**Advanced Greener and Sustainable Methodologies for Organic Transformations**

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**1.1 Introduction**

In the modern progressive era chemist have responsibility to grow environment friendly synthetic routes to achieve their goals without environmental hazards. So, chemists are competing to achieve this under naming of ‘green’ chemical transformations. Achieving such goal is particularly called “Green Chemistry”. Now days in industries various hazardous chemicals are used which causes pollution this is hazardous to environment. The green chemistry is used to reduce carbon footprint and many hazardous by-products. Now intensely established routes in this field includes use of mild reaction conditions, lessening number of reaction steps, switching to less harmful reactants and reagents, use of solvent free processes, use of renewable energy sources, developing proficient purification and isolation processes in synthetic transformation etc.

**Green Chemistry**

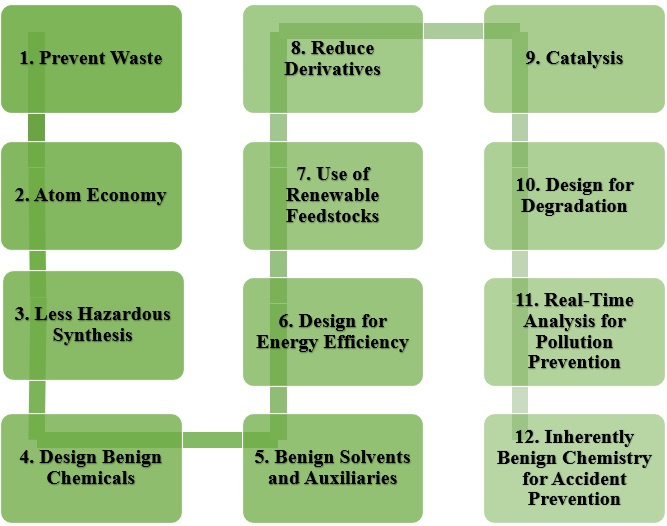
Green chemistry is type of chemistry which performs various chemical processes that reduce or eliminate the usage and generation of hazardous substances. It actually practices techniques that are environmentally friendly. The Green chemistry is applicable in whole sequence of chemical product involving its scheme, manufacturing, use and final disposal. In present era green chemistry plays crucial role in synthetic chemistry. The term green chemistry was first invented by Paul Anastas in 1998 and then John C. Warner set up principles to practice under green chemistry that worldwide known as twelve principals of green chemistry [1], [2].

Nowadays green chemistry works powerful tool and it open up new doors for researchers to think new reaction conditions that have less impact on environment. Considering these new unconventional trends are in progression.

**Need of Green Chemistry**

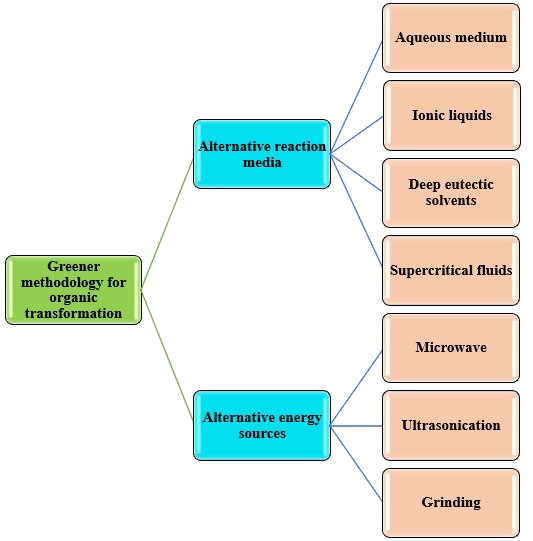
In many ways human impact on the physical environment that triggered lots of pollution that mainly comprise atmosphere change, poor air quality, non-potable water and soil erosion. In that utilization of chemistry is everywhere which acquired principal position for such issue. So, in emerging era use novel compounds and processes had grown up by the researchers that plays vital role to control demolition of environment. Now, researchers adopted various concepts of green chemistry for protection of environment without affecting advancement of chemistry. The fundamental ideas and strategies for green novel techniques based on “Twelve Principles of Green Chemistry” that put forth by Paul Anastas and John C. Warner in 1998.

Thus, to conserve the environment the researchers have no other option than adopting the concept of sustainable development and green chemistry so for that purpose that advancement of chemistry and protection of environment can go on parallel to each other [3], [4]. To analyse sustainability in practises and the involvement of sustainable green approaches in research, evolution, and manufacturing, academic policies have to involvement in green chemistry principles and pointers of sustainability [5], [6]. These principles are listed in following figure 1.1.



**Figure 1.1 12 principles of Green Chemistry**

**Greener methodologies for organic transformations:**



**Figure 1.2 Greener methodologies for Organic Transformations**

**1.2 Aqueous medium**

The water is a desirable medium for various organic synthesis processes. Multi-component reactions (MCRs) carried out in aqueous media enhance the productivity of multi-component reactions as well as save the ecology from hazardous solvents, which would achieve the green chemistry challenge. The use of water as a solvent is more advantageous because it is abundantly available, secure, inexpensive, inoffensive, noncorrosive, nonflammable, and ecologically benignant; alternatively, it is an eco-compatible "green dissolver".

