-1}): 1717.6, 1707.2, 1649.4

MS (m/z): 307.9(ESI); **M.Pt.** 210-212^{0}C; **λ_{max}, nm(MeOH)**: 214, 255, 312, 326

4.5.2 Reaction between 3, 3'-phenylmethylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2b) and DMSO/Ac_2O under microwave conditions to yield 7-Phenyl-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3b)

To 3 gms of 3, 3'-phenylmethylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2b) was added 15 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture contact. The reaction mixture was subjected to microwave irradiation for 2 minutes- medium-hi power (75%) at intervals of 30 second duration to control the heat generated. TLC monitoring indicated the progress of reaction. A dark brownish coloration was developed which on cooling yielded a crystalline

compound. The greenish crystalline product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform. Yield: 1.90 gms

Spectral data of 7-phenyl-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´- c]pyran- 6, 8 – dione – (3b)

^{I}H-NMR (200MHz, $CDCl_3$): δ 5.2, IH, *s*, (Ar-CH)

IR, ν_{max}(KBr, cm^{-1}): 1718.1, 1666.3, 1608.8, 1364.9

MS (m/z): 394(ESI); **M.Pt.** 320^0C

4.5.3 Reaction between 3, 3'-(2-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c) and DMSO/Ac_2O under microwave conditions to yield 7-(2-chlorophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3c)

To 3 gms of 3,3'-(2-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c) was added 9 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture contact. The reaction mixture was subjected to microwave irradiation for 1 minute- medium-hi power (75%) at intervals of 30 second duration to control the heat generated. TLC monitoring indicated the progress of reaction. The white product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform. Yield: 2.32 gms

Spectral data of 7-(2-chlorophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3c)

^{I}H-NMR (200MHz, $CDCl_3$): δ 5.2, IH, *s*, (CH); δ 7-8, 12H, *m*, (12×CH)

IR, ν_{max}(KBr, cm^{-1}): 1743.6, 1726.8, 1611.3, 1459.8, 753.7

MS(m/z): 428(ESI); **M.Pt.** $274\text{-}277^0$C

4.5.4 Reaction between 3, 3'-(3-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2d) and DMSO/Ac_2O under microwave conditions to yield 7-(3-chlorophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3d)

To 3 gms of 3, 3'-(3-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c) was added 6 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture contact. The reaction mixture subjected to microwave irradiation for 5 minutes- medium-hi power (75%) at interval of 30 seconds duration to control the heat generated. TLC monitoring indicated the progress of reaction. The white product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform. Yield: 1.86 gms

Spectral data of 7- (3-chlorophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3d)

^{I}H-NMR (200MHz, $CDCl_3$): δ 5.2, IH, *s*, (CH), δ 7.1-8.2, 12H, *m*, (12×Ar-CH)

IR, ν_{max}(KBr, cm^{-1}): 1727.6, 1651.8, 1629.1, 1610.3, 1602.0, 1367.1, 1111.6, 756.7

MS(m/z): 428(ESI); **M.Pt.** 245-48^{0}C

4.5.5 Reaction between 3, 3'-(4-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2e) and DMSO/Ac_2O under microwave conditions to yield 7-(4-chlorophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3e)

To 3 gms of 3, 3'-(4-chlorophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c) was added 9 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture contact. The reaction mixture subjected to microwave irradiation for 1 minute- medium-hi power (75%) at intervals of 30 seconds duration to control the heat generated. TLC monitoring indicated the progress of reaction. The white product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform. Yield: 1.97gms

Spectral data of 7- (4-chlorophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3e)

^{I}H-NMR (200MHz, $CDCl_3$): δ 5.2, IH, *s*, (CH), δ 7.25-8.2, 12H, *m*, (12×Ar-CH)

IR, ν_{max}(KBr, cm^{-1}): 1728.8, 1714.3, 1667.8, 1611.7

MS(m/z): 427.9(ESI); **M.Pt.** 330^{0}C

4.5.6 Reaction between 3, 3'-(2-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2f) and DMSO/Ac_2O under microwave conditions to yield 7-(2-nitrophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3f)

To 2 gms of 3, 3'-(2-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c) was added 15 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture contact. The reaction mixture was irradiated under microwaves for 4 minutes- medium-hi power (75%) at interval of 30 seconds duration to control the heat generated. TLC monitoring indicated the progress of reaction. The white product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform. Aqueous workup of the mother liquor yielded more of the product which was purified using column chromatography and chloroform as the solvent. Yield: 1.19gms

Spectral data of 7- (2-nitrophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3f)

^{I}H-NMR (200MHz, $CDCl_3$): δ 6.1, IH, *s*, (CH), δ 7.5-8.5, 12H, *m*, (12×Ar-CH)

IR, ν_{max}(KBr, cm^{-1}): 1724.0, 1666.1, 1610.4, 1529.8, 1364.8

MS(m/z): 439(ESI); **M.Pt.** 302^0C

4.5.7 Reaction between 3,3'-(3-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2g) and DMSO/Ac_2O under microwave conditions to yield 7-(3-nitrophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3g)

To 2 gms of 3, 3'-(3-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c) was added 9 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture contact. The reaction mixture was subjected to microwave irradiation for 2 minutes- medium-hi power (75%) at interval of 30 seconds duration to control the heat generated. TLC monitoring indicated the progress of reaction. The white product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform. Yield: 1.22gms

