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Review Article

Overview on microwave synthesis – Important tool for green Chemistry

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ABSTRACT

Green chemistry is also called sustainable chemistry. The term green chemistry is defined as "the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances". The major applications of green chemistry principles and practice renders control, regulation, and remediation, hence resultant environmental benefit can be expressed in terms of economic impact. The main three developments in the concept of green chemistry involves use of aqueous hydrogen peroxide as an oxidizing agent , super critical carbon dioxide as green solvent as well as use of hydrogen in asymmetric synthesis. It also involves replacement of traditional methods of heating with that of modern methods of heating such as microwave radiations which helped to reduce carbon footprint as low as possible. This review emphasize on the concept of Microwave assisted organic synthesis which is an important tool for green chemistry. Microwave radiation, an electromagnetic radiation, which is widely use as a source of heating in organic synthesis. Microwave assisted organic synthesis has emerged as a new "lead" in organic synthesis which makes the chemistry to go green. This technique has provided the excellent momentum for many chemists to switch to microwave assisted chemistry.

Key words: Sustainable Chemistry, Hazardous substances, Microwave assisted organic synthesis

INTRODUCTION

Microwave synthesis is the major breakthrough in the synthetic organic chemistry whereas the conventional heating is the inefficient and time-consuming. Microwave synthesis is the new lead which is being used as the source of heating in the organic synthetic reaction. The present article will give an idea about microwave assisted synthesis.

Microwave Synthesis – an introduction

The great invention of burner was done in organic chemistry 1899 by Robert Bunsen. This invention was so useful that it lead to provide heat in a much focused manner required to carry out any chemical synthesis[1]. But this Bunsen burner was later superseded by microwave energy. Since the first published reports on the use of microwave irradiation to carry out organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986.[3] Microwave heating has been shown to dramatically reduce reaction times, increase product yields and enhance product purities by reducing unwanted side reactions compared to conventional heating methods.

What are Microwaves?

Microwaves are in form of electromagnetic energy which lie in electromagnetic spectrum corresponds to wavelength of 1cm to 1m and frequency of 30GHz to 300MHz .This places it between infrared radiation, which has shorter wavelength in the1-25cm range for radar, whereas remaining section are devoted to telecommunication[1]. Microwave energy consist of both electric as well as magnetic field.

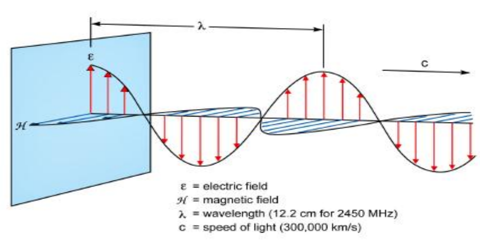


Fig 1

Microwave moves with the speed of light and it have very less energy relative to the energy which is required to break the bond in the chemical molecule thus, microwaves are such a source of energy which will not hamper the structure of the chemical molecule[2].

Advantages[3]:

- Uniform heating occurs throughout the material
- Process speed is increased
- High efficiency of heating
- Reduction in unwanted side reaction
- Purity in final product
- Improve reproducibility
- Environmental heat loss can be avoided

Disadvantages[3]:

- Heat force control is difficult.
- Closed container is difficult because it could burst
- In-situ monitoring
- Expensive setup

Microwaves are used principally in main three areas of drug research:

- The screening of drug formulae which are made of organic compounds and those candidate compounds which are seem to be numerous,
- Microwave-assisted peptide synthesis, in which peptides are used as drug. The synthesis of long chains of peptides is very difficult but microwave approach has been especially effective in the area of peptides synthesis[4].
- The microwave-assisted DNA amplification which is used in disease analysis where there are a number of DNAs which are very difficult to process.

Principles Of Microwave Heating

- ***Dipole interaction[5]***
  Polar ends of a molecule tend to align themselves and oscillate in step with the oscillating electrical field of the microwaves. Collisions and friction between the moving molecules result in heating.
- ***Ionic conduction[5]***
  It 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 super heating.

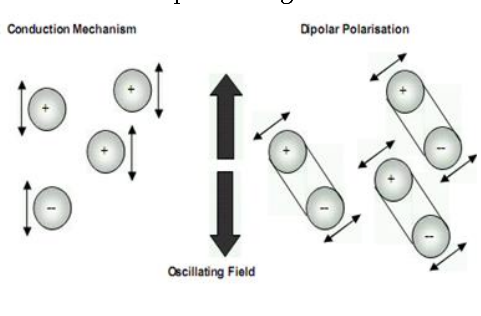


Fig.2

How microwave heating is different from traditional heating?

