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Review Article

MICROWAVE ASSISTED ORGANIC SYNTHESIS: A GREEN CHEMICAL APPROACH**G. G. JOSHI***

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*Received: 08 August 2013,**Revised and Accepted: 14 August 2013***ABSTRACT**

Green chemistry is a revolutionary approach in the field of organic synthesis. It utilizes a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products. Microwave assisted organic synthesis is the noble technique which can be utilized to reach to green chemistry approach. In microwave heating, electromagnetic waves ranging from 0.01 m to 1 m wavelength of frequency 30 GHz to 0.3 GHz are used to generate heat in the material. The region of Microwaves in the electromagnetic spectrum is between I.R. and Radio wave. This technique has numerous advantages over the traditional methods for organic synthesis. The basic mechanisms observed in microwave assisted organic synthesis are dipolar polarization (dielectric polarization) and conduction. Microwave assisted organic synthesis leads us in having synthetic procedures with increased speed, better yield with less time. These are some of the important aspects which explain tremendous use of microwave assisted organic synthesis now days. It has great applications in organic reactions; heterocyclic nucleus synthesis; microwave assisted extraction, drying, sintering, ashing etc.

KEYWORDS: Green Chemistry, Microwave Assisted Organic Synthesis.**INTRODUCTION**

The need of newer, potent and efficient therapies for combating various dreadful diseases in today's world has forced us to invent newer drug molecules. Organic synthetic approach is one of the basic routes which we follow to reach this goal. But these traditional organic synthetic approach is been stucked by the numerous obstacles such as excess use of costly raw materials, great time consumption and most seriously huge chemical wastage adding to bioburden. Hence now days, lots of different techniques are analyzed so as to attempt the green chemical approach in our research works.

The surprising ability of the microwave assisted organic synthesis approach to improve the productivity of chemical reactions by means of improved speed, higher yields, lesser byproducts, pure desired products and cleaner reactions has moved the scientists on the finer track representing one of the important dimensions of modern chemistry.

Microwave heating refers the use of electromagnetic waves ranges from 0.01m to 1 m wavelength of frequency 30 GHz to 0.3 GHz to generate heat in the material. Microwave lie in the region of the electromagnetic spectrum between IR and Radio wave. The basic mechanisms observed in microwave assisted organic synthesis are dipolar polarization (dielectric polarization) and conduction. The tremendous exhaustive study is been carried out on this approach and there is lot of literature available published in the scientific journals (Figure No.1), and the growth rate is still increasing [1].

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WHY GREEN CHEMISTRY?

During the early 1990s the US Environmental Protection Agency (EPA) coined the phrase Green Chemistry 'To promote innovative chemical technologies that reduce or eliminate the use or generation of hazardous substances in the design, manufacture and use of chemical products.' [2] Over the last 10 years Green Chemistry has gradually become recognized as both a culture and a methodology for achieving sustainability. The 12 Principles of Green Chemistry help show how this can be

achieved. Looking Green Chemistry from an industrial perspective, it is a reduction process (Figure No. 2). From this perspective it becomes obvious that through application of Green Chemistry concepts significant savings can be made, arising from reduced raw material use, lower capital expenditure, lower of waste treatment and disposal, etc. providing the benefits to society without overburdening or causing damage to the environment at an acceptable cost.

12 Principles of Green Chemistry [2]

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

Advantages of Microwave Heating Over Conventional Heating [3]

- Microwave heating is an efficient source of heating.
- Increased rate of synthetic reaction.
- Selective heating is possible.
- It leads to higher yields of products.
- These reactions are environment friendly.
- Greater reproducibility of reactions is possible.
- Uniform heating of reaction mixture is possible.

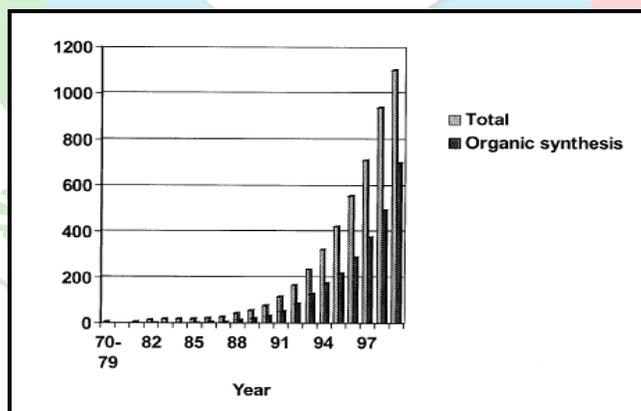


Figure 1: Published articles involving organic & inorganic microwave assisted synthesis, 1970-1999.

MICROWAVE REGION OF THE ELECTROMAGNETIC SPECTRUM [4]

The microwave region of the electromagnetic spectrum lies between infrared radiation and radio frequencies and corresponding to wavelength of 1 cm to 1 m (frequencies of 30

GH to 300 MHz respectively), (Figure No. 3). Domestic and industrial microwave heaters operate at 12.2 cm (2450MHz) or 33.3 cm (900MHz), so that there is no interference. Figure No. 4 gives the schematic of microwave.

PRINCIPLE OF MICROWAVE HEATING [1, 5, 6]

The basic principle behind the heating in microwave oven is the interaction of charged particles of the reaction material with electromagnetic waves of particular frequency. The mechanism of producing heat by electromagnetic irradiation is either by collision or by conduction or sometimes by both.

