

MICROWAVE ASSISTED ORGANIC SYNTHESIS-A POTENTIAL TOOL FOR GREEN CHEMISTRY

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ABSTRACT

Microwave radiation, an electromagnetic radiation, is widely used as a source of heating in organic synthesis. Microwave assisted organic synthesis (MAOS) has emerged as a new “lead” in organic synthesis. The basic mechanisms observed in microwave assisted synthesis are dipolar polarization and conduction. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. Green chemistry efficiently utilizes raw materials, eliminates waste, and avoids the use of toxic or hazardous reagents and solvents in the manufacture and application of chemical products. Microwave assisted technique opens up new opportunities to the synthetic chemist in the form of new reactions that are not feasible using conventional heating and serve a flexible platform for chemical reactions. Over the past five years there has been a dramatic uptake in the use of microwaves as an energy source to promote synthetic transformations. Microwave-assisted synthesis is clearly a method by which the laboratory chemist can achieve goals in a fraction of the time as compared to traditional conductive heating methods. Reaction times in the best cases have been reduced from hours or days to minutes. In the present article an attempt was made to focus on what is microwave assisted synthesis, how is it generated and what importance may it have.

KEYWORDS: Green chemistry, Microwave radiation, electromagnetic spectrum.

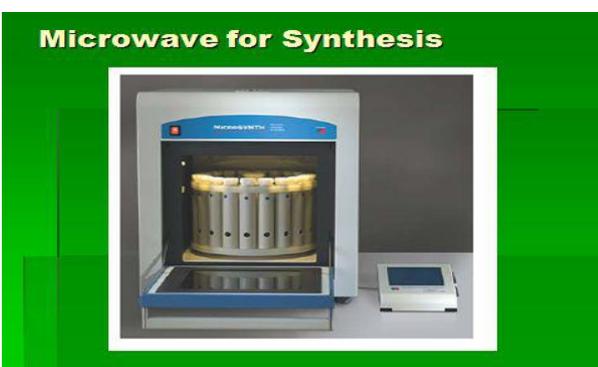
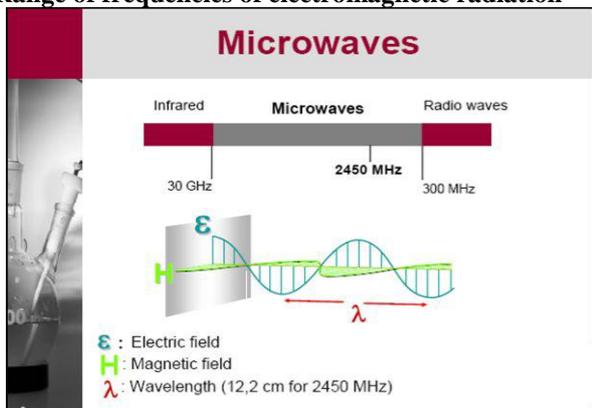
INTRODUCTION

Microwave assisted organic synthesis has revolutionized organic synthesis. Small molecules can be built in a fraction of the time required by classical thermal methods. As a result, this technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes. A microwave is a form of electromagnetic energy, which falls at the lower end of the electromagnetic spectrum and is defined in a measurement of frequency as 300 to 300,000 Megahertz, corresponding to wavelengths of 1 cm to 1m. In order to avoid interference with radar and telecommunication activities, which also operate in this region, most commercial and domestic microwave ovens operate at 2450 MHz (12.25cm). The difference between microwave energy and other forms of radiation, such as X- and γ -rays, is that microwave energy is non-ionizing and therefore does not alter the molecular structure of the compounds being heated it provides only thermal activation. The heating effect utilized in microwave assisted organic transformations is mainly due to dielectric polarization. When a molecule is irradiated with microwaves, it aligns itself with the applied field. The rapidly changing electric field (2.45×10^9 Hz)

