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MICROWAVE - AN EFFECTIVE TOOL IN ORGANIC SYNTHESIS

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ABSTRACT

Microwave-assisted organic synthesis (MAOS) is known for the spectacular accelerations produced in many reactions as a consequence of the heating rate, a phenomenon that cannot be easily reproduced by classical heating methods. As a result, higher yields, milder reaction conditions, and shorter reaction times can often be attained. Its specific heating method attracts extensive interest because of rapid volumetric heating, suppressed side reactions, energy saving, direct heating, decreased environmental pollutions, and safe operations. Microwave-assisted heating under controlled conditions has large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development because it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid optimization of reactions, for the efficient synthesis of new chemical entities, and for discovering and probing new chemical reactivity .Microwave-assisted organic synthesis is now explored for scale-up with the help of continuous flow system. Another parallel technology involves a stop-flow process. These two types of systems would allow the pharmaceutical laboratory to produce large quantities of final products in a safe and efficient manner. This presentation focuses on the principle of microwave activation, various types of microwave reactor and its characteristics, processing techniques, advances in MAOS, application of microwave, advantages and disadvantages, precautions and safety.

KEYWORDS: microwave assisted organic synthesis, time saving, efficient synthesis.

1. INTRODUCTION

Synthesis of new chemical entities is major bottleneck in drug discovery. Conventional methods for various chemical synthesis is very well documented and practiced. The methods for synthesis (Heating process) of organic compounds has continuously modified from the decade. In 1855, Robert Bunsen invented the burner which acts as energy source for heating a reaction vessel, this was latter superseded by isomental, oil bath or hot plate, but the drawback of heating, though method remain the same. Microwave Assisted Organic Synthesis (MAOS), which has developed in recent years, has been considered superior to traditional heating.[2]

Domestic and commercial appliances of microwaves for heating and cooking of foods began to appear in the 1950s. In 1947, the appliances called "Radarange" appeared on the market, it was intended for food processing. The widespread use of domestic microwave ovens occurred during the 1970s and 1980s. The first application of microwaves irradiation in chemical synthesis was published in 1986.

Over the past few decades, many significant advances in practical aspects of organic chemistry have included novel synthetic strategies and methods as well as advent of a vast array of analytical techniques. In these environmentally conscious days, the developments in the technology are directed towards environmentally sound and cleaner procedures.[1]

Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/ reagents lead to environmental pollution.

In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology include highly accelerated rate of the reaction, Reduction in reaction time with an improvement in the yield and quality of the product. This technique is considered as an important approach toward green chemistry, because it is more environmentally friendly. This technology is still under-used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development.

Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic synthesis.

2.Conventional vs Microwave Heating

The mechanism behind microwave Synthesis is quite different from conventional Synthesis. Points enlisted in Table 1, differ the microwave heating from conventional Heating.[13]

Table 1: Difference between Conventional and Microwave Heating[13]

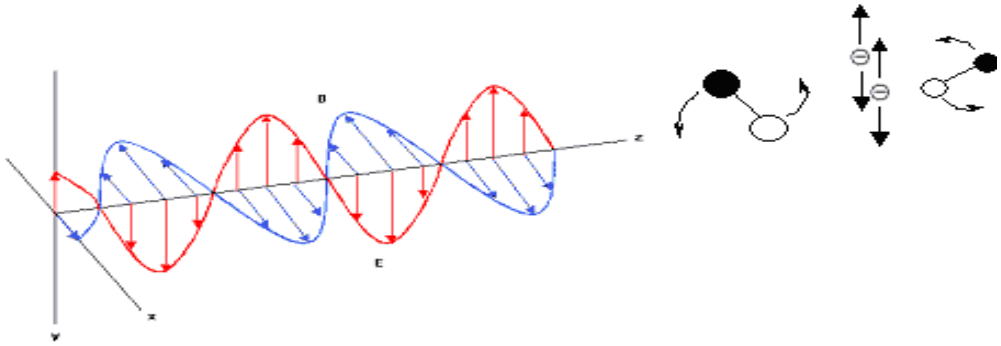
Microwave heating	Conventional heating
Energetic coupling	Conduction/convection
Coupling at the molecular level	Superficial heating
Rapid	Slow
Volumetric	Superficial
Selective	Non selective
Dependent on the properties of the material	Less dependent

Microwave is a collective term for electro magnetic irradiation with frequencies in the range of 0.3-300GHz. For heating purposes it will operate at 2.45GHz corresponding to a wavelength of 12.2cm.[3]

3. PRINCIPLE OF MICROWAVE ACTIVATION

Heating Mechanism[3]