In tradition method of heating chemical synthesis is done by conductive heating with an external source.[5] In this, heat is passed in the substances by passing through the walls of vessel. This results into heating of the reaction vessel more as compared to the reaction mixture. Microwave synthesis being the innovative process of heating instantaneously heats up the molecules present in the reaction mixture as this process does not depend on the thermal conductivity of the vessel.

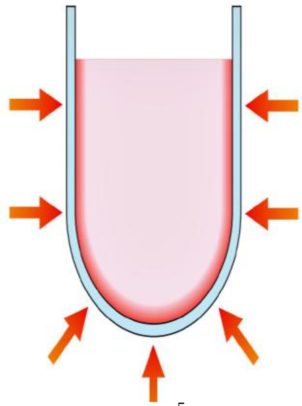


Fig.3 [5]

Sample heating by microwave:

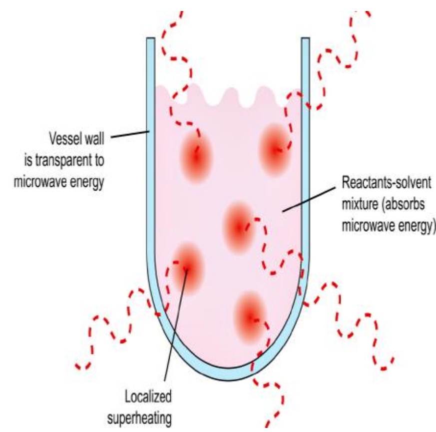


Fig.4 [5]

Microwave heating will result in instantaneous localized heating of the reaction mixture. This is due to the mechanism that microwave directly couple up with the molecules which are present in the reaction mixture.[5] This process of heating is not dependent on the thermal conductivity of the reaction vessel.

How does microwave increase the rate of reaction?

Any chemical reaction begins with A and B which have the certain energy state as E_R as shown in diagram. These reactants react in exact geometrical orientation to get activated to the higher energy transformation i.e. E_{TS}. Thus activation energy E_a is given by $E_a = E_{TS} - E_R$ .Thus activation energy becomes very important which system absorbs from environment. Once the reactants absorbs sufficient amount of activation energy it react and will return to the lower energy states i.e. E_p - the product of reaction A-B.[5] Microwave energy is such a tool which will not affect the activation energy but it provide a great momentum to complete the reaction more quickly and in more efficiently as compared to the conventional heating. In each cycle of electromagnetic energy the microwaves will transfer energy in 10^{-9} sec whereas the kinetic molecular relaxation will take 10^{-5} sec. This indicates that energy transfer is faster than the molecular relaxation.[5] This helps to create the high instantaneous temperature and non equilibrium condition which have a great impact on the kinetics of the reaction. This helps to increase the reaction rate in less time with greater yield[6].

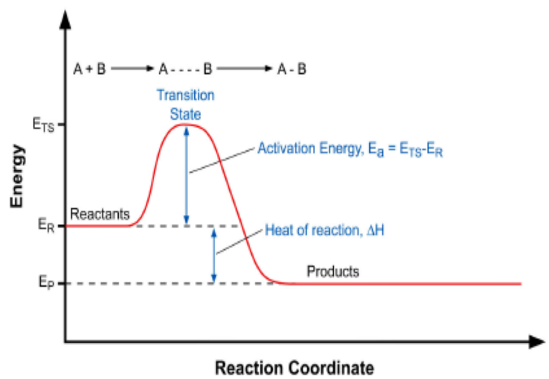


Fig.5 [5]

Microwave Synthesizer Components:

Microwave oven consists of four parts -

1. A high power source.
2. A waveguide feed.
3. The oven cavity.
4. Reaction vessel.

High power source –

A magnetron is a thermo ionic diode having anode and directly heated cathode which generate microwaves.

Waveguide feed - It is a rectangular channel which causes transmission of microwaves from magnetron to microwave cavity. It is have reflective walls made of sheet metal These walls prevent leakage of radiations by increasing the efficiency of the oven.[8]

The oven cavity - The area of oven cavity is designed in such a way so that it receives large amount of energy in the form of electric energy.

Reaction vessel -The reaction vessel for microwave induced organic reactions is a tall beaker, loosely covered which is having the capacity greater than volume of the reaction mixture. Teflon and polystyrene vessels can be used as these are transparent to microwaves. Metallic container gets heated soon due to preferential absorption and reflection of rays, hence those are avoided.

