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Microwave Assisted Synthesis of Heterocycles Green Chemistry Approaches

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ABSTRACT

The field of green chemistry employs many strategies aim at achieving safe, clean, and efficient conversions. Turning into standard synthetic processes. The current investigation focuses on using microwaves to synthesis heterocycle chemicals. According to the study, one new and successful method for organic synthesis that saves time and money is microwave assisted synthesis. When compared to the traditional approach, the chemicals produce well. Microwave radiation also considerably reduces the amount of time needed for synthesis. When compared to conventional synthesis, compounds like phenytoin, benzimidazole can be produced in good yield in a shorter amount of time.

Keywords: *Green Chemistry, Phenytoin Reaction, Benzimidazole, Microwave Assisted Synthesis.*

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INTRODUCTION

"The invention, design, and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances" is the definition of "green chemistry." In process chemistry, acceptability of a chemical process depends on its robustness, efficiency, and affordability.
The artificial plans in green chemistry are made with the least amount of environmental pollution in mind. Conventional techniques are widely used and documented for a variety of chemical syntheses. A new "lead" in organic synthesis is microwave assisted organic synthesis. This method allows for the economical, quick, easy, clean, and effective conversion of a wide range of organic compounds. [1]
Conventional organic synthesis methods typically include lengthy heating times, laborious apparatus setups, and increased process costs due to overuse of solvents and reagents, which pollute the environment. There is a lot of promise for reducing waste output, by products, and energy costs associated with the expansion of green chemistry. The term "microwave heating" describes the process of heating a material by applying electromagnetic waves with wavelengths ranging from 0.01 meters to 1 meter at a specific frequency. [2]
Due to a number of benefits, microwave aided organic synthesis is becoming a more and more common technology in academic and industrial research labs. accelerated chemical reaction optimization and reduced reaction durations. By stabilizing the inactive state of voltage and lowering electrical conductivity between brain cells, phenytoin works to reduce the unwanted, uncontrolled brain activity seen during seizures. sodium channels with gates. Moreover, phenytoin is utilized to treat facial nerve discomfort, migraine headaches, and arrhythmias (irregular heartbeat). The synthesis of novel medications using microwave aided synthesis has become a frontier in pharmaceutical research. It is commonly known that microwave irradiation accelerates chemical processes during the synthesis of a wide range of organic compounds because polar molecules selectively absorb microwave radiation. Every process needs automation in the quickly changing environment to improve quality, productivity, and safety while requiring less labour and time. Microwaves are discovered to be an essential instrument that satisfies these requirements. [3]
Microwave irradiation was initially used on synthetic chemistry in the middle of the 1980s. There are numerous advantages to microwave assisted organic synthesis (MAOS) over conventional heating. Many chemists are moving away from traditional heating methods and towards microwave assisted chemistry because of its advantages, which include speed, increased yield, and clear chemistry.[4] Microwave technology has now ushered in a new age in synthetic chemistry. Every process needs automation in the quickly changing environment to improve quality, productivity, and safety while requiring less labour and time. Microwaves are discovered to be an essential instrument that satisfies these requirements. Microwave irradiation was initially used on synthetic chemistry in the middle of the 1980s. There are numerous advantages to microwave assisted organic synthesis (MAOS) over conventional heating. Many chemists are moving away from traditional heating methods and towards microwave assisted chemistry because of its advantages, which include speed, increased yield, and clear chemistry. [5]
Microwave technology has now ushered in a new age in synthetic chemistry. Less hazardous/toxic chemicals should be used in and produced by synthetic processes.