Spectral data of 7- (3-nitrophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3g)

^{I}H-NMR (200MHz, $CDCl_3$): δ 6.3, IH, *s*, (CH), δ 6.9-8.3, 12H, *m*, (12×Ar-CH)

IR, ν_{max}(KBr, cm^{-1}): 1717.4, 1648.6, 1607.9, 1530.8, 1351.4

MS(m/z): 439(ESI); **M.Pt.** 218^0C

4.5.8 Reaction between 3, 3'-(4-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2h) and DMSO/Ac_2O under microwave conditions to yield 7-(4-nitrophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3h)

To 1 gm of 3, 3'-(4-nitrophenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c) was added 12 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture contact. The reaction mixture was subjected to microwave irradiation for 6 minutes- medium-hi power (75%) at interval of 30 seconds duration to control the heat generated. TLC monitoring indicated the progress of reaction. The white product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform. Yield: 0.6gms

Spectral data of 7- (4-nitrophenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3h)

^{I}H-NMR (200MHz, $CDCl_3$): δ5.3, IH, *s*, (CH), δ 7.3-8.3, 12H, *m*, (12×CH)

IR, ν_{max}(KBr, cm^{-1}):

MS(m/z): 438.9(ESI); **M.Pt.** 314^0C

4.5.9 Reaction between 3, 3'-(4-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2i) and DMSO/Ac_2O under microwave conditions to yield 7-(4-methoxyphenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3i)

To 3 gms of 3, 3'-(4-methoxyphenylmethylene)-*bis*(4-hydroxy-*1H*-benzopyran-2-one)-(2c) was added 6 ml of 2:1 v/v mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture contact. The reaction mixture subjected to under microwave irradiation for 3 minutes- medium-hi power (75%) at interval of 30 seconds duration to control the heat generated. TLC monitoring indicated the progress of

reaction. The white product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, dried and crystallized from chloroform. Yield: 1.84gms

Spectral data of 7- (4-methoxyphenyl)-7H-*bis*[1]benzopyrano[4,3-b: 3´, 4´-c]pyran- 6, 8 – dione – (3i)

^{I}H-NMR (200MHz, $CDCl_3$): δ 7.25, IH, *s*, (CH); δ 7.5-7.7, 12H, *m*, (12×Ar-CH); δ 3.9, 3H, *s*, (OCH_3)

IR, ν_{max}(KBr, cm^{-1}): 1729.9, 1718.0, 1654.0, 1611.1, 1511.9

MS(m/z): 424(ESI); **M.Pt.** 287-88^{0}C

4.5.10. Reaction between 4-hydroxycoumarin (4-hydroxy-*1H*-benzopyran-2-one)- (1a) and DMSO/Ac_2O under microwave conditions to yield 3-dimethylsulphuranylidene chroman-2, 4-dione – (3j) and 4-acetoxycoumarin (3k)

To 1 gm of 4-hydroxycoumarin-(1a) was added 3 ml of 2:1 v/v(ml) mixture of DMSO/Ac_2O in a 50 ml Erlenmeyer flask and covered with a cotton plug to avoid moisture. The reaction mixture was subjected to microwave irradiation for 4 minutes-medium-hi power (75%) at interval of 30 seconds duration to control the heat generated. TLC monitoring indicated the progress of reaction. The white product precipitated out from the reaction mixture was filtered and washed thoroughly with distilled water, to remove DMSO, dried and crystallized from chloroform and identified as **3j**. Yield: 0.86gms

Aqueous workup of the filtrate using extraction by ether yielded a mixture of two compounds. The mixture was subjected to column chromatography to yield further of **3j** using petroleum ether-chloroform 50/50 v/v mixture as the eluant. The other product was identified as 4-acetoxycoumarin **(3k)**; Yield: 0.02gms

Spectral data of 3-dimethylsulphuranylidenechroman-2, 4-dione – (3j)

^{I}H-NMR (200MHz, $CDCl_3$): δ 3.2, 6H, *s*; $S^+(CH_3)$; 7.2-8.1, 4H, (Ar-4×CH)

IR, ν_{max}(KBr, cm^{-1}): 1674.8, 1612, 1598.2, 1556.3, 1358.9, 1291.8, 765.8

MS(m/z): 221.8(ESI); **M.Pt.** 190^{0}C

Spectral data of 4-acetoxy-*1H*-benzopyran-2-one - (3k)

IR, ν_{max}(KBr, cm^{-1}): 1768.1, 1728.3, 1608.6, 1198.2, 1175.5, 1138.6

M.Pt. 110-12^{0}C (similar to one reported in literature)

4.5 Conclusions

Dimethyl sulfoxide activated by acetic anhydride reacts with 4-hydroxycoumarin and various biscoumarins under microwave conditions to yield a variety of products. The transformations are achieved in much lesser time than required under conventional conditions and products obtained have tremendous pharmacological potential.