Working of the microwave oven:

1. In a microwave oven, microwaves are generated by a magnetron. A magnetron is a thermo-ionic diode having an anode and a directly heated cathode. As the cathode is heated, electrons are released and are attracted towards the anode. The anode is made up of an even number of small cavities, each of which acts as a tuned circuit.[9] The anode is, therefore, a series of circuits, which are tuned to oscillate at a specific frequency or at its overtones.
2. A very strong magnetic field is induced axially through the anode assembly and has the effect of bending the path of electrons as they travel from the cathode to the anode. As the deflected electrons pass through the cavity gaps, they induce a small charge into the tuned circuit, resulting in the oscillation of the cavity. Alternate cavities are linked by two small wire straps, which ensure the correct phase relationship. This process of oscillation continues until the oscillation has achieved sufficiently high amplitude. It is then taken off by the anode via an antenna.
3. The variable power available in domestic ovens is produced by switching the magnetron on and off according to the duty cycle. Microwave dielectric heating is effective when the matrix has a sufficiently large dielectric loss tangent (i.e. contains molecules possessing a dipole moment).
4. The use of a solvent is not always mandatory for the transport of heat.[10] Therefore, reactions performed under solvent-free conditions present an alternative in the microwave chemistry and constitute an environmentally benign technique, which avoids the generation of toxic residues, like organic solvents and mineral acids, and thus allows the attainment of high yields of products at reduced environmental costs. This emerging environmentally benign technique belongs to the upcoming area of green chemistry

Microwave in Organic Chemistry:

- ***Solvents Used in Microwave Synthesis***[5,12]
  Solvent being the crucial and important factor in the organic synthesis as most of the organic synthesis will take place in the solution phase of the reactant mixture. Polarity plays major role as more is the polar reaction mixture the reaction mixture will have better ability to couple up with the microwave energy. These are greener reactions because there is less or no use of catalyst, readily recyclable solvent and yield obtained is greater than conventional method. Various factors such as dielectric constant, dipole moment, tangential delta, dielectric loss and dielectric correlation will affect the polarity of the solvents and in turn affect the absorbing power of the solvent.[13] Dielectric constant is also known as relative permittivity of the solvent, ability to store its electric charges.

Table. 1[5]

Name of solvents	Dielectric constant
Water	80.4

Formic acid	58.5
DMSO	45
Methanol	32.6
Acetone	20.7
Ethyl acetate	6
Chloroform	4.8
Toluene	2.4
Hexane	1.9

- ***Microwave Using Solvents***

Example : Water dielectric constant 78 at 25degree while decrease to 20 at 300 degree at elevated temperature hence it perform as the pseudo solvents.[14]

1) Hydrolysis:

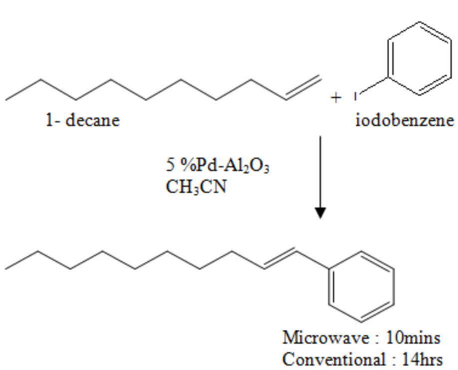
$$\underset{\text{Benzyl Chloride}}{C_6H_5CH_2Cl} + H_2O \xrightarrow{\text{MW, 3MIN}} \underset{\text{Benzyl alcohol 97\%}}{C_6H_5CH_2OH}$$

Water is such a great interesting solvents which show a drastic change at high temperature and pressure. Water show high dielectric constant at normal condition and have hydrogen bonding. But at high temperature and pressure water shows changes its polarity from high value to absolutely non polar solvent. With such a high condition water shows high activity, low density, and less dielectric constant.[17] In microwave, the water has supercritical level of $T_{c:}$ 374 degree cel. , Pc: 218 atm=3204 psi =221 bar.

Organometallic cross coupling reaction in microwave synthesis:

- Heck reaction
- Suzuki reaction
- Stille reaction

Palladium catalyzed reactions are mostly Heck, Suzuki and Stille reactions which are of the great importance in the drug discovery[34]. The use of microwave radiation was done in June 1888 by Mills and co-worker at Glaxo London. The microwave radiation was used in Heck reaction. The reaction was between iodobenzene and 1- decane and the reaction were completed in 10 min whereas as in conventional method 14 hours needed.



