

PART - 1
INTRODUCTION

Microwave-Assisted Organic Reactions

Green chemistry can be defined as the design, manufacture and use of efficient, effective, safe and environmental friendly chemical processes and products. Microwave-assisted organic reactions cover all the principles of green chemistry. Microwave assisted organic reactions are useful in the synthesis of active pharmaceutical ingredients (APIs), drug intermediate and other compounds with chemical and medicinal importance (analytical, diagnostic, research). This technology improves the chemical process and reduces the pollution (solvent free methods). Microwave-assisted reactions maximises the efficient use of safer raw materials and reduces the waste (toxic material) generation.

- 1) **Speed:** Microwave reactions can be completed in minutes. Some chemical reactions complete in seconds. In many cases, it reduces the reaction time from hours to minutes to seconds.
- 2) **Economy:** Microwave reactions utilize no or low volume of solvents.
- 3) **Cost effective:** Microwave reactions reduce the cost per microwave reactions mainly through increasing the reaction rate there by yields.
- 4) **Simplicity:** The products of microwave reactions can be isolated very easily and requires no purification (recrystallization) in most cases.
- 5) **Consistency:** Microwave reactions are reproducible.
- 6) **Rapid optimization:** Microwave reactions complete very fast. Hence, the organic reaction optimization can be achieved faster than the conventional synthesis.
- 7) **Energy efficient reaction:** Microwave reactions offer enhanced reaction conditions.

- 8) **Higher yield:** The rapid-efficient reaction inhibits the byproducts formation and hence offers higher yields of the products.
- 9) **High purity:** The rapid-efficient reaction inhibits the byproducts formation and hence offers highly pure compounds.
- 10) **Superheating:** It takes the reaction environment to very high temperature (super heating). It is very essential for the several reactions such as substitution and coupling reactions.
- 11) **Versatility:** The microwave heating can be utilized for all kinds of organic reactions. It includes substitution, coupling, rearrangement, oxidation and reduction, etc.

Microwave Heating

Electromagnetic waves frequency ranges between 300 MHz and 300 GHz are named as microwaves. Most of the microwave ovens and microwave processors operate at 2.45 GHz (~ 12.2 cm λ). These microwaves penetrate into fogs and clouds and travel in straight lines. Microwave radiations were utilized in the development of Radio Detection and Ranging (RADAR).

In 1946, the American electrical engineer Dr Percy Spenser, noticed the melting of candy bar placed in his pocket under the exposure to microwave radiation once the magnetron was switched on. He was engaged in the experiments to utilize the magnetron in RADAR. This observation stimulated him to develop microwave oven. Based on this, he applied the magnetron heat for cooking popcorn and found working. This is stimuli for the development of the most popular and useful microwave oven in 1970. Initially microwave heating was utilized for heating water, moisture analysis and wet ashing procedures in chemical and biological laboratories. The computerized microwave ovens were used for the acid digestion of ores and minerals. Gedey *et al* and Giguere *et al* (1986) demonstrated the use of microwave ovens in organic reactions for the first time.

Theory of microwave heating: The rotational states of the molecules undergo excitation with electromagnetic radiation. The microwave irradiation, when absorbed by organic molecules induces the rotational changes. The frequency of molecular rotation is similar to the frequency of microwave radiation. The molecule continually attempts to realign itself with the applied electric field and absorbs the energy. This effect is utilized in microwave ovens to heat food materials. Chemists also utilize the microwave irradiation as an energy source for chemical reactions.

- Microwave oven contains microwave generator called as magnetron (inside the string metal box). It receives electricity and converts them into high-energy radio waves.
- Microwave guide (channel) introduces microwave heat energy (radiation) into the heat compartment.
- The microwaves bounce back and forth off the reflective metal walls of the heat compartment.
- The microwaves penetrate the material to be heated (reaction vessel) and vibrate them to cause molecular friction. The rate of vibration decides the heating and initiates the reaction.

Principles

Microwave ovens more efficiently channel heat energy into the molecules. In the microwave heating process energy transfer occurs by three mechanisms namely dipole rotation, ionic conduction and interfacial polarization. Microwave ovens inject the energy directly into the molecules, rather than warming the outside walls of a reaction vessel to spread heat by convection and conduction. High frequency electromagnetic radiations (electric fields) exert a force on charged particles of molecules and that causes molecular friction to generate super heat.

- ***Ionic conduction:*** Ionic conduction is the electrophoretic migration of ions, when an electromagnetic field is applied. The oscillating electromagnetic field generates an oscillation of electrons in a conduction and results electric current.

The conduction mechanism generates heat through resistance friction to the electric current.

- **Dipole rotation:** It means rearrangement of dipoles with the applied field. Polar molecules are the ideal material for dipolar polarization. Dipole polarization depends on the dipole moment of a molecule. The difference in the electro negativity of the atoms and molecular symmetry is responsible for this effect. The alignment of polar molecules with an oscillating electromagnetic field results random motion of particles. This random motion effect generates heat. The dielectric polarization provides the energy to the molecules to rotate into alignment. The polarizations (Maxwell-Wagner effect) contribute heating effect.
- **Interfacial polarization:** A combination of the conduction and dipole polarization mechanism.

How Microwave Radiations are Irradiated? Microwaves are heterogeneously distributed within the cavity and produces defined regions of high and low energy intensity. The energy variation can be minimized by smoothing mechanism, which disperses the incoming energy through a wave stirrer (mode stirrer). It is a reflective, fan-shaped paddle attached to the opening of wave-guide feed. The turn table (rotating platform) present in the microwave oven ensures that an average energy field experienced by the sample is approximately the same in all directions.

Superheating: Superheating of liquids is common under microwave irradiation because of molecular friction. In super heating, a liquid attains a temperature much above its conventional reflux boiling point. This superheating, which is not commonly seen in conventional heating may help in increasing the rate of reaction. Microwave irradiation provides superheating. Superheating in closed vessels and under pressure facilitates the organic reactions. Superheating offers highly accelerated reaction rate and enables chemical synthesis in much lesser time with good yields. Superheating of liquids or solutions under microwave irradiation raises the temperature above the conventional boiling point. It reduces several hour conventional reactions into fewer minutes microwave reactions. Water, for example

reaches 105 °C (5 °C above actual boiling point) and acetonitrile reaches 120 °C (38 °C higher than normal boiling point).

Wall-heat transfer: The wall heat-transfer that occurs with heat resources such as water bath, oil bath and steam bath leads to incomplete reaction. Microwave irradiation produces efficient internal heat transfer (*in situ* heating), and overcomes the wall-heat transfer mechanism. The microwave heating reduces the tendency for seed formation (initiation of boiling).

Microwave Instrument Components

- 1) **Magnetron:** Microwave oven magnetron converts the shortest microwaves (12 cm; 4.7 inches), which carry higher energy into electromagnetic radiations. A magnetron is a microwave source (thermionic diode) consist an anode and a cathode. Cathode releases electrons upon direct heating. The anode consists even numbered small cavities (tuned circuit). The gap across the end of each cavity behaves as a capacitance. The electrons released from cathode are attracted towards the anode. It causes bending of the path of electrons, when they travel from cathode to anode. These deflected electrons pass through the cavity gaps and induces a small charge in the tuned circuit. This is responsible for oscillation of the cavity and microwave generation.
- 2) **Wave-guide feed:** A wave-guide feed is a rectangular channel made from a metal sheet. The reflective walls of wave-guide feed allows the transmission of microwaves from the magnetron to the oven cavity.
- 3) **Oven cavity:** It refers to the place in an oven for placing the material to be heated. It is usually made of glass or fiber material of metal with reflective surfaces. Reflective surfaces increase the oven efficiency and to prevent the hazardous leakage. A wire mesh door of the cavities also prevents the microwave leakage. The ovens are equipped with fans to remove hot air and vapors and prevents oven from getting heated upto higher temperatures.

Microwave Solvents

Solvents serve as energy transfer media and help in coupling the thermal energy with the kinetic energy of the reactants. Solvents are of major concern as environmental pollutants (carcinogenic, mutagenic and allergens). Eco-friendly microwave chemistry requires no solvents or very lesser quantity of solvents as energy transfer medium. Rapid microwave synthesis leads to lesser evaporation of solvents and prevents or reduces environmental pollution. Polar solvents are best for dipolar polarization and microwave heating.

The solvents used in microwave reactions should possess dielectric heating property (Table 1). Dielectric heating ensures the conversion of electromagnetic energy into efficient heating. The ability of the solvent dielectric property is indicated by $\tan \delta$. The solvents with high $\tan \delta$ provide rapid heating. However the solvent with low $\tan \delta$ also can be used, but provide slow heating.

