“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 $1 \times 10^{12}$ - $6 \times 10^{8}$ 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.$^{[1]}$

<table>
<thead>
<tr>
<th>Spectral region</th>
<th>Wavelength range(m)</th>
<th>Frequency range(Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma$-rays</td>
<td>$1 \times 10^{12}$</td>
<td>$3 \times 10^{19}$</td>
</tr>
<tr>
<td>X-rays</td>
<td>$10^{-12}$ - $10 \times 10^{9}$</td>
<td>$3 \times 10^{19}$ - $3 \times 10^{16}$</td>
</tr>
<tr>
<td>Vacuum Ultraviolet</td>
<td>$10^{-9}$ - $200 \times 10^{-9}$</td>
<td>$3 \times 10^{16}$ - $1.5 \times 10^{15}$</td>
</tr>
<tr>
<td>Ultraviolet</td>
<td>$200$ - $400 \times 10^{-9}$</td>
<td>$1.5 \times 10^{15}$ - $7.5 \times 10^{14}$</td>
</tr>
<tr>
<td>Visible</td>
<td>$400$ - $800 \times 10^{-9}$</td>
<td>$7.5 \times 10^{14}$ - $3.8 \times 10^{14}$</td>
</tr>
<tr>
<td>Near Infrared</td>
<td>$0.8$ - $2.5 \times 10^{-6}$</td>
<td>$3.8 \times 10^{14}$ - $1 \times 10^{14}$</td>
</tr>
<tr>
<td>Mid Infrared</td>
<td>$2.5$ - $50 \times 10^{-6}$</td>
<td>$1 \times 10^{14}$ - $6 \times 10^{-12}$</td>
</tr>
<tr>
<td>Far Infrared</td>
<td>$50$ - $300 \times 10^{-6}$</td>
<td>$6 \times 10^{12}$ - $1 \times 10^{12}$</td>
</tr>
<tr>
<td>Microwaves</td>
<td>$0.3 \times 10^{-3}$ - $0.5$</td>
<td>$1 \times 10^{12}$ - $6 \times 10^{8}$</td>
</tr>
<tr>
<td>Radio waves</td>
<td>$0.5$ - $300$</td>
<td>$6 \times 10^{8}$ - $1 \times 10^{6}$</td>
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</table>

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.

![Microwave Reactor Diagram]

**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 irradiation and usually contains a turntable 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 (polytetrafluoroethylene PTFE) has been employed in the manufacture of reaction vessels and tubes that can withstand pressures up to 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 infrared 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.

![Dipolar molecules try to align with oscillating electric field of microwaves.](image)

*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](image-url)
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. 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

\[ \tan \delta = \varepsilon / \dot{\varepsilon} \]
Where $\delta$ = dissipation factor

$\varepsilon$ = dielectric loss

$\varepsilon$ = 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.\textsuperscript{[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.
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.\[^{[10]}\]

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 \textit{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.](image)

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. Microwave assisted synthesis is particularly important for industrial synthesis as it saves time, power and leads to improved yields (figure 10).

![Energy consumption of the syntheses](image)

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. 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°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. \cite{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).

\[
\text{Fig.11. Relative stabilities of more polar transition state (TS) and less polar ground state (GS) in a microwave driven reaction.}
\]

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]\n- 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. 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 organic 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.

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.

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.

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.

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.\[^{[35]}\]

\[\begin{align*}
\text{O} & \quad \text{RNH}_2 \\
\text{\text{CH}_2\text{C}_6\text{H}_5, 4\text{MeOC}_6\text{H}_4, 2\text{ClC}_6\text{H}_4, etc} & \quad (\text{MW, 100-200 W, 0.5-2.0 min., solvent-free})
\end{align*}\]

**1.9.1.2 Imidazoles**

An important preparation of imidazoles is from an \(\alpha\)-diketone, an aldehyde and ammonia. This microwave-assisted synthesis has been achieved in excellent yields in minimum time.\[^{[36]}\]

\[\begin{align*}
\text{O} & \quad \text{O} \\
\text{\text{R}_1} & \quad \text{NH}_4\text{OAc} \\
\text{\text{R}_2} & \quad \text{Al}_2\text{O}_3 \\
\text{\text{R}_3} & \quad \text{NH} \\
\text{\text{R}_2} & \quad \text{R}_1 \\
\text{\text{R}_3} & \quad \text{R}_1 \\
\text{\text{R}_3} & \quad \text{R}_2
\end{align*}\]

\(75-85\%\)

