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Review Article

Microwave-Assisted Organic Synthesis: A Green Chemistry Strategy

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ABSTRACT

Microwave heating, being very quick and specific, is widely used as an easy mode of heating in organic synthesis. Nowadays, the advantages of this technique have made it more widely used. The conventional methods of organic synthesis normally need a longer heating time, elaborate apparatus setup, which result in a higher cost, and the use of excessive reagents and solvents leads to environmental pollution. Microwave-assisted synthesis provides the benefits of higher yields, greater reaction rates and selectivity, at the same time generating new, improved, economically viable, and environment-friendly processes for the synthesis of a large number of organic molecules. This technique is considered an important approach toward green chemistry. Microwave synthesis also opens up new opportunities to the chemist in the form of new reactions that were not possible in conventional heating. This article focuses on the different applications of microwave-assisted synthesis, solid-phase synthesis, green chemistry, and nanotechnology and also discusses the basic mechanism involved in microwave heating.

Key words: Energy-efficient, Environment-friendly, Green chemistry, MAOS, Solvent-free.

1. INTRODUCTION

Microwave chemistry is the science of applying microwave radiation to enable chemical reactions. Earlier, the microwave was only used for domestic purposes for heating and cooking foods. The first microwave oven was introduced by Tappan in 1955 while the first application under organic synthesis was published in 1986. Since the year 2000, microwave-assisted synthesis has gained importance and can easily be used to carry out various syntheses in laboratories [1].

For centuries, conventional heating methods of using Bunsen burners, oil baths, and hot mantles have been used for carrying out chemical reactions. These methods are not only time consuming and tedious, but also energy inefficient and wasteful [2]. They also create a hot surface on the reaction vessel where the reagents decompose over time and creating toxic substances. These methods also require the use of solvents, which are often toxic, harmful to the environment and may require further steps involving their recovery. All these drawbacks of the conventional heating methods can be overcome by the use of alternate methods, use of microwaves being one such method [3,4]. Microwave-assisted synthesis has several advantages over the conventional methods. In this method of synthesis, high temperature is easily and quickly attained and cooling is also fast. Microwave heating does not heat the whole surface inside the appliance, as is the case with conventional heating that heat up the reaction mixture by conduction, but only uses the waves to heat the reaction mixture kept in it. This reduces the formation of unwanted side products, so the yield is enhanced and the synthesis is cleaner. Furthermore, the use of harmful organic solvents in large amounts is avoided, which is usually not possible in conventional synthesis methods. All these features make microwave-assisted synthesis an example of green chemistry, that is, it is energy efficient, atom efficient, faster, uses fewer solvents, and is cleaner [3]. It is also applicable to a large variety of organic reactions, making it highly versatile and useful [4]. The comparison of a conventional oven and microwave oven for synthesis is done in Table 1.

2. MECHANISM OF HEAT GENERATION BY MICROWAVES

The mechanism of heat generation in microwave-assisted synthesis is dipolar polarization [5]. When irradiated with microwaves, the molecules with a permanent dipole moment become aligned with the electric field component of the microwaves. This causes the molecules to oscillate and collide with each other. The oscillation of molecules produces friction between them, resulting in heat generation. Hence, to become microwave active, the reagent molecules should possess a dipole moment and should be polarizable. The greater the polarizability of the molecules more is the heating effect produced in the presence of microwaves.

Solvents also play an important role in this technique and each solvent absorbs energy differently. There are three types of solvents used, namely, low, medium, and high absorber of microwave radiation. While hydrocarbons are low absorbers, polar compounds such as alcohols are high absorbers and the medium one is water, acetone, acetic acid, etc. [7]

3. INSTRUMENTATION

Microwave-assisted synthesis is carried out in special microwave reactors that generally comprise five main components, namely, high voltage transformer, magnetron, waveguide, cooling fan, and cavity, as shown in Figure 1 [8].

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Table 1: Comparison of conventional oven and microwave.