Table 1 Microwave solvents along with their dielectric constant values

High $\tan \delta$ (>0.5)		Medium $\tan \delta$ (0.1- 0.5)		Low $\tan \delta$ (<0.1)	
Ethylene glycol	1.35	2-Butanol	0.45	Chloroform	0.09
Ethanol	0.94	Dichlorobenzene	0.28	Acetonitrile	0.06
DMSO	0.83	N-Methyl-2-pyrrolidone	0.28	Ethylacetate	0.06
2-Propanol	0.80	Acetic acid	0.17	Acetone	0.05
Formic acid	0.72	DMF	0.16	THF	0.05
Methanol	0.70	Dichloroethane	0.13	DCM	0.04
Nitrobenzene	0.59	Water	0.12	Toluene	0.04
1-Butanol	0.57	Chlorobenzene	0.10	Hexane	0.02

Microwave Reaction Vessels

A safe reaction vessel for microwave heating for solvent mediated reflux reactions is essential. Microwave transparent materials such as Teflon, polystyrene, pyrex or borosilicate glass are useful in the vessel fabrication. These materials absorb the radiation poorly and with stand at higher temperatures.

High pressure increases the risk of explosion.

- **Teflon:** Polyterafluoroethylene (Teflon) offers resistant to strong bases and hydrogen fluoride. Longer, microwave exposure (more than 15 minutes) to Teflon materials softens the material, and may lead to loss of reaction content. Hence, the microwave reaction should be conducted in several pulses. Teflon is widely used material for preparation of sealed containers, which are commonly referred to as Teflon bomb.
- **Nalgene:** It is an autoclavable and thermostable polypropylene material.
- **Corian:** A durable and heat resistant polymer preferred for the organic reactions. This material permits the temperature rise to above 200 °C. It is desirable for prolonged reactions with microwave irradiation.
- **Vermiculite:** It consists of hydrous silicates of ferrous, magnesium and aluminium. It is placed in either a Corian box, Nalgene dessicators or a container made of a special polymer.
- **Glass wool:** It can be used as an alternative to vermiculite.
A sealed reaction vessel (Teflon or Pyrex glass) covered with vermiculite absorb the reaction content in the event of explosion.

Open vessel reactions: Borosil beaker, conical flask and Erlenmeyer flask are useful. Glass wares covered with funnel and a watch glass avoids excessive solvent evaporation (incase of domestic microwave ovens). A flask fitted with condenser is available in microwave synthesisers.

Microwave-Assisted Chemical Reactions

1) **Dry media synthesis:** It is a most common microwave method. High pressure and associated danger of explosion can be avoided by dry media synthesis. It includes neat reaction and solid-support reactions.

- **Neat reaction:** It refers to reaction carried out without using solvent. A mixture of reactants without the use of solvent helps to avoid the risk of developing high pressure.
- **Solid-support reactions:** A reaction can be carried out by adsorbing the reactants on an inorganic solid supports under microwave irradiation. Inorganic solids namely in clay, silica, alumina and Zeolite are commonly useful solid supports (catalysts). The reactants adsorbed on the surface of inorganic solids absorb the microwave radiation. These solids prevent development of high pressure in sealed containers. In this kind of experiments, the reactant will be dissolved in organic solvent. Further, the reactant should be mixed with the inorganic solid support and followed by solvent evaporation. This facilitates the adsorption of reactants on the solid surface. Alternatively reactants can be triturated. After the microwave irradiation, the product can be extracted with suitable solvent.

2) **Solvent mediated synthesis:** High boiling polar solvents such as N,N-dimethyl formamide (DMF), *o*-dichlorobenzene, 1,2 dichloroethane (DCE) useful in the microwave reactions. Polar solvents with a high dielectric constant absorb microwave energy better than non-polar solvents due to dipole rotation. These solvents offers higher energy transfer rates. Water is an ideal solvent since it fulfils many criteria; non-toxic, non-inflammable and abundantly available and inexpensive. It possesses high polar character, novel-reactivities and selectivities. At higher temperature it behaves as a pseudo-organic solvent. The higher temperature decreases the dielectric constant and increases the solvating power comparable to ethanol and acetone.

DMF and DCE are heated much faster than hexane or carbon tetrachloride in a microwave oven.

Ionic liquids: Salts (molten salts) in a liquid form at or below 100 °C. Ionic liquids absorb microwave irradiation extremely well and transfer energy quickly by ionic conduction. The major advantage of using ionic liquids in microwave-assisted organic reactions are:

- 1) Extremely low vapour pressure.
- 2) Thermal stability.
- 3) Electrochemical stability.
- 4) Non-flammability.
- 5) Catalytic property.

The instantaneous superheating of the ionic substance due to the ionic motion generated by the electric field. When the temperature increase, the transfer energy becomes more efficient.

Microwave-Assisted Extraction (MAE)

Extraction is one of the most important technique for the isolation, recovery and separation of phytoconstituents. The conventional extraction technique requires longer extraction time, large solvent volume and cause degradation to thermolabile substances. In contrast, the microwave-assisted extraction (MAE) requires less solvent volume, reduces the extraction time and prevents the oxidative degradation of phytoconstituents. Microwave extraction utilizes maceration and percolation principles. The rate of extraction (breaking up of plants cells and tissues) is much higher in microwave extraction. In conventional extraction, the heat transfer occurs from heating medium to the sample. MAE offers heat directly to the medium (dissipation). The penetration of microwave energy depends on the dielectric property on the plant cell structure.

Safety Precautions

Microwave ovens are designed to ensure no leakage of radiation. The microwave ovens with high power capacity are useful. Even if there is any leaking, it is very much small in intensity when compared with cellular phone signals. This radiation

leaking occurs at a distance of 5 cm (2 inch) and is about 5 MW per square cm. Microwave energy penetrates the skin into subcutaneous tissue and therefore also raises the temperature level of tissue and blood. Hence, the protection is required.

- **United States-Food and Drug Administration (US-FDA):** The United States-Food and Drug Administration (US-FDA) limits the leakage of microwave energy and ensures the safety. Shielding or increasing the distance from the oven ensures safety. In title 21 US-FDA states that the power density limit from an operating microwaves oven 'shall not exceed 1 mill watt per square centimetre at any point 5 centimetres or more from the external surface of the oven, measured prior to acquisition by a purchaser and thereafter, 5 milliwatts per square centimetre at any such point.
- **World Health Organization (WHO):** WHO warns that the thermal damage would occur from long exposures to very high power levels. In other words, the radiation is very low to cause damage to the tissue.

Advantages

1. Microwave irradiation penetrates the walls of the vessel and heats only the reactant and solvent, not the reaction vessel.
2. The energy transfer occurs through dielectric ions. In conventional methods, it occurs through conduction and or convection.
3. The commercial microwave systems (specific for synthesis) offer improved reproducibility, rapid synthesis and rapid optimization.
4. Microwave energy offers much higher heating rate (2 to 4 °C/s). In conventional heating it is very difficult to achieve this heating rate.
5. Microwave heating facilitates the solvent-free and solid-supported reactions (dry reactions).
6. The solvents heated under microwave energy, boil at elevated temperature. It increases the reaction temperature by upto 100 °C, above the boiling point. For example, ethanol (b.p 79 °C) provides temperature upto 164 °C (85 °C more).

7. In solid samples, the rate of energy transport is less and develops hotspots. These hotspots enhance the reaction rate as well as shift the equilibrium constant.
8. Microwave reactions offers higher efficiency for the multi-component reactions.
9. Microwave reactions promote the efficiency of combinatorial chemistry reactions.

Applications

- 1) Microwave irradiation is very much useful in the following chemical reactions.
 - Protection and deprotection reactions: Functional group protection and deprotection strategies are important in carbohydrate chemistry and peptide synthesis. Microwave chemistry is more useful in these reactions.
 - Named organic reactions: Gabriel synthesis, Suzuki reaction, Williamson-ether synthesis and Pinacol-Pinacolone rearrangement.
 - Oxidation, esterification, O-alkylation and aromatic electrophilic substitution reactions.
 - Preparation of medicinal compounds such as sildenafil, phenytoin, benzocaine are attempted successfully.
 - Drug intermediates, namely, 1,4-dihydropyridines, chalcones, carvones. Thioflavonoids and γ -carboline also are synthesised.
 - Novel cephalosporins are synthesised using microwaves.
 - Asymmetric reactions were also successfully attempted.
- 2) In analytical chemistry
 - Ashing: The ash content determination such as loss on ignition (LOI) and residue on ignition (ROI) is an important quality control procedure. Microwave ashing provides reduced time, cost and reduced exposure to fumes.