Part II

"UV Monitoring of the base hydrolysis of a dihydrofurocoumarin - the product from DMSO-Ac_2O oxidation of dicoumarol"

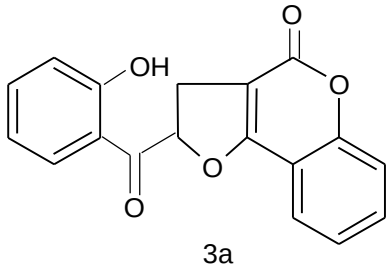
Abstract

"Base hydrolysis of a dihydrofurocoumarin obtained from the DMSO/Ac_2O oxidation of simple dicoumarol has been monitored by UV spectroscopy to asses its sensitivity under different basic conditions. The product has been found to be extraordinarily stable under basic conditions contrary to our belief."

4.6 Introduction

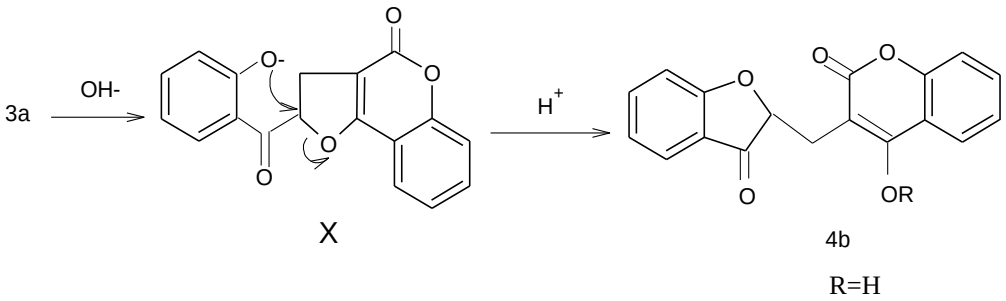
The most important chemical method used for structure determination of oxygen heterocycles including coumarins is the alkali induced degradation. Just as with other coumarins, aqueous hydrolysis begins with attack at the carbonyl group, though attack may also occur at the phenolic hydroxyl but experiments with deuteriated 4-methoxycoumarin, which serves as a model for the dihydrofurocoumarin, rules out the possibility.[29] In contrast to the expected two-stage hydrolysis, first the opening of the lactone ring and the second being further hydrolysis leading to cleavage of the ring, the hydrolysis stops at the lactone stage. In this work, alkaline hydrolysis of dihydrofurocoumarin synthesized from the DMSO/Ac_2O oxidation of dicoumarol under microwave conditions was monitored under UV spectrophotometry. The reaction was also carried out insitu within the UV spectrophotometer fitted with a temperature regulator.

4.7 Results and Discussion



3a

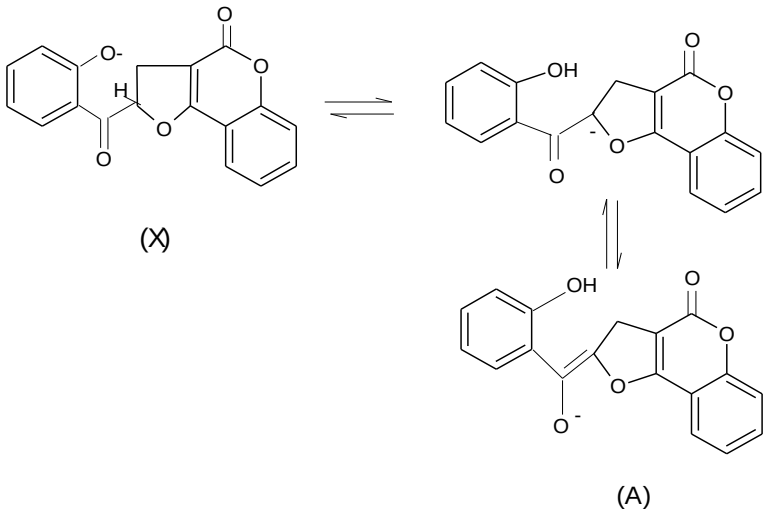
The compound (**3a**) has been found to be extremely sensitive to base. On treatment with methanolic alkali, the reaction requires only five minutes for completion at water bath temperature. However, as reported in literature, if the reaction time or the base strength is increased, a number of products result. [23]



Scheme 24. Mechanism of the base catalysed isomerisation of dihydrofurocoumarin derivative of dicoumarol.

When the reaction was monitored under a UV spectrophotometer, results came as a surprise in contrast to those reported in literature as well as an outcome of a possibility of cleavage of a similar analogue. Even after five minutes of heating, the base hydrolysis product was found to be stable enough to undergo further cleavage under basic conditions and no byproduct formation took place. The reaction was repeated under different conditions – strongly basic NaOH/KOH, aqueous alkaline, aqueous methanolic KOH/NaOH (50/50 v/v), but no significant results were obtained in each case (*figures 1-11*) except the first stage of hydrolysis to yield **4b**. The reaction is represented in scheme 24 but the situation is not as simple to explain as it appears (*scheme 24*).

There are several points where the attack of hydroxide ion might be expected to be fast. As regards the cleavage of C—O bond, it must be kept in mind that the leaving group is not equivalent to hydroxyl or methoxyl in character but, as the enol of the *β*-ketolactone, is rather like acetoxyl, which makes the observed reaction more understandable. This has to be weighed against the fact that the phenoxide is a poor nucleophile and the stretching of the C—O bond in the transition state would place a partial positive charge *α* – to the carbonyl group. According to older work, however, nucleophillic substitution is assisted by presence of an *α* – carbonyl.[29] Another factor of importance in this context, is enolisation of **X** to **A** which should atleast slow down the cleavage of the five membered ring required for transformation of **3a** to **4b** (*scheme 25*). The most important thing from the point of view of hydrolysis is that the hydroxide ion does not attack the conjugated double bond at all. In the light of these results, the reaction was monitored by UV spectrophotometry.