affects the molecule and consequently the molecule continually attempts to align itself with the changing field and energy is absorbed. The ability of a material to convert electromagnetic energy into thermal energy is dependent on the dielectric constant. The larger the dielectric constant the greater is the coupling with microwaves. Thus, solvents such as water, methanol, DMF, ethyl acetate, acetone, acetic acid, etc. are all heated rapidly when irradiated with microwaves. However, solvents with low dielectric constants such as hexane, toluene, carbon tetrachloride, etc. do not couple and therefore do not heat that rapidly under microwave irradiation. Microwave heating has thus been found to be a very convenient thermal source not only in the kitchen but also in a chemical laboratory. Chemists have explored the possibility of the application of a conventional microwave oven to carry out chemical reactions. It has been found that many reactions progress much faster upon microwave irradiation than with traditional heating techniques. The application of microwave irradiation to activate and accelerate organic reactions has taken a new dimension and has experienced exponential growth in the last ten years. Microwave

chemistry is becoming increasingly popular both in industry and in academia.

Range of frequencies of electromagnetic radiation



Principles of Green Chemistry

Green Chemistry aims to eliminate hazards right at the design stage. The practice of eliminating hazards from the beginning of the chemical design process has benefits for our health and the environment, throughout the design, production, use/reuse and disposal processes.²⁹ Practitioners of Green Chemistry strive to protect the environment by cleaning up toxic waste sites and by inventing new chemical methods that do not pollute and that minimize the consumption of energy and natural resources. In 1998, two US chemists, Dr. Paul Anastas and Dr John Warner outlined Twelve Principles of Green Chemistry to demonstrate how chemical production could respect human health and the environment while also being efficient and profitable. Guidelines for developing Green Chemistry technologies are summarized in the "Twelve Principles of Green Chemistry," shown in the following.

1. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

The occurrence of accidents in chemical industry must be avoided. It is well known that the incidents in Bhopal (India) and Seveso (Italy) and many others have resulted in the loss of thousands of life. It is possible sometimes to increase accidents potential inadvertently with a view

to minimize the generation of waste in order to prevent pollution. It has been found that in an attempt to recycle solvents from a process (for economic reasons) increases the potential for a chemical accident or fire.

2. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

It is extremely important that the products designed to be synthesized should be biodegradable. They should not be persistent chemicals or persistent bio accumulators. It is now possible to place functional groups in a molecule that will facilitate its biodegradation. Functional groups which are susceptible to hydrolysis, photolysis or other cleavage have been used to ensure that products will be biodegradable. It is also important that degradation products do not possess any toxicity and detrimental effects to the environment. Plastic, Pesticides (organic halogen based) are examples which pose to environment.

3. Analytical methodologies need to be further developed to allow for real time, In process monitoring and control prior to the formation of hazardous substances.

Methods and technologies should be developed so that the prevention or minimization of generation of hazardous waste is achieved. It is necessary to have accurate and reliable reasons, monitors and other analytical methodologies to assess the hazardous that may be present in the process stream. These can prevent any accidents which may occur in chemical plants.

4. A raw material or feedstock should be renewable rather than depleting, Whenever technically and economically practicable. Non reversible or depleting sources can exhausted by their continual use. So these are not regarded as sustainable from environmental point of view. The starting materials which are obtained agricultural or biological processes are referred to as renewable starting materials. Substances like carbon dioxide (generated from natural sources or synthetic routes like fermentation etc) and methane gas (obtained from natural sources such as marsh gas, natural gas etc) are available in reasonable amounts and so are considered as renewable starting material. Methane, a constituent of biogas and natural gas can easily be converted into acetylene by partial combustion. Acetylene is a potential source of number of chemicals such as ethyl alcohol, acetaldehyde, vinyl acetate etc.

5. Catalytic reagents (as selective as possible are superior to stoichiometric Reagents.

The catalyst as we know facilitates transformation without being consumed or without being incorporated into the final product. Catalysts are selective in their action in that the degree of reaction that takes place is controlled, e.g. mono addition v/s multiple addition. A

typical example is that reduction of triple bond to a double bond or single bond. In addition to the benefits of yield and atom economy, the catalysts are helpful in reducing consumption of energy. Catalysts carry out thousands of transformation before being exhausted.