All the wave energy changes its polarity from positive to negative with each cycle of the wave. This cause rapid orientation and

reorientation of the molecules, which cause heating by collision. The physical properties of materials predict their behavior in a microwave field. One calculated parameter is the “Dissipation Factor” or “Loss Tangent”. The dissipation factor is a ratio of the dielectric loss (loss factor) to the dielectric constant. The dielectric loss is a measure of how well a material absorbs the electromagnetic energy to which it is exposed, while the dielectric constant is a measure of the polarizability of a material, essentially how strongly it resists the movement of either polar molecules or ionic species in the material.

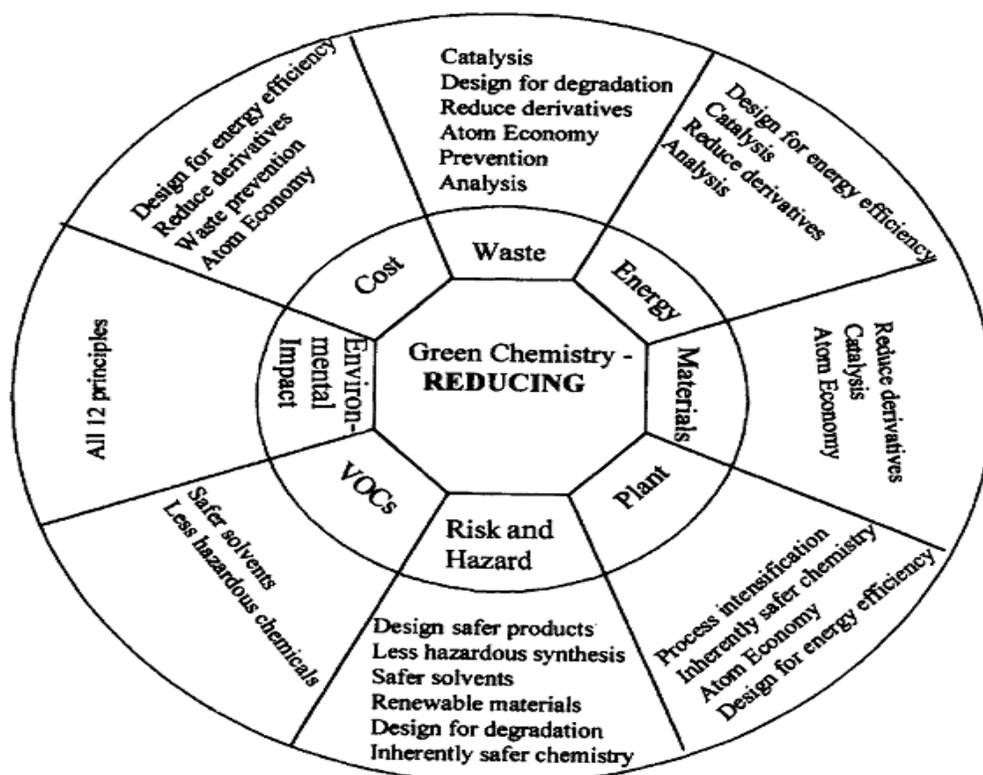


Figure 2: Green Chemistry-Reduction Process.

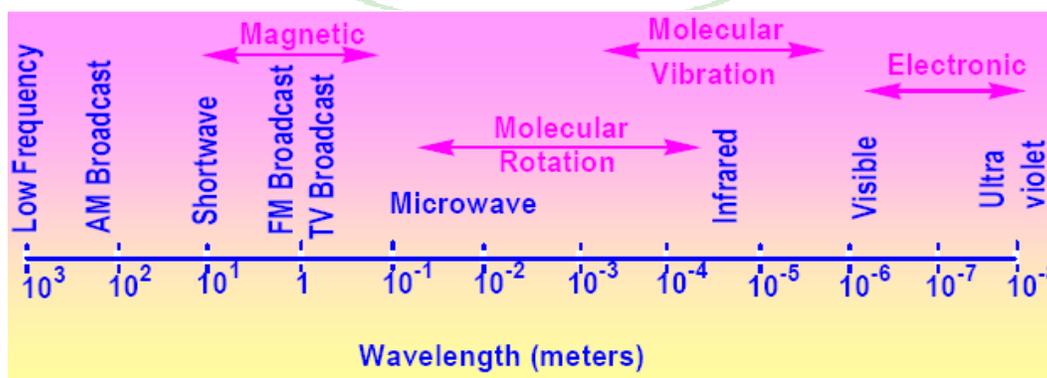


Figure 3: The Electromagnetic Spectrum and Quantum and Transition.

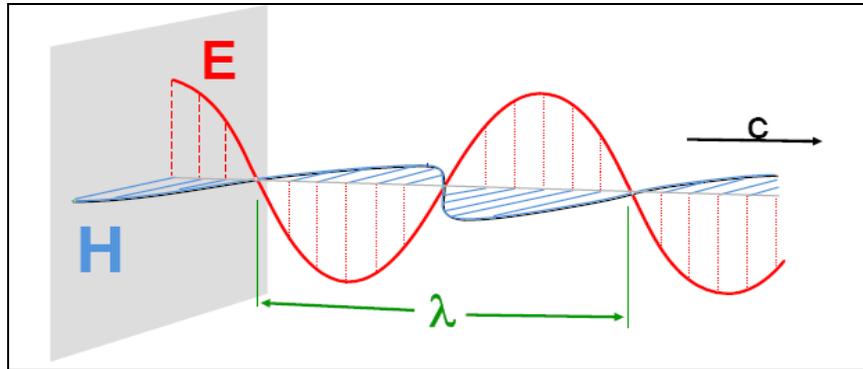


Figure 4: Schematic of a Microwave.