Scheme 25

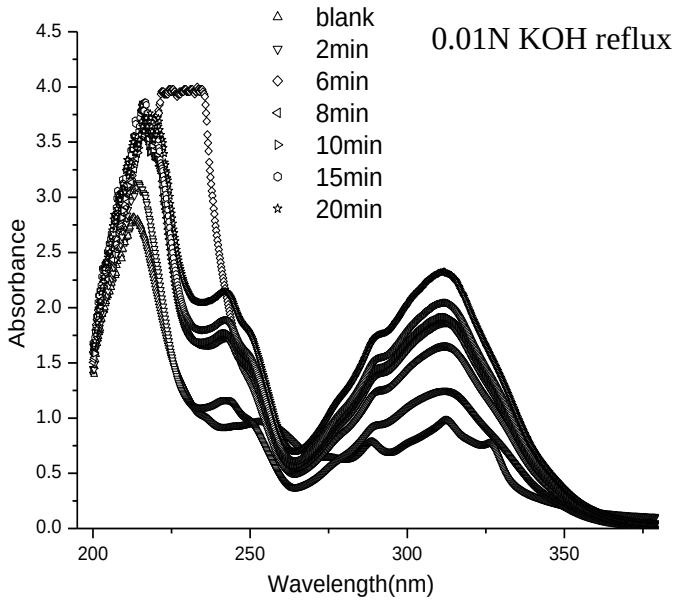


Figure 1. UV spectra of the base hydrolysis of 3a in 0.01N methanolic KOH at reflux temperature.

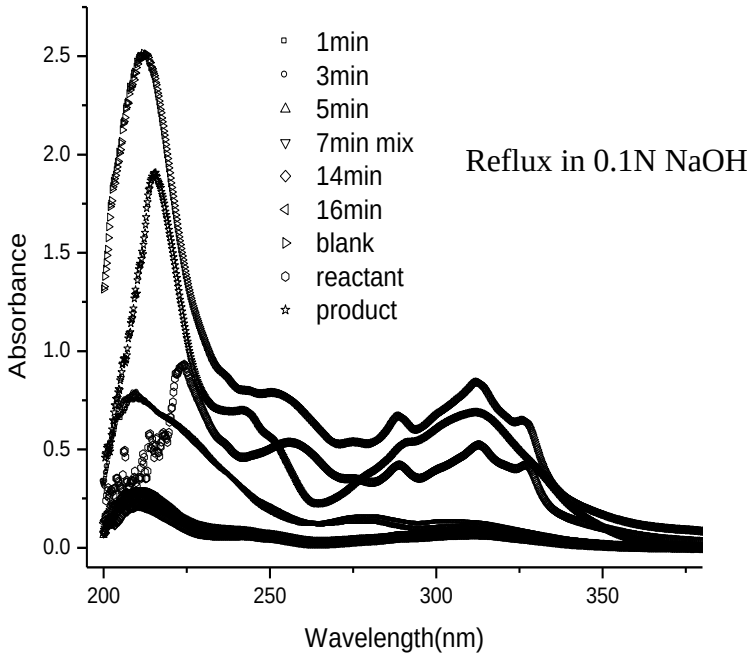


Figure 2. UV spectra of the base hydrolysis of 3a in 0.1N methanolic NaOH at reflux temperature

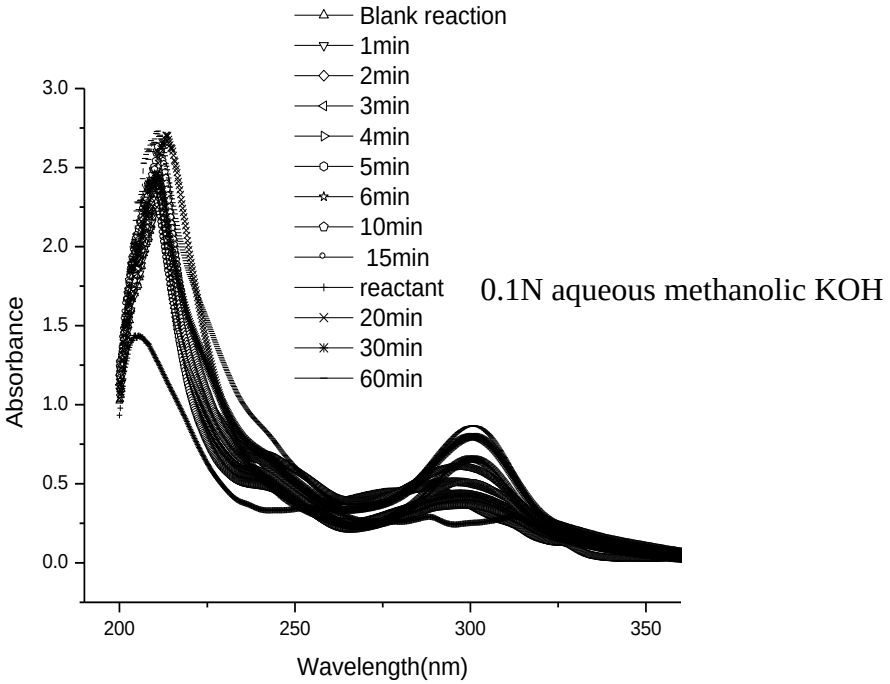


Figure 3. UV spectra of the base hydrolysis of 3a in 0.1N 50/50 v/v aqueous methamolic KOH at reflux temperature