6. Unnecessary derivatization (blocking group, protection, deportation, temporary modification of physical/chemical processes) should be avoided whenever possible.

A commonly used technique in organic synthesis is the use of protecting or blocking group. These groups are used to protect a sensitive moiety from the conditions of the reaction, which may make the reaction to go in an unwanted way if it is left unprotected. This procedure adds to the problem of waste disposal.

7. The use auxiliary substances (e.g. solvents, separating agents) should be made Unnecessary wherever possible and innocuous when used.

An auxiliary substance is one that helps in manufacture of a substance, but does not become an integral part of the chemical. Such substances are used in the manufacture, processing at every step. Major problem with many solvents is their volatility that may damage human health and the environment. Even processes like recrystallisation require energy and substances to change the solubility. The problem of solvents has been overcome by using such solvents which do not pollute the environment. Such solvents are known as green solvents. Examples include liquid carbon dioxide (supercritical CO₂), ionic liquid water. Even reactions have been conducted in solid state. For example the condensation reaction of orthoesters with *o*-phenylenediamines in presence of KSF clay under solvent free conditions using microwave. Many solvents used in traditional organic synthesis are highly toxic. The Green Chemistry approach to the selection of solvents has resulted in several strategies. One method that has been developed is to use supercritical carbon dioxide as a solvent. Supercritical carbon dioxide is formed under conditions of high pressure in which the gas and the liquid phases of carbon dioxide combine to a single – phase compressible fluid that becomes an environmentally benign solvent (temperature 31°C, 7280 kPa, or 72 atmospheres). Supercritical CO₂ has remarkable properties. It behaves as a material whose properties are intermediate between those of a solid and those of a liquid. The properties can be controlled by manipulating temperature and pressure. Supercritical CO₂ is environmentally benign because of its low toxicity and easy recyclability. Carbon dioxide is not added to the atmosphere; rather, it is removed from the atmosphere for use in chemical processes. It is used as a medium to carry out a large number of reactions that would otherwise have many negative environmental consequences. It is even possible to perform stereo selective synthesis in supercritical CO₂. Some reactions

can be carried out in ordinary water, the most green solvent possible. Recently, there has been much success in using near-critical water at higher temperatures where water behaves more like an organic solvent. In the past 5 years, many new ionic liquids have been developed with a broad range of properties. By selecting the appropriate ionic liquid, it is now possible to carry out many types of organic reactions in these solvents. In some reactions, a well –designed ionic solvent can lead to better yields under milder conditions than is possible with traditional solvents. Another approach to making organic chemistry greener involves the way in which a reaction is carried out, rather than in the selection of starting material, reagents, or solvents. Microwave technology can be used in some reactions to provide the heat energy required to make the transformation go to completion. With microwave technology, reactions can take place with less toxic reagents and in a shorter time, with fewer side reactions, all goals of Green Chemistry. Microwave technology has also been used to create supercritical water that behaves more like an organic solvent and could replace more toxic solvents in carrying out organic reactions. Another Green Chemistry approach is the use of a catalyst which facilitates transformations without the catalyst being consumed in the reaction and without being incorporated in the final product. Therefore, use of catalyst should be preferred whenever possible.

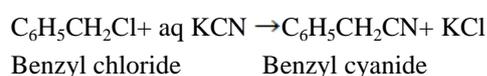
8. It is better to prevent waste than to treat or clean up waste after it is formed. It is most appropriate to carry out a synthesis by following a pathway so that formation of waste is minimum or absent. One type of waste product common and often avoidable is the starting material or reagent that remains unreacted. The wellknown saying “Prevention is better than cure should be followed”.

9. Whenever practicable synthetic methodologies should be designed to use and generate a substance that poses little or no toxicity to human health and the environment.

