# MW ASSISTED TECHNIQUE IN HETEROCYCLE SYNTHESIS

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**Summary**

Green chemistry today has to take into consideration, the ecological aspect, toxic waste generation, formation of unwanted by products and cost of manufacture no matter how innovative chemistry is employed in the process.
Microwave assisted technique opens up new opportunities to the synthetic chemist in the form of new reactions that are not possible using conventional heating and serve a flexible platform for heterocycles ring formation viz. five membered ring (pyrrolo, imidazole, triazole), Benzo derivatives of five membered ring (indole, isatin), six membered ring (dihydropyridine, dihydropyrimidine), polycyclic six membered ring (quinoline,) etc.

**Key word:** Heterocycle, Microwave synthesis, Microwave technique, Green chemistry.

**Introduction**

## 1. General Introduction

The chemistry in new millennium has accepted the concept of **'Green Chemistry'** and adopted it widely to meet the challenge of protecting the human health and environment, a necessity which has arisen due to the indiscriminate use of hazardous chemicals and solvents. It has been realized lately that operation of any synthesis today has to take into consideration, the ecological aspect, toxic waste generation, formation of unwanted by products and cost of manufacture no matter how innovative chemistry is employed in the process.

Following twelve basic principles of green chemistry have been formulated by Paul T. Anastas[1].

1. It is better to prevent waste than to treat or clean up after it is formed.
2. Synthetic processes, materials should be designed to maximize the incorporation of all materials used in the process, into the final product.
3. Wherever practicable synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy while reducing toxicity.
5. The use of auxiliary substances should be made unnecessary whenever possible and, when used it should be innocuous.
6. Energy requirement should be recognized for their environmental and economic impacts and should be minimized.
7. A raw material or feedstock should be renewable rather than depleting, it should be technically and economically practicable.
8. Unnecessary derivatization should be avoided whenever possible.
9. Catalytic reagents are superior to stoichiometeric reagents.
10. Chemical products should be so designed that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed, to allow for real time in-process monitoring and control prior to the formation of hazardous substances.
12. Substance should be chosen so as to minimize the potential for chemical accidents, including explosions and fires.

To meet this demand, chemists have resorted to using wide variety of techniques in synthesis such as the microwave technique, photochemical, electrochemical, sonochemical and enzymatic methods. With the easy availability of microwaves its use in chemistry has gained momentum and this has led the microwave heating to emerge as powerful technique to promote a wide variety of chemical reactions. Since the appearance of first article[2] in 1986 on the use of microwaves in chemical reactions, the approach has blossomed into a useful technique for a variety of application in organic synthesis and in functional group transformations. The technique has great potential and can be utilized as an innovative synthetic tool for accessing the highly functionalized products.

The recent use of microwave irradiation techniques for acceleration of organic reactions has placed a milestone in field of Green Chemistry. The recyclability of the mineral supports used and their application under solvent free conditions render these processes truly eco-friendly clean protocols. The technique has emerged as promising synthetic tool with great potential and the practical utility of MW assisted green protocols has been realized in several synthetic operations such as protection/deprotection condensation, oxidation, reduction, rearrangement reaction and in the synthesis of various heterocyclic systems[3-6]. Several reviews which have appeared on this subject clearly illustrate the ingenuity and imaginative breadth of the work carried out in this area in the past twenty years.

### 1.1 Microwave assisted technique- A new tool for Green chemistry

In recent years, the use of microwave technology in organic synthesis has received considerable attention[7]. Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions. Although first reported by the group of Gedye[1] and Gigure Majetich[8] in 1986, the use of microwaves in organic synthesis was initially hampered by a lack of understanding of the basic principle of MW dielectric heating and the inability to obtain reproducible results with domestic microwave ovens. Today microwave irradiation in organic synthesis has readily gained popularity as it accelerates variety of organic reactions[9]. Solvent free organic reactions (dry media techniques) under microwave irradiation are one of the main concerns of research in recent time[10-12] which were originally developed in late eighties[13]. Synthesis without solvent, in which reagents are absorbed on mineral support has a great potential as it offers an eco-friendly green protocol in synthesis.

