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Review Article

AN OVERVIEW ON MICROWAVE MEDIATED SYNTHESIS

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ABSTRACT

Microwave-assisted organic synthesis is an enabling technology for accelerating drug discovery and development processes. Microwave organic synthesis opens up new opportunities to the synthetic chemist in the form of new reaction that are not possible by conventional heating and serve a flexible platform for chemical reaction. This review focuses on the advances in the developing of innovative application of microwave mediated synthesis. The efficiency of microwave flash-heating chemistry in dramatically reducing reaction times (reduced from days and hours to minutes and seconds) has recently been proven in several different fields of organic chemistry. The time saved by using focused microwaves is potentially important in traditional organic synthesis but could be of even greater importance in high-speed combinatorial and medicinal chemistry. The study presents examples that demonstrate the significance of these advantages to industrial application.

Keywords: microwave, green synthesis, organic synthesis.

INTRODUCTION

Traditionally, organic synthesis is carried out by conductive heating with an external heat source (for example, an oil bath). This is a comparatively slow and inefficient method for transferring energy into the system, since it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture[1]. Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat[1]. Microwaves are defined as electromagnetic waves with vacuum wavelength ranging between 0.1to 100cm or, equivalently, with frequencies between 0.3 to 300GHz. Although the first reported by group of Gyedye and Gigure Majetih in 1986, the use of microwaves in organic synthesis was initially hampered by a lack of understanding of the basic principal of MW heating and the inability to obtain reproducible results with domestic microwave oven[7]. With microwave heating, the energy can be applied directly to the sample rather than conductively, via the vessel. Heating can be started or stopped instantly, or the power level can be adjusted to match the required[2]. Microwave dielectric heating is a non-quantum mechanical

effect and its leads to volumetric heating of the samples. Therefore, it is necessary to question whether it has any significant advantages compared to thermal heating of chemical reactants[7].

The interest in the microwave assisted organic synthesis has been growing during the recent years. Drug companies are exploiting microwave in the area of organic/pharmaceutical synthesis for drug screening and discovery. Microwave heating is also called as green chemistry and the development of cleaner technologies is a major emphasis in green chemistry. Among the several aspects of green chemistry, using efficient and less hazardous energy sources such as microwave energy is recommended. The goal of the present review is to present microwave assisted synthesis with special emphasis on aspects that relevance to drug discovery[3]. The microwave enhanced kinetics in synthesis of organometallic compound was reported by Geyde et al in 1991, when they synthesized $(C_6H_5)_3SnCL$ and $(C_6H_5)_3SnOH$ in sealed vessel under microwave radiation in 7 and 4 minutes respectively[6]. With microwave heating energy can be directly applied to the reaction not to the vessel where it takes time for the reaction to be completed and also the time taken is less and there is the consumption of time[2]. Microwave heating is based on dielectric heating, i.e., molecule exhibiting a permanent dipole moment will try to align to the applied electromagnetic field resulting in rotation, friction and collision of molecules and, thus in heat generation. Microwave irradiation in chemical reaction enhancement has been well recognized for increasing reaction rates and formation of clear[7].

What Microwave Are:-

A microwave (MW) is a form of electromagnetic energy that falls at the lower frequency at the end of electromagnetic spectrum (300-300000 MHz). Microwave heating is the best process due to the microwave couple directly with the molecule that are present in the reaction mixture, leading to fast rise in temperature, faster reaction and cleaner chemistry[5]. In older days kitchen microwaves are used for the chemical synthesis in respect to the microwave reactor but they are not so much efficient because they work in the low power which is not sufficient for the microwave synthesis that's why the microwave reactors are introduced in the green chemistry.

The microwave chemistry is also called as green chemistry because it does not produce any hazardous material like gas fumes or heating using external energy source. Microwave uses electromagnetic radiation that passes through material and causes oscillation of molecule which produces heat[2]. Microwave heating produces heat in the entire material in the same rate and at the same time at a high speed and at a high rate of reaction. Microwave assisted synthesis has become an important tool to the medicinal chemist for rapid organic synthesis[1]. A huge number of research papers have appeared over the last decades on the application of microwave technology in organic synthesis. Some of the major advantages include spectacular decrease in reaction time, improved conversions, clean product formation and wide scope for the development of new reaction conditions[11]. Recent reports have shown that microwave heating can be very convenient for use in a large number of organic synthetic methods. Microwave heating is instantaneous and very specific and there is no contact required between the energy source and the reaction vessel. Microwave dielectric heating is a non quantum mechanical effect and it leads to volumetric heating of the samples[8, 10].