Figure No.1: Microwave Heating

Principle of Microwave Heating:

The fundamental idea underlying microwave oven Heating is the result of charged particle interacting with the substance used in the reaction that has a specific electromagnetic wavelength. Heat can be produced by electromagnetic radiation either by conduction or impact or occasionally by both.[6]

The following are the fundamental mechanisms involved in material heating:

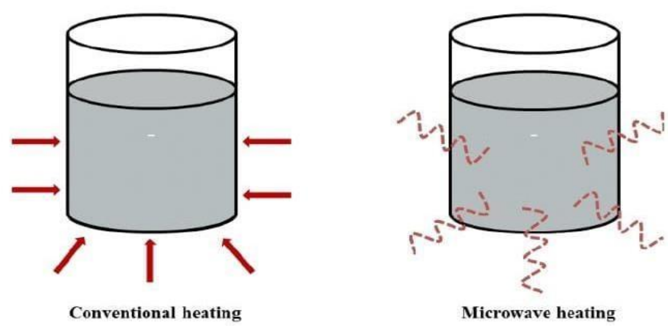


Figure No.2: Conventional Heating and Microwave Heating

Dipolar Polarization:

Heat is produced in polar molecules by a process called dipolar polarization. Polar molecules attempt to follow and align themselves in phase with an oscillating electromagnetic field of a suitable frequency when exposed to it. Heat can be produced by dipolar polarization in one or both of the following methods. A substance needs a dipole moment in order to produce heat when exposed to microwave radiation. It's the Molecular friction causes a dipole to lose energy in the form of heat when it tries to realign itself in respect to an alternating electric field.[7] Instead of the magnetic field component that generates heat, this is the electric field component of microwave radiation. Dipolar polarization can occur when pole solute molecules, such as ammonia and formic acid, combine with polar solutions molecules, such as water, methanol, and ethanol, to produce heat. If the frequency range is large enough, intermolecular interactions will prevent a polar molecule from moving before it tries to follow the field, leading to insufficient inter-particle interaction. On the other hand, if the frequency range is narrow, there will be sufficient time for the polar molecule to phase-align with the field.

The frequency range of microwave radiation (0.3-30 GHz) is suitable for polar particle oscillation and sufficient inter-particle interaction. It is therefore the best option for heating polar solutions. [8]

Conduction mechanism:

Heat is produced by the conduction mechanism when an electric current encounters resistance. An oscillation of electrons is produced by the oscillating electromagnetic field or ions in a wire, causing a current to flow across it. The conductor gets heated as a result of internal resistance to this current. Ions in a solution containing ions, or even a single detached ion with a hydrogen bonded cluster, will move through the solution in the presence of an electric field because it is thought that the more polar the solvent, the more easily the microwave radiation is absorbed and the higher the temperature obtained. Energy will be used as a result of this.[9] The carriers of charge, such as ions, electrons, etc. are transported through the material when the irradiated sample is an electrical conductor due to the influence of the electric filed, resulting in a Polarization. Heat is produced by the conduction mechanism when an electric current encounters resistance. An electric current is produced when an oscillating electromagnetically field causes an oscillation of electrons or ions in a conductor. The conductor gets heated as a result of internal resistance to this current. There are numerous ways in which microwave heating differs from traditional heating. [10]

Interfacial polarization:

The conduction and dipolar polarization mechanisms can both be combined in this technique of polarization. Take into account, for instance, how metal particles disperse in Sulphur. Metals absorb most of the microwave energy they come into contact with, whereas Sulphur does not react to microwaves. When the two are combined, the result is a substance that is effective in absorbing microwave radiation. However, metals must be used in powder form for this to happen. [11]

This is due to the fact that metal powder effectively absorbs microwave radiation, in contrast to a metal surface. It heats up through a process akin to dipolar polarization and absorbs radiation. The metal powder's environment works as a solvent for polar molecules and uses forces similar to those found in inter-particle interactions in polar solvents to limit the migration of ions. These constraining forces cause an oscillating field to cause a phase lag in the ion motion, which leads to random ion motion and eventually system heating.[12]

MECHANISM OF MICROWAVE HEATING:

Since different materials react differently to microwave radiation, not all materials can be heated by microwaves. According to how materials react to microwaves, can categories general as follows:

Materials that reflect microwaves, like copper,

Materials such as sulfur that are transparent to microwaves,

Substances like water that can absorb microwaves Dipolar polarization, conduction mechanism, and interfacial polarization are the three primary mechanisms involved in the heating of microwave-absorbing materials, which are crucial for understanding microwave chemistry. [13]

Advantage and Disadvantage of Microwaves:

Advantages:

Quickly responses Superior quality of goods Reduce byproduct

Enhanced yield Enhanced and streamlined synthetic process

Greater temperature range that can be used Increased energy economy

Advanced safety and measurement technologies.[14]

Disadvantages:

It's difficult to regulate the heat force.

Freshwater evaporation

There is a chance that a locked vessel will explode.[15]

MICROWAVE VERSUS CONVENTIONAL SYNTHESIS:

Conventional synthesis typically uses an oil bath or furnace to heat the reactor walls via convection or conduction. It takes a lot longer for the sample's core to reach the desired temperature. Energy is transferred into the responding system in a delayed and ineffective manner using this strategy. The use of microwaves in microwave-assisted synthesis offers various benefits over traditional reactions, including faster reaction rates, quicker reaction optimization, and quicker analogue synthesis. [16]

It also makes complex compound synthesis possible and requires less energy and solvent. In particular, lead creation, hit-to-lead efforts, and lead optimization are the three main stages of the drug development process where medicinal chemistry activities may be impacted by microwave synthesis. Utilizing specialized blades or microtiter plate devices, microwave chemistry can be carried out in a parallel arrangement with significant effectiveness. A single radiation experiment can include a few hundred reactions when using multimode microwave equipment. Benefits of combining combinatorial chemistry with microwave heating have been demonstrated by researchers. [17]

LIMITATIONS OF MICROWAVE ASSISTED SYNTHESIS:

Even if there have been advancements lately on the scalability of microwave equipment, a gap still needs to be filled in order to achieve scalability in the technology. Materials that absorb microwaves have limited applications when it comes to microwave heating. Materials like sulphur, which are transparent to microwave radiation, cannot be heated by them. Uncontrolled radioactive decay can occur when microwave heating is used improperly to speed up chemical reactions involving radioisotopes. When performing polar acid-based reactions, certain issues have also been noted that can have severe outcomes. For instance, microwave irradiation of an activity using concentrated sulphuric acid may cause damage. While performing polar acid- based reactions, other issues have also been noted that can have severe outcomes.[18]

For instance, heating a concentrated sulfuric acid reaction in a polymer vessel using microwave radiation may result in damage. Explosions and uncontrollable reactions can also occur when microwave processes are conducted under high pressure. Microwave penetration is the source of health risks associated with microwaves. Low-frequency microwaves can only penetrate human skin, whereas higher-frequency microwave can penetrate organs in the body. Studies have demonstrated that extended exposure to microwave radiation can cause bodily tissues and cells to completely degenerate. Additionally, it has been demonstrated that exposing DNA to high-frequency microwaves continuously while it is undergoing a biological response may cause total degeneration. [19]

Microwave-assisted synthetic applications include:

The utilization of microwave radiation in chemical synthesis entails utilizing it to expedite the process. Microwave-accelerated synthesis leads to faster reactions, higher yields, and purer final product. Furthermore, the possibility of high-capacity microwaves equipment has allowed the investigations' yields to readily scale up from milligrams to kilograms not requiring any changes to reactivity parameters. One good use for microwave-aided synthesis is drug discovery. [20]

Synthesis of organic matter:

Organic synthesis aided by microwaves has been the most popular is among the most extensively studied uses of microwaves in chemical processes. A review of the literature shows that a wide variety of organic reactions have been successfully carried out by scientists.[21] The pharmaceutical industry makes extensive use of microwave-assisted organic synthesis, especially when creating molecules for the lead optimization stage of drug discovery and development. During this stage, chemists create candidate pharmaceuticals from lead molecules using a variety of synthetic approaches. The following methods can be used to conduct organic synthesis reactions, depending on the conditions of the reaction.[22]