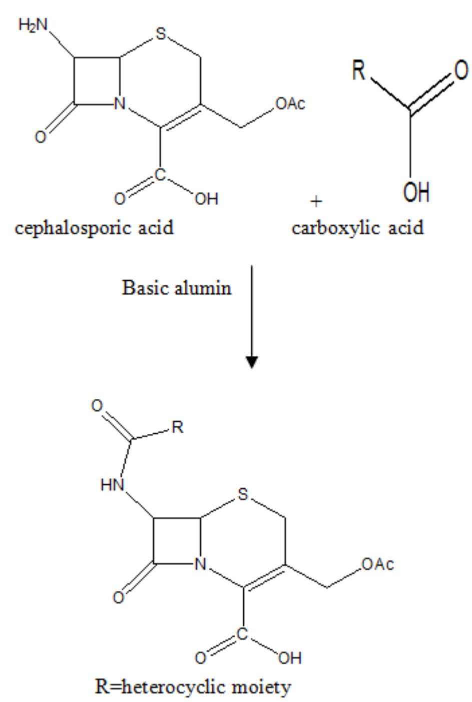
- ***Microwave using solvent free condition:***

Reactions performed in solvent free conditions are becoming more prevalent in organic synthetic reactions[15]. Less hazardous reaction conditions in environmental friendly methods is the main purpose of this process. 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.[19, 20.] Furthermore, microwave-assisted solvent-free organic synthesis 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.

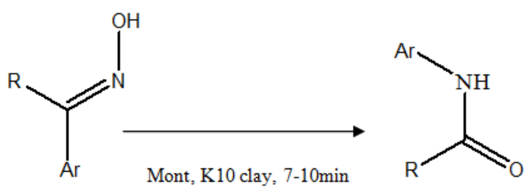
The microwave-assisted solvent-free organic synthesis reactions are of three types:

- *Reactions using neat reactants;*
- *Reactions using solid-liquid phase transfer catalysis (ptc);*
- *Reactions using solid mineral supports.*

1. Kidwai and co-workers have done extraordinary work to carry out the organic chemical reaction without the use of any solvents. Their work involve microwave synthesis of N- acetylated cephalosporin without use of solvent.[25] The cephalosporic acid is such a carboxylic acid which get adsorb on the basic alumina and it is then brought in contact with microwave radiation only for 2min.The yield of antibacterial obtained was 82-93% in 2 min time. In comparison with the conventional method (time: 2-6 hours) the time required is very less with greater yield.

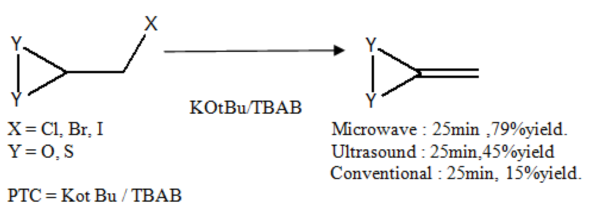


2. The most important pioneer in microwave assisted solvent free reaction is Andre Loupy[5,27].In this Beckmann's reagent was used. This reaction rearranges ketoximes to amides or lactums in presence of an acid. In conventional method carboxylic acid was used to promote this reaction to carry out reaction. But Loupy performed this reaction on montmorillonite k10 clay under microwave radiation with yield of 68-90 %.



R =Me, Ph
Ar =Ph, p-oMeC_6H_4,p-Cl C_6H_4, p-NO_2C6H4
Mont, K10 clay = montmorillonite k10 clay

3. Phase transfer catalysis in Microwave[5,32]:
Andre Loupy has also done very interesting work involving PTC which is coupled with microwave radiations. Example of this can be β-elimation of the precursors with the potassium t-butoxide or tetrabutyl ammonium precursor provided new way of synthesis of ketene[32]. Compared to the conventional method microwave radiation have provided a greater yield.



CONCLUSION

The obvious features of microwave technology include carrying out solvent free reactions, reduction of time for a chemical/pharmaceutical reaction, instantaneous and uniform heating and possibility of parallel chemical reaction. This has proved as a bonanza for the researchers involved in drug discovery and development processes like high-speed combinatorial and medicinal chemistry. The combination of ionic liquids and microwave heating encourage scientists to initiate new unexplored areas of complex pharmaceutical systems. Microwave synthesis in macro-scale (synthesis of active pharmaceutical ingredient synthesis), microscale (integrated 'lab-on-achip' type approaches where synthesis and biological screening are integrated) and meso-scale flow units should be actively pursued.

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