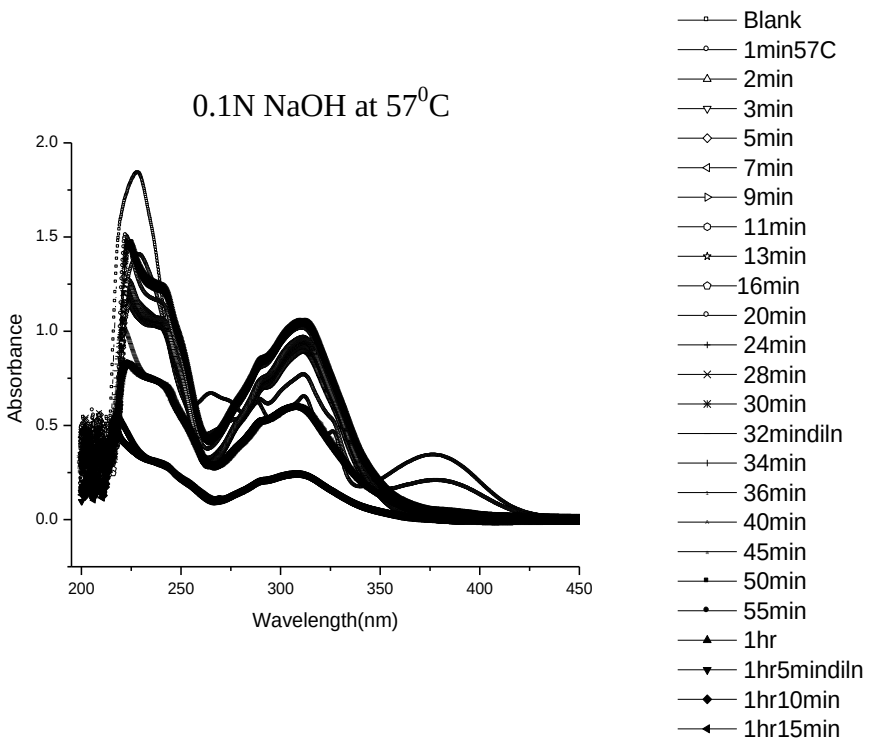


Figure 4. UV spectra of the base hydrolysis of 3a in 0.1N NaOH insitu in temperatute regulator UV of the instrument.

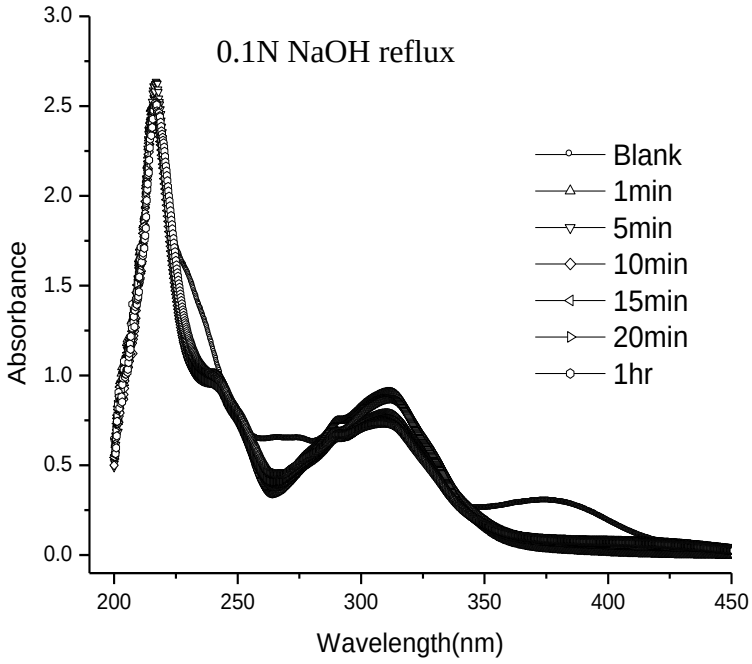


Figure 5. UV spectra of the base hydrolysis of 3a in 0.01N methanolic NaOH at reflux temperature.

