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AQUEOUS MICROWAVE CHEMISTRY: NOVEL SYNTHETIC METHODOLOGY

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ABSTRACT

Chemistry is the scientific study of interaction of chemical substances that are constituted of atoms or the subatomic particles; protons, electrons, and neutrons. Traditional chemistry involves study of interaction between substances in a chemistry laboratory using various forms of laboratory glassware. Traditional chemistry is perhaps the most established method for organizing atoms. Microwave irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules. Microwave reactions involve selective absorption of MW energy by polar molecules, non-polar molecules being inert to MW (microwave) dielectric loss. Microwave synthesis is facile and offers synthesis of variety of chemical compounds.

Keywords: - *DNA fragmentation, DNA smearing, Free radicals, Antibiotics, Proven Antimicrobial Plant*

INTRODUCTION

Antibiotics Conventional synthesis employs wide range of reactants, reagents, catalysts and solvents. The time required for completion of reaction is high and yield of products formed by this kind of synthesis is considerably low. The reactions accompanied may form non-selective products and also the by-products formed from reactants as well as organic solvents are not so easily eliminated from the reaction mixture. Sometimes they may cause hazardous undesired effect. However traditional synthesis has its own merits and demerits.

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ADVANTAGES

1. Synthesis of wide variety of molecular components and characterization using traditional tools.

2. Convenient to perform on laboratory scale.
3. Less cost of equipment and instruments.

DISADVANTAGES:

1. Lower rate of reaction.
2. High energy consumption.
3. Low yield.
4. Formation of bye-products as chemical wastes.
5. Less reproducibility.

INTRODUCTION TO MICROWAVES [3]

Microwaves are electromagnetic waves having a frequency range from 1000 MHz to 300000 MHz corresponding to wavelength range from 300mm to 1mm. Like light waves microwaves travel essentially in straight lines. They are used in radar (detection of ships, aircrafts by means of reflecting the radio waves), in communications, spanning moderate distances and in other applications such as "Microwave ovens".

MECHANISM OF MICROWAVE CHEMISTRY

The principle of microwave chemistry is that enhanced collisions between various reaction components upon interaction with microwaves, which is associated with "Microwave Dielectric Effect", the process depends on the specific polarity of molecules. For example as water is polar in nature, it has excellent potential to absorb MW radiation and convert it to heat energy. There are two ways through which the irradiation of reaction mixture can be achieved viz., Dipolar Polarization and Ionic Conduction.

1. SPECIFIC MICROWAVE EFFECT [4]

Irradiation of reaction mixture in presence of microwaves results in the electrostatic polar effects which produce the dipole-dipole type interaction of the dipolar water molecules and reactants with the electric field component of microwave, resulting in energy stabilizations of an electrostatic nature.

2. THERMAL EFFECT

The dielectric heating that results from the tendency of dipoles to follow the inversion of alternating electric fields and induce energy dissipation in the form of heat through molecular friction and dielectric loss, which allows more regular repartition in reaction temperatures compared to conventional heating.

It is noteworthy to mention that various organic reactions can be carried out in an aqueous medium using microwave irradiation without using any phase-transfer catalysts (PTC). This is because water at higher temperature behaves as a pseudo-organic solvent, as the dielectric constant decreases substantially and an ionic product increases the solvating power towards organic molecules to be similar to that of ethanol or acetone.

MICROWAVE CHEMISTRY [5]

Microwave chemistry is the science of applying microwave irradiation to chemical reactions.

Microwaves act as high frequency electric fields and will generally heat any material containing mobile electric charges, such as polar molecules in a solvent or conducting ions in a solid.

PRINCIPLES OF MICROWAVE CHEMISTRY [2]

Microwave chemistry can also be considered as Green chemistry. Twelve principles of green chemistry can be used to assess a specific synthetic protocol.