Why Microwave Irradiation Speed UP the Reaction:-

Since the introduction of microwave assisted organic synthesis in 1986, the main debt has dealt with the question that what actually alters the outcome of the synthesis. Is it merely an effect of the thermal heat generated by microwave or is it an effect specific for microwave heating. But the conclusion of the debt comes out be that the microwave heating depends upon two major factors first is the pre-exponential factor 'A' which describe the molecular mobility and depends upon the frequency of vibrations of the molecule at reaction interface. The other reason is the alteration in the exponential factor by affecting the free energy of activation ie. ΔG[4]. With microwave heating heat is directly applied to the sample not to the vessel or container that's why it increases the rate of reaction very quickly. We know that with every 10° rise in temperature the rate of reaction become double ie. If for a reaction is to be completed it

takes 80 min in conventional system but if the same reaction takes place in microwave irradiation it will takes only 10 min this shows that in microwave irradiation the rate of reaction speeds up[4]. Also in microwave there is no interference of external atmospheric pressure which will lead to direct action of microwave heating on the reaction or synthesis and the rate of reaction speeds up. All microwave reactions were conducted using a single mode Biotage Initiator 2.0. The H NMR and the C NMR were obtained using a Bruker Advance 400 HMz NMR and were recorded at 400 MHz and 100 MHz, respectively, due to these factors rate of reaction increases and reaction speeds up[2].

Microwave Vs Conventional Synthesis:-

Microwave-assisted organic synthesis has several advantages over conventional reactions in that the microwave allows for an increase in reaction rate, rapid reaction optimization, and rapid analogue synthesis. It also uses both less energy and solvent, and it enables difficult compound synthesis In general, drug discovery can be broken down into five steps: i) target and synthesis design, ii) reaction, iii) work- up (usually extraction and evaporation), iv) purification (usually chromatography), and v) spectral analysis registration[3]. Microwave heating has been shown to dramatically reduce reaction times, increase product yields and enhance product purities by reducing unwanted side reactions compared to conventional heating methods. Conventional organic synthesis is carried out by conductive heating with an external heat source (for example, an oil bath). This is a comparatively slow and inefficient method for transferring energy into the system, since it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture[2]. In contrast, microwave irradiation produces efficient internal heating (in-core volumetric heating) by direct coupling of microwave energy with the molecules (solvents, reagents, catalysts) that are present in the reaction mixture[3]. Microwave irradiation can be used as a simplistic and general method for the construction of a wide variety of triazoloquinazolinones and benzimidazo quina zolinones. The basic principles behind microwave technology and recent trends and areas in drug discovery have been reported. Regiospecific microwave-assisted synthesis of novel purine derivatives as antitumor agents was reported. The pharmacophoric requirements for compounds to exhibit anticonvulsant activity that includes one aryl unit in proximity to a hydrogen donor-acceptor domain and an electron donor have been justified with the molecular orbital surface analysis of the synthesized compounds using microwave-assisted synthesis[3,17].

There are various examples which explain about the advantages of microwave heating over conventional heating system:-

Herein, we describe a simple and efficient microwave-mediated procedure for the solid-phase synthesis (SPS) of pyrimidin 5(1H)-ones (R^1=H, R^2=C_2H_5) using a conventional heating procedure that involves condensing ethyl 3-oxopentanoate with thiourea in the presence of NaOEt/EtOH under reflux. The reaction was monitored by TLC and found tobe completed after 24 h. The crude mixture was purified by flash chromatography (CH_2CL_2/MeOsH) 30:1) to provide 2-(benzylthio)imidazoin 75% yield. To facilitate the rapid synthesis of 2-(benzylthio)imidazo, microwave irradiation was explored and found that compound 2-(benzylthio)imidazowas obtained in the highest yield (83%) when the reaction was performed in EtOH/DMF mixture at 130 °C for 30 min. S-Benzylation of 2-(benzylthio)imidazowith benzyl bromide in EtOH under microwave irradiation for 10 min at 100, 110, and 120 °C gave 2-(benzylthio)-6-ethylpyrimidin-4-one in 90%, 96%. and 90% yields, respectively[9].