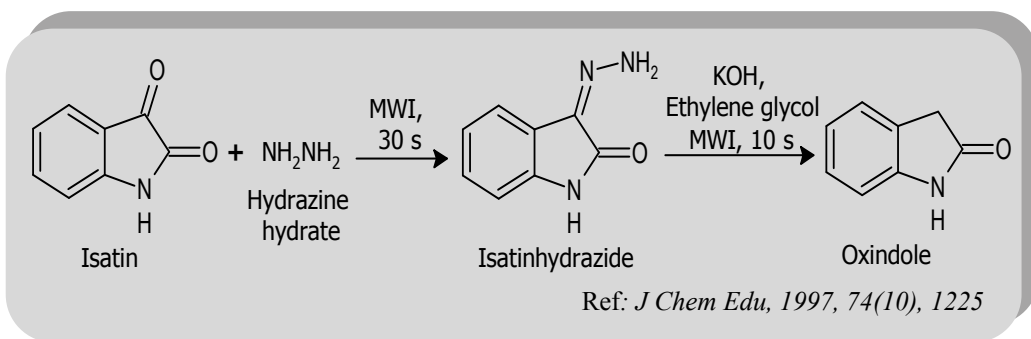
- Digestion: Microwave digestion assists in dissolving the metals in minutes during elemental analysis. Microwave digestion can oxidize compounds more effectively than conventional methods.
 - Moisture analysis: The microwave-assisted moisture analysis overcomes the limitations of Karl-Fischer (destructive). Microwave analyzers work on higher dielectric constant (attenuate energy transfer) and offers non-destructive moisture measurement.
- 3) In natural product extraction and isolation: Extraction and isolation of active principles from plant materials is very critical. The conventional methods require longer extraction procedures and higher solvent volume. Longer extraction and high volume of solvents pose the thermal degradation issues. Microwave-assisted extraction (MAE) is useful in the extraction of plant tissues using relatively less volume of solvent with higher extraction power. Thus it helps in overcoming the issues of conventional methods.
- 4) In food industry: Microwave heating is successfully applied in the food processing such as pasteurization and preservation. Microwave pasteurization is an efficient technique for milk and fruit juice. Microwave blanching is another important application for the food industry. For freezing, canning and drying processes.

Important Microwave Reactions

Fewer important microwave reactions

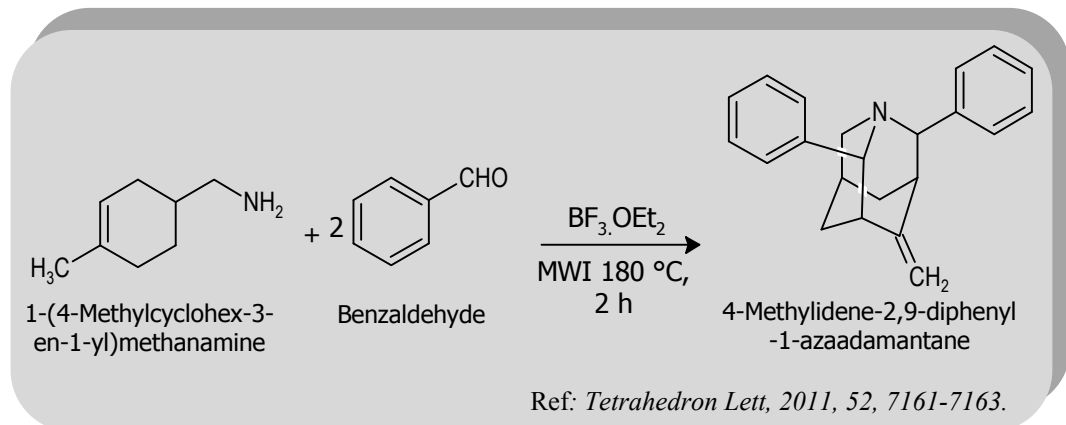
1) Microwave-assisted Wolf-Kishner reduction

Wolf-Kishner reduction converts a carbonyl compounds (aldehyde or ketone) into an alkane using hydrazine hydrate and potassium hydroxide. The conventional reaction requires elevated temperatures and prolonged heating. Parquet and Lin (1997) reported the microwave assisted conversion of isatin into oxindole. Isatin was mixed with hydrazine and ethylene glycol and irradiated (microwave heating) for 30 seconds. This produced hydrazide product. The mixture of isatin hydrazide and potassium hydroxide in ethylene glycol was further irradiated for 10 seconds to obtain oxindole.



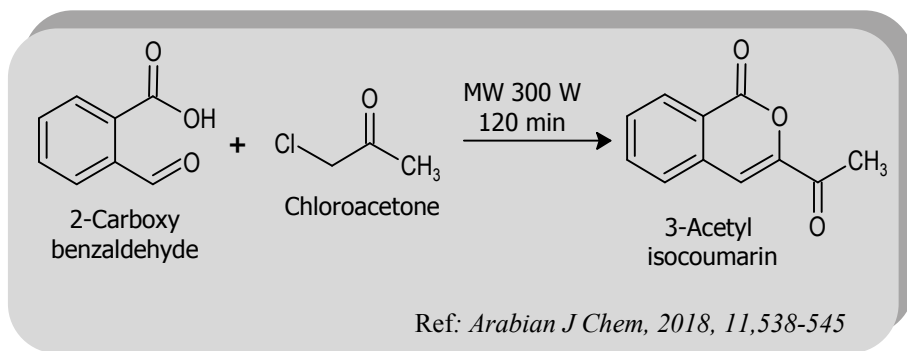
2) Microwave-assisted Aza-Prins cyclization

Aza-Prins cyclization involves the condensation of homoallylic amine with an aldehyde in the presence of an acid to generate piperidines. Parchinsky et al (2011) reported the microwave assisted generation of 1-azaadamantanes (piperidines) from (4-methylcyclohex-3-ene-1-yl)-methyl amine. The microwave condensation of 1-(4-methylcyclohex-3-ene-1-yl)-methanamine with benzaldehyde (2 equivalent) in the presence of boron trifluoride diethyl etherate at 180 °C for 2 hours generated 4-methylidene-2,9-diphenyl-1-azaadamantane (83%).



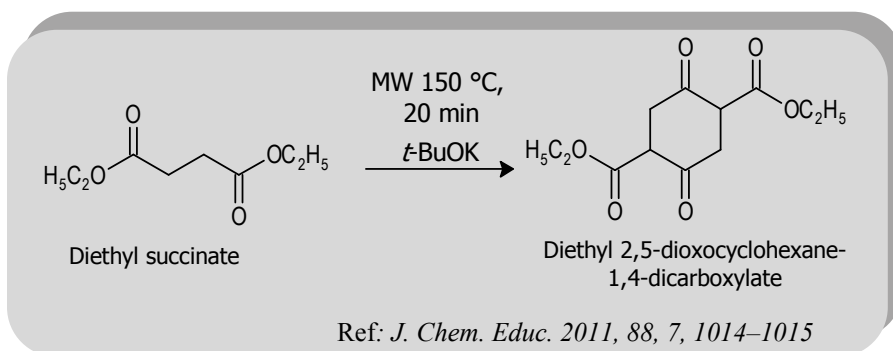
3) Microwave-assisted intermolecular Aldol condensation

Aldol condensation involves the condensation of enolate ion with a carbonyl compound in the presence of catalyst (acid/base) to generate β -hydroxy aldehyde (or β -hydroxy ketone). The dehydration of the β -hydroxy product forms conjugated enone. Molecules with dicarbonyl functionalities (e.g. 2-carboxybenzaldehyde) undergo special kind of aldol condensation called as intermolecular aldol condensation. This reaction constructs 5 or six membered rings. Koca et al (2018) reported the synthesis of 3-acetyl isocoumarin through intermolecular aldol condensation. The condensation of 2-carboxybenzaldehyde with mono-chloroacetone using triethyl amine as a base catalyst under microwave heating (300 W, 120 min) generated 3-acetylisocoumarin.