1. Prevention of waste
2. Atom Economy
3. Less Hazardous Chemical Synthesis
4. Design Safer Chemicals
5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use Renewable Feedstock's
8. Reduce Derivatives
9. Catalysis
10. Design for Degradation
11. Real-time Analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

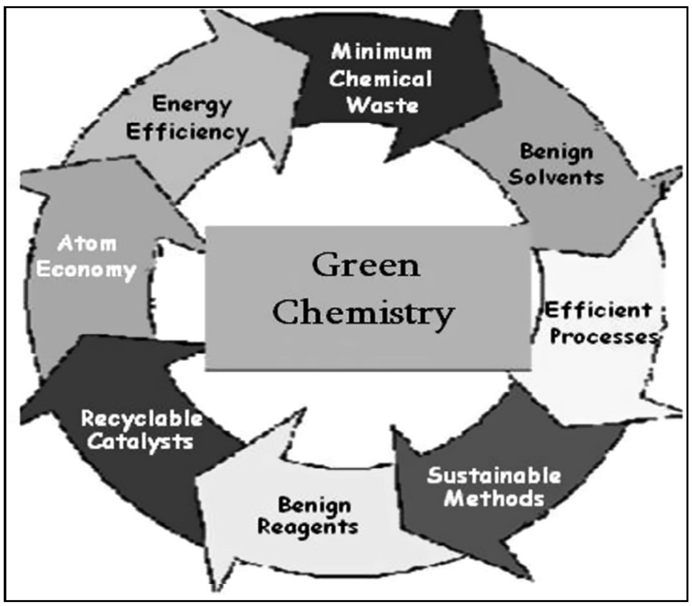


Fig: 1. Schematic diagram of Green Chemistry

INSTRUMENTATION

Microwave Synthesizers [12]

Herley General Microwave has been a leader in the field of microwave PIN diode control components for more than 30 years. A natural extension to its product line, microwave oscillators, was launched in 1989. In a relatively short period of time, General Microwave has established itself as an industry leader in manufacturing microwave oscillators as well.

Principle of Operation

An oscillator has at least one active device, such as a transistor, that acts as an amplifier. When power is first applied, random noise is generated within the active device, and then amplified. This noise is fed back positively through frequency-selective circuits to the input, where it is amplified again. Ultimately a state of equilibrium is reached: the losses in the circuit are balanced by consuming power from the power supply, and the amount of positive feedback to sustain oscillation, as well as the frequency of oscillation, is determined by the external components. These external components may be inductors and capacitors, as in an LC circuit, or a crystal, in a crystal oscillator.

Modern microwave oscillators utilize a solid-state device, such as a transistor or diode, together with a resonant circuit and matching network, to convert DC power to microwave power at a specified microwave frequency. By appropriate choice of these elements, oscillators may be designed for an extremely wide range of applications. Signals produced by oscillators are extremely precise and can be used in a variety of consumer electronic products. In addition, low frequency digital and analog control circuitry may be incorporated to provide further flexibility.

Types of Oscillators

Herley General Microwave has a complete line of high-performance **voltage-controlled oscillators** (VCOs) and **digitally-tuned oscillators** (DTOs).

A **voltage-controlled oscillator** provides a signal whose frequency is controllable using an analog voltage signal. When employing an LC oscillator, for example, there are high costs and other difficulties encountered when employing quality variable capacitors. This often makes VCOs an extremely attractive alternative. This is because diodes, when they have a reverse voltage applied, exhibit the characteristics of a capacitor. Altering the voltage alters the capacitance. This is where voltage-controlled oscillators enter the picture.

VCOs can be generally categorized into two groups based on the type of waveform produced:

1. **Harmonic oscillators**, which generate a sinusoidal waveform, and
2. **Relaxation oscillators**, which can generate a saw tooth or triangular waveform.

A **Digitally-tuned oscillator** was designed as an attempt to increase stability in tuning the frequency of a VCO having a quartz crystal. The VCO is synchronized by an external frequency reference. The reference in this case is reset pulses produced by a digital counter—digital tuning input. The DTO thus provides the desired output frequency in response to a digital control signal.

The DTO features also a modulator circuit that produces a digitally-modulated output signal by noise shaping or oversampling a multi-bit input signal. The modulator circuit includes an input for the multi-bit input signal and an output that has a lower number of bits than the input. A DTO can also include a tuning capacitor to further tune the frequency of the crystal oscillator circuit.

Herley offers a line of single-band DTOs, employing a single VCO, or multiband, employing a range of VCOs. Multiband DTOs achieve broadband frequency coverage and improve settling speed.