E= electric field, H= magnetic field, λ= wavelength (12.2 cm for 2450 MHz), c= speed of light (300,000 km/s)

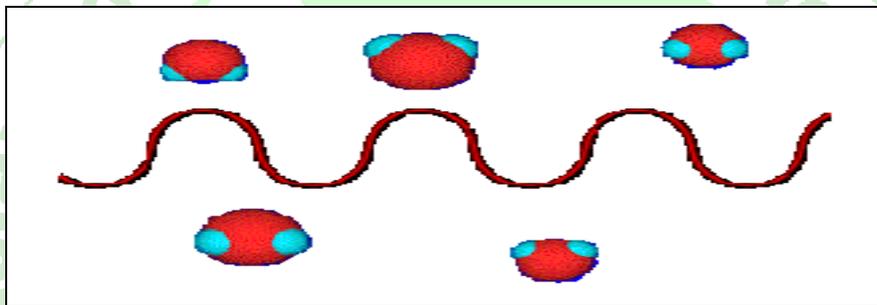


Figure 5: Dipolar molecules try to align to an oscillating field by rotation.

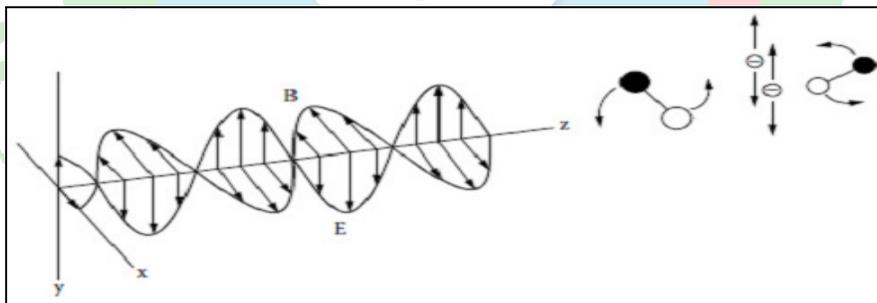


Figure 6: Dipolar Polarization.

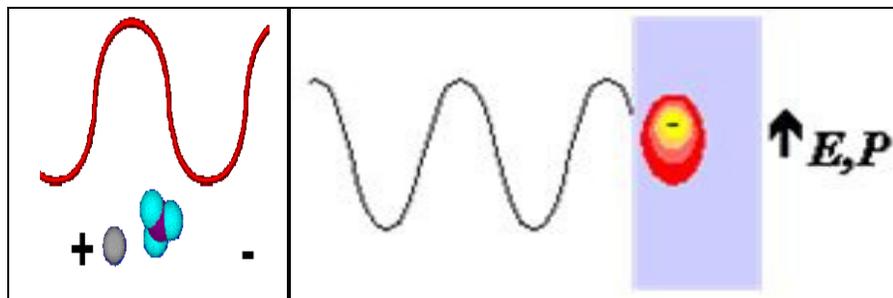


Figure 7: Ions in solution will move by the applied electric field.

Mechanisms

Dipolar polarization

Dipolar polarization is the phenomenon responsible for the majority of microwave heating. It depends upon nature (polarity) of solvent and compound. Electric dipole of molecules is sensitive to external oscillating electric field of microwave. Due to which polar molecules rotate to continuously align with it called dipole rotation. As the field alternates, the molecules reverse direction (Figure No. 5 and 6). Rotating molecules push, pull, and collide with other molecules (through electrical forces), distributing the energy to adjacent molecules and atoms in the material. Collisions and friction between the moving molecules result in the heating.

Conductivity heating

Ionic conduction is only minimally different from dipole interactions. Obviously, ions in solution do not have a dipole moment. When the irradiated sample is an electrical conductor, the charge carries (electrons, ions, etc.) are moved through the material under the influence of electric field (E), resulting in a polarization (P). This induced current will cause heating in the sample due to any electric resistance. For a very good conductor, complete polarization may be achieved in approximately 10-18 seconds.

Loss angle

In order to be able to compare the abilities of different solvents to generate heat from microwave irradiation, their capabilities to absorb microwave energy and to convert the absorbed energy into heat must be taken into account. These factors may be considered using the loss angle, which is usually expressed in the form of its tangent.

$$\tan \delta = \epsilon'' / \epsilon'$$

The dielectric constant, or relative permittivity, ϵ' , represents the ability of a dielectric material to store electrical potential energy under the influence of an electric field. At room temperature and under the influence of a static electric field, ϵ' , is equal to the dielectric constant, ϵ_s .

The loss factor, ϵ'' , quantifies the efficiency with which the absorbed energy is converted into heat.

REACTION MEDIUM: REQUIRMENTS

[7]

There are various solvents that can be employed in this technique (Table No. 1). Requirements for solvents to be used in MW assisted organic synthesis are,

- The solvent must have dipole moment so as to absorb MW and boiling pt. at least 20-30⁰C higher than the desired reaction temperature. An excellent energy transfer medium for many types of reactions in domestic microwave oven is N, N-dimethylformimide (DMF).
- A good solvent with high boiling point (160) & higher dielectric constant ($\epsilon = 36.7$). The solvent can retain the water formed in the reaction, thus, obviating the need for a water separator. The temperature can be raised to about 140⁰C without noticeable vaporization.
- The presence of salts in polar solvents can frequently enhance microwave coupling.
- Hydrocarbon solvents such as hexane ($\epsilon = 1.9$), benzene ($\epsilon = 2.3$), toluene ($\epsilon = 2.4$) & xylene, because of less dipole moment, are unsuitable as they absorb MW poorly. But the addition of alcohol or water to these solvents can leads to dramatic coupling effects. Hence, a 1:4 ethanol:toluene mixture can be heated to boiling in few minutes in a standard microwave oven. Coupling reactions of hexane, benzene, toluene & xylene with alcohol or water.