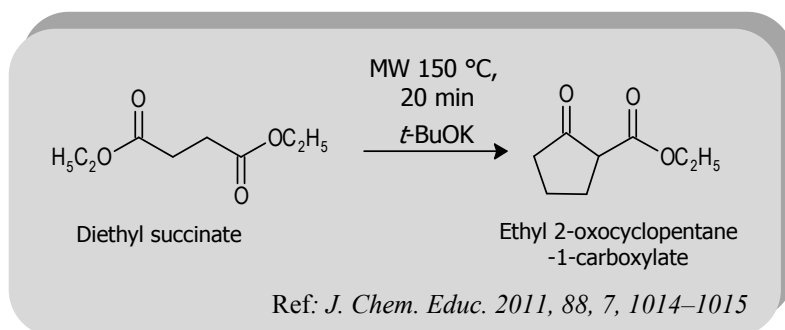
4) Microwave-assisted Claisen condensation

Claisen condensation involves the condensation of two esters in the presence of strong base to generate β -ketoester. The condensation between one ester and another carbonyl compound also considered as claisen condensation (claisen reaction). Horta (2011) reported the synthesis diethyl-2, 5-dioxocyclohexane-1,4-dicarboxylate through intramolecular claisen condensation. The self condensation of diethyl succinate using *t*-butoxide as a base catalyst under microwave heating (150 °C, 20 min) generated the diethyl-2, 5-dioxocyclohexane-1,4-dicarboxylate (80%).



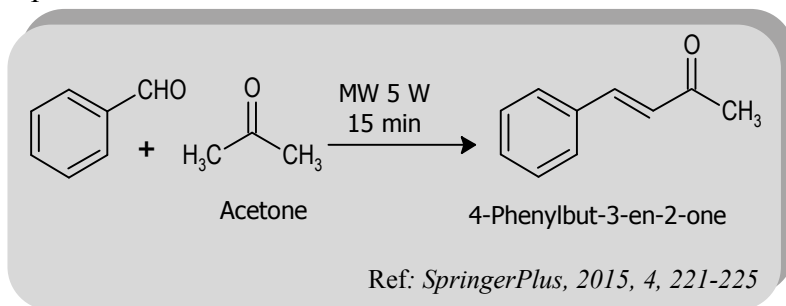
5) Microwave-assisted Dieckmann condensation

Dieckmann condensation involves the intramolecular condensation of diesters containing carbon length of 6 and 7 in the presence of strong base to generate cyclic β -keto ester. Horta (2011) reported the synthesis ethyl 2-cyclopentanecarboxylate through Dieckmann condensation. The self condensation of diethyl adipate using *t*-butoxide as a base catalyst under microwave heating (150 C, 20 min) generated the 2-cyclopentanecarboxylate (~90%).

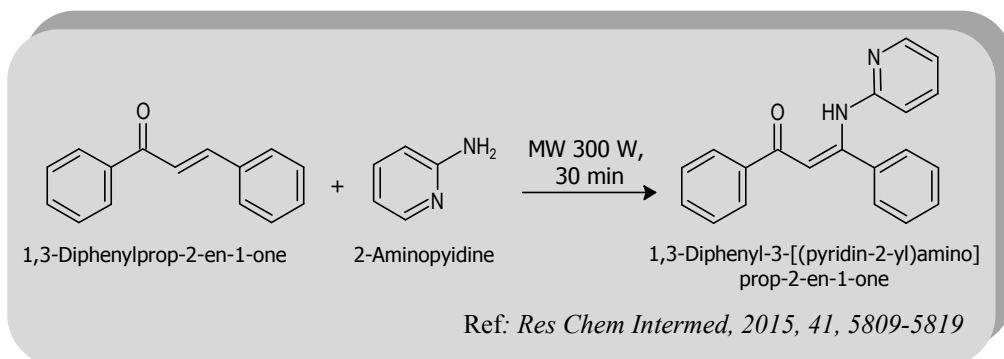


6) Microwave-assisted Claisen-Schmidt reaction

The condensation of aromatic carbonyl compound (lacking α -hydrogen) with carbonyl compound (aldehyde or ketone) having α -hydrogen in the presence of base is known as Claisen-Schmidt reaction. This reaction generates α , β -unsaturated aldehyde or α , β -unsaturated ketone. Rayar et al (2015) reported the microwave condensation of benzaldehyde and acetone using sodium hydroxide to generate 4-phenylbut-3-en-2-one. The microwave heating of 5 W for 15 min offered the product.

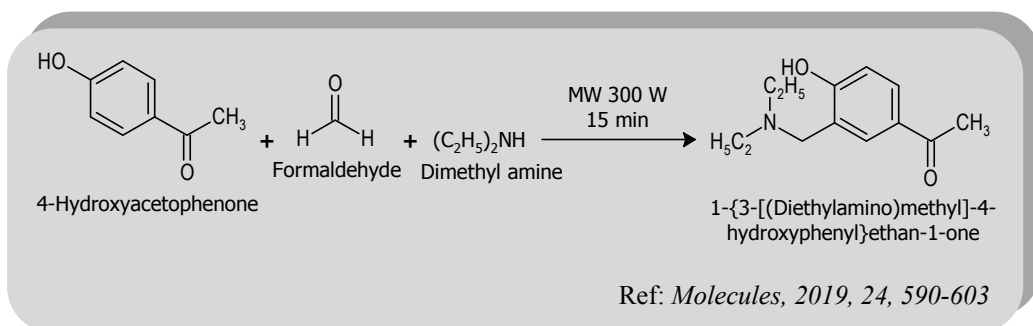
**7) Microwave-assisted Michael reaction**

The addition of carbanion (or enolate, an amine; nucleophile) to the β -unsaturated systems (enone, enal) generates carbo-carbon bond at the β -carbon. This reaction is known as Michael addition reaction. Zhao et al (2014) reported the microwave assisted Michael reaction for the synthesis of 1,3-diphenyl-3-[(pyridine-2-yl)-amino]prop-2-ene-1-one. The mixture of 2-amino pyridine and 1,3-diphenyl prop-2-en-1-one (chalcone) in ethanol upon microwave mediated heating (300 W, 30 min) produced 1,3-diphenyl-3-[(pyridine-2-yl)-amino]prop-2-ene-1-one (90%).



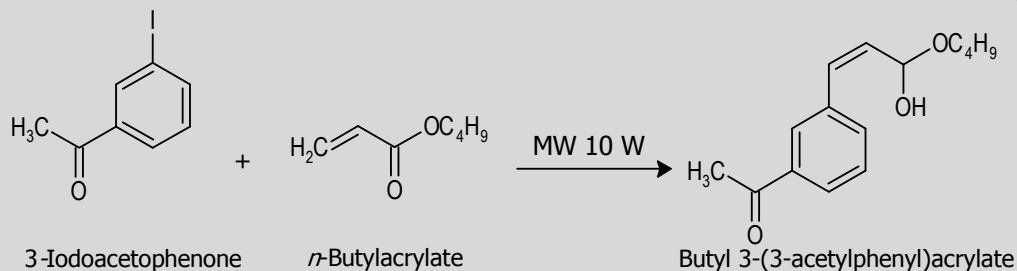
8) Microwave-assisted Mannich reaction

The reaction between amine (1°, 2°, ammonia) and enolizable carbonyl compound (formaldehyde, methanal) produces β -amino carbonyl compound. This reaction is known as Mannich reaction. Aljohani et al (2019) reported the microwave assisted Mannich reaction for the synthesis of 1-{3-[(diethylamino)-methyl]-4-hydroxyphenyl}-ethan-1-one. The mixture of 4-hydroxybenzaldehyde, formaldehyde and diethylamine upon microwave heating (300 W, 15 min) produced 1-{3-[(diethylamino)-methyl]-4-hydroxyphenyl}-ethan-1-one (77%)



9) Microwave-assisted Heck reaction (Mizoroki-Heck reaction)

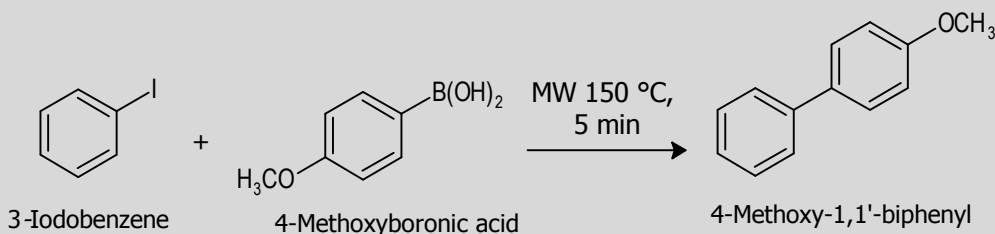
The palladium catalysed cross-coupling reaction between alkenes and aryl (or vinyl) halides (or triflates) in presence of base to generate substituted alkenes is known as Heck reaction (one step synthesis of olifines). Ichikawa et al (2018) reported the Heck reaction for the synthesis of several alkenes. The cross-coupling reaction between the 3-iodoacetophenone and *n*-butylacrylate using tributylamine as a base catalyst and *N,N*-dimethylacetamide as a solvent under microwave heating (10 W) in flow chemistry principle generated butyl-3(3-acetyphenyl)acrylate (93%).