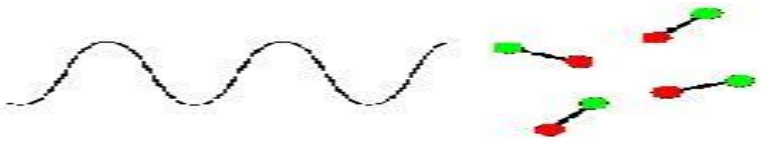
Energy in the form of microwaves can be transferred to substances that are present in the beam line of the microwave radiation. Absorption of the energy occurs when dipolar molecules rotate to align themselves with the fluctuating electric field component of the irradiation or when ions move back and forth by the same phenomena.[3]



There are **four principles** involved in heating methods[3]

- Dipolar Polarization
- Ionic Conduction
- Loss Angle
- Superheating Effect

1) Dipolar Polarization[3]



A substance possessing a dipole moment when irradiated with microwaves will generate heat. A dipole is sensitive to external electric fields and will attempt to align itself with the field by rotation. The frequency of the microwave radiation is low enough so that the dipoles have time to respond to the alternating electric field and rotate. The frequency is, however, not high enough for this rotation to precisely follow the field. So as the dipole re-orients to align itself with the electric field, the field is already changing and generates a phase difference between the dipole and the orientation of the field. This results in increased molecular friction and collisions, giving rise to dielectric heating.[3]

2) Ionic Conduction[3]

A solution containing ions or even a single isolated ion with a hydrogen bonded cluster in the sample will move through the solution under the influence of an electric field, resulting in an increased collision rate.[3]

3) Loss Angle[3]

The ability of a substance to heat in a microwave field is dependent upon two factors: (1) the efficiency with which the substance adsorbs the microwave energy, normally described by its dielectric properties, ε' and (2) the efficiency with which the adsorbed energy can be converted to heat, described by the loss factor, ε''.

A convenient way to evaluate the ability of two closely related substances to convert microwave energy into heat is to compare their respective "loss tangent" values, where the loss tangent is defined as the tangent of the ratio of the loss factor and the dielectric properties (Eqn 1). $\tan \delta = \varepsilon''/\varepsilon'$ Eqn (**1**)

A reaction medium with a high tan δ value is required for efficient absorption and consequently, for rapid heating.

4) Superheating Effect[3]

Microwaves ability to superheat solvents beyond their normal boiling points –because the even spread of heat through the liquid allows it to reach a higher temperature before bubbles form.[12] Superheating may result in the boiling points of solvents being raised by upto 26^0c above their conventional values.[3] example ,water reaches 105^0 c before boiling in a microwave oven; whereas the solvent acetonitrile boils at 120^0c instead of its usual 82^0c.[12]

Solvents in microwave assisted organic synthesis[3]

Every solvent and reagent will absorb microwave energy differently. They each have a different degree of polarity within the molecule, and therefore, will be affected either more or less by the changing microwave field. Most organic solvents can be broken into three different categories: low, medium, or high absorber, The low absorbers are generally hydrocarbons while the high absorbers are more polar compounds, such as most alcohols shown in Table 2.[2]

Table 2: Physical Properties Of Common Solvents[4]

Solvent	b.p. (^{0}C)	ε'	ε''	tan δ	Microwave absorbance
Ethylene Glycol	197	37.0	49.950	1.350	Very Good
DMSO	189	45.0	37.125	0.825	Good
Ethanol	78	24.3	22.866	0.941	Good
Methanol	63	32.6	21.483	0.659	Good
Water	100	80.4	9.889	0.123	Medium
DMF	154	37.7	6.070	0.161	Medium
Acetonitrile	81	37.5	2.325	0.062	Medium
MDC	40	9.1	0.382	0.042	Low
THF	66	7.4	0.348	0.047	Low
Toluene	110	2.4	0.096	0.040	Very Low

3.WHY DOES MICROWAVE IRRADIATION SPEED UP CHEMICAL REACTIONS?

Chemical reactions, performed using MAOS (Microwave Assisted Organic Synthesis) techniques, are rapid mainly because the reactions are performed at temperatures higher than their conventional counterparts. Quantitatively the relationship between the reaction rate and its temperature is determined by the Arrhenius Equation.