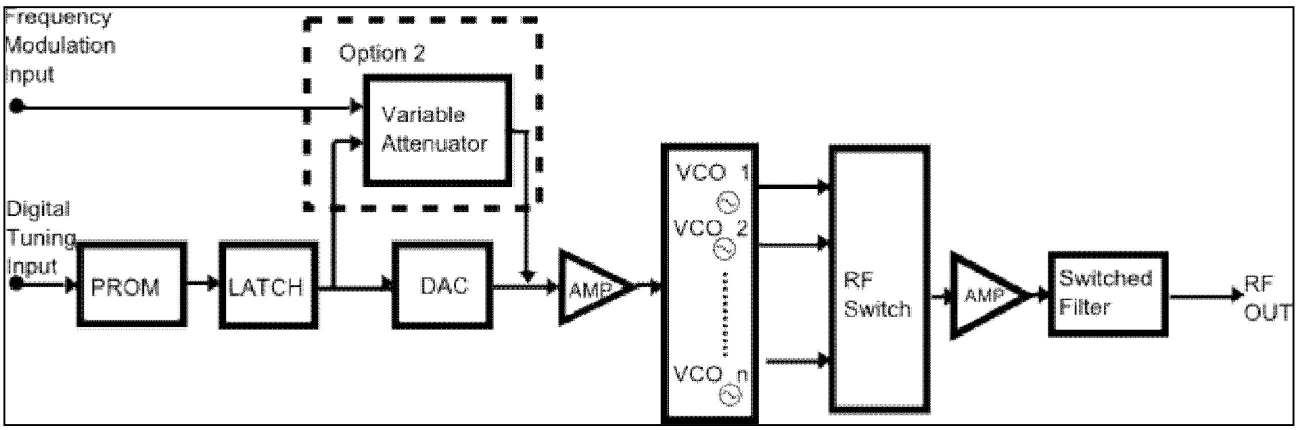


Fig: 2. Multi Band DTO Block Diagram

AQUEOUS MICROWAVE SYNTHESIS

It is a new kind of Green Chemistry. It is clean and synthetic tool for rapid drug discovery.

Water as Green Solvent [1]

A green solvent is the one which does not generate toxic pollutants, hazardous by-products. They aim to be ecofriendly and exhibit less impact on environment. Use of no-solvent, i.e. solvent-free reactions is another solution, but can't be adopted for all reactions as lack of reaction medium may lead to overheating of the reaction mixture, yielding a mixture of by-products. Ionic liquids are good solvents as they have negligible vapor pressure and does not evaporate into environment. However, the cost and toxicity of ionic liquids are regulating factors in using them as a solvent. Thus, the last option remains is naturally abundant water as a solvent which is nontoxic, nonflammable, abundantly available, and inexpensive.

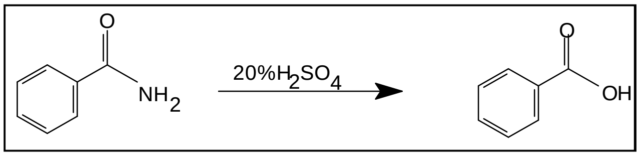
APPLICATIONS OF MICROWAVE CHEMISTRY

A comparative analysis of some routinely employed conversion depicts the significance of Aqueous Microwave Chemistry.

1. Hydrolysis of Benzamide to Benzoic Acid [6]:

The hydrolysis of benzamide to benzoic acid in the acidic conditions by conventional heating was found to occur in **1 hour** and yield is **90%**

whereas by microwave heating it took only **10min** and yield is **99%**

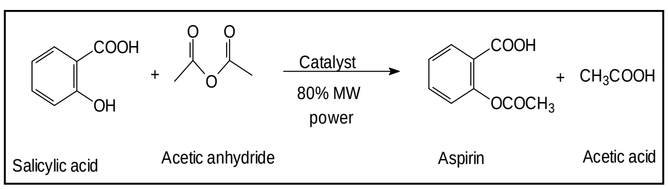


Conventional heating: 1hr 90%

Microwave heating: 10 min 99%

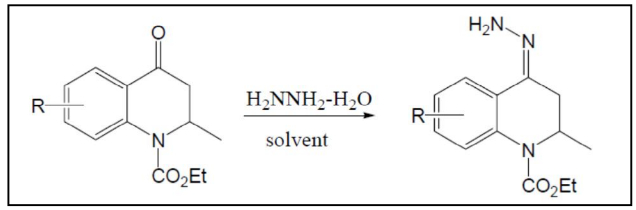
2. Synthesis of Aspirin

Reaction mixture of salicylic acid and acetic anhydride is placed in microwave oven for 2min at 80% power. Mixture is removed from microwave, stirred and again placed for 2min at 80% power. After this period microwave radiation is continued and reaction mixture is monitored every 5min using TLC. Formation of solid indicates presence of product which can be obtained by recrystallization.



