CHAPTER-V

Microwave assisted organic synthesis

PART A

Introduction to microwave chemistry and microwave assisted organic reactions
VA. 1. INTRODUCTION TO MICROWAVE CHEMISTRY

VA. 1.1. INTRODUCTION[1]

Microwave irradiation provides an alternative to the conventional methods, for heating or introducing energy into the system. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Microwave-assisted reactions are fast, clean,[2] economic and eco-friendly and this technique has been proposed as the “technology of tomorrow”.

Microwave heating began to gain wide acceptance following papers in 1986 by the groups of Gedye and Giguere / Majetich. The use of microwave heating in chemical[3, 4] modification can be traced back to the 1950 s. In the early days of microwave synthesis, experiments were typically carried out in sealed teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. Microwave chemistry involves the use of microwave irradiation to conduct chemical reactions, and essentially pertains to chemical analysis and chemical synthesis. Microwaves lie in the electromagnetic spectrum between infrared waves and radio waves. They have wavelengths between 0.01 and 1 meter, and operate in a frequency range between 300 and about 300,000 MHz (Fig. VA.1). However, for their use in laboratory reactions, a frequency of 2,450 MHz is preferred, since this frequency has the right penetration depth for laboratory reaction conditions.


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Microwaves are powerful and reliable source of energy that may be adapted to many fields. Understanding the basic theory behind microwaves will provide the organic chemists the right tools and knowledge to effectively apply microwave energy to many synthetic route. Microwave synthesis gives organic chemists more time to expand their scientific creativity, try new theories and develop new processes. Microwave energy (Fig. VA.2) consists of an electric and a magnetic field, though only the electric field transfers energy to a heat substance.[5] Magnetic field interactions do not normally occur in chemical synthesis.


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Microwaves move at the speed of light (300,000 km/sec). The energy in microwave photons (0.037 kcal/mole) is very low relative to the typical energy required to cleave molecular bonds (80–120 kcal/mole) thus, microwaves will not affect the structure of an organic molecule. When there is excitation of molecules, the effect of microwave absorption is purely kinetic.

Traditionally, chemical synthesis has been achieved through conductive heating with an external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and reactants (Fig. VA.3). This is a slow and inefficient method for transferring energy into the system because it depends on the thermal conductivity of the various materials that must be penetrated. It results in the temperature of the vessel being higher than that of the reaction mixture inside until sufficient time has elapsed to allow the container and contents to attain thermal equilibrium. This process can take hours. Conductive heating also hinders the chemist’s control over the reaction. The heat source must physically be removed and cooling administered to reduce the internal bulk temperature. Here temperature on the outer surface is greater than the internal temperature.

**Fig. VA.3. Schematic representation of sample heating by conduction**

Microwave heating, on the other hand, is a very different process. As shown in (Fig. VA.4), the microwaves couple directly with the molecules that are present in the reaction mixture, leading to a rapid rise in temperature. Because the process is not dependent upon the thermal conductivity of the vessel materials, the result is an instantaneous localized superheating of anything that will react to either dipole rotation or ionic conduction, the two fundamental mechanisms for transferring energy from microwaves to the substance being heated. Microwave heating also offers facile reaction control. It can be described as “instant on-instant off”.

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**Fig. VA.4. Schematic representation of sample heating by microwaves**

When the microwave energy is turned off, latent heat is all that remains. Dipole rotation is an interaction in which polar molecules try to align themselves with the rapidly changing electric field of the microwave. The rotation motion of the molecule as it tries to orient itself with the field results in transfer of energy. The coupling ability of this mechanism is related to the polarity of the molecules and their ability to align with the electric field. There are number of factors that determine the dipole rotation coupling efficiency. However any polar species (solvent and/or substrate) that are present will encounter this mechanism of energy transfer. The second way to transfer energy is ionic conduction, which results if there are free ions or ionic species present in the substance being heated. The electric field generates ionic motion as the molecules try to orient themselves to the rapidly changing field. This causes the instantaneous superheating previously described. The temperature of the substance also affects ionic conduction. As the temperature increases the transfer of energy becomes more efficient.

**Interaction of microwaves with different materials**

Heating in microwave cavities is based upon the ability of some liquid and solids to absorb and transform electromagnetic energy into heat. In general, during the interaction of microwaves with materials three different behaviors of a material can be observed depending whether the material is counted among:

1) Electrical conductors [e.g. metals, graphite (Fig. VA.5a)]

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(2) Insulators, which are considered as materials with good dielectric properties extremely poor conductors [e.g. quartz glass, porcelain, ceramics, Teflon (Fig. VA.5b)]

(3) Lossy dielectrics, which are materials that exhibit so called dielectric losses, which in turn results in heat generation in an oscillating electromagnetic field [e.g. water (Fig. VA.5c)].

