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MICROWAVE ASSISTED ORGANIC SYNTHESIS: A GREEN CHEMISTRY APPROACH

[1]A.B. Patil, [2]P. M . Phole, [3]M. S. Charde, [4]R. D. Chakole, [5]N.S. Mali.

[1]Research Scholar , [2]Research Scholar , [3]Assitant Professor , [4]Associate Professor, [5]Research Scholar

Department of Pharmaceutical Chemistry.

Government Collage of Pharmacy, Vidyanagar, Karad, Satara,

Pin: 415124, Maharashtra, India.

***For correspondence,**

Mr. Adarsh Balasaheb Patil

Department of Pharmaceutical Chemistry,

Government Collage of Pharmacy, Vidyanagar, Karad, Dist: Satara, Maharashtra, India 415124

Abstract:

Green chemistry utilizes renewable materials it eliminates waste greatly and also avoiding the use of hazardous and toxic materials and solvent in the preparation of the chemical product. Microwave and electromagnetic radiations is greatly used as a source for heating in the synthesis of organic products. Dipolar polarization and ionic conduction are the mechanisms seen in the microwave-assisted synthesis. Microwave heating is fast, specific and ecofriendly method. These advantages of this method have made it more widely used. The conventional heating method needs longer time, complex apparatus which makes it costlier and use of excessive material and solvent leads to more environmental pollution than microwave synthesis. Microwave assisted synthesis method is greatly becoming the method of choice for chemical synthesis. The article also highlights the various applications of microwave assisted synthesis in organic, inorganic, nanoparticle synthesis and also in the drug discovery and drug development process.

Keywords: Green chemistry, Microwave assisted synthesis and ecofriendly.

1) Introduction:

The design of chemical products and processes that minimize or completely avoid the usage or synthesis of harmful chemicals is becoming known as "green chemistry" throughout the world. The US Environmental Protection Agency is credited with coining the word, which is described as: "the application of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design. Application and manufacture of the chemical products, the following twelve Green Chemistry principles can be used to accomplish this goal. (1) Preventing waste is preferable than treating or cleaning up waste after it has been produced. (2) The goal of synthetic methods should be to incorporate as many raw components as possible into the finished product. (3) Less hazardous/toxic chemicals should be used and generated via synthetic processes. (4) Chemical goods should be made with the least amount of toxicity possible while yet performing the specified purpose. (5) The use of solvents and auxiliary compounds should be minimized and, where necessary, made harmless. (6) Chemical operations should use as little energy as feasible, and wherever possible, synthetic methods should be carried out at room temperature and pressure. (7) A raw material should, if possible, be renewable rather than depleting. (8) If at all feasible, avoid or minimize the need for derivation. (9) Stoichiometric reagents are inferior to catalytic reagents. (10) Chemical products should be made to degrade into harmless degradation products that disappear from the environment after they have served their purpose. (11) analytical methods needs to be enhanced to enable in process monitoring and control in real time before any hazardous compound arise. (12) To reduce the risk of chemical mishaps, substances and the type of substances employed in a chemical process should be chosen. Because it is more environmentally benign, microwave synthesis is regarded as a key strategy for green chemistry. Microwave irradiation has been utilized to enhance various organic syntheses because it may couple directly with the reaction molecule and by passing thermal conductivity, which causes a fast rise in temperature. The significant development in synthetic organic chemistry is microwave heating, which is faster and more efficient than traditional heating. The latest development in heating sources for organic synthetic reactions is microwave synthesis. The information in this page will help you understand microwave aided synthesis.[1]

2) Microwave Apparatus:

A microwave system consist of

- Magnetrons
- Waveguide feed
- Reactor
- Mode stirrer

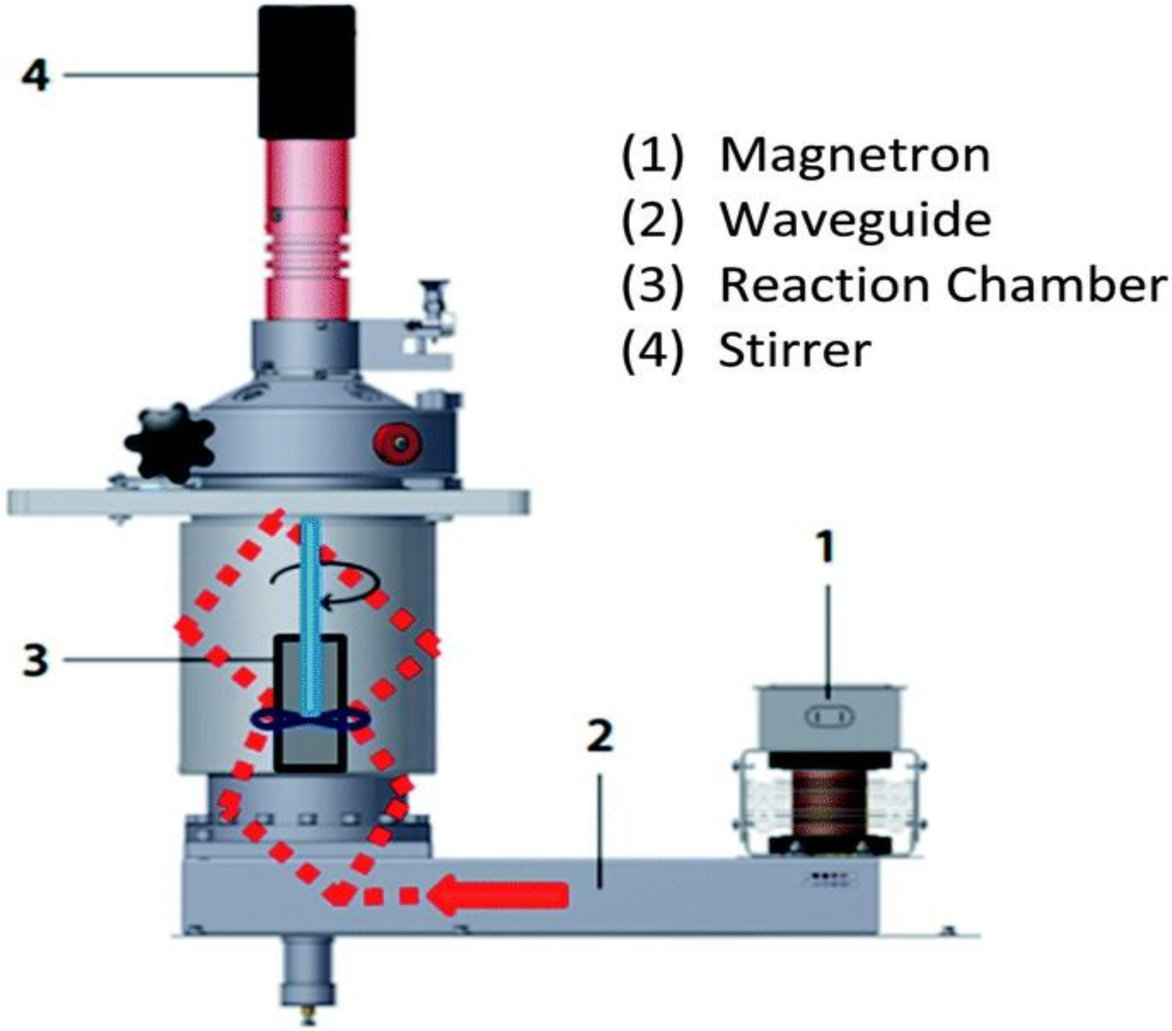


Figure 1: Microwave apparatus [2]

2.1) Magnetrons:

In a vacuum tube known as a magnetron, electrons are impacted by magnetic and electric fields in a way that results in the production of microwave radiation with a certain wavelength.

2.2) Waveguide feed:

It is a rectangular channel that allows microwaves to go from the magnetron to the microwave cavity. It has metal sheet-made reflecting walls. These barriers improve the efficiency of the oven by preventing radiation leakage.

2.3) Reactor:

Two types of reactors are used for microwave assisted organic synthesis: multimode reactors and mono mode reactor.