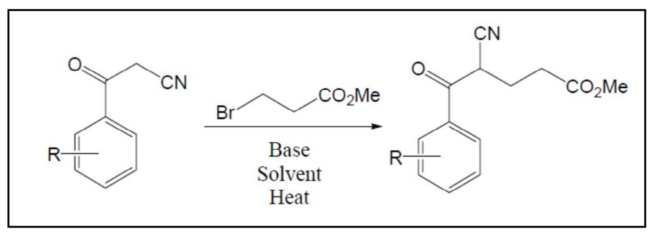
3. Rapid Method Development

Synthesis of hydrazine derivatives of 1, 4-dihydro-4-oxo-2-methylethyl-1-carboxylate can be achieved by condensation between 1,4-dihydro-4-oxo-2-methylethyl-1-carboxylate and hydrazine hydrate in presence of toluene as solvent. The reaction mixture was condensed at RT, for 48 hours, yielding an amount of 25-50%, while the same can be called out by Microwave synthesis to get same yield in the similar solvent, which requires only 10 minutes.



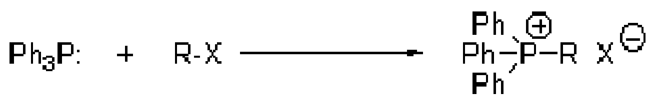
4. Alkylation

Alkylation of substituted α-cyanomethylphenylketone with methyl-β-bromopropionate is carried out in presence of chloroethane at 50^{0}C to get the product yield of 50%. If the same reaction is carried out at 151^{0}C in a microwave synthesizer using Dimethyl sulfoxide solvent, the reaction completes within 5 minutes with high yield than the conventional synthesis.



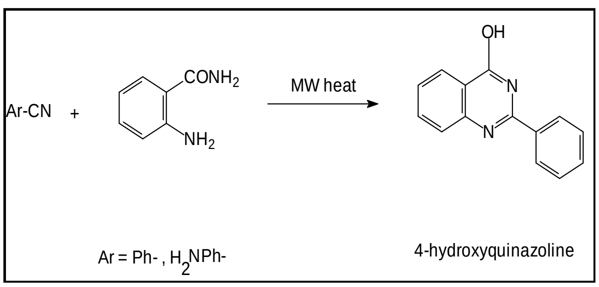
5. Wittig reagents – Synthesis of Phosphonium salts [7]

Several phosphonium salts have been prepared using a domestic microwave oven. The microwave enhanced reaction of triphenyl phosphine and an organic halide shows remarkable rate acceleration under microwave irradiation and allows the general and facile synthesis of both stabilized and non-stabilized phosphonium salts.



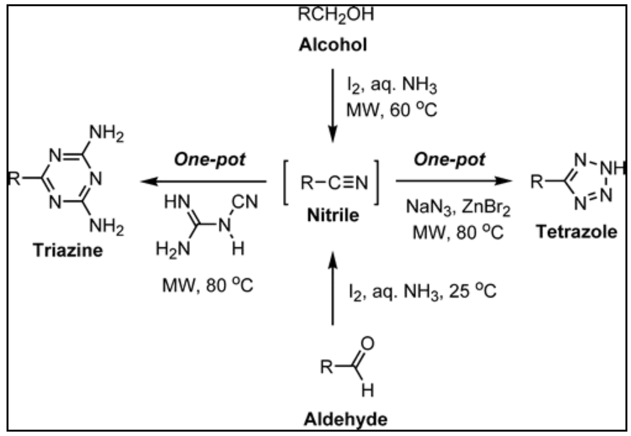
6. Microwave synthesis of 4-hydro quinazoline

The microwave enhanced synthesis of 4-aminoquinazolines from anthranilonitrile and several aromatic nitriles. In the absence of another nitrile, anthranilonitrile dimerized to gave the corresponding 4-amino-2-(2'-aminophenyl) quinazoline. There we reported a reduction in reaction times together with an improvement in yields regarding to the methods using conventional heating.



7. Synthesis of Triazoles and Tetrazoles [8]

A series of primary alcohols and aldehydes were treated with iodine in ammonia water under microwave irradiation to give the intermediate nitriles, which without isolation underwent [2+3] cycloadditions with dicyandiamide and sodium azide to afford high yields of the corresponding triazines and tetrazoles, including the α-amino and dipeptidyl tetrazoles in high optical purity.