Arrhenius Equation

$$K=Ae^{-\Delta G/RT}$$

where k is the rate coefficient, A is a constant, Ea is the activation energy, R is the universal gas constant (8.314×10^{-3} kJ $mol^{-1}K^{-1}$) and T is the temperature (in degrees).By considering above equation ,there are basically two ways to increase rate of reaction.First ,pre-exponential factor, A,which describes the molecular mobility and depends on frequency of vibrations of the molecules at reaction interface. Other one is alteration of exponential factor, by affecting the free energy of activation, ΔG.[3]

4. MICROWAVE EQUIPMENT

4.1 Working of the Microwave Oven

- 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.
- The anode is, therefore, a series of circuits, which are tuned to oscillate at a specific frequency or at its overtones. 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**
- **Wave-guide** that delivers the microwave energy from the magnetron to the **microwave cavity.**
- Microwave dielectric heating is effective when the matrix has a sufficiently large dielectric loss tangent (i.e. contains molecules possessing a dipole moment).
- The use of a solvent is not always mandatory for the transport of heat.[15]

4.2 Aspects of temperature measurement in microwave field

Commonly employed mercury thermometers cannot be used for temperature measurements in the microwave field. It causes a spark discharge (compensation of potential) that destroys the thermometer.[18]

Three essential methods for the measurement of temperature in the presence of microwaves exist[18]

(i) Shielded thermocouples

(ii) IR-sensors

(iii) Fibre optics

4.2.1 Shielded thermocouples

These thermocouples can be used up to 300 °C, which is a temperature higher than typically useful for organic synthesis. Since those thermocouples have significant volume due to the shielding, reaction volumes should have a minimum size of approximately 30 ml. This measurement method is only available from MLS GmbH/Milestone Ltd.[18]

4.2.2 IR-sensors

The measuring range of IR-Sensors currently used is between -40 and +1000 °C. Such sensors are used by all manufacturers of technical microwave systems and are fairly widespread. For devices from CEM and Personal Chemistry, the IR-sensor is the lead-sensor and controls the power input. MLS/Milestone uses the IR-sensors in several systems for secondary measurements that explicitly control the temperature on the reactor surface.[18]

4.2.3 Fibre optics

A fibre-optic sensor with gallium arsenide crystal on the tip is placed inside a protective tube directly into the reaction mixture .Due to the low volume requirements, the sensors can also be applied to small scale reactions. A disadvantage compared to other measurement systems is the more narrow operating range of 0 to 330 °C.[18]

It must be concluded that the problem of temperature measurement within the microwave field is mostly solved.

4.3 Types of Reactors

Two types of microwave reactors can be used in the Laboratory-

1.Multimode Microwave Reactors

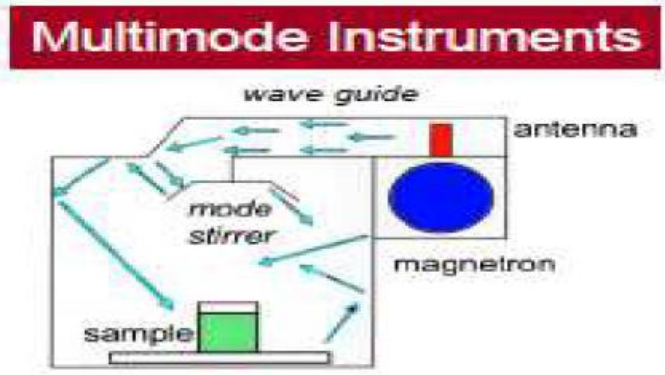


Figure:1 Multimode Microwave Reactor

- In multimode cavities several reaction vessels can be irradiated simultaneously in multivessel rotors (parallel synthesis),deep-well microtitre plates.
- In the much larger multimode instruments several liters can be processed under both open- and closed-vessel condition .
- The microwaves enter the cavity are reflected by the walls and load over large cavity therefore energy distribution is heterogeneous.[1,5]

2.Monomode Microwave Reactors

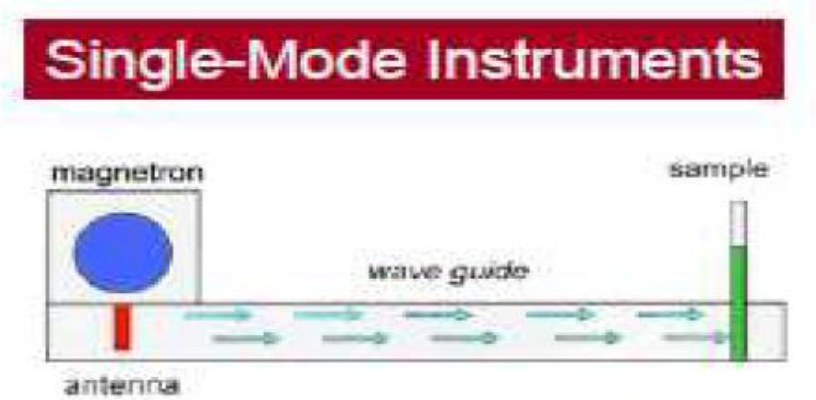


Figure :2 Monomode Microwave Reactor

- In the monomode cavities, the electromagnetic irradiation is directed through an accurately designed rectangular or circular wave guide onto the reaction vessel mounted at a fixed distance from the radiation source, thus creating a standing wave.
- In monomode systems only one vessel can be irradiated at the time.