Aqueous medium has a wide spectrum of applications in numerous areas involving supramolecular structures [7], interactions between protein molecules [8], etc. In recent years different groups working on aqueous mediated synthesis so they observed that water could catalyse chemical transformations through the hydrogen bonding with substrates [9]. Breslow’s group carried out Diels-Alder synthesis in water and got excellent results because water accelerates the reaction by forming hydrophobic interactions with non-polar groups [10]. Although organic preparations in aqueous media are very few due to the sparingly or incompletely soluble nature of the many organic composites. An interesting study to achieve aqueous solubilities of substrates is the utility of amphiphiles, including hydrotropes and surfactants.

**1.2.1 Hydrotropes**

Hydrotropes are immensely aqueous-solvable, surface-active organic salts that boost the solubilities of operationally unsolvable or sparely soluble organic composites in aqueous medium [11]. In 1916, *Carl Neuberg* was first time invented the term “hydrotropes” for surface-active organic salt [12]. As reported by Neuberg, “the phenomena of accelerating the solubilities of unsolvable organic molecules in water by a third ingredient or additive are referred to as hydrotropism or hydrotropy” [13]. Neuberg furthermore recorded environmentally friendly character of various hydrotropes as a result of their basic nature and the potential there within. The salts of different organic constituents such as benzoic, benzyl sulfonic, 1-naphthyl, thiophene carboxylic, 2-furoic, and phenylacetic acid derivatives, as well as few of aromatic fatty acids, are hydrotropic substances. The concept hydrotropes comes from the word hydro means water and tropes means something other. Hydrotropic salts decrease the interfacial surface tension at a particular concentration, mentioned as the *Minimum Hydrotropic Concentration* (MHC) [14]–[18]. Hydrotropes have similarities as well as differences to surfactants in the form of molecular structure and association **(Figure 1.3)**. Hydrotropes contain the hydrophilic and hydrophobic groups; however, hydrophobic groups are incapable to form micelle as result of its very small structural arrangement in contrast with a hydrophobic group of surfactants. The diversity between surfactant and hydrotrope is substantially higher Hydrophile/Lipophile balancing (HLB). Hydrotrope generates stacks type aggregates in an aqueous medium which creates associated structures that are accountable for hydrotropic behaviour. The distinctive aggregation of hydrotrope is the source of the dissolution process of a moderately soluble hydrophobic compound in an aqueous medium, which is analogous to the micellization process. Saleh and co-workers considered the importance of planer structure for the association and hydrotropic effect.

**Figure 1.3. Difference between Hydrotrope and Surfactant.**

The capacity of hydrotrope to enhance the solvability of organic material in aqueous media is highest whenever the hydrotrope concentration is enough to stimulate the creation of associated structure and maintain the solubility same after that point. Surfactant carry out greatest solubility at critical micelle concentration (CMC) while hydrotrope shows highest solubility at minimum hydrotrope concentration (MHC). Hydrotropes are excellent in solubilising organic compounds in aqueous media and more exclusive than surfactant. Hydrotrope reduces the surface tension of water and at particular point surface tension becomes constant at that point self-aggregation of hydrotrope occurs. Several theories and practical approaches are used to explain the mechanistic pathway of hydrotrope in organic transformation. The reported mechanism of hydrotrope in organic transformation are show by following figure **(Figure 1.4)** [19]–[23].



**Figure 1.4 Proposed mechanism of Hydrotropes**

Friberg and Blute mentioned the historical growth of hydrotrope and its involvement in industrial applications [24]. Hydrotropes are mostly utilized in cleaning agent, medical treatment such drug dissolutions [25]. The different fields take advantages of hydrotropes including shampoo, creams, lotion and printing press [26].

Sodium xylene sulfonate maximizes the efficiency of water to solubilise other organic substances. Johnson and Johnson firm put to use hydrotrope sodium xylene sulfonate in cosmetics mainly in shampoos. Sodium toluene sulfonate be applied as hydrotrope and viscosity modifying agent in detergent formulations which reduces the viscosity of chain of Linear Alkyl Benzene Sulfonic Acids (L.A.B.S.).

**Application of Hydrotropes in organic transformation**

In supplement to industrial application hydrotropes also take part in organic transformation as a reaction medium, for example preparation of quinolines [27]. Hydrotropes also enhance the speed of multiphase synthesis which results in alkaline hydrolysis of aromatic esters [28], [29].

Bhushan M. Khadilkar and Virendra R. Madyar [30] reported synthesis of clinically important dihydropyridine in presence of aq. 50% sodium butyl monoglycol sulphate (NaBMGS) under microwave irradiation **(Scheme 1.1)**.