![Interaction of microwaves with different materials](image)

**Fig. VA.5. Interaction of microwaves with different materials**

(a) Electrical conductors (b) Insulators (c) Lossy dielectrics

When a strongly conducting material (e.g. a metal) is exposed to microwave irradiation, microwaves are largely reflected from its surface (Fig. VA.5a). However, the material is not effectively heated by microwaves, in response to the electric field of microwave irradiation, electrons move freely on the surface of the material, and the flow of electrons can heat the material through a resistive heating mechanism. In opposite, in the case of insulators (e.g. porcelain), microwaves can penetrate through the material without any absorption, losses or heat generation. They are transparent to microwave (Fig. VA.5b). Passage of microwave radiation which is electromagnetic in nature can give rise to absorption of microwave energy and heat generation due to the so called dielectric heating mechanism (Fig. VA.5b).[6]


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VA. 1.2. APPLICATION OF MICROWAVES

(1) Application of Microwaves in material Chemistry
The use of microwave for synthesis of inorganic solid is very efficient and useful technique in material chemistry. Microwave has been used in preparation of ceramics and theoretical modeling of microwave interaction with ceramic material have been studied by few people[7–10] and reported that when Si and C (Charcoal) in their powder form is taken in silica crucible and is exposed to microwave for 4 to 10 min in domestic microwave oven operating at 2.45 GHz, SiC is obtained. SiC is a large volume ceramic and is extensively used for industrial application such as for grinding wheels and in manufacture of abrasion tools.

(2) Preparation of catalyst under microwave irradiation
Synthesis of a high permeance NaA zeolite YBa2Cu3O7-X membrane[11] was prepared from an aluninate and silicate sodium with molar ratio of 5 SiO2 : Al2O3 : 50 Na2O:1000 H2O in a modified domestic microwave oven operating at 2450 MHz in 15 min. It was observed that the permeance of the zeolite membrane synthesized by the microwave heating is 4 times higher than that of the zeolite membrane synthesized by conventional heating.

(3) Application of Microwave Technology for Nanotechnology
Today nanotechnology[12, 13] is being applied in the fields of synthesis of single-site catalyst, antimicrobial nanocomposites, fire retardant materials, novel electro-optical devices, sensors, ultra soft magnets and also in the area of drug delivery systems.

(4) Application of Microwaves in polymer synthesis
The synthesis of polyacrylamide(PAM) was studied under microwave irradiation. PAM is used as a flocculating agent in waste water treatment. Effects of microwave radiation power on acrylamide molecular transformation ratio, with respect to PAM molecular weight, initiation and dissolve time were discussed.


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(5) Analytical Chemistry

The application of microwave irradiation is immense in the field of analytical chemistry. Microwave irradiations are routinely used for sample digestion and solvent extraction techniques. They have also been put to use for gravimetric, moisture determination and to find out enthalpy of vaporization of solvents.

(6) Digestion

Development of high pressure Asher focused microwave(HPAFM) a novel approach to microwave digestion is described by H. Matusiewics.[14] The system uses focused MW operating at 2.45 GHz at 650 W power. The pressure vessels are made up of quartz discover pressure and temperature can be conducted up to 130 bar and 320 °C respectively. Using this apparatus the methodology was developed for digestion of biological reference material such as bovine liver.

(7) Microwave irradiation in waste management

Microwave heating is playing an important role in treatment of domestic and hazardous industrial and nuclear waste. Microwave heating can be advantageously used for waste management in areas where human exposure can cause health problems. The MW and high frequency technology needed for handling such type of hazardous waste is ready to use. A process for carbonization of organic waste for manufacturing of activated carbon using MW heating has been patented by Kasai et al.[15] Activated carbon can be manufactured form organic wastes such as used paper, wood, waste plastic etc. in high carbonization efficiency using MW heating. The method and apparatus for continuous and batch process is developed for waste treatment by Roszel.[16] In this process waste such as automobile shedder waste, medical wastes, ores, sludge etc are treated by MW energy in anaerobic atmosphere.


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VA. 1.3. ADVANTAGES AND DISADVANTAGES OF USE OF MICROWAVES IN CHEMICAL SYNTHESIS

Rapid reactions, high purity of products, less side-products, improved yields, simplified and improved synthetic procedure, wider usable range of temperature, higher energy efficiency, sophisticated measurement and safety technology, modular systems enable changing from mg to kg scale. Heat, force control and water evaporation is difficult, closed container is dangerous as it could burst.