CLASSIFICATION OF MICROWAVE SYNTHESIS [7]

A. Solvent Assisted Synthesis

Solvent assisted synthesis proceeds in presence of solvent with good polarity, high boiling point and sufficient chemical stability as explained earlier.

B. Solvent Free Synthesis

Solvent free conditions offer safe and efficient reaction pathway, which are time saving, economic & often enable

elimination of waste treatment. Solvent free synthesis is subdivided into following:

- Solid supported reactions
- Neat reactions

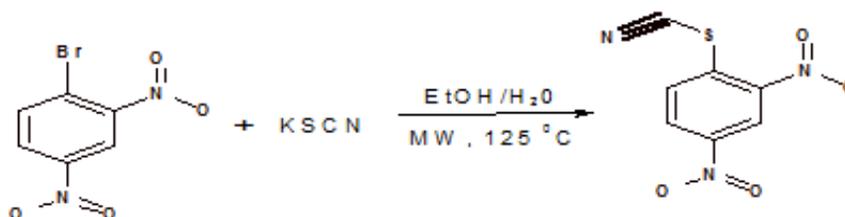
Table 1: Solvents for Microwave assisted Organic Synthesis

<i>SR. NO.</i>	<i>SOLVENT</i>	<i>DIELECTRIC CONSTANT</i>	<i>BOILING PONT °C</i>	<i>DIELECTRIC LOSS</i>
1	Water	80.4	100	9.88
2	Formic Acid	58.5	100	42.37
3	DMSO	45	189	37.12
4	DMF	87.7	153	-
5	Acetonitrile	37.5	82	2.32
6	Ethylene Glycol	37	197	49.95
7	Nitro methane	36	101	2.3
8	Nitrobenzene	34.8	202	20.47
9	Methanol	32.6	65	21.48
10	Ethanol	24.3	78	22.66
11	Acetone	20.7	56	1.16
12	1-Propanol	20.1	97	15.21
13	1-Butanol	17.1	118	9.76
14	2-Butanol	15.8	100	7
15	Isobutanol	15.8	108	8.24
16	Dichloromethane	9.1	40	0.38
17	THF	7.4	66	0.34
18	Acetic Acid	6.2	113	1.07
19	Ethyl Acetate	6	77	0.33
20	Chloroform	4.8	66	0.43
21	Chlorobenzene	2.6	132	0.26

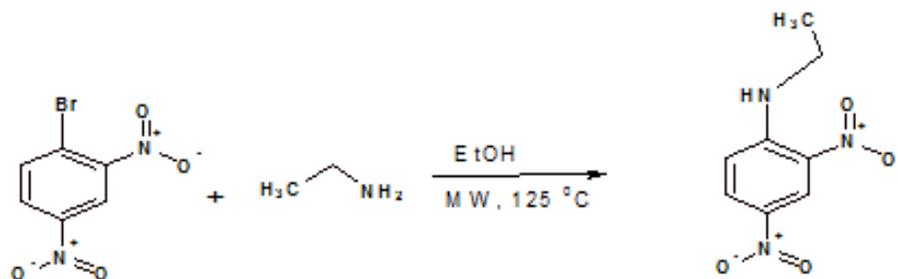
APPLICATIONS [8, 9, 10]

1. Nucleophilic aromatic substitution

a. Synthesis of 2, 4-dinitrophenyl thiocyanate

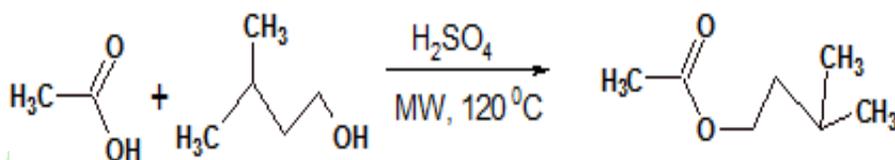


b. Synthesis of 2,4-dinitro-N-ethylaniline

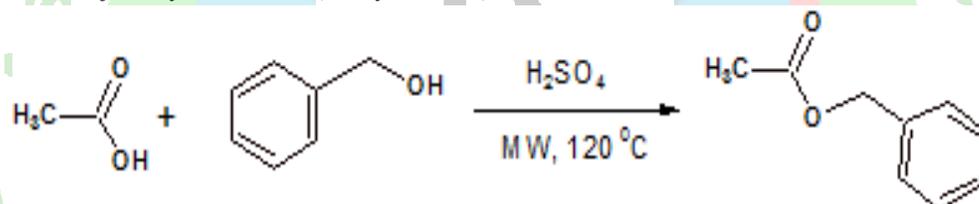


2. Esterification

a. Synthesis of 3-methyl butyl ethanoate (isoamylacetate)

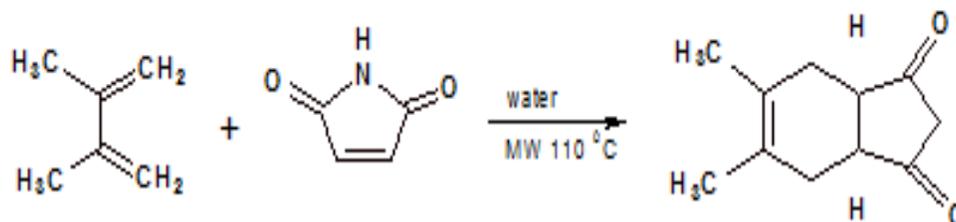


b. Synthesis of benzyl ethanoate (benzyl acetate)