- The most popular tools used in organic synthesis are household microwave ovens (multimode reactors), as they are very affordable and easily accessible. With a household microwave, a lot of rewarding organic synthesis has been accomplished. Areas of high and low field strength, or "hot and cold spots," are provided by multimode reactors. The heating efficiency varies significantly across various places of the sample as a result of the non-uniformity of the field. The single mode reactor has helped to solve this problem.

- As its name suggests, a single mode can only enter a single mode cavity through waveguide. "Hot and cold" patches can be avoided by using a single mode cavity or reactor that has been correctly built. This benefit, which allows for control over the actual heating pattern, is crucial for organic synthesis. Higher repeatability and predictability are thereby attained.

2.4) Mode stirrer:

The instantaneous field pattern within the cavity is continually changed by a mode stirrer, which is commonly a periodically moving metal vane. The microwave field is continually churned due to the vane's shape and motion, which causes the field intensity to be uniform throughout the cavity in all directions and at all points. As a result of the cavity's uniform magnetic field, microwave-absorbing materials may be positioned anywhere inside the cavity.[3]

3) Microwave heating mechanism:

Because different materials react differently to microwave radiation, not all materials can be heated by them. Materials can be divided into the following major categories based on how they react to microwaves:

(1) Substances that are microwave-transparent, like sulphur

(2) Microwave-reflective materials, such as copper

(3) Microwave-absorbing materials, such as water The heating of microwave absorbing materials involves two primary distinct mechanisms: dipolar polarization mechanism, and ionic conduction mechanism. Microwave absorbing materials are of the highest importance for microwave chemistry.

3.1) Dipolar polarization mechanism

Polar units of reactants or solvents starts to align with the applied oscillating electric field and try to pursue the alternating and such a procedure is in charge of energy loss in form of thermal energy through the molecular friction as well as dielectric loss. The amount of thermal energy produced which is connected to the capacity of reaction dipoles with microwave frequency which is applied is an benefit of this mechanism. If a reaction dipoles does not meet with the essential condition to realign or to redesign quickly with the connected EF, no MW warming can be observed therefore the frequency of 2.45 GHz which is a acceptability frequency provide the dipoles with the time to line up them with EF .[4]

3.2) Ionic conduction mechanism

The dissolved ions in a reaction mixture oscillates back and fourth under the MW field. In this phenomenon these ions collide with each other and generate the heat. It provides with the better heat liberating capacity than the dipolar mechanism. Free ions in the reaction mixture will try to orient themselves in the direction of the applied field due to ionic motion, which will result in immediate super heating .[5]

4) How microwave heating is different from traditional heating:

Chemical synthesis is traditionally heated using conductive heating from an external source. Through the vessel walls, heat is transferred to the things in this. This causes the reaction vessel to heat up more than the reaction mixture as a result. Since microwave synthesis does not rely on the thermal conductivity of the vessel, it is a new method of heating that instantly warms up the molecules present in the reaction mixture.

The reaction mixture will instantly become locally heated when heated with a microwave. This is caused by the microwaves that interact directly with the molecules in the reaction mixture. The reaction vessel's thermal conductivity has no bearing on the heating process.[6]