VA. 2. MICROWAVE ASSISTED ORGANIC REACTIONS

VA. 2.1. MICROWAVE ASSISTED REACTIONS USING SOLVENTS

In the case of the microwave-assisted reactions using (organic) solvents, the reactants are usually dissolved in the solvent, which often couples effectively with microwaves and thus acts as the energy transfer medium. The use of aqueous media for organic reactions[17–21] is also under active investigation and temperatures of up to 100 °C and above have been employed for the syntheses[22–24] often intended to exploit the hydrophobic effect.[25] Water has a dielectric constant 78 at 25 °C which decreases to 20 at 300 °C; the latter value being comparable with that of the solvents, such as acetone, at ambient temperature.[24] Thus, water at elevated temperature can behave as a pseudo-organic solvent[26] and is a possible environmentally benign replacement for organic solvents.


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In addition to the environmental advantages[27,28] of using water instead of the organic solvents, isolation of the products is often facilitated by the decrease of the solubility of the organic material upon post-reaction cooling.[29] An alternative method for performing microwave assisted organic reactions, termed enhanced microwave synthesis (EMS),[30] has also been examined. By externally cooling the reaction vessel with compressed air, while simultaneously administering microwave irradiation, more energy can be directly applied to the reaction mixture. In the conventional microwave synthesis (CMS), the initial microwave power is high, increasing the bulk temperature (TB) to the desired value very quickly. However, upon reaching this temperature, microwave power decreases or shuts off completely in order to maintain the desired bulk temperature without exceeding it. When microwave irradiation is off, classical thermal chemistry takes over, losing the full advantage of microwave irradiation, which is used to reach TB faster. Microwave enhancement of chemical reactions will only take place during the application of the microwave energy. This source of energy will directly activate the molecules in a chemical reaction, and therefore it is not desirable to suppress its application. EMS ensures that a high, constant level of microwave energy is applied, resulting in the significantly greater yields and cleaner chemistries. Recently, the combination of two prominent green chemistry principles, namely microwaves and water has become very popular and received substantial interest. A plethora of very recent synthetic applications describes a variety of new chemistries that can be performed with microwave irradiation but a wide range of microwave-assisted applications is still waiting.[31] Many organic transformations proceed via radical chemistry. As chemists wonder if microwave irradiation can promote radical transformations, microwave-assisted freeradical chemistry is increasingly being explored.[32] Microwave irradiation is applicable not only to the solvent phase chemistry, but also to the solid-phase organic synthesis. Following are the example of microwave assisted reaction using solvents.


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Hydrolysis of benzyl chloride with water in microwave oven gives 97 % yield of benzyl alcohol in 3 min. The usual hydrolysis in normal way takes about 35 min (Scheme VA.1).[26]

\[
\text{Scheme VA.1.}
\]

Oxidation of toluene with KMnO₄ under normal conditions of refluxing takes 10–12 hr compared to reaction in microwave conditions, which takes only 5 min and the yield is 40 % (Scheme VA.2).[31]

\[
\text{Scheme VA.2.}
\]

A mixture of benzoic acid and n-propanol on heating in a microwave oven for 6 min in presence of catalytic amount of conc. Sulfuric acid gives propylbenzoate (Scheme VA.3).[33]

\[
\text{Scheme VA.3.}
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Conventional decarboxylation of carboxylic acids involve refluxing in quinoline in presence of copper chromate and the yields are low. However, in the presence of microwaves decarboxylation takes place in much shorter time (Scheme VA.4).[33]

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1,3-Dipolar cycloadditions are important reactions in organic synthesis. Cycloadducts were prepared by carrying out the reaction between an azide and a substituted amide in toluene. This reaction was carried out under microwave irradiation at 120 W at 75 °C for 1 h. The product was isolated in 70–80 % yield (Scheme VA.5).[34]

Scheme VA.5.

N-Acylations were carried out using secondary amines and isocyanate in dichloromethane under microwave irradiation (8–10 min), yielding the product in 94% yield (Scheme VA.6).[35]
VA. 2.2. MICROWAVE ASSISTED REACTIONS UNDER SOLVENT-FREE CONDITIONS

Due to the environmental concerns, there has currently been an increasing demand for efficient synthetic processes and solvent-free reactions. Some old and new methodologies are being used to diminish and prevent pollution caused by chemical activities. In this context, the microwaves have become an important source of energy in many laboratory procedures.[36] Furthermore, microwave-assisted solvent-free organic synthesis (MASFOS) has been developed as an environmentally friendly process as it combines the selectivity associated with most reactions carried out under microwaves with solvent and waste-free procedures in which organic solvents are avoided throughout all stages.[37] In these environmentally conscious days, the research and development are directed towards devising cleaner processes. Environmental hazards and the subsequent degradations are instrumental for the rapid evolution of green chemistry concept involving benign reagents and conditions. The MASFOS reactions are of three types:

1. Reactions using neat reactants
2. Reactions using solid-liquid phase transfer catalysis (PTC)
3. Reactions using solid mineral supports.