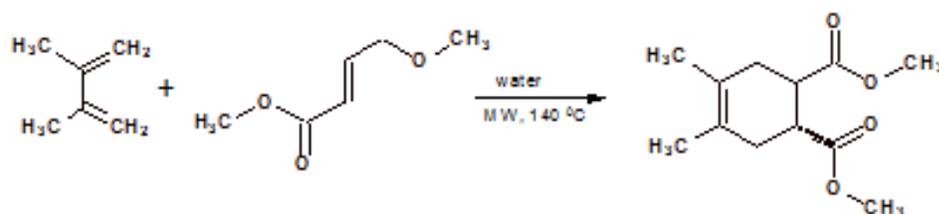


3. Diels alder reaction

a. Reaction of 2, 3-dimethyl-1,3-butadiene & maleimide

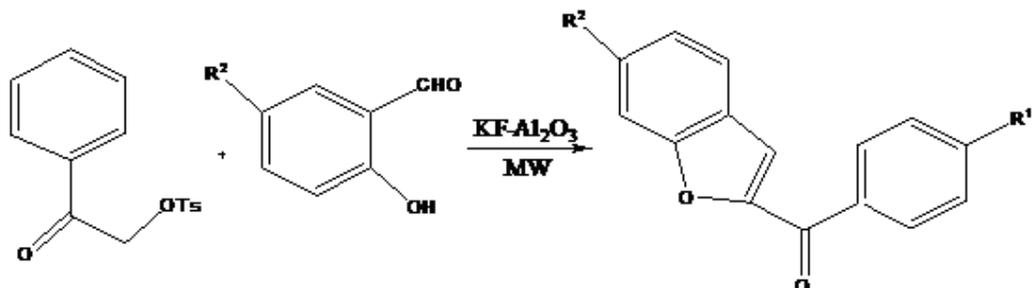


b. Reaction of 2,3-dimethyl-1,3-butadiene & dimethyl fumarate



4. MW assisted synthesis of heterocycles

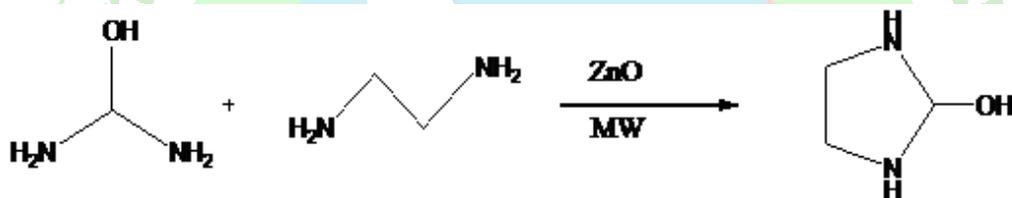
a. Synthesis of 2-arylbenzo[b]furans



A rapid solvent-free synthesis has been developed, from readily accessible α -tosyloxyketones and mineral oxides that is accelerated by exposure to MWs.

b. MW assisted synthesis of imidazolidine-2-one

A MW-assisted protocol for the direct synthesis of cyclic ureas has been developed that proceeds expeditiously in the presence of

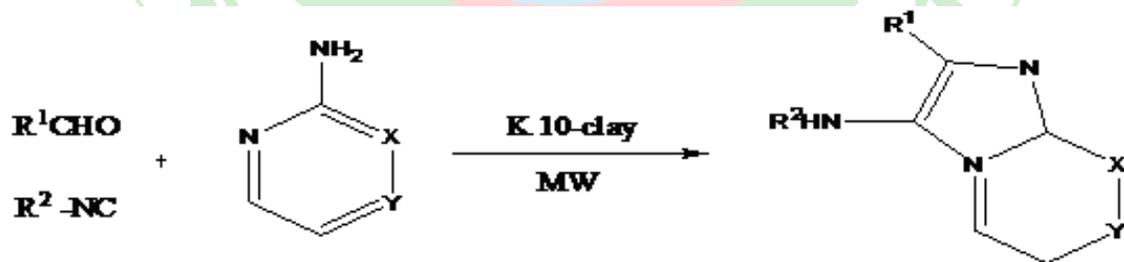


ZnO. The reaction was not only accelerated upon exposure to MW irradiation but also the formation of by-products was eliminated when compared to the conventional heating methods.