- The single-mode instruments available today can process volumes ranging from 0.2 to about 50 mL under sealed vessel conditions (250 8C, ca. 20 bar), and somewhat high volumes (ca. 150 mL) under open-vessel reflux conditions. [1,5]

5. MICROWAVE ASSISTED SYNTHESIS TECHNIQUES

1. Solvent-free reactions

a) Reactions using supported reagents on solid mineral supports in "dry media" by impregnation of compounds on silica, alumina, or clays.
b) Reactions using neat reactants.
c) Solid –liquid Phase-transfer catalysis (PTC) conditions in the absence of organic solvent, i.e., when a liquid reagent acts both as a reacting and an organic phase. This method is specific for anionic reactions as it involves "anionic activation". ("dry-media") procedures.[9]

2. Reflux system

A number of reflux system have been developed in an effort to use solvents in microwave assisted organic synthesis without the risk of explosion. Some systems are modified domestic ovens, while other have been designed with a single mode cavities. There is a little risk of explosion with reflux systems, since the systems are at atmospheric pressure and flammable vapours cannot be released into the microwave cavity. The temperature however cannot be increased by more than 13-26 ^{o}C above the normal boiling point of the solvent and only for a limited time.[14]

3. Pressurised systems

Reactions performed under pressure in a microwave cavity also benefit from the rapid heating rates and remote heating of microwave dielectric heating, this type of experiments lead to the one of very earlier development using microwave assisted organic synthesis.[14]

4. Continuous flow system

If the outcome of a reaction is strongly dependent on the heating profile of the reaction mixture, it is crucial to maintain that heating profile when scaling up the reaction. If for example, 3 ml of a solvent is heated to 150 ^{o}C in 20 s using microwave irradiation at 300 W, it will be necessary to use at least 15 kW power to heat 150 ml of same solvent,in order to maintain the same heating profile.[14]

6. ADVANCES IN MICROWAVE ASSISTED SYNTHESIS

Current applications of microwave chemistry have motivated researchers to test the viability of microwave technology in other categories of reactions, and explore its newer applications. In addition to these developments, leading market players have tried to address the issue of scalability by developing products that have scaled up chemical reaction from milligrams to kilograms.[16]

Scaling Up of Reactors to a Higher Volume of Yields

Two main approaches have evolved to address the issue of scaling up microwave reactors. The first approach scales up single-mode reactors through a flow-through reactor, and the second scales up multi-mode reactors to a batch reactor.[16]

- **Flow-through Microwave Reactor**

A flow-through microwave reactor is capable of scaling up single-mode yield from grams to kilograms. CEM Corporation has developed a patented technology for its *Voyager*[21] flow-through single-mode reactor. An advantage of the flow-through reactor is its ability to perform dual-mode operations between liquid and solid phase reactions. Milestone s.r.l's flow SYNTH continuous flow reactor allows scale up from grams to kilograms with full temperature and pressure control. It provides precise monitoring and control of the process parameters. Though the flow-through single mode microwave reactor has been a breakthrough product in meeting chemists' requirements pertaining to liquid phase reactions, the product has limitations with regard to handling solids and admixture-based reactions.[16] Example of flow-through organic microwave synthesis, the synthesis of 5-amino-4-cyanopyrazoles and preparation of 3-methyl cyclopent-2-enone etc.[10]

- **Batch Reactor**

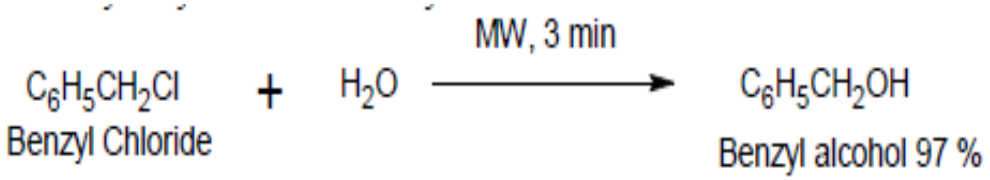
Another breakthrough related to successful scaling up is multi-mode reactors. Batch reactors are capable of accommodating larger volumes of reactants in a multi-mode operation in one go, and therefore can conduct reactions to produce higher yields. Biotage AB and Milestone s.r.l have developed batch reactors to scale up the yields of reactions - Biotage AB with a batch reactor called Emrys™ Advancer, and Milestone s.r.l with its MRS batch reactor.[16] Example, Grandberg synthesis of 2-methyltryptamine, synthesis of pyranoquinoline.[10]

7. APPLICATIONS OF MICROWAVE

1) Application of Microwave in Chemical synthesis

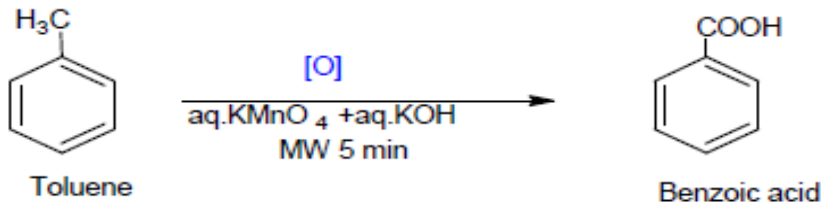
I. Hydrolysis[1]

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.