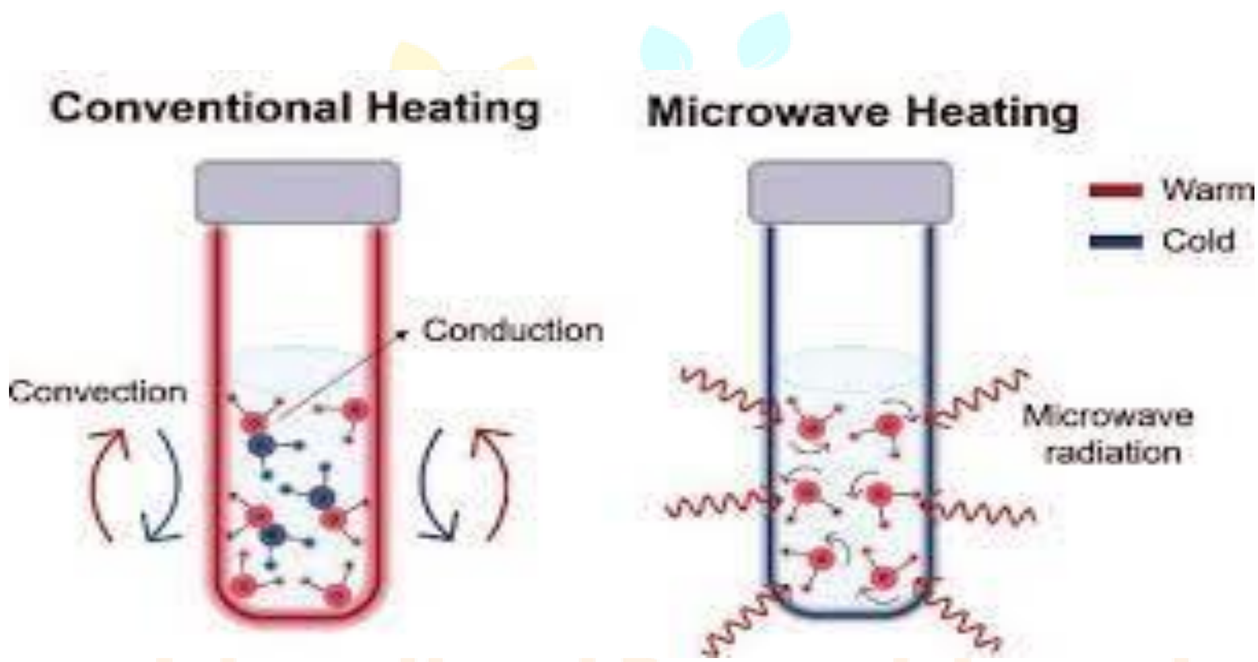


Fig 2. Conventional heating versus microwave heating [7]

A few processes that were heated utilizing microwave technology and compared to traditional heating are gathered, showing the time and energy efficiency of the method. (Table 1)

Table 1: Comparison of reaction time using microwave verses conventional heating [8]

Compound synthesized	Microwave Reaction time	Conventional Reaction time
Methyl benzoate	05 minutes	08 hours
4-nitrobenzylester	02 minutes	90 minutes
Zeolitesynthesis	30 seconds	60 minutes
Cubanite	03 minutes	03 days
Sodium aluminium hydride	120 minutes	08 hours
4-nitrobnzyl ester	02 minutes	90 minutes

5) Application of microwave assisted synthesis:

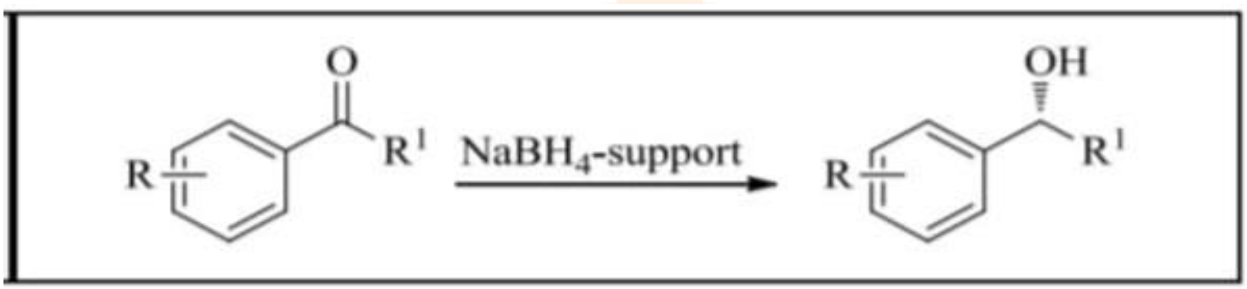
The application of microwave irradiation in chemical synthesis includes the speeding of the process. Faster reactions, greater yields, and improved product purity are the outcomes of microwave-enhanced synthesis. Additionally, the yields of the tests have now been readily scaled up from milligrams to kilograms without the need to change reaction conditions, thanks to the accessibility of high-capacity microwave equipment.