c. Mw assisted clay catalyzed synthesis of nitrogen heterocycles

A one-pot MW protocol for the synthesis of imidazo [1, 2-a]-annulated pyridines,

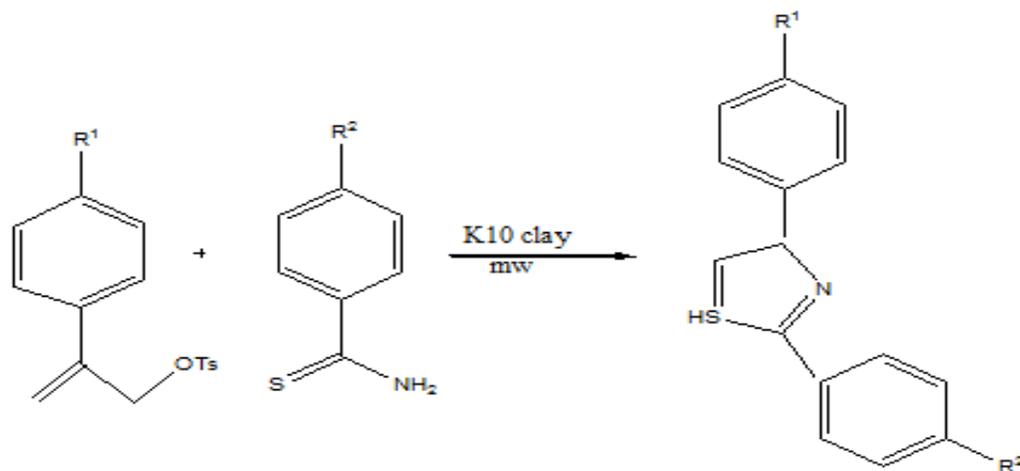
pyrazines and pyrimidines has been developed (Scheme 8.20) that proceeded in the presence of solid catalyst montmorillonite K10 clay under solvent-free conditions.



d. MW assisted solvent free synthesis of 1, 3-thiazoles

1, 3-Thiazoles have been readily obtained from thioamides and α -tosyloxy- ketones,

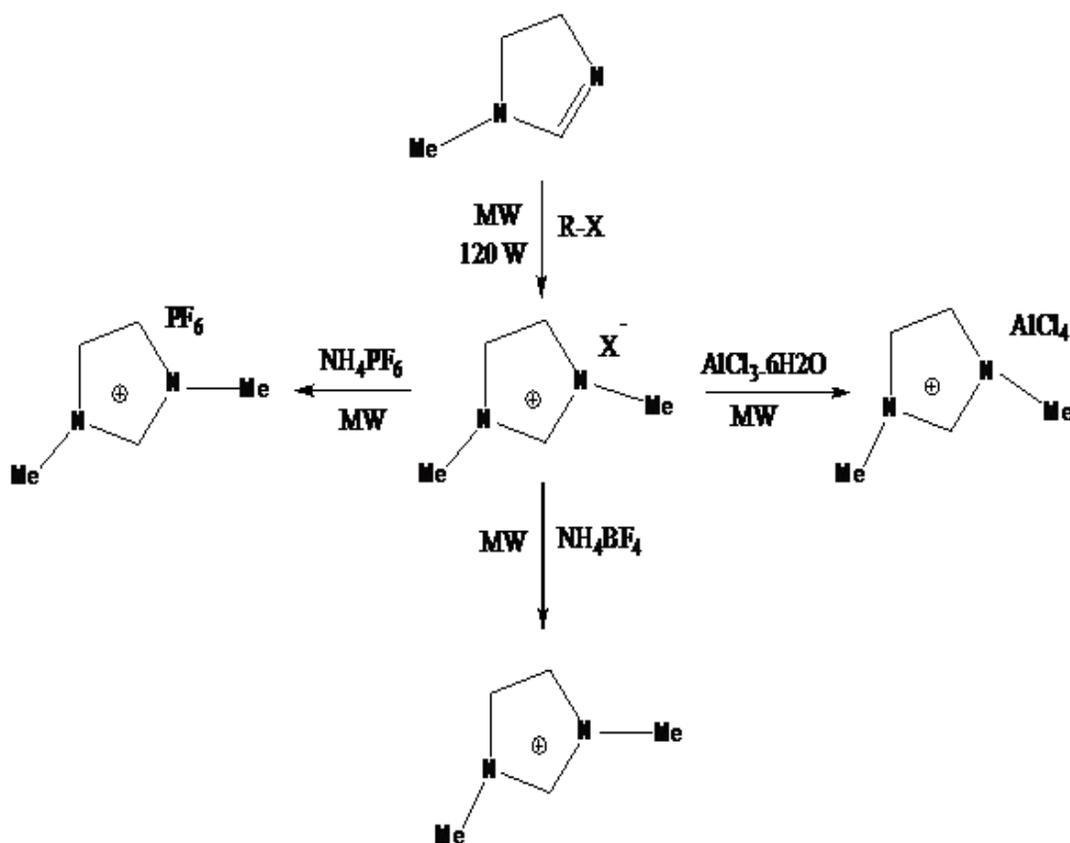
catalyzed by montmorillonite K-10 clay under MW irradiation, in excellent yields. These compounds are very difficult to synthesize under conventional heating conditions.



5. MW – assisted synthesis of Ionic Liquids

IL's are polar but consists of poorly coordinating ions and provide a polar alternative for biphasic systems. Other important attributes of these IL's include negligible vapor pressure, potential for recycling, compatibility with various organic compounds and organometallic catalysts, and ease of separation of products from reactions. ILs, being polar and ionic in character, couple

with MW irradiation very efficiently and are, therefore, ideal MW-absorbing candidates for expediting chemical reactions. The first efficient preparation of 1, 3-dialkylimidazolium halides via MW irradiation was developed by Varma and co workers. The reaction time was reduced from several hours to minutes and it avoids the use of a large excess of organic solvents as the reaction medium.