Wherever practicable, synthetic methodologies should be designed to use and generate substances that pose little or no toxicity to human health and the environment. Redesigning existing transformations to incorporate less hazardous materials is at the heart of Green Chemistry.

10. Energy requirements should be recognized for their environmental and economic impacts and should be minimized.

Energy generation, as we know has a major environmental effect. The requirement of energy can be kept to a base minimum in certain cases by the use of a catalyst. For example in conversion of benzyl chloride into benzyl cyanide if we use phase transfer catalyst, the conversion goes to completion in a very short time.



Conventionally, we have been carrying reaction by heating on wire gauze, in oil bath or heating mantels. It is now possible that the energy to a reaction can be supplied by using microwaves, by sonication or photo chemically. Simple examples are,



Esterification



11. Synthetic methods should be designed to maximize the incorporation of all the materials used in the process into the final product.

If one mole of the starting material produces one mole of the product, the yield is 100 %. However, such a synthesis may generate significant amount of waste or by product which is not visible in the above calculation. Such a synthesis, even though gives 100% yield, is not considered to be green synthesis. In order to find, if a particular reaction is green, the concept of atom economy was developed by Berry Trost of Stanford University. This considers the amount of starting materials incorporated into the desired final product. Thus by incorporation of greater amounts of the atoms contained in the starting materials (reactants) into the formed products, fewer waste by products are obtained. In this way, using the concept of atom economy along with ideas of selectivity and yield, "greener" more efficient synthesis can be developed. The atom economy for a reaction can be calculated using the following equation:

$$\text{Percent atom economy} = \frac{\text{Molecular weight of desired product}}{\text{Molecular weights of all reactants}} \times 100\%$$

To illustrate the benefits of atom economy, consider the synthesis of ibuprofen. In the former process, developed in the 1960s, only 40% of the reactant atoms were incorporated into the desired ibuprofen product; the remaining 60% of the reactant atoms found their way into unwanted by-products or waste that required disposal. The new method requires fewer reaction steps and recovers 77% of the reactant atoms in the desired product. This 'green' process eliminates millions of pounds of waste chemical by-products every year, and it reduces by millions of pounds the amount of reactants needed to prepare this widely used analgesic.

12. Chemical products should be designed to preserve efficiency of function while reducing toxicity.

The designing of safer chemical is now possible since there have been great advances in the understanding of chemical toxicity. It is now fairly understood that a correlation exist between chemical structure e.g. presence of functional groups and the existence of toxic

effects. The idea is to avoid the functionality related to the toxic effect. Chemical properties of a molecule, such as water solubility, polarity etc. so that they can manipulate molecules to the desired effects.

Microwave Synthesis on Solid Supports

Microwave heating for carrying out reactions on solids has also attracted considerable attention in recent years. For such 'dry media' reactions, solid supports such as alumina, silica, montmorillonite clay and zeolites have been investigated. The practical feasibility of microwave assisted solvent-free protocols has been demonstrated in useful transformations like protection, deprotection, condensation, oxidation, reduction, rearrangement reactions and in the synthesis of various heterocyclic systems on solid supports. A wide variety of industrially important compounds and intermediates such as enones, imines, enamines and nitro alkenes have been prepared by this environmentally friendly solvent-free approach. In these reactions, the organic compounds adsorbed on the surface of inorganic oxides, such as alumina, silica and clay or 'doped' supports absorb microwaves whereas the solid support does not absorb or restrict their transmission. The bulk temperature is relatively low in such solvent free reactions. Environmental concerns in synthetic chemistry have led to a reconsideration of reaction methodologies. This has resulted in investigations into atom economy, the use of supercritical CO_2 , ionic liquids, and other procedures to reduce the disposal problems associated with most chemical reactions. One obvious route to reduce waste entails generation of chemicals from reagents in the absence of solvents. Therefore the design of green processes with no use of hazardous and expensive solvents, e.g., "solvent-free" reactions, has gained special attention from synthetic organic chemists. As a result, many reactions are newly found to proceed cleanly and efficiently in the solid state or under solvent-free conditions. Less chemical pollution, lower expenses, and easier procedures are the main reasons for the recent increase in the popularity of solvent-free reactions. While an obvious approach to chemical synthesis, there are many problems associated with this approach, the chief of which is the role of diffusion/interactions between reactants. Further, it is never clear that the reactions in the solid state will generate the same products as those found in the presence of solvents. Generally, Michael additions are conducted in a suitable solvent in the presence of a strong base either at room temperature or at elevated temperatures. Due to the presence of the strong base, side reactions such as multiple condensations, polymerizations, rearrangements and retro-Michael additions are common. These undesirable side reactions decrease the yields of the target adduct and render their purification difficult. Better results can be obtained by employing weaker bases such as piperidine, quaternary ammonium hydroxide, tertiary amines etc. There have been some reports on Michael reactions catalyzed by potassium carbonate in organic solvents, and water in the presence