8. Tandem bis-aldol Reaction [9]

A novel Tandem bis-aldol reaction of ketone with paraformaldehyde catalyzed by polystyrene sulfonic acid in aqueous medium delivers 1, 3-dioxanes in high yields. This one-pot, operationally simple microwave-assisted synthetic protocol proceeds efficiently in water in the absence of organic solvent, with excellent yield.

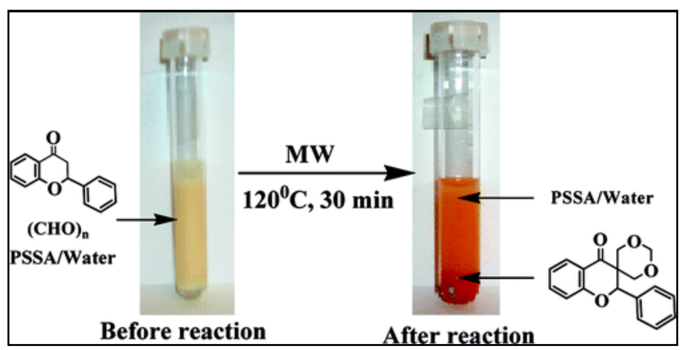
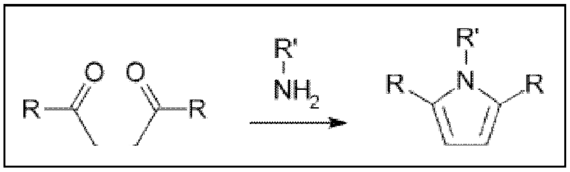


Fig: 3. Tandem bis-aldol Reaction

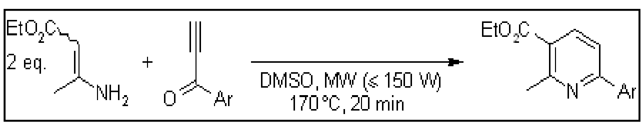
9. Paal-Knorr Pyrrole Synthesis [11]

The condensation between 2, 5-heptanedione (1) and a primary amine (2) yields 2, 5 dimethylpyrroles (3) under solvent-free conditions in excellent yields and purities. Reaction times are reduced to seconds rather than days in conventional thermal synthesis. Energies around 100-200 watts are required for the completion of the reactions, which can be scaled up to 3 g of the product.



10. Synthesis of Pyridines [10]

Tri- or tetra substituted pyridines are prepared by microwave irradiation of ethyl β-aminocrotonate and various alkynones in a single synthetic step and with total control of regiochemistry. This new one-pot Bohlmann-Rahtz procedure conducted at 170°C gives superior yields to similar experiments conducted using conductive-heating techniques in a sealed tube.



RECENT ADVANCES

Recently, an alternative method for performing microwave assisted organic reactions, termed "Enhanced Microwave Synthesis" (EMS), has been implemented, which facilitates externally cooling of the reaction vessel with compressed air, while simultaneously administering microwave irradiation, more energy can be directly applied to the reaction mixture.

Microwave enhancement of chemical reactions will only take place during application of microwave energy. This source of energy will directly activate the molecules in a chemical reaction; therefore it is not desirable to suppress its application. EMS ensures that a high, constant level of microwave energy is applied. This results in significantly greater yields and cleaner chemistries.

Enhanced Microwave Chemistry was employed in the synthesis of a variety of keto amides to support a protease inhibitor discovery project. Coupling of acyl chlorides with various isonitriles gave Keto imidoyl chloride as intermediates, which were then converted to the keto amides upon hydrolysis. Under conventional heating conditions, this reaction took place for 2 to 6 hours whereas under optimized Enhanced Microwave Synthesis conditions, the two steps were completed in 2 min and the yield was found to be 21–74%.

CONCLUSION

Microwave technology is emerging as an alternative energy source to accomplish chemical transformations in minutes, instead of hours or even days, witnessed by its exponential increase as a technique for chemical synthesis. Microwave synthesis creates new possibilities in performing chemical reactions. Because microwaves can transfer energy directly to the reactive species, they can promote transformations that are currently not possible. Microwave irradiation has emerged as a powerful tool for organic synthesis.

In concert with a rapidly expanding applications base, microwave synthesis can be effectively applied to any type of chemistry, resulting in faster reaction times and improved product yields. Scaling up syntheses from gram quantities to kilograms is essential for drug development, as this can be achieved with Microwave Chemistry.

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