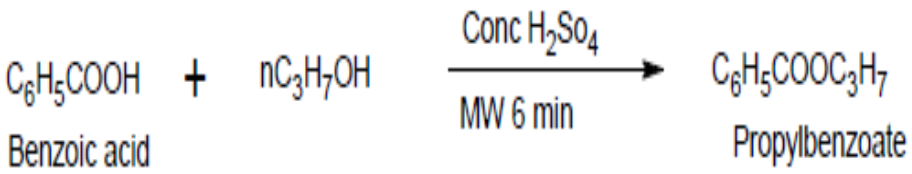
II.Oxidation[1]

Oxidation of toluene with KMnO4 under normal conditions of refluxing takes 10-12 hrs as compared to reaction in microwave conditions, which takes only 5 min and the yield is 40 %.



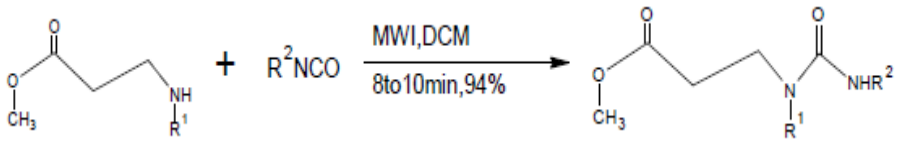
III. Esterification[1]

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.

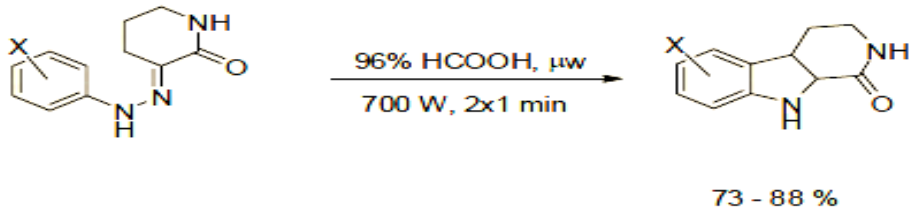


IV. N-Acylations[1]

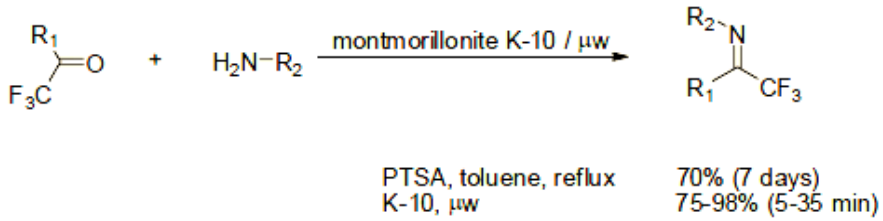
N-Acylations were carried out using secondary amines and isocyanate in dichloromethane under microwave irradiation (8–10 min), yielding the product in 94% yield



V. Synthesis of Heterocycles[6]

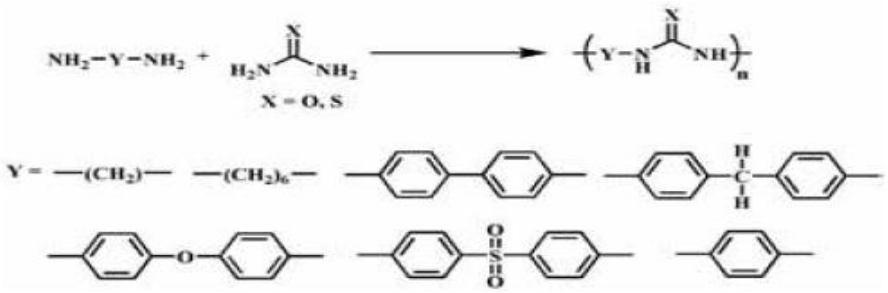


VI. Condensation[6]



2) Microwave-assisted Reactions in Step-growth Polymerization[11]

The synthesis of high-molecular-weigh polyureas and polythioureas via the reaction of aromatic and aliphatic amines with urea and thioureas in the presence of a catalytic amount of *p*toluenesulphonic acid using a microwave oven (for duration of 12 min) at 400 W. The reactions are being performed in different solvents such as dimethyl sulphoxide, *N*,*N*dimethylacetamide (DMAc), chlorobenzene, dioxane and toluylene. DMAc was chosen as the most appropriate solvent owing to the greater solubility of the substrates, the higher rate of the reactions, and the excellent energy-transfer properties.