Inorganic synthesis:

A wide range of substances have been created by this process, including apatite, carbides, nitrides, complicated oxides, silicide's, zeolites, and others use microwaves. A variety of A3B and A4 type mesoporphyrinic combinations have been produced with increased rates using free of solvents microwave irradiation. [23] Mesoporphyrinic compounds have been successfully produced via solvent-free synthesis utilizing microwave irradiation because the elimination of solvent from the reaction environment reduces the amount of time it takes for reactant molecules to interact and boost's reaction yield. Two novel ionized metal-organic foundation isostructural polymer coordination polymers were synthesized with the aid of a microwave. A palladium/imidazolium salt combination was used to catalyze the synthesis of pinacol boronated from aryl chlorides with the use of a microwave.[24]

MATERIAL AND METHODOLOGY:

The melting points of the synthetic compounds used in this study were measured using open capillary tubes and a paraffin bath; the results are uncorrected. One of the best methods for monitoring the development of organic chemical reactions and determining the purity of organic molecules is thin layer chromatography. [25] Using precoated aluminium sheets (E-Merck) and silica gel coated on glass plates, thin layer chromatography was carried out. The spots were visible when exposed to iodine vapors. A Cary-630 model Agilent FTIR (ATR) spectrophotometer from Core Analytical Laboratory was used to record IR spectra. [26]

EXPERIMENTAL WORK:

Synthesis of Phenytoin:

Microwave Assisted Reaction:

Using a 250 ml RBF, a combination of 2.0 gm of benzil and 1.13 gm of urea was taken in ethanol. A 30% NaOH solution was introduced to the mixture, and the reaction was microwaved at 425 W for 10 minutes, intermittently recording TLCs. Conc. HCl was used to turn the reaction mixture acidic. Alcohol was used to cleanse the different product after it was filtered at the pump. [27]

Conventional Synthesis:

Fill a 250 ml RBF with 5.3 g of benzil, 3 g of urea, 15 ml of 30% sodium hydroxide, and 75 ml of ethanol. For two hours, heat the reaction solution while attached to the reflux condenser. Fill the flask with 125 milliliters of cold water after cooling it. Filter, then use concentrated HCl to make the filtrate highly acidic. Filter the precipitates, then use industrial spirit to recrystallize them. [28]

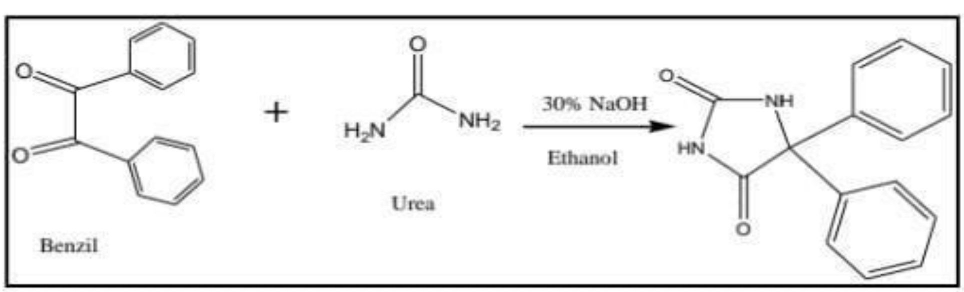


Figure No.3: Synthesis of Phenytoin

Synthesis of Benzimidazole:

Microwave Assisted Reaction: In RBF, a mixture of o-phenylene diamine (2.7 gm) and 90% formic acid (1.6 ml) was heated to 595 W for a duration of 7 minutes. After the reaction mixture had cooled for seven minutes, 10% sodium hydroxide was used to precipitate crude benzimidazole, that was then recrystallized by water via a little amount of decolorizing agent. [29]

Conventional synthesis:

In a 250 ml round-bottom flask, add 17.5 g of 90% formic acid in addition to 2.7 g of o-phenylenediamine. For two hours, the mixture is heated at 100°C in a water bath. Once the liquid is somewhat alkaline to litmus, cool it down and gradually add 10% sodium hydroxide solution while shaking continuously. At the pump, filter off the crude benzimidazole. After washing in ice-cold water, thoroughly drain and then wash again in 25 ml of cold water. Add 2g of discoloring carbon, dissolve the crude product in 400ml of boiling water, and let it digest for 15 minutes. Filter quickly at the pump using a flask and Buchner funnel that have been heated. Wash with 25 milliliters of cold water, filter off the benzimidazole, cool the filtrate to roughly 10°C, and then dry at 100°C. [30]

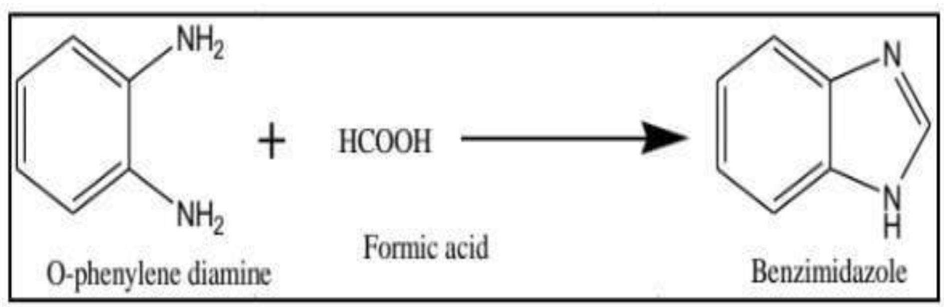


Figure No.4: Synthesis of Benzimidazole

RESULT:

Compound Code	Name of Compound	%Yield from MWI	Time taken by Conventional Synthesis in hours	Time taken by MWI in minutes
MS1	Phenytoin	74	4	11
MS2	Benzimidazole	63	2	7

Table No.1: A Comparison of the Time Required for Conventional Synthesis and Microwave Irradiation

Table 2 listed the physical characteristics of the heterocyclic compound. The product produced under safe conditions and with higher quality using microwave irradiation. Certain reactions don't require the use of a solvent, which lowers the cost. Because no solvent is required for the reaction to occur, no harmful vapors are also released.

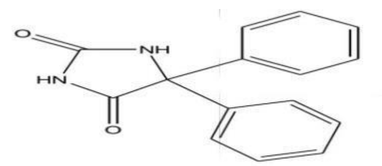
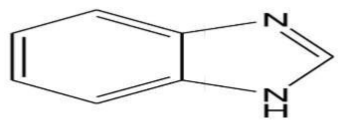
Compound code	**Name of compound**	**Structure**	**Mol. formula**	**Melting point (C)**	**Rf value**
MS1	Phenytoin		C15H12N2O2	294-296	0.93(Chloroform ethyl acetate 1:1)
MS2	Benzimidazole		C7H6N2	170-172	0.3(n -Hexane: ethyl acetate7:3)

Table No.2: The Physical Characteristics of Heterocyclic Substances

DISCUSSION

Microwave radiation is one of the best substitutes for traditional heating. The product obtained in a shorter amount of time with a satisfactory yield using microwave irradiation. The time needed to synthesize heterocyclic compounds using conventional and microwave irradiation is compared in Table 1. Heterocycle that, when heated by a traditional approach, would take hours to complete are produced in minutes with high-quality microwave radiation. Certain products obtained with higher purity than through traditional heating.

CONCLUSION

Microwave assisted synthesis is a better, quicker, and safer approach to environmentally friendly chemistry than traditional named reactions. The microwave-assisted organic synthesis considerably shortens the synthesis time. Thus, microwaves turned out to be a useful alternative to traditional heating methods. It's the surroundings friendly method to quickly obtain the chemical.

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