	Conventional oven	Microwave
Heating method	Uses fans to circulate hot air, hence creating a uniform heating environment	Heats by polarizing effect [5]
Heating times	Slow heating, may take several hours	Fast heating, takes few minutes [6]
Heating characteristics	Heats the material from outside and then toward the inside of the material	Heats the material inside out

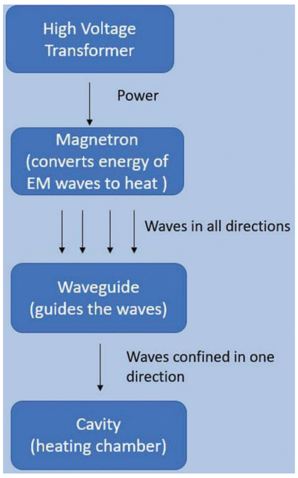

Figure 1: Main components of a microwave reactor.

3.1. High Voltage Transformer

A microwave reactor requires a high voltage (min of 3000–3400 V) to work. To achieve this voltage, a high voltage transformer is required, which uses a variety of capacitors that wind electric current, multiplying their power. In this way, the required power that the reactor needs to work is attained.

3.2. Magnetron

The magnetron consists of two parts - a vacuum tube and two ring-shaped magnets surrounding this tube. Furthermore, the vacuum tube has two parts - a copper anode and a central filament that are made of tungsten and thorium. The magnetron receives a high voltage from the transformer and converts the energy of microwaves into heat energy and to do this it creates a diode that directs electrons using magnetic fields. The ring-shaped magnets divert the electrons to make them move back to the central filament; this creates an oscillating wave.

3.3. Waveguide

Its prime function is to direct the waves that are produced by the magnetron in all directions, toward one direction, working as a guide. It is a hollow tube made up of metal whose internal walls are reflective, hence reverberating the waves back and forth until they reach the cavity [9].

3.4. Cooling Fan

To prevent the microwave oven from getting overheated, it is provided with a cooling fan which serves to eliminate excess heat.

3.5. Cavity

The cavity is a closed metal structure that works as an oscillator. Microwaves oscillate within the cavity in the form of standing waves. These waves oscillate back and forth by striking on the walls of the metal structure with the help of an arrangement of two reflectors on each side, making these waves superimpose one another hence creating higher intensity.

4. APPLICATIONS OF MICROWAVE-ASSISTED ORGANIC SYNTHESIS MAOS

Organic synthesis often requires the use of organic solvents such as benzene, chloroform, acetone, and methanol which then have to be removed and disposed of. Hence, in this field, microwave-assisted synthesis has been a great boon as it offers a greener approach to organic synthesis, from using greener solvents such as water to solvent-free reactions. A lot of research has been carried out in the field of microwave-assisted organic synthesis. Some of these organic syntheses have been reviewed below (Table 2).

4.1. Microwave-assisted Reactions Using Solvents

In this method, the reactants are dissolved in suitable solvents which have the tendency to couple with microwaves and act as an energy transfer medium. One of the most investigated among these is the use of aqueous media for organic synthesis; it was found out that at an elevated temperature, water can behave like a pseudo–organic solvent [10]. The use of water can be a perfect replacement for organic solvents, making the process eco-friendly.

When using solvents, another thing to consider is open or closed vessel reactions. When using low-boiling solvents in open vessels, they get heated up by microwave irradiation at atmospheric pressure, which limits the reaction temperature; so the rate of reaction is affected. This can be avoided using high-boiling solvents such as dimethyl sulfoxide, 1,2-dichlorobenzene, or ethylene glycol; however, this would involve the removal of the solvents after completion of the reaction. Other than this, the reaction can be performed with low-boiling solvents, with frequent disruption of heating; the problem in this is that high temperatures, that increase the rate of reaction, are not attained and also there is a potential fire hazard if suitable precautions are not taken. Therefore, a better alternative is to conduct the reactions in a closed vessel, and with the help of more advanced microwave reactors, where temperature and pressure can be monitored; this method is becoming the most suitable one for carrying out a microwave-assisted synthesis. However, in case, the by-products of the reaction are volatile, pressure build-up in a sealed vessel can pose a problem; in such cases, an open vessel is more suitable [11].