Ref: *Tetrahedron* 2018, 74, 1810-1816

10) Microwave-assisted Suzuki reaction (Suzuki-Miyaura reaction)

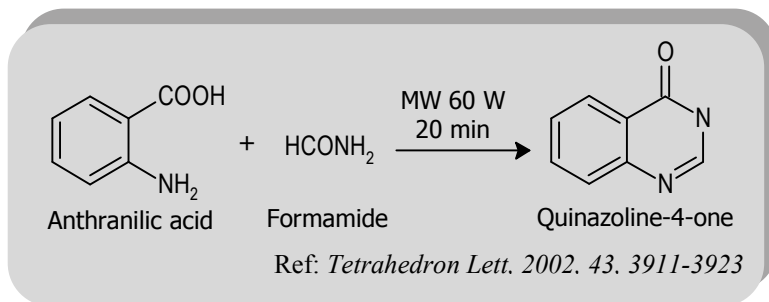
The palladium catalysed cross-coupling reaction between aryl (or vinyl) boronic acids with aryl (or vinyl) halide (or triflates) to generate alkenes, styrenes, biphenyls is known as Suzuki reaction. Dhara et al (2019) reported the Suzuki reaction for the synthesis of biphenyl compounds. The cross-coupling reaction between the iodobenzene and 4-methoxyboronic acid using palladium nanoparticles and under microwave heating (150 °C, 5 min) generated 4-methoxy-1,1'-biphenyl compound (95%).



Ref: *Synth Commun*, 2019, 49(6), 859-868.

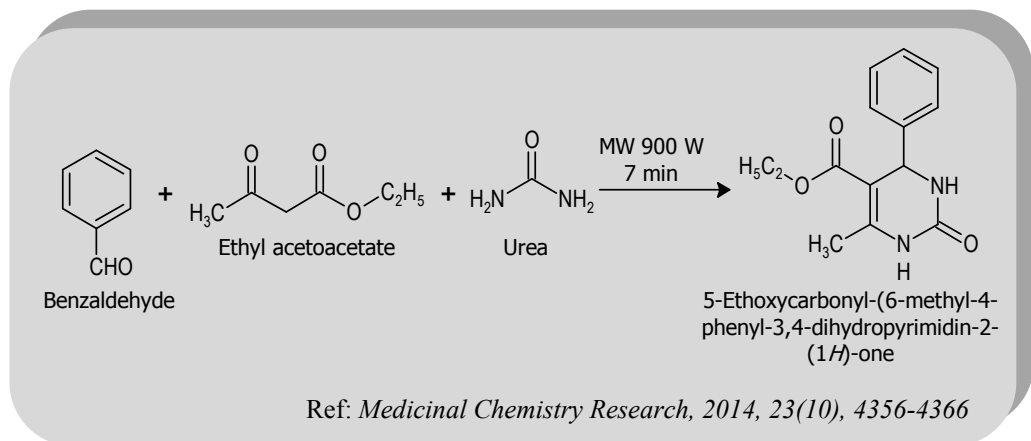
11) Microwave-assisted Niementowski cyclocondensation

The cyclocondensation reaction between anthranilic acid and amides generate quinazolin-4-ones. This reaction is known as Niementowski cyclocondensation. Alexandre et al (2002) reported the condensation of anthranilic acid and formamide under microwave irradiation (60 W, 20 min) to generate quinazolin-4-one (90%).



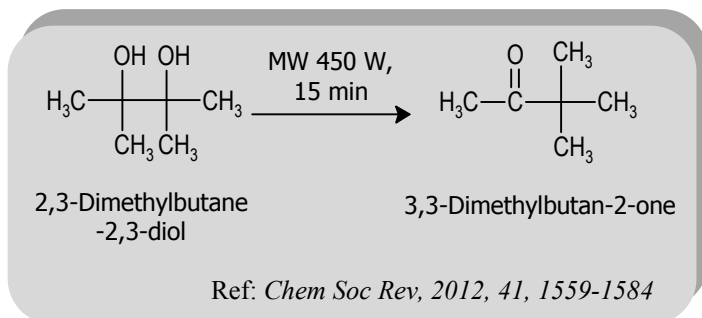
12) Microwave-assisted Biginelli reaction

A one pot condensation of aryl aldehyde, β -ketoester and urea (or thiourea) in acid catalysed reaction produces 3,4-dihydropyrimidine-1-ones (or 1-thiones). This reaction is known as Biginelli reaction. Jeti et al (2014) reported the synthesis of 3,4-dihydropyrimidine-1-ones (or 1-thiones) derivatives using microwave heating. The condensation of benzaldehyde, ethyl acetoacetate and urea under silica sulphuric acid catalysed microwave irradiation (900 W, 7 min) produced 5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (95%).

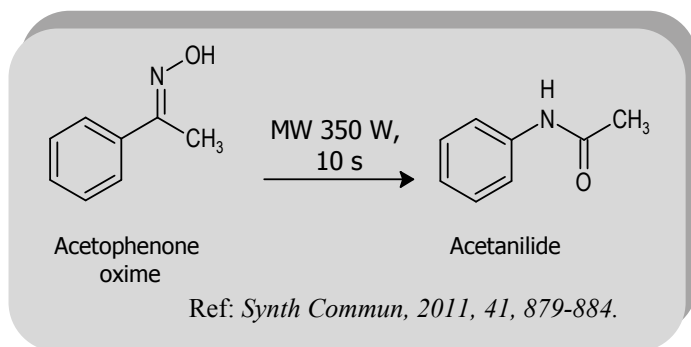


13) Microwave-assisted Pinacol-Pinacolone rearrangement

The chemical conversion of 1,2-diols into carbonyl compounds through 1,2-migration reactions are known as Pinacol-Pinacolone rearrangement. Gutierrez et al (1989) reported the chemical conversion 2,3-dimethyl-butane-2, 3-diol (gem-diols, pinacol) into 3,3-dimethyl butan-2-one (pinacolone) using Al (III)-Monmorillonite K10 clay under microwave irradiation (450 W, 15 min). The reaction produces excellent yield (99%).

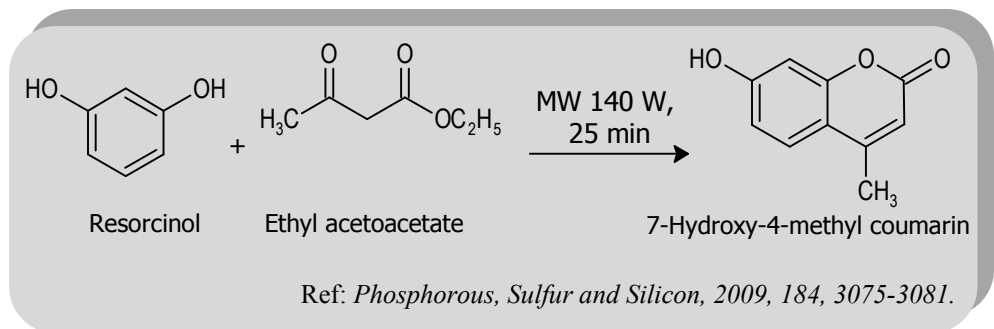
**14) Microwave-assisted Beckmann Oxime rearrangement**

The acid catalysed chemical conversion of oximes into amide (e.g. acetanilide) through selective migration of one group (rearrangement) is known as Beckmann oxime rearrangement reaction. Sugamoto et al (2011) reported the microwave assisted (350 W, 10 s) chemical conversion of acetophenone oxime into acetanilide (amide; 89%). This reaction is catalysed by the use of indium triflate and [Bdimim][PF₆].



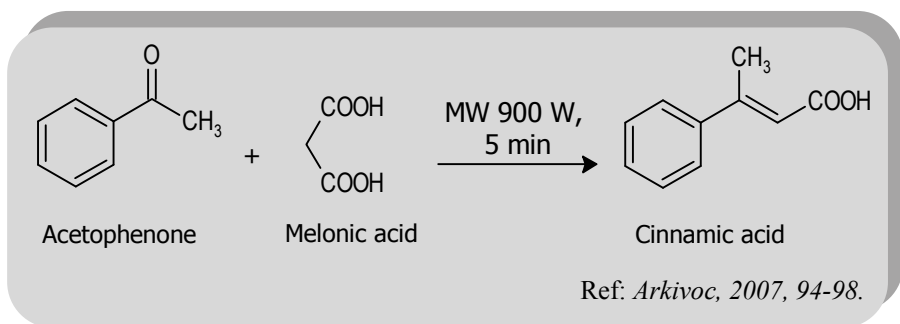
15) Microwave-assisted Pechmann reaction

The acid catalysed condensation of phenols with carboxylic acid or esters containing β -carbonyl functionality generates coumarins. This reaction is known as Pechmann reaction. Valizadeh et al (2009) reported the condensation of resorcinol and ethyl acetoacetate under microwave irradiation (140 W, 25 min) to generate 7-hydroxy-4-methylcoumarin (85%). This reaction utilized imidazolium dihydrogenphosphate as a catalyst.