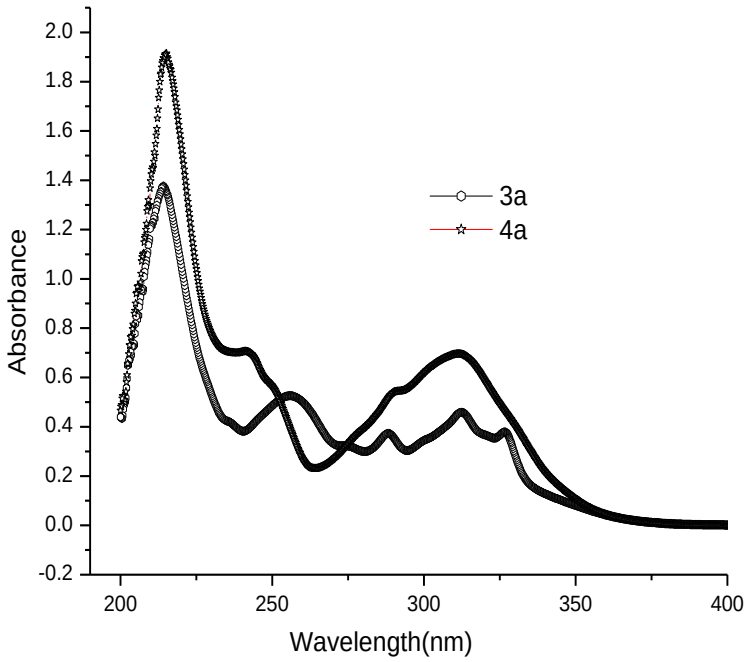


*Figure 6. UV spectra of **3a** and **4b** in methanol.*

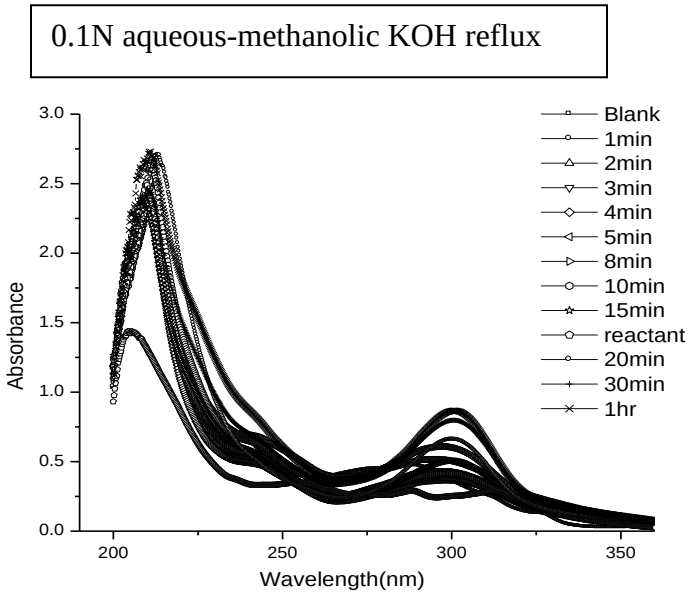


Figure 7. UV spectra of the base hydrolysis of 3a in 0.1N aq-methanolic KOH at reflux temperature

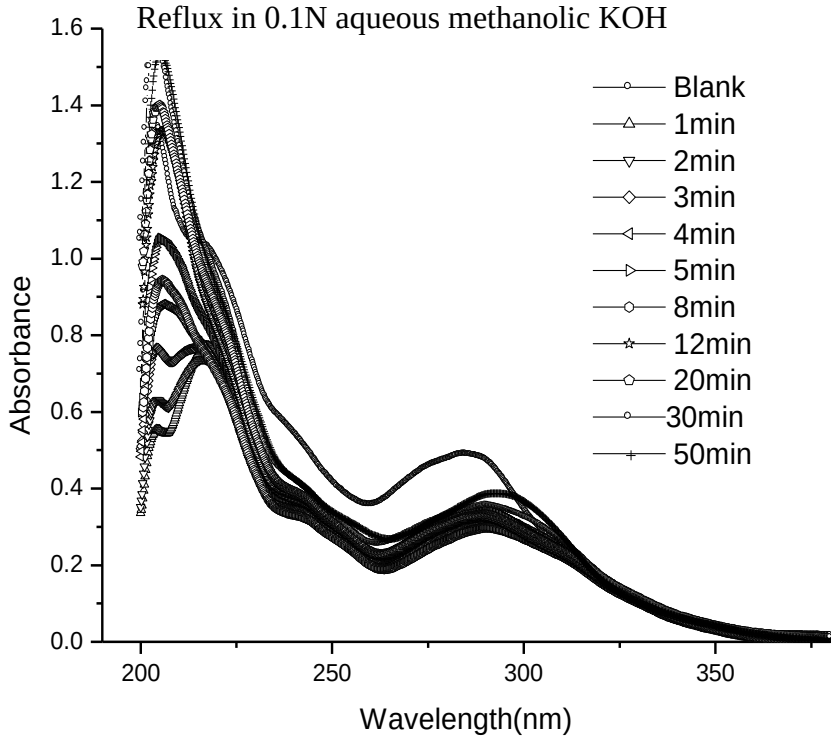


Figure 8. UV spectra of the base hydrolysis of 3a in 0.01N aqueous methavolic KOH at reflux temperature.