5.1) Organic synthesis

The most common and well-studied use of microwaves in chemical processes is microwave-assisted organic synthesis. A variety of organic reactions have been successfully carried out by scientists

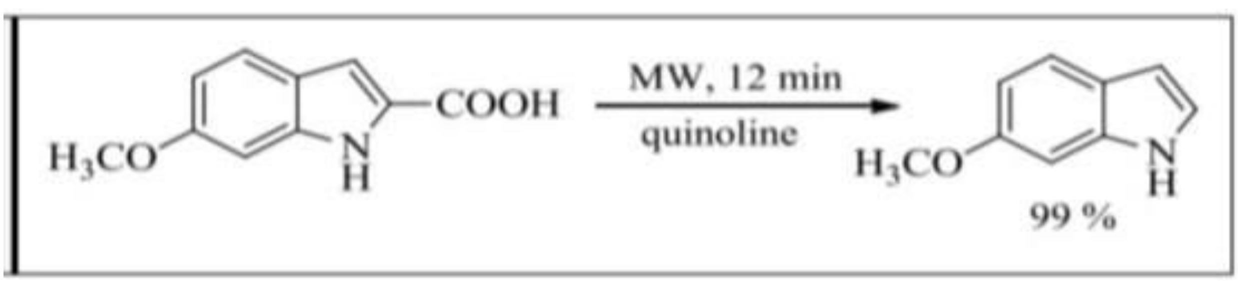
5.1.1) Reduction

In a microwave, acetopehenone and NaBH4 are reduced to generate 92% of benzyl alcohol in 2 minutes.



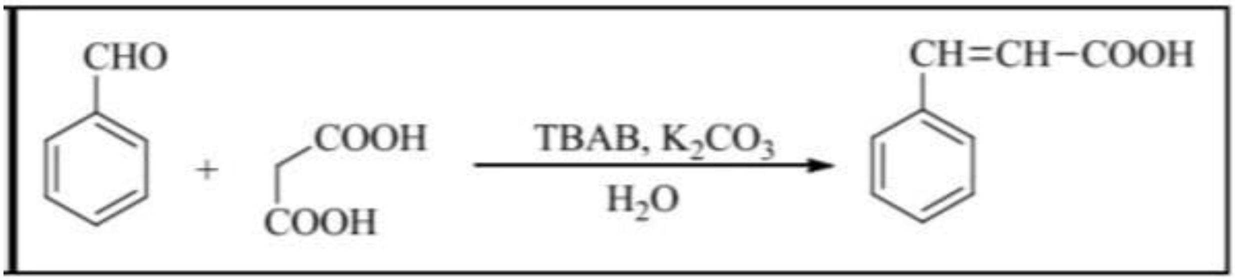
5.1.2) Decarboxylation

The yields are poor when carboxylic acids are decarboxylated conventionally, which involves refluxing in quinoline while copper chromate is present. However, decarboxylation occurs considerably more quickly in the presence of microwaves.



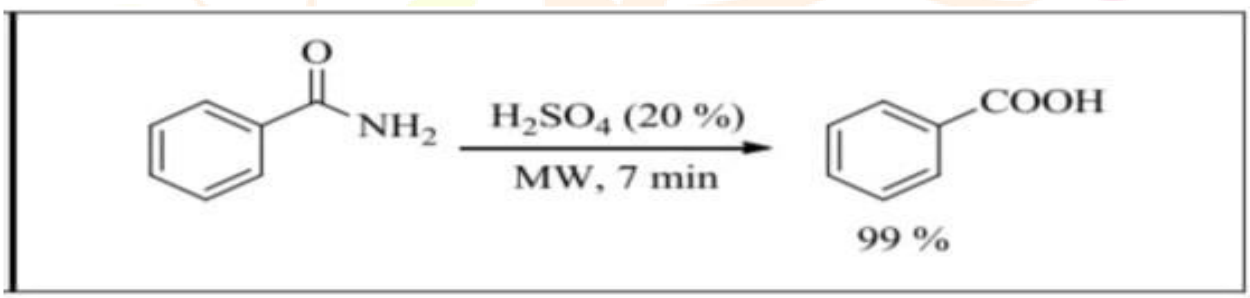
5.1.3) Knoevenagel Condensation

A well-known chemical process called knoevenagel condensation is also used to create unsaturated acids, which are utilized as building blocks for numerous heterocycles, flavonoids, and scent precursors. Tetrabutylammonium bromide and potassium carbonate in water were used to study knoevenagel condensation between carbonyl compounds and active methylene compounds, such as malonic acid, generating unsaturated acids with outstanding yield and purity when microwave radiation was used.