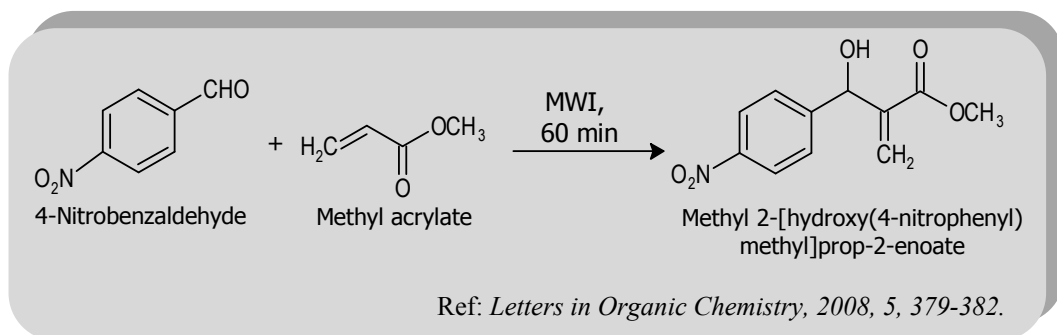
16) Microwave-assisted Knoevenagel condensation

The base (e.g. piperidine) catalysed condensation of active hydrogen containing compound with carbonyl compound is known as Knoevenagel condensation. In general, this reaction produces α , β -unsaturated ketone (conjugated enone). Gupta et al (2007) reported the microwave assisted synthesis of cinnamic acid through Knoevenagel condensation. The condensation of benzaldehyde and melonic acid in the presence of TBAB and potassium carbonate under microwave irradiation (900 W, 5 min) produced cinnamic acid (85%).



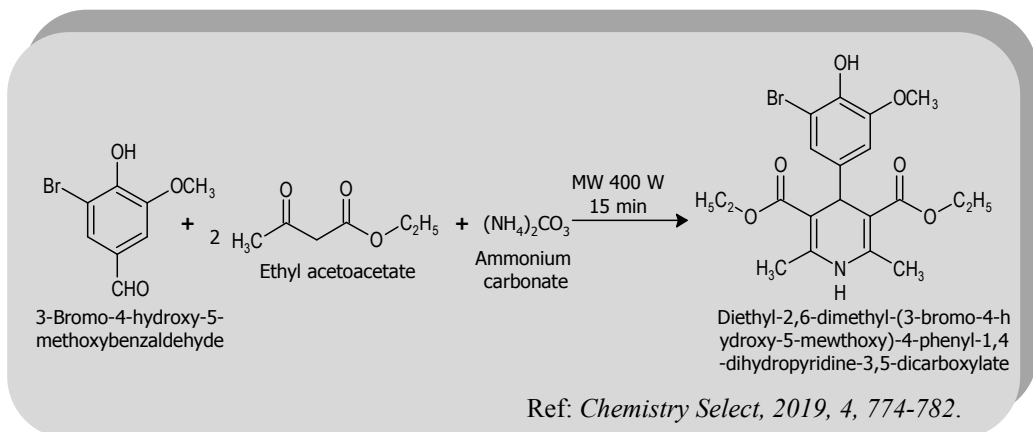
17) Microwave-assisted Baylis-Hilman reaction (Morita-Baylis-Hilman reaction)

The coupling reaction between an aldehyde (electrophile) and an activated alkene containing an electron withdrawing group in the presence of a Lewis base catalyst generates α -hydroxyalkylated compounds. This reaction is known as the Baylis-Hilman reaction. 1,4-diazabicyclo [2.2.2]octane (DABCO) is the most commonly used catalyst. De Souza et al (2008) reported the microwave assisted synthesis of methyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate through the Baylis-Hilman reaction. The DABCO catalyzed reaction between 4-nitrobenzaldehyde and methyl acrylate under microwave irradiation (60 min) produced methyl methyl 2-[hydroxy(4-nitrophenyl)methyl]prop-2-enoate (90%).



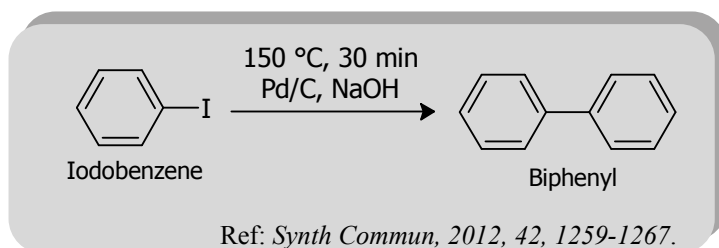
18) Microwave-assisted Hantzsch 1,4-dihydropyridine synthesis

The condensation of an aryl aldehyde, β -ketoester, and ammonia (amines) in an acid-catalyzed reaction produces 1,4-dihydropyridines. This reaction is known as Hantzsch 1,4-dihydropyridine synthesis. Maru et al (2019) reported the synthesis of 1,4-dihydropyridine. The microwave-assisted (400 W, 15 min) catalyst-free cyclocondensation of 3-bromo-4-hydroxy-5-methoxybenzaldehyde, ethyl acetoacetate, and ammonium carbonate generated the 1,4-dihydropyridine (97%).



19) Microwave-assisted Ullman reaction

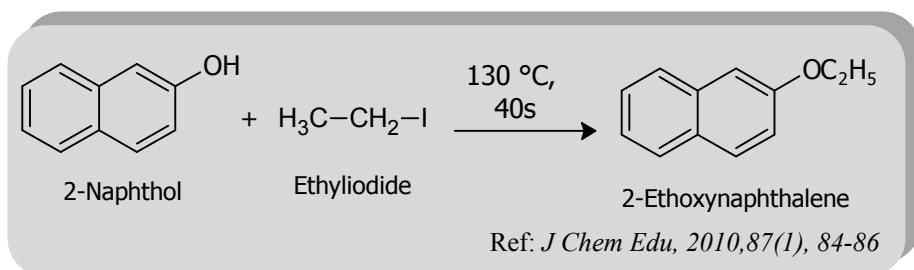
The copper metal catalysed coupling reaction between two molecules of aryl halides to form biaryl compound is known as Ullman reaction. Gadda et al (2012) reported the microwave assisted synthesis of biphenyl compound. Gadda et al (2012) reported the microwave assisted synthesis biphenyl compound. The coupling reaction between two molecules of iodobenzene using Pd/C and sodium hydroxide base under microwave irradiation (150 °C, 30 min) generated biphenyl compound (97%).



20) Microwave-assisted Williamsons ether synthesis

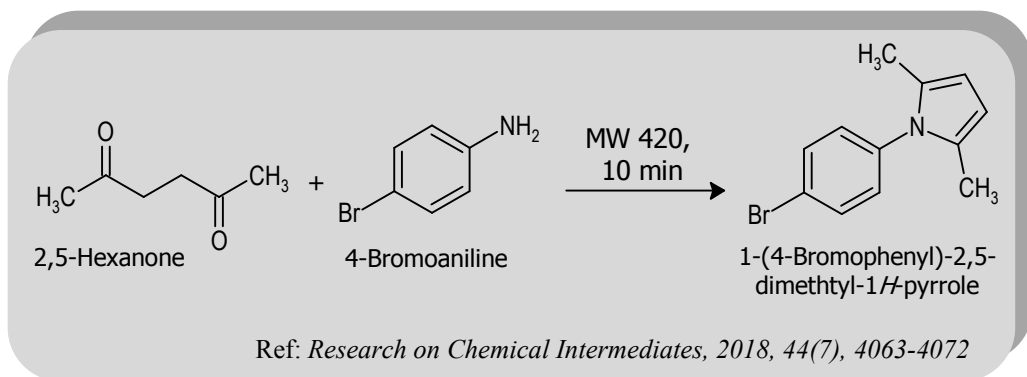
The reaction between alkoxide ion (nucleophile) and alkyl halide and generates ether through halide ion displacement ($\text{S}_{\text{N}}2$ reaction). This reaction is known as Williamsons ether synthesis. Baar et al (2010) reported the microwave assisted

synthesis of 2-ethoxynaphthalene. The reaction between potassium 2-naphtholate and ethyl iodide in methanol under microwave irradiation (130 °C, 40s) produced 2-ethoxynaphthalene (47%).