For carrying out reactions with neat reactants i.e. without the use of a solvent or a support (heterogeneous reactions), at least one of the reactants at the reaction temperature should normally be liquid. In such a set-up, either the solid is partially soluble in the liquid phase or the liquid is adsorbed onto the surface of solid with the reaction occurring at the interface. There is also another possibility, namely that both the reactants are solid. Usually, they melt during the reaction course and then undergo reaction as described above.[38] Following are the examples of microwave assisted reactions with neat reactants.

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Aromatic nucleophilic substitutions are carried out using sodium phenoxide and 1,3,5-trichlorotriazine under microwave irradiation (6 min). The products are obtained in 85–90% yield (Scheme VA.7).[39,40]

![Reaction scheme](image)

**Scheme VA.7.**

Aldehydes, phenol and alcohols are protected by acetylation. After the reaction, the deacetylation of the product is carried out usually under acidic or basic conditions, the process takes long time and the yields are low. Use of microwave irradiation reduces the time of deacetylation and the yields are good (Scheme VA.8).[41]

![Reaction scheme](image)

**Scheme VA.8.**


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VA. 2.3.  MICROWAVE ASSISTED REACTIONS USING SOLID LIQUID PHASE

Solid liquid phase transfer catalysis (PTC) has been described as an effective method in organic synthesis and is under active investigation. This methods is specific for anionic reactions as it involves anionic activation. A catalytic amount of a tetralkylammonium salt or a cation complexing agent is added to the mixture (in equimolar amounts) of both pure reactants. Reactions occur in the liquid organic phase, which consists here only of the electrophilic R-X.

The presence of an additional liquid component is disadvantageous as it induces a dilution of reactants and consequently a decrease in reactivity. The electrophile R-X is therefore both the reactant and the organic phase for the reaction. Following are the examples of microwave assisted reaction using solid liquid phase.

Preparations of ethers were carried out from β-naphthol using benzyl bromide and 1-butyl-3-methyl-imidazolium tetrafluoroborate under microwave irradiation (6-12 min) the products were isolated in 75-90% yields (Scheme VA.9).[42]

\[ \text{Scheme VA.9.} \]

\( \text{N-Alkylations under microwave irradiation using phase transfer catalysts occupy a unique place in organic chemistry. Bogdal and co-workers reported the synthesis of N-alkyl phthalimides using phthalimide, alkyl halides, potassium carbonate and TBAB which gave products in 45–98% yields (Scheme VA.10).}[43] \]


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Scheme VA.10.

Oxidation of secondary alcohols to acetone derivatives was carried out using phase transfer catalyst (PCC), tetrabutylammonium bromide and dichloromethane under microwave irradiation (6–8 min), products were isolated in 70–99% yields. Oxidation of benzyl alcohols was conducted using BIFC under microwave irradiation (1–8 min) yielding benzaldehyde derivatives in 70–92% yields (Scheme VA.11,12).[44]

Scheme VA.11.

Gupta and Wakhloo studied Knoevenagel condensation between carbonyl compounds and active methylene compounds, such as malonic acid, using tetrabutylammoniumbromide, potassium carbonate in water forming unsaturated acids in excellent yield and purity under microwave irradiation (Scheme VA.13).[45]

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VA. 2.4. MICROWAVE ASSISTED REACTIONS ON MINERAL SUPPORTS IN DRY MEDIA

Solid supports are often very poor conductor of heat but behave as very efficient microwave absorbents. This, in turn results in very rapid and homogeneous heating. Consequently, they display very strong specific microwave effect with significant important in temperature homogeneity and heating rates enabling faster reactions and less degradation of final products as compared to the classical heating. Following are the Example of the Microwave Activation with Supported Reagents

*N*-Alkylation were carried out between piperidines and chloroalkanes in the presence of silica as the solid support under microwave irradiation (6-10 min). *N*- Alkyl products were isolated in 79–99% yields (Scheme VA.14).[46]

*S*-Alkylation was accomplished by carrying out the reaction between mercaptobenzene and alkyl halides using potassium carbonate and alumina under microwave irradiation (4-10 min). Products were isolated in 70-89% yields (Scheme VA.15).[47]


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Scheme VA.15.

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