4.2. Microwave-assisted Reactions Using Solvent-free Conditions

Due to the environmental concerns and wastage involved, there has been an increasing demand for efficient synthetic processes and solvent-free reactions. The use of microwaves can be done for solvent-free synthesis, making MAOS an environment-friendly green process [12]. Solvent-free reactions can be performed in three ways:

- Reactions using neat reactants, when at least one of the reactants is a liquid or the reactants melt during heating and undergo reaction [13].
- Reactions using solid-liquid phase transfer catalysis. In these, a catalytic amount of a tetra-alkylammonium salt or a cation complexing agent is added to the reaction mixture
- Reactions using solid mineral support. Solid supports, such as silica, alumina, and clay, often behave as very efficient microwave absorbents, helping in rapid and homogeneous heating.

Table 2: Different reactions using MAOS.

S. No.	Type of reaction	Reactants/reagents	Reaction conditions	Advantage of using MAOS	Reference
1	Hydrolysis	(1) Benzyl chloride, water	Aqueous medium	Yield 97%; Time 3 min	[14]
		(2) Benzamide, sulfuric acid	Aqueous medium	99%; 7 min	[14]
		(3) 3-hydroxyacetals, pyridinium tosylate	Solvent free and silica gel supported	High yield, less time	[15]
2	Oxidation	(1) Primary and secondary alcohols with 30% aqueous H_2O_2	Aqueous medium	Time 10–20 min	[16]
		(2) Benzyl alcohol with BIFC	Solvent-free and phase transfer catalyst	Time 1–8 min	[17]
		(3) Primary alcohol with clay-supported iron (III) nitrate	Solvent free and clayfen	Time 15–60 s	[18]
3	Reduction	Acetophenone with $NaBH_4$	Solvent free and solid-support	Yield 92%, time 2 min	[19]
4	Esterification	Benzoic acid with n-propanol, conc. H_2SO_4	Neat	Time 6 min	[20]
5	Decarboxylation	Malonic acids	Aqueous medium	Yield 80–90%, time 15 min	[21]
6	N-Alkylation	(1) Phthalimide, alkyl halides, potassium carbonate, and TBAB	phase transfer catalysis	Yield about 45–98%	[22]
		(2) Piperidines and chloroalkanes	silica as solid support	Time 6–10 min	[23]
7	N-Acylations	Secondary amines and isocyanate	DCM	Yield 94%, Time 8–10 min	[24]
8	S-Alkylation	Mercaptobenzene and alkyl halides	Alumina is used as the solid support	Yield 70–89%	[25]
9	Aromatic Nucleophilic Substitutions	Sodium phenoxide and 1,3,5-trichlorotriazine	Neat	Yield 85–90%, Time 6 min	[26]
10	Knoevenagel Condensation	Benzaldehyde, malonic acid, tetra butyl ammonium bromide, K_2CO_3	Aqueous medium	Yield 85%, Time 5 min	[27]

Using these reactions, several important organic compounds have been synthesized. A few examples are discussed below.

- Synthesis of cephalosporin derivatives (antibiotics) can be done in high yield by adsorbing the reactants on basic alumina and irradiating with microwaves for just 2 min [28] (Figure 2)
- Synthesis of N-acetyl-p-aminophenol (paracetamol) and acetylsalicylic acid (aspirin). The synthesis of these well-known drugs can be carried out using MAOS using acetic anhydride and no catalyst. While the synthesis of aspirin can be done from salicylic acid in 3 min, with 82% yield (Figure 3), that of paracetamol can be done in 2 min, with 92% yield, from 4-aminophenol [29].

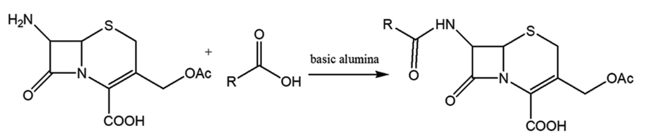

Figure 2: Synthesis of cephalosporins using microwaves.

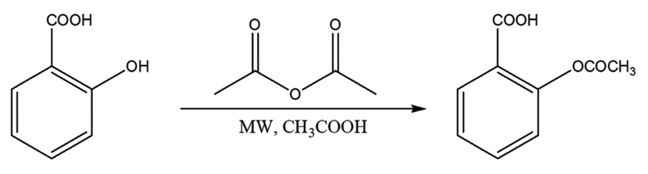

Figure 3: Synthesis of aspirin using microwaves.