21) Microwave-assisted Paal-Knorr pyrrole synthesis

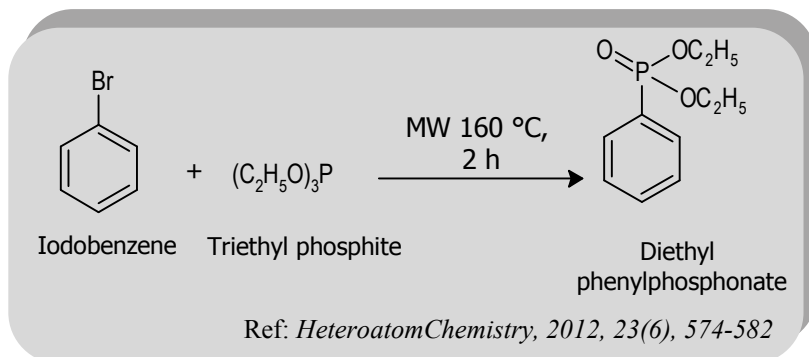
The generation of pyrrole derivatives from 1,4-carbonyl compounds and ammonia (or primary amines) in acid catalysed reaction is known as Paal-Knorr pyrrole synthesis. Aghpoor et al (2018) reported the calcium chloride catalysed microwave assisted synthesis of *N*-substituted pyrroles. The reaction between 2,5-hexanone and 4-bromoaniline under microwave irradiation (420 W, 10 min) produced 1-(4-bromophenyl)-2,4-dimethyl-pyrrole (100%).



22) Microwave-assisted Arbuzov reaction (Michaelis-Arbuzov reaction)

The reaction between a trialkylphosphite (trivalent) and an alkyl halide produces a phosphonate (pentavalent). This reaction is known as Arbuzov reaction. Heglivich et al (2012) reported the nickel chloride catalysed synthesis

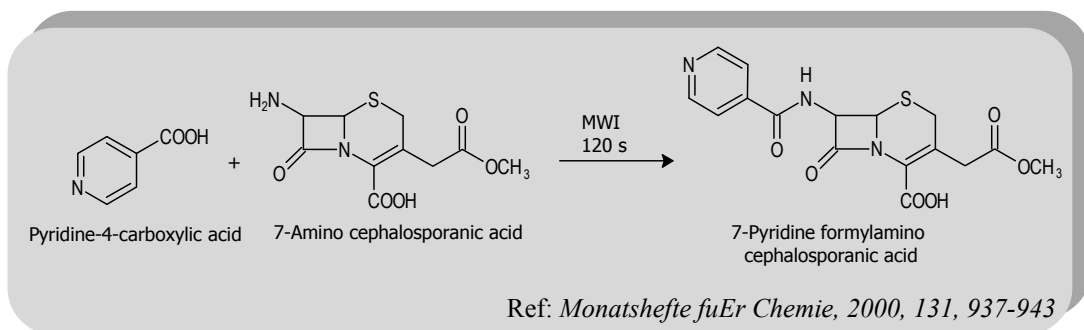
of diethyl phenylphosphonate (90%) by the reaction between the bromobenzene and triethylphosphite under microwave irradiation (160 °C, 2 h).



Important microwave assisted drug synthesis

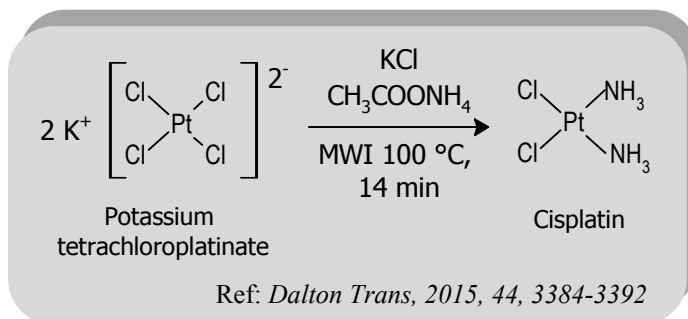
1) Microwave-assisted synthesis of cephalosporin derivatives

Cephalosporins are broad spectrum antibacterial agents which produce low toxicity. Kidwai et al (2000) reported the synthesis of 7-aminosubstituted cephalosporinic acid derivatives through microwave assisted reaction. The reaction between 7-amino cephalosporanic acid and 4-pyridine carboxylic acid under microwave irradiation (120 s) produced 7-pyridine formylamino cephalosporinic acid (92%).



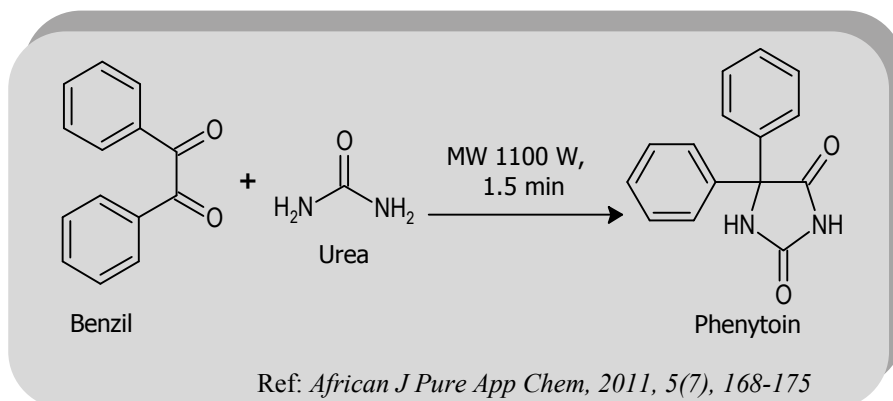
2) Microwave-assisted synthesis of cisplatin

Cisplatin (cisplatinum) is chemically *cis*-diamminedichloroplatinum. It is used in the treatment of bladder, lung, ovarian and testicular cancers. Petruzzella et al (2015) reported the microwave assisted synthesis for the cisplatin. The reaction between potassium tetrachloroplatinate, potassium chloride and ammonium acetate under microwave irradiation (100 °C, 14 min) produced cisplatin (47%).



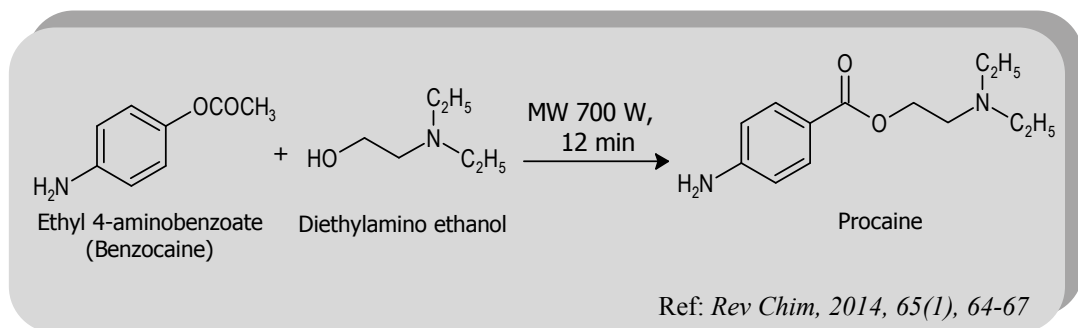
3) Microwave-assisted synthesis of phenytoin

Phenytoin is chemically 5,5-diphenylhydantoin. It is useful in the treatment of wide variety of seizure disorders. Gbaguidi et al (2011) reported the microwave assisted synthesis of phenytoin. The mixture of benzil, urea and potassium hydroxide in dimethylsulphoxide upon microwave irradiation (1100 W, 1.5 min) produced phenytoin (87%).



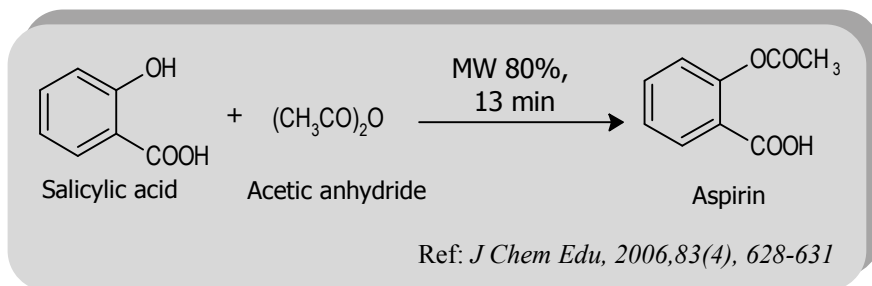
4) Microwave-assisted synthesis of procaine

Procaine is chemically an ester of 4-aminobenzoic acid. It is useful in inducing local anaesthesia. Noditi et al (2014) reported the synthesis of procaine through microwave irradiation. The reaction between ethyl 4-aminobenzoate (benzocaine) in sodium ethoxide and 2-(diethylamino)ethanol upon microwave heating (700 W, 12 min) produced procaine (86%).