3) Microwave Impact on Drug Discovery Process[4]

Lead Discovery

The impact of MAOS is not only limited to organic chemistry but it now also being used in the areas like lead discovery and optimization. The current trend in the pharmaceutical industry is to generate comparatively small, focused libraries containing ~30-300 compounds

for a typical drug discovery project.[4] The technology of running parallel chemical reactions is an intensively investigated area of research. The goal of this effort is to transfer the advantages associated with microwave-assisted reaction engineering to combinatorial chemistry.[19] The method was able to produce libraries of diverse pyridines high throughput, automated, single step, and parallel synthesis. Today the main use of MAOS for combinatorial chemistry and high speed parallel synthesis is in the area of multi-component reactions such as Biginelli reaction.

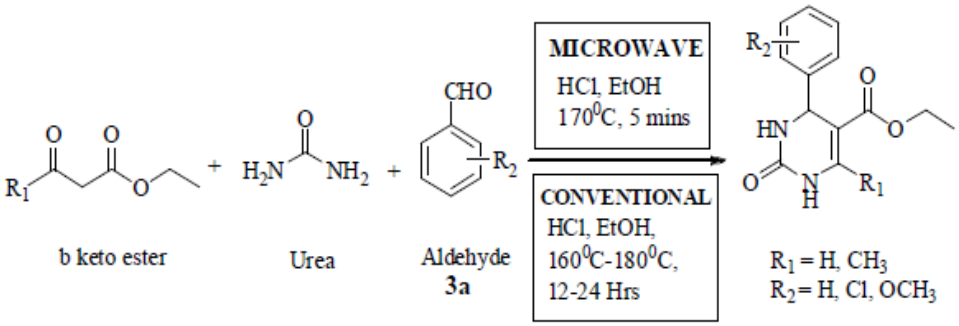


Fig 5: Biginelli synthesis of tetrahydropyrimidines

4) Microwave Impact on Drug Development[4]

Development of Active Drug Isomer

Microwave is beginning to play a greater role in process of drug development, especially in cases where classical methods require prolonged reaction times and forced conditions. A most interesting and important application of microwave activation is the epimerization of optically active compounds. A wide range of amino acids has been epimerized quantitatively within two minutes, thus avoiding the decomposition that is associated with the use of classical heating. Similarly, the complete epimerization of (-)-vincadifformine (figure 7) is achieved in <20 minutes to generate (+) isomer.

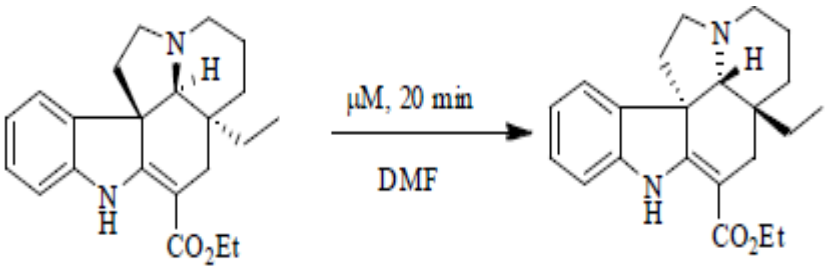


Figure 7: Epimeization of (-)-vincadifformine

5) Microwaves in Processing of dosage forms[4]

Microwaves in recent years can be used during the preparation process of dosage form and/or directly onto the preformed products. Alternatively, the microwave can be applied to process the excipients prior to their use in the formulation of drug delivery systems. Also it is possible to modify the physicochemical properties of excipients to provide the intended release properties of drugs in dosage forms.

Drying of Agglomerates

When drying is carried out under microwave-assisted conditions, materials with higher moisture contents interact more readily with the waves as they possess higher dielectric constants and losses. As a result, these materials may potentially experience greater heating and drying rates than those which are comparatively drier. Such moisture-targeting effects are beneficial when drying products of large volumes since moisture is seldom uniformly distributed within the product load undergoing drying. This selective nature of microwave energy enables moisture leveling and maintenance of overall product quality. Thus microwave drying is especially useful for moisture sensitive materials. In addition, microwave drying technology is useful for production of very high potency dosage forms because it provides the possibility of drying in same production container. Thus, it reduces the likelihood of cross contamination and human contact with high potency drug.