of surfactants or phase-transfer catalysts. To a large extent, mild bases restrain the formation of side products, thus improving the yield of the desired Michael adducts. Recently, non-conventional procedures like conducting the reaction on the surface of a dry medium or under microwave irradiation were found to facilitate the Michael reaction. For the purposes of eco-friendly "Green Chemistry", a reaction should ideally, be conducted under solvent-free conditions with minimal or no side-product formation and with utmost atom-economy.

Reaction Medium (In Presence of Solvent)

The reactions are carried out in a solvent medium or on the solid support (in which no solvent is used). For a reaction in solvent medium, the solvent must have a dipole moment so as to absorb microwaves and a boiling point at least 20-30 higher than the reaction temperature. In this respect N,N-dimethylformamide (DMF), is an excellent solvent used in microwave oven with high b.p. (160°C) and high dielectric constant ($\epsilon = 36.7$). Other solvents used are: formamide (b.p. 216°C, $\epsilon = 111$), methanol (b.p. 65°C, $\epsilon = 32.7$), 1, 2 dichlorobenzene (b.p. 83°C), dioxane (b.p. 101°C). The presence of salt in polar solvents can.

Frequently enhance, microwave coupling. Hydrocarbon solvents such as hexane ($\epsilon = 1.9$), toluene ($\epsilon = 1.9$), because of less dipole moment are unsuitable as they absorb microwave radiation poorly but addition of small amounts of alcohol or water can lead to a dramatic Coupling effect.

Microwave Heating in Drug Discovery

During the past fifteen years there is a tremendous growth and efforts to prepare organic, inorganic and organometallic compounds via green chemical approach. Introduction of Green technology in drug discovery, can help streamline process improvements in the R&D field. Microwave assisted green synthesis is a very good technique in the field of green chemistry by offering a flexible platform for many named organic reactions. 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. The compiled review gives an idea on MW green chemistry, its principle, its assembly and enlists some research work which will be beneficial for promising scientists.

CONCLUSION

The entry of microwave ovens in the chemistry laboratory has made it possible to carry out many transformations with greater efficiency and ease of workup. In recent years, the use of microwave has become very attractive in the field of pharmaceutical science. In today's competitive era microwave is one of the major tools for the rapid lead generation and optimization through which medicinal chemist will be able to deliver critically need new chemical entities and

candidate drug. Microwave also used in pharmaceutical drying that can change the drug release properties by polymeric cross linkages and drug interaction improves drug dissolution. We believe that in the future many more microwave-assisted reactions will be developed which will simplify time consuming conventional procedures. It is also hoped that appropriate technology will develop so that some of these fascinating microwave-assisted transformations could be done on industrial scales thereby increasing the overall efficiency of the processes and reducing pollution of the environment through the use of solvent free reaction protocols. The exploitation of microwaves for assisting different organic reactions has blossomed into an important tool in synthetic organic chemistry. The future for the application of microwave technology looks bright because of its efficiency and its potential to contribute to clean products.

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