### 1.2 Principle behind microwave effects

The energy of a MW photon (0.037 Kcal/mol) is too low to break chemical bonds or induce reactivity. In comparison, the energy of Brownian motion is 0.392 Kcal/mol and the energy contained within hydrogen bonds ranges from 0.908 to 10.038 Kcal/mol)[14] While conventional heating provides energy to reaction vessels via conduction or convection, MW enhanced chemistry is based on temperature increase by dielectric heating, which operates through two mechanisms: **dipolar polarization and ionic conduction**. The electric field component of MW irradiation causes dipoles and ions to align, and as the applied electric field oscillates, the dipole-ion field is forced to realign itself. In this process energy is lost as heat through both molecular friction and dielectric loss[15] The greater the polarity of a molecule (for instance a solvent) the more pronounced microwave effect when one considers the rise in temperature.

### Thermal Effects

A substance ability to convert electromagnetic radiation into heat depends on dielectric properties[16] and is calculated by the loss angle, $\tan \delta = \varepsilon'' / \varepsilon'$. The loss factor $\varepsilon''$ quantifies the efficiency with which the absorbed energy is converted into heat, while $\varepsilon'$, the dielectric constant describes the ability of molecules to be polarized by an electric field.

A reaction medium with high $\tan \delta$ values are considered transparent to microwaves. Thermal effects are accelerations in rate that cannot be achieved by conventional heating but are essentially the result of dielectric heating.

These includes the superheating of solvents up to 40°C above their boiling points under MW irradiations at normal atmospheric pressure, as well as selective heating of strongly MW-absorbing catalysts or reagents in a heterogeneous reaction mixture[17].

### Specific MW Effects

The possibility of specific MW effects, are characterized by rate accelerations, yield improvements, or selectivity changes that cannot be obtained by thermal effects. The existence of non-thermal MW effects is often explained in the literature by considerations of the terms in the Arrhenius equation, $K=Ae^{-Ea/RT}$ The pre-exponential term A describes molecular mobility and depends on the frequency of vibrations at the reaction interface[18,19]. Since microwaves induce an increase in molecular vibrations, it was proposed that this could also cause an increase in the A factor of the Arrhenius law. Some have predicted that microwaves might increase reaction rate, decrease ΔG# especially if polarity increases from reactant to transition state during the course of reaction. But the exact source of MW enhancement is the subject of much controversy [20, 21]. In many cases, where temperature, pressure and concentration have been carefully monitored, specific microwave effects have not been observed. On the other hand, since the magnitude of the proposed microwave effect may be smaller than imagined, it is expected that only reactions involving polar transition states under low temperature conditions (in non polar solvents) might exhibit specific effects[22]. Careful research efforts in future will be necessary to truly understand microwave enhancements in organic synthesis.

### 1.3 Advantages, limitations and precautions

**Advantages[23]**

Microwave assisted organic synthesis have several significant advantages over conventional technology:

1. Microwaves generate rapid intense heating of polar substances with consequent significant reductions in reaction times.
2. Many reactions occur by conventional heating results in very low yields but under MW irradiations results in higher yield.
3. The main advantage of MW heating is “incore” heating of materials in homogenous and selective manner.
4. The smaller volume of solvent required contribute to a savings in cost and diminish the waste disposal problem.
5. The method provides rapid and relatively inexpensive access to very high temperatures and pressures.
6. Microwave technology with reactions performed on solid support constitutes an environmentally benign technique which results in no highly contaminating residues.
7. The method provides rapid and relatively inexpensive access to very high temperatures and pressures.
8. Microwave chemistry is the current approach in green chemistry which involves the design and redesign of chemical synthesis and chemical products to prevent environmental pollution.

**Limitations[24]**

Although microwave chemistry has many advantages but it has certain limitations which should be kept in mind while carrying out reactions in microwaves.

1. Reactions carried in microwave are in millimoles and results in generation of small amounts of products which cannot fulfill the requirements of industries.
2. These procedures are strongly limited by the presence of solvents which reach their boiling points within very short time in (≅ 1min) of exposure to microwaves.
3. Reaction over solid supports may run more slowly due to diffusional constraints.
4. Side reactions with the polymer support itself may occur.

**Precautions**[24]

1. Although microwave technique is a safe source of heating, yet may be hazardous also when chemical reaction is not carried out in controlled manner Volatile reactants under superheated condition may result to explosive conditions
2. The volume of the reaction mixture is kept between 10 and 5% of the volume of the container
3. Toxic, explosive and noxious reagents are often more safely handled when contained on a solid support.
4. Microwave radiations are proved fatal for health. Its prolonged exposure may result in the complete degeneration of body tissues and cells. It may penetrate the skin and affect body organs.