6) Microwaves in Analytical Chemistry[16]

The various applications of microwave radiation in analytical chemistry encompass the following processes

1. Ashing
2. Digestion
3. Extraction
4. Protein hydrolysis
5. Moisture/solids analysis
6. Spectroscopic analysis

7) Microwave irradiation in waste management[1]

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. 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. In this process waste such as automobile shedder waste, medicalwastes, ores, sludge etc are treated by MW energy in anaerobic atmosphere.

8) Organometallic Synthesis[20]

Microwave radiation has been successful in accelerating the reaction rate for the generation of organometallic and coordination compounds, which are produced by generating covalent bonds between organic compounds and metals. It improved synthesis of $(C_6H_5)_3SnCl$, $(C_6H_5)_3SnOH$.

9) Microwave-Assisted Carbocyclizations on solid support[22]

Solid phase synthesis techniques have been the primary method utilized in combinatorial chemistry. Transition metal mediated carbocyclization on solid support are viable approach for the synthesis of pharmacologically active small molecules on solid support. Microwave assisted method for synthesis of differentially substituted aromatic ,heteroaromatic ,phenolic scaffolds privileged by biological receptors for combinatorial/solid phase organic synthesis.

10) Application in proteomics[23]

Microwave technology have been applied into proteomics so as to carry out enzymatic protein digestions. This non-classical proteomics method is identified to have enhanced digest efficiency and sequence coverage and also accelerate degradation rates. The difference between conventional and microwave assisted digestions termed as non-thermal microwave effects.Interaction between proteins or enzymes and 2.45 GHz electromagnetic field is responsible for these differences.If there is no idea about exact internal reaction temperature, this type of reaction can not be carried out or they may be given incorrect output.

8. KEY USERS OF PRODUCTS RELATED TO MICROWAVE CHEMISTRY

Are as follows

1. Pharmaceutical and biotechnology companies
2. Chemical companies
3. Educational and research institutions

1.Pharmaceutical and biotechnology companies[16]

Pharmaceutical and biotechnology companies are increasingly turning to microwave Chemistry. Pharmaceutical companies comprise the largest consumer segment in the market. They are using microwave synthesisers in their research laboratories to develop compounds for the lead optimisation phase in drug development. The reduced reaction time for chemical synthesis, using microwave radiation, gives chemists an ideal response period to apply diverse synthesis methods iteratively to new chemistries and develop proprietary compounds. Pharmaceutical companies such as GSK, Merck, Eli Lilly, and AstraZeneca are already using these instruments in their drug development processes.

2. Chemical companies[16]

Companies producing chemicals and chemical products, such as ChevronTexaco, have been using microwave technology to conduct various chemical analyses. The application of microwave chemistry in these companies has resulted in improved quality, higher yields and lower costs.

3. Educational and research institutions[16]

Educational and research institutions are slowly shifting to microwave chemistry instrumentation from conventional techniques, to conduct their laboratory experiments. However, these institutions find it difficult to acquire microwave technology for their laboratories because of the high set-up costs involved.

9. KEY SUPPLIERS PROVIDING DEDICATED INSTRUMENTATION FOR MICROWAVE CHEMISTRY

There are three main suppliers[16]

1. CEM Corporation (the US)
2. Milestone s.r.l (Italy)
3. Biotage AB (Sweden)

10. ADVANTAGES AND DISADVANTAGES OF MICROWAVE

Advantages

1. Rapid reactions
2 .High purity of products
3. Less side-products
4. Improved yields

5. Simplified and improved synthetic procedure

6. Higher energy efficiency

7. Sophisticated measurement

8. Modular systems enable changing from mg to kg scale.

Disadvantages

1. Heat force control is difficult

2. Water evaporation

3. Closed container is dangerous because it could be burst

4.Rapid cooling of reaction mixture on leaving irradiation zone may cause crystallization .

5. In microwave synthesis sudden increase in temperature may led to the distortion of molecules which may lead to distortion of the reaction.[25]

6. Reactions are very vigorous and which may be hazardous.[24]

7. Microwave reactors are expensive and very delecated so there must be a care to be taken during their use.[24]

8. Various reactions which have short reaction time are not be undertaken in microwave reactor due to sudden increase in the temperature it may be hazardous and it may lead to reaction crises.[24]

9. Many other things like, temperature sensitive reactions, reactions involving bumping of material, and reaction in which effervescences and colour reaction are not be done in microwave reactor.[24]

11. PRECAUTIONS AND SAFETY[12]

Microwave techniques introduce unique safety considerations that are not encountered by technicians using traditional laboratory heating devices. Microwave irradiation has the capability of rapid hightemperature heating, with the potential for vaporization and pressurization. The majority of unsafe conditions or practices that can arise during the use of microwave systems in the laboratory are avoidable. It is essential that microwave units be operated in a manner that ensures maximum safety to the operator and laboratory personnel. In the U.S., many regulatory bodies (e.g., Food and Drug Administration [FDA], Occupational Safety and Health Administration [OSHA]) require compliance with provisions of the Code of Federal Regulations (CFR) and testing laboratories and certification organizations (e.g., Underwriters' Laboratories [UL]). One such provision for laboratory equipment is 29 CFR 1910.399. This requirement states that an installation of equipment