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

\(\text{R}_1 = \text{C}_6\text{H}_5, 4\text{ClC}_6\text{H}_4, 2\text{-thiophenyl etc.}
\)

\(\text{R}_2 = \text{R}_3 = \text{C}_6\text{H}_5, 4\text{MeC}_6\text{H}_4\)

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 benzyolated 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 \( o \)-hydroxydibenzoylemethanes adsorbed on montmorillonite K 10 clay for 1–2 minutes. Rapid and exclusive formation of cyclized flavones occurs in good yields.[38]
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.\(^{[40]}\)

\[
\text{PHTHALIMIDE} + \text{R} - \text{X} + \text{K}_2\text{CO}_3, \text{TBAB} \xrightarrow{\text{MW}= 4-10 \text{ min}} \text{PHTHALIMIDE-}N-R
\]

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 acetox 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.\(^{[41]}\)
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 (MnO₂), potassium permanganate (KMnO₄), chromium trioxide (CrO₃), potassium chromate (K₂CrO₄), and potassium dichromate (K₂Cr₂O₇), 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]

\[
\begin{align*}
R_1 \quad \text{Clayfen} \quad R_2 \\
\xrightarrow{\text{MW 50-60sec}} \\
\text{CH} \quad \text{OH} \quad \xrightarrow{\text{Clayfen}} \\
\text{C} \quad \text{O} \\
(87-96\%)
\end{align*}
\]

\[R_1 = \text{Ph, 4MeC}_6\text{H}_4, 4\text{MeOC}_6\text{H}_4; R_2 = \text{H}\]

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]

\[
\begin{align*}
R_1 \quad \text{CH} \quad \text{OH} \\
\xrightarrow{\text{MnO}_2\text{-Silica}} \\
\text{C} \quad \text{O} \\
(67-96\%)
\end{align*}
\]

\[R_1 = \text{Ph, 4MeC}_6\text{H}_4, 4\text{MeOC}_6\text{H}_4, \text{Ph-CH=CH}; R_2 = \text{H}\]

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]

\[
\begin{align*}
\text{KMnO}_4 \text{ on Alumina} \\
\xrightarrow{\text{MW}} \\
\text{O}
\end{align*}
\]
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]

\[
\begin{align*}
\text{OH} & \quad \text{OH} & \quad \text{Al}^{3+} \text{ Montmorillonite} \\
\text{OH} & \quad \text{OMW 15min} & \quad \text{98-99%}
\end{align*}
\]

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]

\[
\begin{align*}
\text{R}_1 \quad \text{C} = \text{N} & \quad \text{OH} & \quad \text{Montmorillonite K}0 \text{ Clay} \\
\text{MW 7-10 min} & \quad \text{O} & \quad \text{R}_1 \\
\text{NH} & \quad \text{R}_2
\end{align*}
\]

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 \textit{via} the reactions of primary and secondary amines with aldehydes and ketones, respectively.\cite{48}

\[
\text{X = H, 2-OH, 4-OH, 4-Me, 4-OMe, 4-NMe}_2
\]

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.\cite{49}

The useful synthesis of coumarins \textit{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.\cite{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.\[53\]

\[\text{CHO} \quad R \quad R_1 \quad \text{OH} \quad + \quad \text{Piperidine} \quad \xrightarrow{\text{MW}} \quad \text{CN} \quad R \quad R_1 \quad \text{CO}_2\text{Et} \]

\( R_1 = \text{H, R}_2 = \text{H, OMe, NO}_2, \text{OH, Br, Me} \)

\( R_1 = R_2 = \text{OMe} \)

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 $\alpha$-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. 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, 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)$_2$·8H$_2$O, surface which demonstrates the first application of this reagent in a solvent-free crossed Cannizzaro reaction. 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.

\[
\text{RCHO} + (\text{CH}_2\text{O})_n \xrightleftharpoons{\text{MW, Ba(OH)}_2\cdot8\text{H}_2\text{O}} \text{RCH}_2\text{OH} + \text{RCOOH} \\
(80-99\%) \quad (1-20\%)
\]

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, Acetylations, Asymmetric Reactions Carbohydrates, CO Insertions Condensations, Cyanations, Cycloadditions, Reactions Involving Ionic Liquids, Michael Reactions, Multicomponent Synthesis, Photochemistry, Polymerisation, Solid-Phase Reactions, and so on.

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.

1.11 References

15. Loupy, A. Solvent free microwave organic synthesis as an efficient procedure for green chemistry, Chimie, (2004), 7, 103-112.