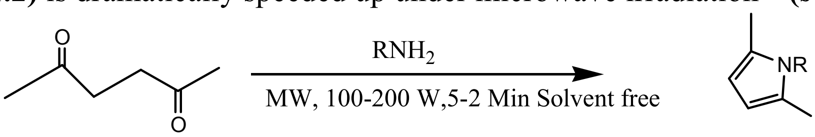
## 2. Applications of microwaves in heterocyclic ring formation

Microwave synthesis has gained popularity among the synthetic chemist community. Some of the applications of microwave methodology in presence of solvent and over solid supports are:

**2.1 Five-membered héterocyclic rings**

**(a) Synthesis of pyrroles (1.2)**

The classical Paal-Knoor cyclization of 1, 4 —diketones **(1.1)** to give pyrroles **(1.2)** is dramatically speeded up under microwave irradiation[25] **(scheme 1)**



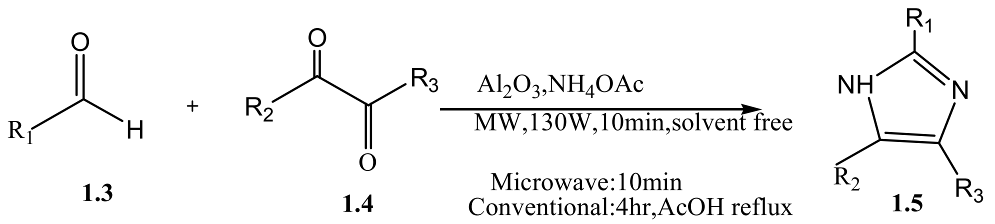

**1.1** **1.2**

Microwave:2Min
convential:Lewis acid activation 12 hr

**(Scheme 1)**

**(b) Synthesis of imidazoles (1.5)**

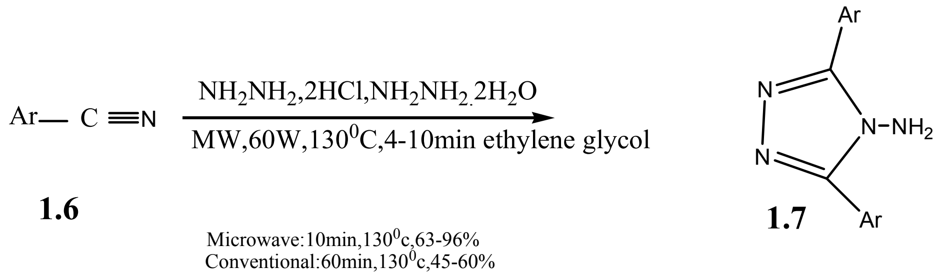
An important classical preparation of imidazoles **(1.5)** is from an aldehyde **(1.3),** an a-diketone **(1.4)** and ammonium acetate which allows the imidazole **(1.5)** to be obtained in few minutes[26]. **(scheme 2)**




**(Scheme 2)**

**(c) Synthesis of triazoles (1.7)**

The scheme shown below illustrates the advantageous preparation of 1,2,4-triazoles **(1.7)** using microwaves [27]. **(scheme 3)**