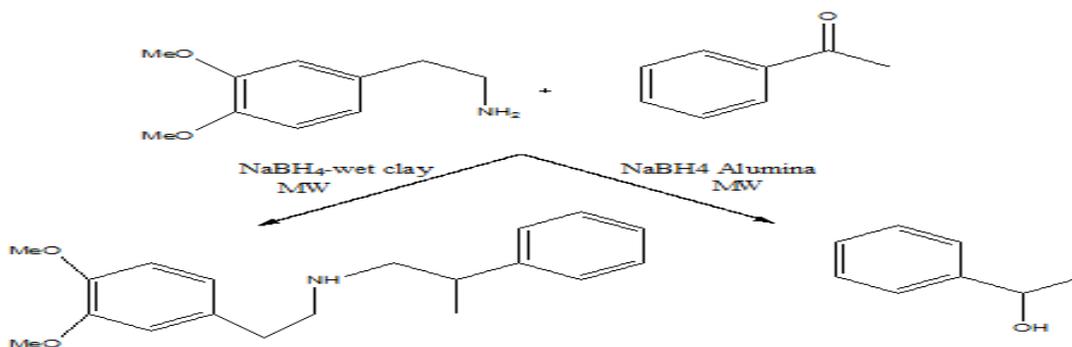
6. MW –assisted solvent free oxidation reduction reactions

MW protocols for oxidation–reduction reactions using immobilized reagents on solid supports have been extensively explored.

a. The oxidation of sulfides to sulfoxides and sulfones

It was also developed under MW irradiation with good selectivity to either sulfoxides or sulfones using sodium periodate (NaIO_4) on

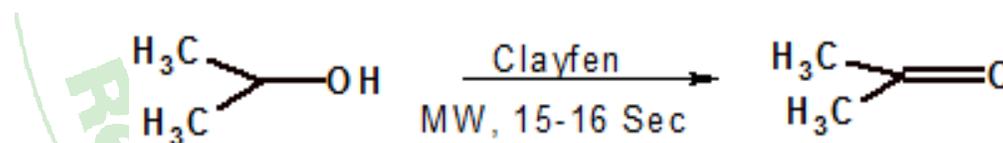
silica. A rapid and chemo selective reduction of aldehydes and ketones, which) and proceeds in the uses alumina-supported sodium borohydride (NaBH_4) solid state, was also accelerated by MW irradiation. A solvent-free reductive amination protocol for carbonyl compounds using sodium borohydride supported on moist montmorillonite K10 clay was carried out under MW irradiation. Clay serves as a Lewis acid and provides water from its inner layers that enhances the reducing ability of NaBH_4 .



b. Oxidation of alcohols

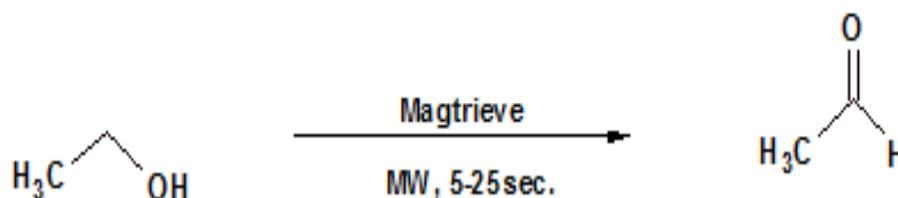
Alcohols are readily adsorbed on clay fen and rapidly oxidized to corresponding carbonyl

compounds upon exposure to microwave under solvent free conditions.



Under MW irradiation primary & secondary alcohols selectively oxidized to corresponding aldehydes & ketones within 5-25 s. using

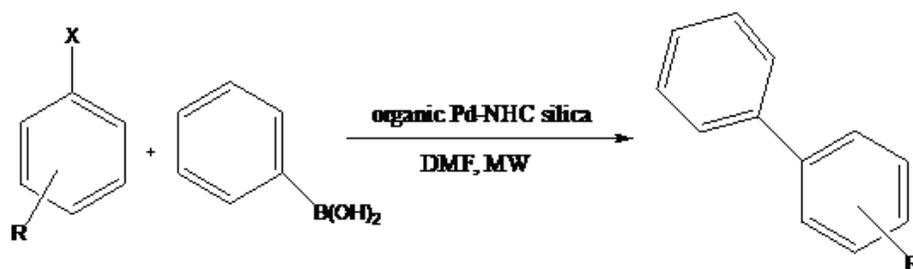
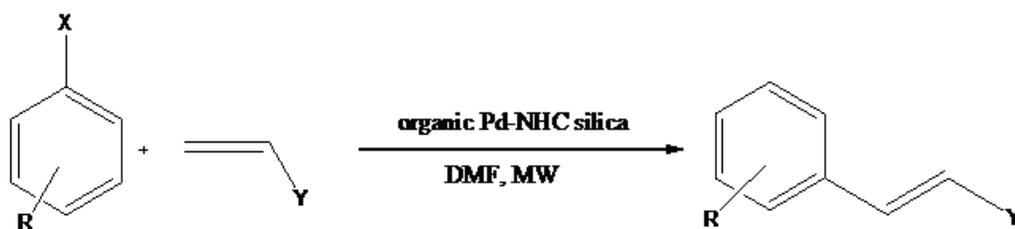
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7. PD-NHC silica catalyzed Heck and Suzuki reactions

This catalyst was then used for Heck and Suzuki reactions under MW irradiation condition. These C–C coupling reactions

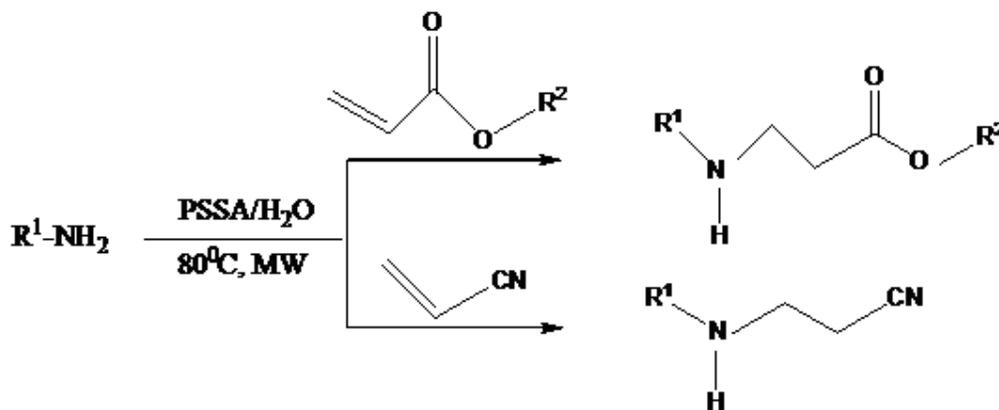
proceeded efficiently under the influence of MW, with excellent yield and high turnover frequency (TOF), without any change in catalytic activity for at least five reaction cycles.