(including household microwave ovens) could be acceptable (to OSHA) and approved within the meaning of Subpart S requirement if it is accepted, certified, listed, labeled, or otherwise determined to be safe by a nationally recognized testing laboratory (NRTL). However, even if a device or equipment is "approved," 29 CFR 1910.303(b) (2) requires that the "listed or labeled equipment should be used or installed in accordance with any instructions included in the listing or labeling."

NOTE: Current FDA and OSHA regulations do not prevent anyone from purchasing and using a microwave oven for other than its intended purpose. However, once a household or commercial microwave unit has been modified for use in a clinical laboratory (i.e., it is no longer considered to have been "designated to heat, cook, or dry food"), the original oven manufacturer is neither liable nor responsible for the compliance of the modified ovens. Thus, the person who is modifying the oven is subject to the provisions of Chapter V, Subchapter A- Drugs and Devices of the Federal Food, Drug, and Cosmetic (FFD&C) Act. Microwave-accelerated sample preparation is not exempt from traditional safety considerations, and references to general laboratory safety are available. (Please refer to the most current edition of CLSI/NCCLS document GP17—*Clinical Laboratory Safety* for additional information.)

Recommended Safety Procedures for Microwave Devices

Microwave devices designed for the laboratory may include safety features such as isolation of the fume exhaust from the device electronics, high volume exhaust, safety interlocks, and sensors for flammable solvents

Procedure Safety

1. **Leakage** – A certified personnel must do annual monitoring for microwave leakage (<5 mW of microwave radiation per square centimeter at 5 cm from the surface). This safety check should be done to meet appropriate radiation regulatory standards for the institution.
2. **Spills** – For some applications, a secondary container must be used to collect spills (e.g., tray or plastic bag with a vent). Operators must use extra caution when using secondary containers not specifically designed for microwave procedures due to the higher risk of container leakage and contamination. **NOTE:** Secondary containers are very important when transporting samples to and from the microwave device.

3. **Handling** – Utensils designed should be used to handle containers after microwave heating to protect the operator from burns. Thermal mitts should be used to prevent thermal burns from handling containers after microwave heating. Chemically resistant gloves should be used to prevent skin exposure to hazardous chemicals or their vapors, which may have contaminated the outside of the container during microwave heating.
4. **Temperature** – Temperature should be monitored to prevent overheating and specimen damage.

Equipment Safety

1. A nonabrasive disinfectant should be use to keep interior surfaces clean. Blot interior surfaces dry after each use to prevent local hot spots and corrosion.Spills must be clean immediately.

2. Yearly inspections of a microwave's fume exhaust system (check owner's manual) should be done.

3. Flammable and/or corrosive reagents must be removed from the fume hood prior to microwave device operation to prevent ignition of the reagents or chemical damage to the electronic safety systems in the device.

4. Microwave devices without a built-in exhaust should be placed six inches from the plane of the hood face and not block airflow to slots of the baffle. Sash height should be adjusted to the lowest possible position to maximize containment (see the institutional safety officer for this determination).

5. Routine performance tests on ventilation hoods such as face velocity and smoke visualization are required on ventilation hoods containing microwave devices and microwaves with extractor fans connected to a ventilation hood or other exhaust system.

6. Regularly inspection and cleaning of dirty microwave door seals should be done. Microwave with any evidence of damaged door frames, hinges, or door latches should not be operated. Containers made from microwave-compatible materials (e.g., polyethylene, polypropylene, PTFE, PFA, borosilicate glass) must be used.

7. Pressurization during microwave procedures can only be done in devices approved by the manufacturer for this purpose.

8. In particular, containers with screw-type cover lids should not be used.

9. Temperature measurement devices must be manufacturer approved for use in a microwave cavity.

10. Microwave devices should have UL, CSA certification for laboratory use.

12. CONCLUSION

Microwave heating is very convenient to use in organic synthesis. Due to instantaneous, selective, uniform heating this technique offer high yield and greater reproducibility. Microwave assisted organic synthesis is a technique which can be used to rapidly explore 'chemistry space' and increase the diversity of compounds produced. More growth of microwave chemistry occuring due to increasing level of research and innovation being conducted. Increasing awareness amongst the scientific community about technology and benefits therein.

With the advent of newer techniques it is much more easier to scale-up the processes that are followed in the lab and make it applicable in industries.

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