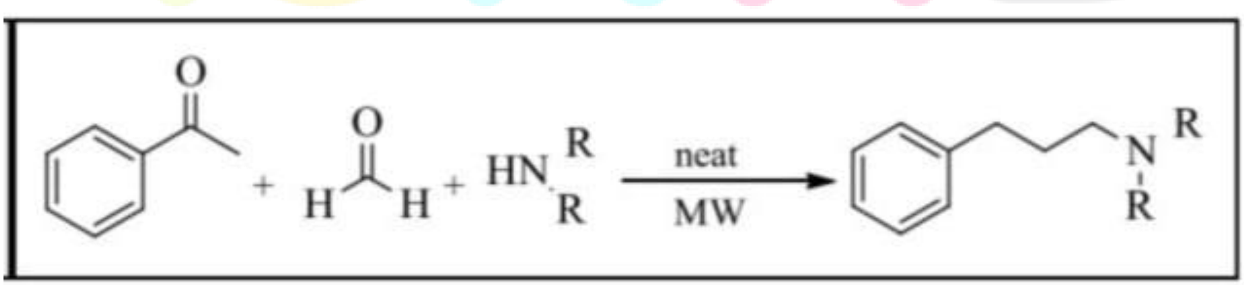
5.1.4) Hydrolysis

In 3 minutes, 97% of the benzyl alcohol produced by the hydrolysis of benzyl chloride with water in a microwave oven is produced. Common hydrolysis in the standard method takes roughly 35 minutes. Typically, benzamide hydrolysis takes one hour. Under microwave conditions, however, the hydrolysis is finished in 7 minutes with a 99% yield of benzoic acid.



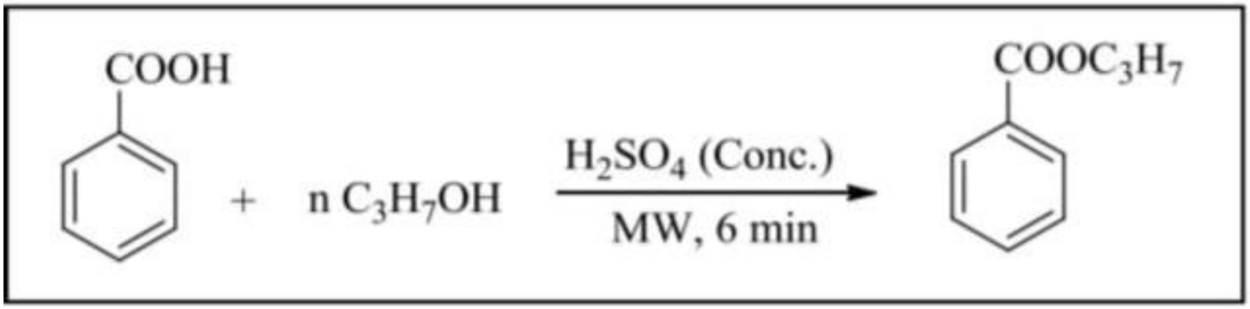
5.1.5) Mannich reaction

By using a microwave process, a number of Mannich base derivatives were quickly and with high to outstanding yields produced. Outcomes from a microwave deliver greater returns in less time than traditional outcomes do. In the pharmaceutical business, microwave-assisted organic synthesis is often used, notably for creating compounds during the lead optimization stage of drug discovery and development.