4.3. Benefits of MAOS

- Higher temperatures: The microwave uses a higher temperature than the conventional method and hence the reaction rate is automatically increased
- Faster reactions: Microwave reactions are faster than conventional methods as per many pieces of research [28]
- Lesser by-products or side products: This gives better yield and higher purity. For example, the synthesis of aspirin results in an increase of yield to more than 80% [29]
- Energy-efficient: This is because microwaves only heat the sample and not the apparatus and hence the consumption of energy is less
- Green synthesis: Reactions conducted by microwaves are cleaner and more environmentally friendly than conventional heating methods. It has great potential as it offers eco-friendly routes in synthesis. The work-up and purification, that were earlier done at the end of the reaction, are also not required in microwave-assisted reactions.

5. DRAWBACKS OF MICROWAVE-ASSISTED SYNTHESIS

It has been observed that the use of microwaves for synthesis can sometimes pose certain problems.

- Some solvents absorb microwaves much more readily than others which mean certain solvents are unsuitable
- Heating reactions far past the boiling point of the solvent can cause a build-up of pressure which may cause the microwave vial to explode
- Reactions involving volatile substances need more consideration as pressure here also can cause an explosion. Large scale reactions also cannot be done for the same reason (especially when volatile compounds are involved) [11]
- Unless we are using a very expensive microwave reactor, they often achieve uneven heating of the solvent, so yields are not reproducible.

6. CONCLUSION

Microwave-assisted synthesis is a suitable alternative to conventional synthetic procedures as it is environment-friendly and follows the principles of green chemistry. The reactions have been found to be energy-efficient, high yielding, and fast. High temperatures are quickly reached due to microwave irradiation, so prolonged heating is not needed and also the yield is high due to lesser side reactions. The reactions can be carried out in solvent-free conditions as well, either neat or with solid-support or phase transfer catalysts, making them less toxic and less wasteful. Moreover, a variety of organic reactions can be conducted by microwave irradiation, which has made this method highly versatile and useful in synthetic organic chemistry. With the development of safer and less expensive microwave reactors, this technique has the potential to become more acceptable and commonly used, and can become an eco-friendly approach to chemistry.