Various Techniques Of Microwave System:-

1. ***Domestic house hold ovens – 'solvent-free' open vessel reactions:-***

Most of published chemistry has been performed using domestic microwave ovens. The key reasons for using a device intended for heating items to perform synthesis are that they are readily available and inexpensive. The use of domestic ovens might be one of the main reasons why microwave assisted organic synthesis has not increased greatly in popularity, due to factors outlined earlier, and conducting synthesis in domestic microwave ovens is clearly not the intended application, as stipulated by the CE code

for electrothermal appliances. These type of experiments are therefore conducted with an increased risk to the user, and the use of domestic microwave ovens for microwave chemistry should be considered to be entirely at risk of the operator[4].

2. Reflux system:-

A number of reflux system have been developed in an effort to use solvents in microwave assisted organic synthesis without the risk of explosion. Some systems are modified domestic ovens, while other have been designed with a single mode cavities. There is a little risk of explosion with reflux systems, since the systems are at atmospheric pressure and flammable vapours cannot be released into the microwave cavity. The temperature however cannot be increased by more than 13-26°C above the normal boiling point of the solvent and only for a limited time[4].

3. Pressurised systems:-

Reactions performed under pressure in a microwave cavity also benefit from the rapid heating rates and remote heating of microwave dielectric heating this type of experiments lead to the one of very earlier development using microwave assisted organic synthesis[4].

4. Continuous flow system:-

If the outcome of a reaction is strongly dependent on the heating profile of the reaction mixture, it is crucial to maintain that heating profile when scaling up the reaction. If for example, 3 ml of a solvent is heated to 150°C in 20 s using microwave irradiation at 300 W, it will be necessary to use at least 15 kW power to heat 150 ml of same solvent, in order to maintain the same heating profile[4].

There are some reactions that are easily proceed by microwave synthesis:-

Microwave synthesis for Nanomaterials:-

Amongst the several methods that exist for synthesizing of nanoparticles, the use of microwave assisted synthesis has shown promise. Synthesis of silver nanoparticles from silver nitrate employing starch as the reductant cum stabilizing agent has been carried out under direct heating, controlled heating and microwave irradiation. The microwave irradiation was considered as better for reduction of silver ions to silver nanoparticles. It also afforded smaller particle sizes and particle size distribution. Compared to conventional methods, microwave assisted synthesis was faster and provided particles with an average particle size of 12 nm[3].

Microwave-Assisted Peptide Synthesis:-

A microwave-assisted, rapid solid phase peptide synthesis procedure has been reported. The application of microwave heating to solid-phase peptide synthesis is particularly advantageous as the acceleration of coupling and deportation reactions should lead to shorter cycle times, higher repetitive yields, and ultimately purer peptides. The protocols for the synthesis of cystine-rich peptides in the presence of microwave radiation with Boc-solid phase peptide synthesis have been reported[3,15].

Polymer Chain Reactions:-

Polymerase chain reactions with focused microwave irradiation as the source of heat were demonstrated and the results indicated the possibility to shorten the total reaction time as well as the possibility to perform PCR reactions in millilitre scale. Scientists focused on the microwave technology for advance to the various chemical and biological reactions and the microwave irradiatation to rooling circle amplification reaction on controlling the temperature. The extract and detection of anthrax DNA from spores and vegetative cells in two steps within 1 min has been reported. Microwave energy is highly focused using thin-film aluminum "bow-tie" structures in a cavity, to extract DNA from whole spores within 20 s, followed by the detection of the released DNA, by employing the microwave-accelerated metal-enhanced fluorescence technique[3,16].

Microwave Assisted ILs Synthesis:-

The first step in the synthesis of ILs is the quaternization of a nitrogen containing hetrocycle, such as 1-subsituted imidazole, pyridine or isoquinoline, amine, mercaptants or phosphane to it form the cation. In a second step, the halogen ion is interchanged for the desired anions, it must be ensured that no halide ions remain in the system. Employing conventional synthetic methods, ILs synthesis in refluxing solvent required several hours (8-72 h) at a relatively high temperature, depend on the reactivity of the alkylating reagent, to afford reasonable yield and employing a large excess of alkyl halides and organic solvent at the reaction medium[5].