5) Microwave-assisted synthesis of aspirin

Aspirin is chemically acetylsalicylic acid. It is used as an analgesic, antipyretic, antiplatelet and anti-inflammatory agent. Montes et al (2006) reported the solvent free synthesis of aspirin using microwave heating. The acetylation reaction between the salicylic acid and acetic anhydride upon microwave irradiation (80% MWI, 13 min) offered aspirin (97%).



Optimal Conditions for Microwave-Assisted Organic Synthesis

Microwave-assisted reactions, in comparison with prolonged thermal conventional heatings are much-faster (requires fewer minutes) and yields high quality products.

Similar to conventional organic reactions, the microwave reactions also demands the reaction optimization. The parameters namely solvent, power, temperature, reaction time, etc need to be optimized for the efficient reactions. The parameters also include the reactant stoichiometry, and catalyst concentration. In order to utilize the full benefits of microwave heating, the following sections need to be done and conditions need to be maintained.

1) Solvent: The solvents used in microwave reactions should possess dielectric heating property. Dielectric heating ensures the conversion of electromagnetic energy into efficient heating. The ability of the solvent dielectric property is indicated by $\tan \delta$. The solvents with high $\tan \delta$ provide rapid heating. However the solvent with low $\tan \delta$ also used to some extent in microwave heating depending on necessity of reaction conditions can be utilized (Table 2).

Table 2 Microwave solvents with dielectric constant values

High $\tan \delta$ (>0.5)		Medium $\tan \delta$ (0.1- 0.5)		Low $\tan \delta$ (<0.1)	
Ethylene glycol	1.35	2-Butanol	0.45	Chloroform	0.09
Ethanol	0.94	Dichlorobenzene	0.28	Acetonitrile	0.06
DMSO	0.83	N-Methyl-2-pyrrolidone	0.28	Ethylacetate	0.06
2-Propanol	0.80	Acetic acid	0.17	Acetone	0.05
Formic acid	0.72	DMF	0.16	THF	0.05
Methanol	0.70	Dichloroethane	0.13	DCM	0.04
Nitrobenzene	0.59	Water	0.12	Toluene	0.04
1-Butanol	0.57	Chlorobenzene	0.10	Hexane	0.02

- Polar solvents (e.g. methanol, ethanol) are very suitable for microwave reactions (heating). The dielectric properties of ionic liquids make them highly suitable for use as solvents or additives in microwave-assisted organic synthesis.
- Non-polar solvents such as toluene, dioxane, THF also can be used, if other components in the reaction mixture respond to microwave energy.
- Low boiling point solvents (e.g. methanol, dichloromethane and acetone) develops pressure in the vessel, hence offers lower reaction temperatures.

2) Reaction phase: Microwave reactions can be performed in solution, solid, solvent free (dry) and polymer supported medium. Microwave reactions are beneficial under solvent free conditions. This dry reaction (neat) offers several benefits. Mainly it reduces the explosive risks associated with the solution phase reactions. This kind of reaction conditions offer the microwave induction for the reactants and reagents, hence promotes the rate of reaction (efficient).

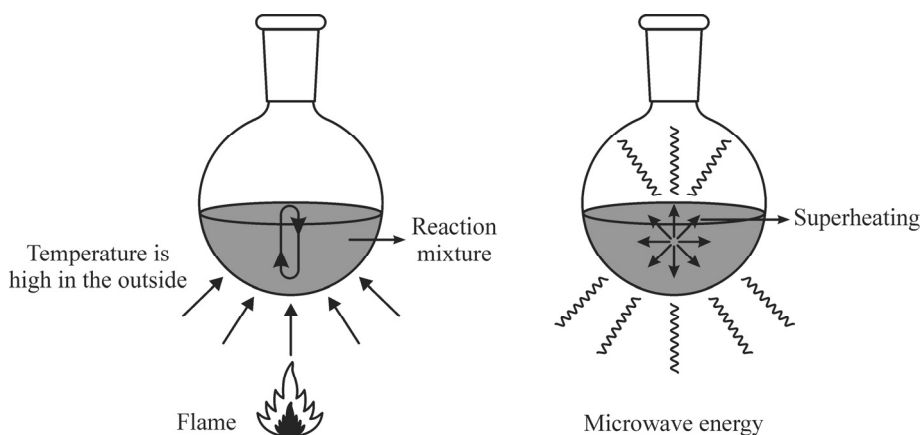
Inert atmosphere: The reactions with sensitivity for oxygen and moisture requires inert gas environment. Purified argon and liquid nitrogen are the most common inert gases used in the organic reactions. But, microwave reactions do not require such conditions. The microwave reaction vessel can be flushed (washed) with the inert gas, if it is necessary.

3) Power (temperature): Microwave power has direct influence on the reaction progress and rate of reaction. The exothermic nature of the reaction decides the power requirement. Hence, chemical reactions like dehydration require high power. In general, different instruments use different magnetron and their capacity slightly differs. This in turn decides the power levels to be set for given reaction. The most general power set up is given in the Table 3.

Table 3 Microwave power levels

Power	Temperature	
	in degree Celsius (°C)	in Watts
90 - 100	220 - 260	900 (100%)
80	190 - 220	600 (67%)
70	175 -190	
50 - 60	150 - 175	450 (50%)
30 - 40	110 - 150	300 (33%)
20	90 -110	180 (20%)
10	65 -90	100 (11%)

Microwave heating through the super heating property enhances the reactivity and product purity (yield). Super heating refers to the ability of solvents to boil above their boiling points. Microwaves also avoid the surface heating and, over heating of the specific components. In other words, microwave offers the uniform heating to the mixture causes molecular friction and facilitates the reaction rates.



Intermittent cooling: This is very important for the exothermic reactions. Intermittent cooling prevents the decomposition of reactants. In general, the low temperature reactions do not require intermittent cooling.

In microwave heating, the heat is generated inside the material. There is no direct contact between the energy source and the sample undergoing heating. This offers higher heating rate. In conventional heating, the outside of the vessel is heated first and it leads to thermal stress and cracking in the glassware.

- 4) **Reaction vessel:** The reaction vessels should be selected based on the quantities of the reactants (in grams, moles). Specially designed glassware are available for the microwave reactions. The design aspect also includes the pressure withstanding property (more than 30 bars). In general the capacity of the reaction vessel should be less than 50 ml. It can still lower depending upon the reactant concentration. Microwave transparent materials such as Teflon, polystyrene, pyrex or borosilicate glass are useful in the vessel fabrication. These materials absorb the radiation poorly and with stand at higher temperatures.
- 5) **Stirring:** To stir well is the universal instruction for chemical reactions. It is very essential for heterogeneous and solid phase reactions. Stirring the reaction mixture with the aid of in-built stirring enhances the heating process. In case of solvent less reactions (solid-phase), the mixture can be stirred using spatula during intermittent cooling
- 6) **Reaction time:** Microwave-assisted organic reactions are much-faster. Hence, most of the reactions can be completed in minutes (<15 minutes) and some of the reaction occur in seconds. The duration of the microwave heating can be optimized depending upon the reaction nature and instrument (model). The property of super heating in microwaves offers the multi fold increase in the reaction rate.
- 7) **Stoichiometry:** It refers to the quantitative relationship between the reactant and products. The relative quantities of the reactants influence the chemical

reactions. The quantities determine the equilibrium of the reactions. This is also applicable for microwave assisted reactions.

- Unimolecular reactions are independent of reactant concentration.
- Bi and trimolecular reactions depend on the reactant concentration. Higher concentrations enable the reaction rate.

Special Guidelines

a) General

- Special precautions are required for handling the reaction flasks.
 - Monitor through the glass window, alone.
 - Never remove the reaction vessel immediately after the microwave irradiation. Allow it to cool for few seconds.
- Monitor the progress of reactions through thin-layer chromatography (TLC)

b) To promote the reaction/drive the reaction to completion:

The difficult reactions can be facilitated by adopting the following:

- Increase the reaction duration
- Increase the reaction temperature (Watts)
- Increase the concentration of reactants and reagents
- Replacing the solvent (increasing the polarity, dipolar constants)
- Replacing the reagents with more microwave absorbing reagents

c) To prevent the decomposition of reactants and products

The difficult reactions can be facilitated by adopting the following:

- Lower the temperature (Watts)
- Shorten the reaction time
- Decrease the concentration of reactants and reagents
- Replacing the reagents with less microwave absorbing reagents

Microwave Instruments

a) Domestic microwave ovens



SAMSUNG



Whirlpool



IFB

b) Microwave synthesizers (specially designed for chemical synthesis)