7. REFERENCES

1. M. A. Surati, S. Jauhari, K. R. Desai, (2012) A brief review: Microwave assisted organic reaction, ***Archives of Applied Science Research***, **4**(**1**): 645-661.
2. S. Nain, R. Singh, S. Ravichandran, (2019) Importance of microwave heating in organic synthesis, ***Advanced Journal of Chemistry***, **2**(**2**): 94-104.
3. A. K. Nagariya, A. K. Meena, A. K. Yadav, U. S. Niranjan, A. K. Pathak, B. Singh, M. M. Rao, (2010) Microwave assisted organic reaction as new tool in organic synthesis, ***Journal of Pharmacy Research***, **3**(**3**): 575-580.
4. A. S. Grewal, K. Kumar, S. Redhu, S. Bhardwaj, (2013) Microwave assisted synthesis: A Green chemistry approach, ***International Research Journal of Pharmaceutical and Applied Sciences***, **3**(**5**): 278-285.
5. A. de la Hoz, Á. Díaz-Ortiz, A. Moreno, (2005) Microwaves in organic synthesis: Thermal and non-thermal microwave effects, ***Chemical Society Rev*iews**, **34:** 164-178.
6. D. Bogdal, (2005) ***Microwave Assisted Organic Synthesis***, UK: Elsevier Publications, p13.
7. B. M. Sahoo, (2016) Microwave assisted drug synthesis: A green technology in medicinal chemistry, ***Journal of Applied Pharmacy***, **8:** 1.
8. C. O. Kappe, (2004) Controlled microwave heating in modern organic synthesis, ***Angew Chemie International Edition***, **43**(**46**): 6250-6284.
9. T. V. C. Chan, H. C. Reader, (2000) **Understanding Microwave Heating Cavities**, Boston, London: Artech House Publishers.
10. V. Polshettiwar, R. S. Varma, (2008) Aqueous microwave chemistry: A clean and green synthetic tool for rapid drug discovery, ***Chemical Society Reviews***, **37:** 1546-1557.
11. A. Stadler, (2002) Microwave-enhanced reactions under open and closed vessel conditions: A case study, ***Tetrahedron***, **58:** 3177-3183.
12. R. S. Varma, (2006) Greener organic syntheses under non-traditional conditions, ***Indian Journal of Chemistry***, **45B**, 2305-2307.
13. A Seijas, M. P. Vazquez-Tato, (2007) Microwaves: A new tool for an ancient element. solvent and support-free microwave-assisted organic synthesis, ***Chimica Oggi***, **25:** 20-26.
14. R. N. Gedye, W. Rank, K. C. Westaway, (1991) The rapid synthesis of organic compounds in microwave ovens II, ***Canadian Journal of Chemistry***, **69:** 700.
15. Y. He, M. Johansson, O. Sterner, (2004) Mild microwave-assisted hydrolysis of acetals under solvent-free conditions, ***Synthetic Communication***, **34:** 4153-4158.
16. D. Bogdał, M. Łukasiewicz, (2000) Microwave-assisted oxidation of alcohols using aqueous hydrogen peroxide, ***Synlett***, **1**(**1**): 143-145.
17. V. Sivamurugan, G.A. Rajkumar, B. Arabindoo, V. Murugesan, (2005) Selective and Clean Oxidation of Alcohols with Benzimidazolium Fluorochromate (BIFC) under Solvent Free Conditions, ***Indian Journal of Chem*istry**, **44B**: 144-147.
18. R. S. Varma, R. Dahiya, (1997) Microwave assisted oxidation of alcohols under solvent free conditions using clayfen, ***Tetrahedron Letters***, **38**(**12**): 2043-2044.
19. V. Polshettiwar, M. N. Nadagouda, R. S. Varma, (2009) MW-assisted chemistry: A rapid and sustainable route for synthesis of organics and nanomaterials, ***Australian Journal of Chemistry***, **62:** 16-26.
20. R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, (1986) The use of microwave ovens for rapid organic synthesis, ***Tetrahedron Letters***, **27:** 279-282.
21. G. B. Jones, B. J. Chapman, (1993) Decarboxylation of indole-2-carboxylic acids: Improved procedures, ***Journal of Organic Chemistry***, **58:** 5558-5559.
22. D. Bogda, J. Pielichowski, A. Borona, (1996) Remarkable fast microwave-assisted N-alkylation of phthalimide in dry media, ***Synlett***, **37:** 873-874.
23. M. M. Heravi, N. Farhangi, Y. S. Beheshtiha, M. Ghassenizade, K. Tabar-Hydar, (2004) Sulfuric acid adsorbed on silica gel and chromium (VI) oxide: Rapid and selective oxidation of alcohol in solvent-free condition, ***Indian Journal of Chem*istry**, **43B**: 430-431.
24. A. Vass, J. Dudas, R. S. Varma, (1999) Solvent-free synthesis of N-sulfonylimines using microwave irradiation, ***Tetrahedron Letters***, **40:** 4951-4954.
25. Q. Xu, B. Chao, Y. D. Wang, C. Dittmer, (1997) Tellurium in the "no-solvent" organic synthesis of allylic alcohols, ***Tetrahedron***, **53:** 2131-2134.
26. A.D. Sagar, D.S. Patil, B.P. Bandgar, (2000) Microwave Assisted Synthesis of Triaryl Cyanurates, ***Synthetic Communication***, **30**, 1719-1723.
27. M. Gupta, B. P. Wakhloo, (2007) Tetrabutylammoniumbromide Mediated Knoevenagel Condensation in Water: Synthesis of Cinnamic Acids, ***ARKIVOC***, **1:** 94-98.
28. M. Kidwai, P. Misra, K. Bhushan, M. Singh, (2000) Microwave-assisted solid-phase synthesis of cephalosporin derivatives with antibacterial activity, ***Monatshefte für Chemie***, **131:** 937-943.
29. S. Lenuta-Maria, C. M. Popoiu, I. Ledeti, G. Simu, G. Savoiu, A. Fulias, (2014) Alternative synthesis of paracetamol and aspirin under non-conventional conditions, ***Revista de Chimie***, **65:** 621-623.

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