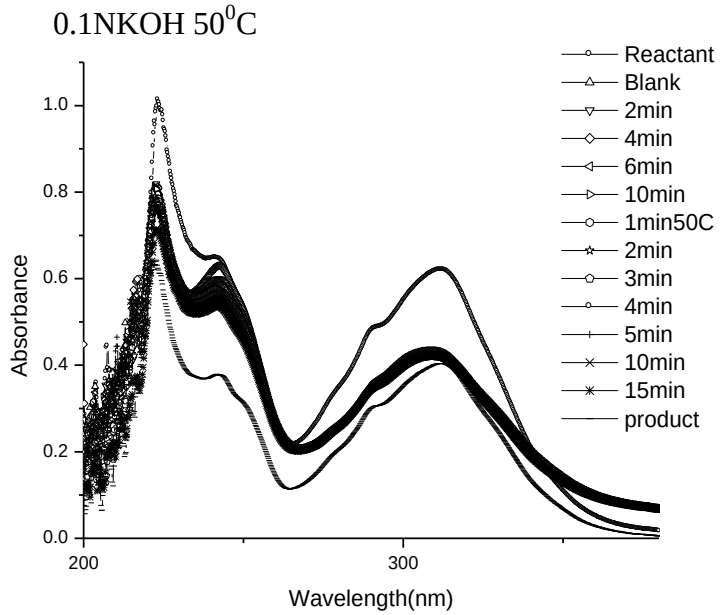


Figure 9. UV spectra of the base hydrolysis of 3a in 0.1N KOH at 50^{0}C in the instrument.

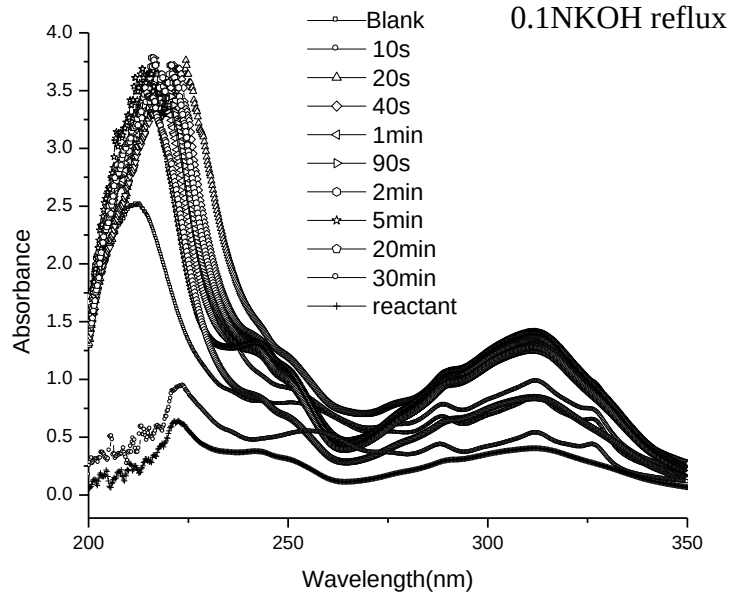


Figure 10. UV spectra of the base hydrolysis of 3a in 0.1N KOH at reflux temperature

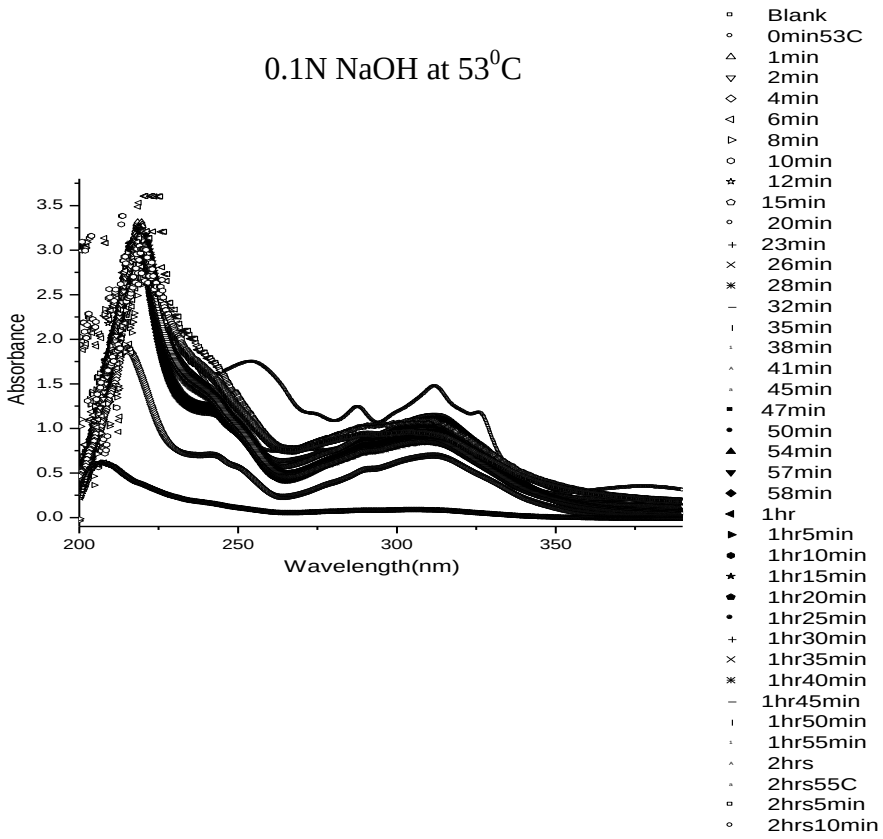


Figure 11. UV spectra of the base hydrolysis of 3a in 0.1N NaOH at 53^{0}C in the instrument(insitu).