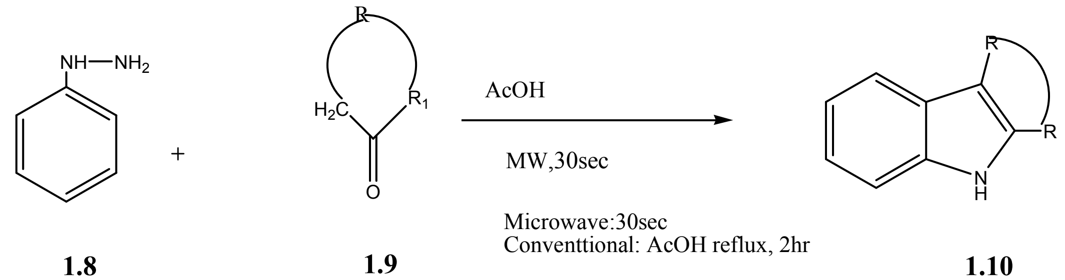



**(Scheme 3)**

**2.2 Benzo derivatives of five membered rings**

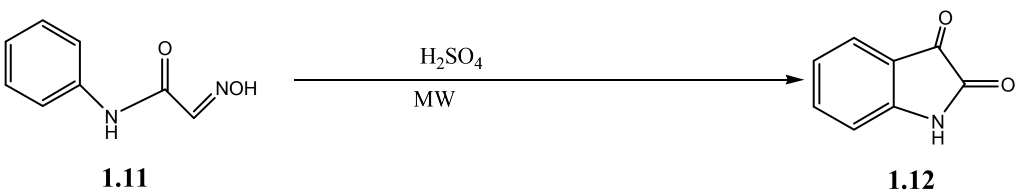
**(a) Synthesis of indoles (1.10)**

The classical Fisher-indole synthesis from any aryl hydrazine **(1.8)** and a ketone **(1.9)** is speeded up several folds by microwave irradiation[28] **(scheme 4)**




**(Scheme 4)**

**(b) Synthesis of isatin (1.12)**[29] **(scheme 5)**

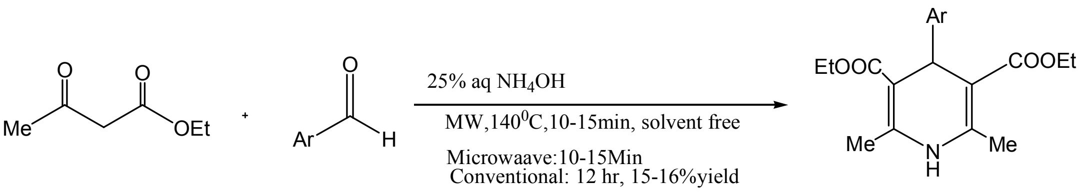



**(Scheme 5)**

**(c) Six-membered rings**

**2.3 Synthesis of dihydropyridines (1.15)**

The Hantzsch dihydropyridine synthesis remains one of the most important routes to pyridine ring systems. Microwaves dramatically reduce the heating time and significantly increase the yields[30]. **(scheme 6)**

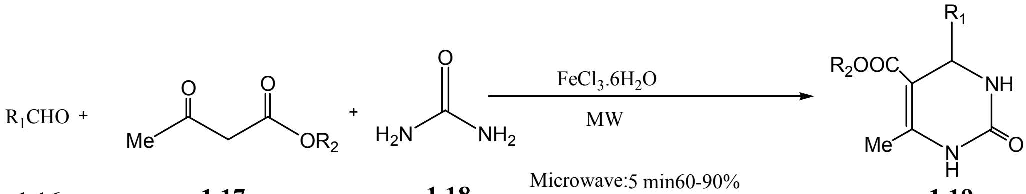



**1.13** **1.14** **1.15**

**(Scheme 6)**

**Synthesis of dihydropyrimidines (1.19)**

The Biginelli reaction is important for the preparation of dihydropyrimidine derivatives **(1.19)** and excellent results are obtained in microwave **(scheme 7)**



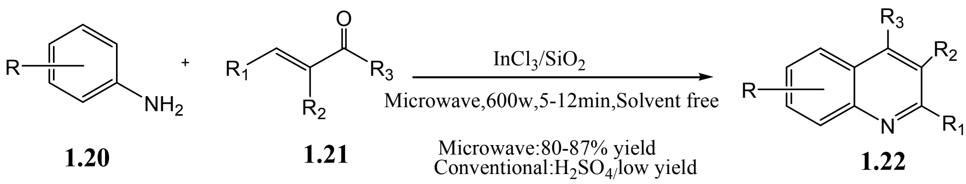

**1.16** **1.17** **1.18** **1.19**

**(Scheme 7)**

**2.4 Polycyclic six-membered rings**

**Synthesis of quinolines (1.22)**

Recently, the Skraup synthesis has been reported under microwave conditions to give **1.22** in a few minutes and with high yield[31] from **1.20** and **1.21** **(scheme 8)**




**1.20** **1.21** **1.22**

**(Scheme 8)**

## 3. Conclusion

Microwave assisted green synthesis is a very good technique in the field of green chemistry by governs a flexible platform for heterocycles ring formation. The compiled review gives an idea on MW green chemistry, their principle, advantage limitation and precaution, and application of MW in heterocycle ring formation which is beneficial for research ara.

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