Development In Microwave Reactor Techniques:-

An established approximation is that, for each 10 °C increase in reaction temperature, the required time is halved. A reaction taking 18 h at 80 °C could give a comparable result within 30 s at 200 °C provided that the components survived the conditions. At around 200 °C, though, reactions are inconvenient to carry out with conventionally heated flasks at atmospheric pressure[13].

Solvents boiling in that region are difficult to recover and purify. With microwave heating, the energy can be applied directly to the sample rather than conductively, via the vessel. Heating can be started or stopped instantly, or the power level can be adjusted to match that required. Safety, the highest priority, was achieved through appropriate engineering, comprehensive control of reactions, reproducibility of performance, and effective, automated emergency procedures if necessary. Other major technical issues concerned scale, vessel design, means for stirring of reaction mixtures, temperature measurement, control of microwave power, sample or product withdrawal, reactant addition, and postreaction cooling. Some are irrelevant for digestion, and all were resolved by the mid 1990s. In 1995, we reported a microwave batch reactor which operated on a scale of 25-200 mL (a range selected to facilitate scaling up and scaling down), at temperatures up to 260 °C and pressures up to 10 MPa (100 atm) in a standard organic laboratory. It superseded an earlier prototype and enabled rapid heating (typically 1-2 °C per second on the 100-200 mL scale), infinitely variable control of microwave power, and measurement of absorbed and reflected microwave energy[2,14].

Some Common Reactions Occur In Microwave Synthesis:-

Cycloaddition Reaction:-

Cycloaddition reactions were among the first transformations to be studied by using microwave heating technology, and numerous examples have been summarized in previous review articles and book chapters. Conventional cycloaddition reactions require, in many cases, the use of harsh conditions such as high temperatures and long reaction times, but they can be performed with great success with the aid of microwave heating. Which can be shown by two recent examples of Diels–Alder cycloadditions performed by microwave dielectric heating? In both cases the diene and dienophile were reacted neat without the addition of solvent. For the transformation described by Trost and Crawley, irradiation for 20 minutes at 165 °C (or for 60 min at 150 °C) gave the cycloadduct which is in near quantitative yield.

In the above reaction 4n+ 2 cycloaddition reaction occurs[1].

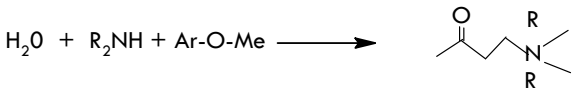
Asymmetric AllylicAlkylations:-

A frequent criticism of microwave synthesis has been that the typically high reaction temperatures will invariably lead to reduced selectivity's. This is perhaps the reason why comparatively few enantioselective processes driven by microwave heating have been reported in the literature. For a reactions to occur with high enantioselectivity there must be a large enough difference in the activation energy for the processes leading to the two enantiomers. The higher there action temperature, the larger the difference in energy required to achieve high selectivity. Despite these limitations, a number of very impressive enantioselective reactions involving chiral transition-metal complexes have been described. The research groups of Moberg, Hallberg, and Larhed reported on microwave-mediated palladium-andmolybdenum-catalyzed asymmetric allylic alkylation reactions involving neutral carbon, nitrogen, and oxygen[1,12].

Glycosylation Reaction:-

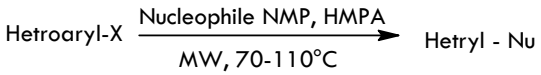
Glycosylation reactions involving oxazoline donors are generally rather slow and require prolonged reaction times because of the low reactivity of the donors. Oscarson and co-workers have reported the preparation of dimers of Nacetyllactosamine linked by alkyl spacers by microwave assisted glycosylations with oxazoline donors in the presence of pyridiniumtriflate as a promoter. Rapid and efficient coupling was achieved in dichloromethane with four different diols using 2.2 equivalents each of the oxazoline donor and pyridiniumtrflate as a promoter[1].