8. MW-assisted Aza-Michel reaction

The aza-Michael addition is an important class of carbon–nitrogen bond forming reactions, and has been demonstrated to be a powerful tool in organic synthesis. Efficient aza Michael

addition reactions of alkyl amine and tandem bis aza-Michael addition reactions of alkyl diamine with methyl acrylate and acrylonitrile catalyzed by PSSA in aqueous medium have been developed.



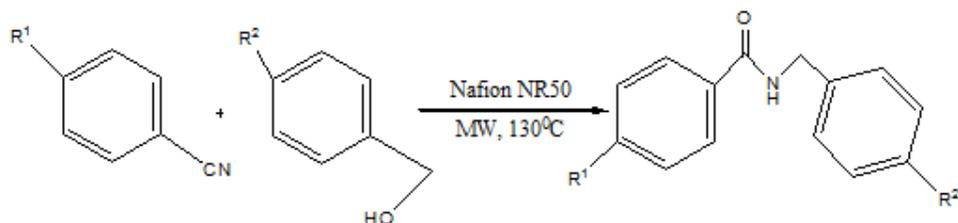
$R^1 = \text{Ph, Cy, 4-ClPh, PhCH}_2\text{ Bu, etc.}$

$R^2 = \text{Me, n-Bu}$

9. MW-assisted Ritter reaction

An efficient synthesis of amides by the Ritter reaction of alcohols and nitriles under MW irradiation was developed under solvent-free

conditions. This green protocol is catalyzed by solid-supported Nafion NR50 with improved efficiency and reduced waste production.



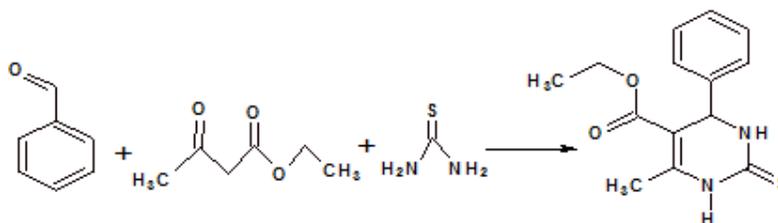
$R^1 = H, OMe, Cl$

$R^2 = H, Me, OMe, Cl, Naphthyl$

10. Modified Biginelli reaction

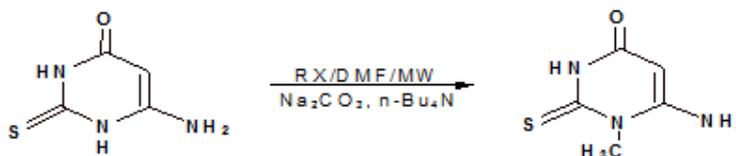
and neat reactants. This is Condensation reaction. 9-12 min., traditionally 2 hr.

3, 4-dihydropyrimidine compounds can be prepared by using modified Biginelli Reaction



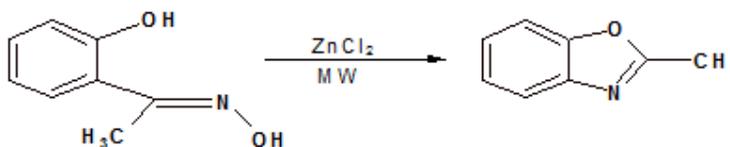
11. Microwave assisted alkylation

MW assisted selective N alkylation of 6- amino -2-thiouracil in DMF using different alkyl halide.

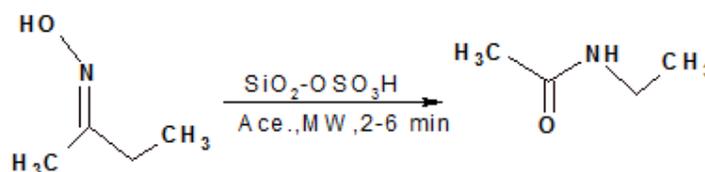


12. MW assisted rearrangement reaction

Comparison of Beckman rearrangement of benzaldehyde and 2 hydroxy acetophenones oximes by conventional and MW heating was done. Yields are significantly enhanced under MW exposure.



- a. Beckman rearrangement in acetone under MW irradiation using silica sulphate as an efficient & recyclable catalyst.



CONCLUSION

The most important goal of chemists is in ensuring that our next generation of synthetic protocols for drugs & fine chemicals are more sustainable & greener than the current generation.

The uses of emerging MW- Assisted Chemistry in conjunction with utility of greener reaction media or solvent free conditions are effective & sustainable techniques to reduce chemical waste & reaction time in organic synthesis. It is a technique which can be used to rapidly explore

'chemistry space' & increase the diversity of the compounds produced. Now a days, it could be considered that all the previously conventionally heated reactions could be performed using this technique.

ACKNOWLEDGEMENTS

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