4.8 Experimental

All the reactions were monitored using a Schimadzu (1650PC) UV spectrophotometer fitted with a temperature regulator. The solvent used was methanol that was dehydrated according to the standard procedure.

A methanolic solution of sodium hydroxide was added to 20 mg of 3a. Yellow colored solution obtained was diluted with water, concentrated to half of its volume and acidified with hydrochloric acid. The solid that precipitated out was filtered, washed with distilled water and dried. It was crystallized from methanol.

Spectral data of 4-hydroxy-3-[methylenebenzofuran-3(2H)-one-2-yl][1]benzopyran-2-one (4b)

^{I}H-NMR (90MHz, $CDCl_3$):δ 4.72, IH, *t*, (O= C—CH—); 3.22, 2H, *d*, (—CH—CH_2—)

IR, ν_{max}(KBr, cm^{-1}): 1705, 1655, 1620, 1605

MS(m/z): 308(ESI); **λ_{max}, nm(MeOH)**: 255, 305; **M.Pt.** 218^{0}C

4.9 Conclusions

Since the UV spectra of both **3a** and **4b** are almost identical and supposedly a conversion of **3a** to **4b** occurs, progress of such a transformation cannot be assessed by UV spectrophotometry. However, survival of **4b** possessing both coumarin and coumaranone moieties under basic conditions is intriguing. It may be assessed that although, in accordance with literature, hydrolysis of the dihydrofurocoumarin is very sensitive to dilute alkaline conditions, ultraviolet spectrophotometry may not be the suitable technique to follow its course especially those like **3a**.

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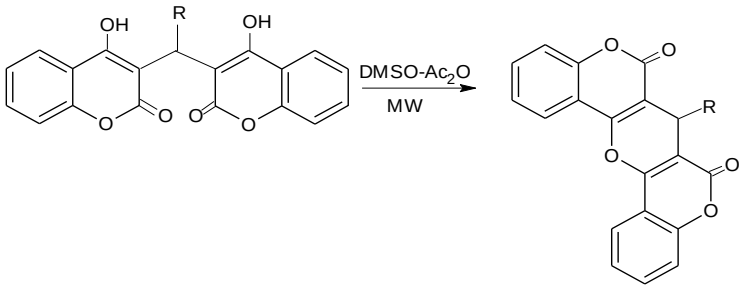
Summary

Microwave-assisted organic synthesis has blossomed into a useful technique and accelerations have been observed in a wide range of reactions. Microwaves have been successfully applied to combinatorial chemistry whereby synthesis of large numbers of molecules is achieved by varying combinations of molecular building blocks and permutations of modular components. Control of the desired selectivity (chemo, regio, stereo and enantioselectivity) is the most important objective in organic synthesis.The application of microwave irradiation involves the modifications of the reactivity as well as selectivity in relation to conventional heating.

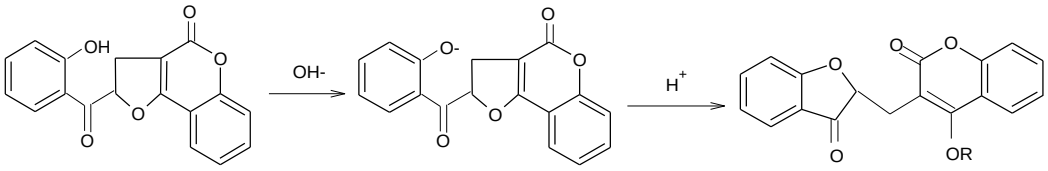
Microwave-assisted organic synthesis is a convenient and cost effective method of synthesizing potentially important compounds in an environmentally favorable way. A convenient synthesis of various biscoumarins is described by condensing a series of aldehydes with 4-hydroxycoumarin under microwave conditions for the first time along with a comparative account of their syntheses under conventional conditions. The reactions have been carried out in solvent media as well as under solvent-free conditions. The reaction times have been shortened considerably with improvement in yield in comparison to classical methods and the adopted procedure provides an energy and time-saving protocol. These biscoumarins have been prepared in good yields in minimum time through easy workups using this technique and a comparison has been drawn under solvent, solvent-free and conventional conditions.

Moreover, the synthesis has been supported by a UV monitoring of the reactions and a comparative account has been drawn between the calculated percentage conversions from UV data with the observed/isolated yields. The kinetics of the reactions have been studied by calculating percentage conversions with time and a comparison has been made from the data with that observed for the same reactions during the microwave-assisted synthesis of biscoumarins.

Synthetic transformations of various biscoumarins involving oxidative rearrangements using DMSO/Ac_2O oxidation has been carried out to get more derivatives of biscoumarins under ecofriendly conditions. 4-Hydroxycoumarin and various biscoumarins synthesized under microwave conditions were treated with DMSO-Ac_2O reagent under same conditions to yield different products including some novel ones. A comparative account of the reactions with conventional procedure, as reported in literature, has been drawn and improved yields have been obtained in minimum time under microwave conditions.



Base hydrolysis of a dihydrofurocoumarin obtained from the DMSO/Ac_2O oxidation of simple dicoumarol has been monitored using ultraviolet spectrophotometry to asses its sensitivity and stability under different basic conditions. The product has been found to be extraordinarily stable under basic conditions contrary to our belief.



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