Eg.-:



Neucleophillic Aromatic Subsitution:-

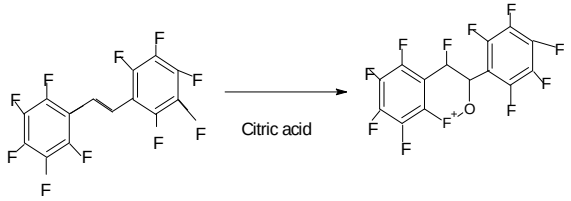
An alternative to the palladium-catalyzed Buchwald–Hartwig reactions and the related copper-catalyzed methods for C(aryl)- N, C(aryl) -O, and C(aryl)- S bond formations are nucleophilic aromatic substitution reactions. A benzene derivative substituted by a leaving group may be treated, for example, with an amine, but here the benzene derivative must generally also contain an electron-withdrawing group. Such nucleophilic aromatic substitution reactions are notoriously difficult to perform and often require high temperatures and long reaction times[1].



Oxidations:-

The osmium-catalyzed dihydroxylation reaction, the addition of osmium tetroxide to olefins to produce a vicinal diol, is one of the most selective and reliable organic transformations. Recent work by Sharpless, Fokin, and co-workers has uncovered that electron-deficient olefins can be converted into the corresponding diols much more efficiently when the reaction medium is kept acidic. One of the most useful additives in this context is citric acid. Which in combination with 4-methylmorpholine N-oxide (NMO) as the reoxidant for OsVI and K2OsO2(OH)4 (0.2 mol%) as a stable, nonvolatile substitute for OsO4, allows the conversion of many olefinic substrates into their corresponding diols at ambient temperatures.

Eg.-: It is osmium–catalysed dihydroxylation of electron deficient alkenes at 120° 150mm[1].

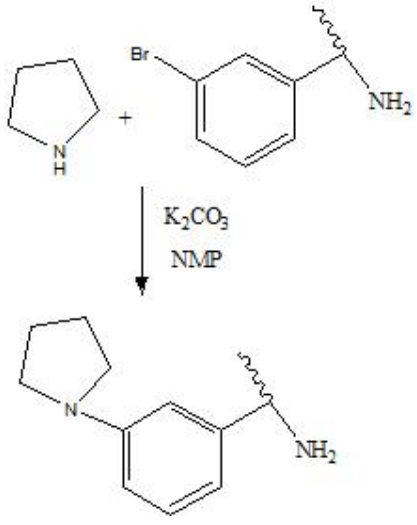


Buchwald-Hartwig Reaction:-

The research groups of Buchwald and Hartwig have developed a large variety of useful palladium-mediated methods for C-O and C-N bond formation. These arylations have been enormously popular in recent years. A vast amount of published material is available describing a wide range of palladium-catalyzed methods, ligands, solvents, temperatures, and substrates which has led to a broad spectrum of tuneable reaction conditions that allows access to most target molecules that incorporate an aryl amine motif[1,11].

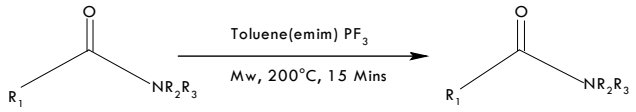
Ullmann Condensation Reactions:-

A recent survey of the literature on the Ullmann and related condensation reactions has highlighted the growing importance and popularity of copper-mediated C-N, C-O and C-S bond forming protocols. Examples of microwave-assisted Ullmann-type condensations from researchers at Bristol–Myers Squibb. In the first example, (S)-1-(3-bromophenyl) ethylamine was coupled with eleven heteroarenes containing N-H groups in the presence of 10 mol% CuI and 2.0 equivalents of K_2CO_3 base. The comparatively high reaction temperature (195 8C) and the long reaction times are noteworthy. For the coupling of 3,5-dimethylpyrazole, for example, microwave heating for 22 h was required to afford a 49 % yield of the isolated product eg. The following reaction occurs at 195°C, for 1-22 hr[1].



Polymer-Supported Reagents, Catalysts, and Scavengers:-

The use of PSRs combines the benefits of SPOS with many advantages of traditional solution-phase synthesis. The most important advantages of these reagents are the simplification of reaction work-up and product isolation, with the former being reduced to simple filtrations. In addition, PSRs can be used in excess without affecting the purification step. Reactions can be driven to completion more easily by using this technique than in conventional solution-phase chemistry. The combination of MAOS and PSR technology is a rapidly growing field. An early example of microwave assisted PSR chemistry published by Ley et al. involves the rapid conversion of amides into thioamides by employing a polystyrene-supported Lawesson-type thionating reagent. A range of secondary and tertiary amides was converted within 15 min with 3–20 equivalents of the PSR into the corresponding thioamides in high yield and purity by using microwave irradiation at 2008°C. These thionation reactions showed a marked acceleration in the reaction rate compared to classical reflux conditions, with reaction times being reduced from 30 hours to 10–15 minutes. Interestingly, heating at these elevated temperatures caused no damage to the polymeric support. As toluene itself is a less than optimum solvent for absorption and dissipation of microwave energy a small amount of ionic liquid (1-ethyl-3-methyl-1H imidazolium hexafluorophosphate) was added to the reaction mixture to ensure an even and efficient distribution of heat.