5.1.6) Esterification

a combination of n-propanol and benzoic acid heated for 6 minutes in a microwave in the presence of catalyst , Propyebenzoat is produced by sulfuric acid.[9]



Other organic reactions include prins reaction, protection and deprotection, Heck reaction, Suzuki reaction, oxidation,[10] coupling reactions , insertion reactions .[11]

5.2) Heterocyclic Nucleus Synthesis

Microwave is used in synthesis of

- Five-Membered Heterocyclic Rings: Pyrroles, Pyrazoles, Imidazoles, Oxazolines, Triazoles and Tetrazoles, Oxadiazoles, Isoxazolines and Pyrazolines
- Benzo-Derivatives of Five-Membered Rings: Benz-imidazoles, Benz-oxazoles, and Benz-thiazoles, Indoles
- Six-Membered Rings: Dihydropyridines, Dihydropyridopyrimidinones, Tetrazines, Dihydropyrimidines
- Polycyclic Six-Membered Rings: Quinolines, Pyrimido [1, 2-a] pyrimidines

Microwave is used in heterocyclic C-Alkylations, Heterocyclic N-Alkylation, Nucleophilic Substitutions, Hetero-Diels-Alder Reactions, Intramolecular Reactions, Intermolecular Reactions, 1,3-Dipolar Cycloaddition Reactions.[3]

5.3) Inorganic synthesis

5.3.1) Synthesis of organometallic and coordination compounds

Organometallic and coordination compounds are created by creating covalent bonds between organic compounds and metals, and microwave radiation has been successful in speeding up this reaction rate.

5.3.2) Synthesis of intercalation compounds

Recently there have been studies for the application of microwave chemistry for intercalation compounds. Compounds known as intercalation compounds are organic or organometallic substances that are sandwiched between oxide and sulphide layers. The production of intercalation compounds using conventional heating techniques, such as the intercalation of pyridine or its derivatives, is slow and has limitations in terms of yield.

5.3.3) Synthesis of ceramic products

Ceramic materials may now be microwave processed to a very high level of maturity. A crucial phase in the creation of ceramic goods in the ceramic manufacturing sector is the elimination of moisture or solvent. Microwaves were first only used to efficiently remove solvents from solid samples. According to estimates, microwave drying is more effective than traditional drying techniques for materials with a water content below 5%.however over the past few years Other benefits have boosted the usability of microwaves. It has been demonstrated that microwave heating produces a more even heat than traditional heating techniques. Ceramics are widely employed in a variety of sectors, including those that produce sanitary ware and electrical components.[12]

5.4) Synthesis of Nanoparticles

Among the several technologies now used for the synthesis of organic compounds, microwave aided synthesis is the most promising for nanoparticles. Microwave aided synthesis was quicker than traditional methods and produced particles with an average particle size of 12 nm. Microwave heating produced nanostructures that were smaller, narrower in size distribution, and more crystallized than those produced by traditional oil-bath heating.[13]

5.5) Drug discovery

MAOS is currently becoming more widely accepted in drug development labs. The fast popularity of this technology mirrors the rising expense of R&D and decline in the number of FDA approvals, which have led to what is regarded as a productivity crisis. The most effective way to increase R&D productivity is to lower the cost of failure, either by rejecting candidates earlier or by increasing the likelihood that candidates will succeed in the end. Through the reduction of chemical processes from hours or days to minutes, microwave technology produces speedy results. On occasion, microwave heating makes it feasible to create chemistries that were not previously achievable using traditional techniques.[14]

5.6) Drug development

The advantageous effect of microwave irradiation are greatly used in process chemistry especially when the classical methods require increased reaction time . Microwaves have also demonstrated a benefit in procedures involving delicate reagents or when compound degradation under prolonged reaction conditions is a potential. The use of concentrated microwave radiation to minimize reaction durations and enhance yields has recently been demonstrated in the multi-step synthesis of a thiazole [5,4-f] quinazoline . Instead of employing traditional heating methods, focused microwaves (irradiation in solution, 300 W) produced the necessary compounds with a better overall yield, quicker reaction times, and purifiable end products. The epimerization of substances with optical activity is a fascinating use of microwave activation. Within two minutes, a large variety of amino acids have been quantitatively epimerized, avoiding the significant breakdown brought on by the use of conventional heating.