Eg. Thionation of amides using a polymer-supported thionation reagent[1].

Some Miscellaneous Aspects Of microwave synthesis:-

Microwave applications in radoilabelling traces for Positron Emission Tomography, paralleling and sometimes preceding developments in other areas of microwave enhanced chemistry were reported. Dihydropyridones were prepared by microwave assisted reaction microwave synthesis is considered the cutting-edge methodology today between curcumin and primary amines or their acetates n in the presence of Montmorillonite (K-10) as a catalyst. In most pharmaceutical and biotechnologies companies, microwave synthesis is considered as cutting edge methedology today. The synthetic methodology for the preparation of trimethoprim via microwave assisted synthesis has reported. A rapid open –vessel focused microwave assisted extraction method was followed by LC analysis was developed for the determination of naproxen in suppositores[3].

Commercial Developments In Microwave Reactor :-

The dedicated microwave reactors and associated chemistry stimulated other researchers to construct systems for laboratory and even pilot-scale studies. Units were also designed for solvent-free reactions. Since about 2000, various commercial microwave reactors have appeared. Some, based on patents embodied by the CMR and MBR, were manufactured under license. Commercial batch systems now are produced in Europe, Asia, and North America. They operate typically on scales from around 1 mL to 2 L and may employ multimodal cavities as with the CMR and MBR or monomodal cavities for so-called "focused" 3a microwaves. The modality though has little influence on reactions conducted above the multimilligram scale in appropriately designed systems. With commercial systems, microwave reactions maybe performed with or without magnetic stirring in vessels of glass, ceramic, or polymeric materials. Reactions mayor may not be externally air-cooled. Cooling may be direct, by the cold finger. Reactors may have the capability for "simultaneous heating and cooling" as advocated by one manufacturer or for concurrent heating and cooling as we originally termed it. Temperatures may be measured remotely by infrared pyrometer rather than intimately by optic fibre thermometer or by grounded thermocouple. There are many other things which makes microwave reactor as the first choice for companies for undertaking heating reactions. Various other reactions which are cited above undertaken by microwave synthesis in the development of microwave reactor[2].

Demerits of Microwave Synthesis:-

- In microwave synthesis sudden increase in temperature may led to the distortion of molecules which may lead to distortion of the reaction[3].

- Reactions are very vigorous and which may be hazardous[2].
- Microwave reactors are expensive and very delectated so there must be a care to be taken during their use[2].
- Short reaction period ,so a care must be taken during the process[4].
- Various reactions which have short reaction time are not be undertaken in microwave reactor due to sudden increase in the temperature it may be hazardous and it may lead to reaction crises[2].
- Many other things like, temperature sensitive reactions, reactions involving bumping of material, and reaction in which effervescences and colour reaction are not be done in Microwave reactor[2].

CONCLUSION

The obvious features of microwave technology like reduction of time for a chemical/pharmaceutical reaction, instantaneous and uniform heating, carrying out solvent free reactions and possibility of parallel chemical reactions has proved as a bonanza for the researchers involved in drug discovery and development processes like high-speed combinatorial and medicinal chemistry. Microwave synthesis in macro-scale (synthesis of active pharmaceutical ingredient synthesis), micro scale (integrated 'lab-on-achip' type approaches where synthesis and biological screening are integrated) and meso-scale flow units should be actively pursued[3]. Through their capability for rapid, direct syntheses by the generation and control of higher temperatures, the MBR and CMR were the first major departure from traditional hardware for preparative organic chemistry. Now, other innovations such as combinatorial systems for parallel synthesis have appeared. Although most of those developments are beyond the present scope, the rate of advancement in analytical techniques no longer outstrips that for practical methods. In the end we can say that microwave mediator synthesis is most efficient and most effective method than that of conventional technique and it is the future of chemical synthesis.

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