5.7) Process development

Growing importance in process development is being given to microwave-assisted organic synthesis, particularly when forced conditions and lengthy reaction periods are required by traditional techniques. For effective, environmentally friendly synthesis of low-boiling solvents at high temperatures in confined containers, continuous and batch microwave reactors have been built. Based on these discoveries, commercial microwave systems are available.[15]

5.8) Synthesis of radiopharmaceuticals

Radiopharmaceuticals have been created in the pharmaceutical business using microwave-assisted organic synthesis at an increased pressure. These radiopharmaceuticals are employed as tracers in pre-clinical trials to provide nuclear medical images. The first trial of this sort was conducted using a multi-mode microwave oven, and it was found that the pace of response significantly increased. The production of radiopharmaceuticals using microwaves has increased as a result. The quick reaction speeds and high reaction yield are two benefits of microwaves. This is explained by the short half-lives of the reactants; for instance, shortening a synthesis with carbon-11 by five minutes increased output by 15%. Additionally, it has been shown that some reactions could only be accomplished by employing microwave.[16]

6) Benefits of microwave assisted synthesis:

6.1) Faster reaction

According to experimental evidence, microwave-enhanced chemical reaction rates can be quicker than those of traditional heating techniques. The synthesis of fluorescein, it requires normally 10 hours using conventional heating methods, it can be completed in only 35 minutes using microwave heating because the microwave can use higher temperatures than conventional heating systems. As a result, reactions are completed in a matter of minutes rather than hours.

6.2) Better yield and higher purity

Utilizing microwave irradiation, less side product production is seen, and a larger yield of the product is recovered . As a result, the purifying process goes more quickly and easily. For instance, the yield of the process increases from 85% to 97% during the microwave synthesis of aspirin.

6.3) Energy saving

The use of microwave radiation for heating is a very effective method that saves a lot of energy. This is largely due to the fact that microwaves only heat the sample and not the equipment, using less energy in the process.

6.4) Uniform and selective heating

In traditional heating, the solvent is heated last while the oil bath's walls are heated first. due to the dispersed heating in an oil bath there is a difference in the temperature between the walls and the solvent . When using a microwave to heat a substance, only the solvent and solute particles are stimulated, which causes the solvent to be heated evenly. The idea behind selective heating is that various materials react to microwaves in various ways. While certain substances are transparent, others absorb microwaves.

6.5) Eco-friendly

Microwave reactions are more hygienic and ecologically friendly than traditional heating techniques. The need of solvents in chemical reactions can be decreased or eliminated since microwaves heat the compounds directly. For instance, Hamelin invented a method for conducting a solvent-free chemical reaction on a sponge-like material with the use of microwave heating. Heat is applied to a porous substance, such as alumina, to initiate the reaction. When exposed to microwaves, the chemical reactants are adsorbed on alumina and react more quickly than with normal heating. The quantity of purification needed for the byproducts of chemical processes involving harmful chemicals has also decreased as a result of the employment of microwaves.

6.6) Reproducibility

Because of homogenous heating and improved process parameter control, reactions with microwave heating are more repeatable than reactions with traditional heating. It is also simple to keep track of a chemical reaction's temperature. .This is especially pertinent to pharmaceutical firms during the lead optimization stage of the drug development process.[9]

7) Drawbacks of microwave assisted synthesis:

It has been noted that using microwaves for synthesis might occasionally provide certain issues.

• Some solvents are inappropriate because they absorb microwaves much more readily than others.

• Reactions involving volatile compounds require extra caution since pressure in these reactions might also result in an explosion

• Heating reactions much above the boiling point of the solvent can increase the pressure which can cause vials to explode.

• They frequently accomplish inconsistent solvent heating, making yields unpredictable, unless we are employing a very costly microwave reactor.[17]

Conclusion:

Microwave assisted synthesis is one of the best methods for the achievement of goal of green chemistry. It is a very suitable alternative for conventional method of synthesis for the chemical synthesis of various products. microwave assisted synthesis has a advantage over conventional method of heating as its improves the isolated yields with green synthesis and also it is very energy efficient , the other advantage has also been exploited in the context of inorganic synthesis , drug development and other processes like synthesis of nanoparticles and radiopharmaceuticals. The exploitation of microwave in assisting various organic reactions has increased its importance as an important tool for the synthetic organic chemistry, in order to gain further development in this field in the place of domestic microwave ovens novel instruments which gives reproducible performances and also with minimal hazards should be used. because of its efficiency and also its potential to contribute to clean products the future of the application of microwave technology looks bright .

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