**Scheme 1.1**

Sharmad J. Chandratre and Zoeb A. Filmwala [31] developed synthesis quinolines in aqueous hydrotropic medium. Condensation between 2-amino ketones with aldehydes or ketones in the aqueous hydrotropic solution of sodium xylene sulphonate (SXS) afford the desired quinolines derivatives **(Scheme 1.2)**.



**Scheme 1.2**

Synthesis of 5-arylidine barbituric acid derivatives in aqueous hydrotropic medium reported by Santosh Kamble and co-workers [17]. They use an efficient Knoevenagel reaction of barbituric acid with different substituted aromatic aldehydes in 50 % aq. NaPTS solution at room temperature providing the respective 5-arylidine barbituric acid derivatives **(Scheme 1.3)**.



**Scheme 1.3**

Kamble et al. [32] uses same hydrotrope for the synthesis of 1,8-dioxooctahydroxanthenes **(Scheme 1.4)**.



**Scheme 1.4**

In the absence of ligand Suzuki-Miyaura and without base Heck-Matsuda cross-coupling schemes developed by Sanjay N. Jadhav and co-workers [33]. In this protocol, they developed a new catalyst by palladium grafting on activated carbon (Pd/C) in an aqueous hydrotropic environment **(Scheme 1.5)**.

 **Scheme 1.5**

**1.2.2 Surfactant**

A surfactant is a combination of surface-active agents or compounds having surface-active properties that are called surfactants. Surfactants having a hydrophilic head (polar molecule) and a hydrophobic tail (non-polar molecule), such kind of structure with two different functions, are called amphiphilic substances. Surfactants are entities that generate self-assembled molecular clusters called micelles in a solution as well as interfacial adsorption, which are characteristics properties of a surfactant [34] **(Figure 1.5)**. That has different dissolution characteristics in similar solutes. Hydrophobic group is alkyl chain with 8-12 carbons atoms that does not show affinity toward water in aqueous system but in lipid system they are called as lipophilic groups. The hydrophilic group they are functional group such as RCOO-, RSO3-, ROSO3-, R4N+ etc.has affinity toward water. Thus, hydrophobic groups of surfactants attract nonpolar environment while hydrophilic groups attract with polar environment if aqueous system during aggregation. This is a characteristic property of surfactant, due to which it becomes a surface active and able to decrease the surface/ interfacial tension by aggregating at interface of two immiscible liquids which results into maximise the solubility, mobility and biodegradation of sparingly soluble organic substance. At a certain concentration, surfactant molecules form the micelle that concentration is known as critical micelle concentration (CMC).



**Figure 1.5: Structure of micelle formation**

**Classification of surfactant:**

Classification of surfactant based on charge as anionic, non-ionic, cationic, amphoteric, and also on their source of availability as a biosurfactant **(Figure 1.6)**.

**Figure 1.6 Classification of surfactant**

**I) Chemical or synthetic surfactant:**

**1.2.1 Anionic Surfactant:**

In these surfactants hydrophilic group dissociate into amphiphilic anions and alkaline cations (Na+, K+) or a quaternary ammonium cation when dissolved in aqueous system. Anionic surfactant is mostly used in industry as a detergent such as soap. The hydrophilic head groups are carboxylate, sulfonate, sulphate and alkyl chain of hydrocarbons C12 to C18 acts as hydrophobic.

*Examples:* Sodium dodecyl sulphate, Sodium dodecylbenzene sulfonate, Dioctyl sodium sulfosuccinate, Sodium stearate, petroleum sulfonates, lignin sulfonates, ester sulfonates etc **(Figure 1.7)**.



**Figure 1.7 Examples of anionic surfactant**

**1.2.2 Cationic Surfactant:**

**In the aqueous system, cationic surfactant dissociates as an amphiphilic cation and halogen as an anion.** These types of surfactants correspond to large proportions of nitrogen compounds such as fatty amine salts, natural fatty acids, and quaternary ammonium compounds. These surfactants are mostly used for surface modification as softeners in hair conditioners, but they also have bactericidal properties as antibacterial in hygiene formulations.

*Examples:* Hexadecyl trimethyl ammonium chloride, Hexadecyl pyridinium chloride, Benzethonium chloride **(Figure 1.8)**.



**Figure 1.8 Examples of cationic surfactant**

**1.2.3 Amphoteric or Zwitterionic Surfactant:**

Amphoteric surfactant exhibits dissociation of both cationic and anionic functional groups in their polar hydrophilic portion often depending on the pH but amphoteric behaviour shows at intermediate pH and its application in cosmetic, personal care products due to which they are quite expensive. Alkyl amino acids, alkylbetains, alkylaminobetaines are common classes of amphoteric surfactants.

*Examples:* N-Dodecyl-N, N-dimethylglycinate, Dipalmitoylphosphatidylcholine (Lecithin), Cocamidopropyl betaine **(Figure 1.9)**.



**Figure 1.9 Examples of amphoteric surfactant**

**1.2.4 Non-ionic surfactant:**

These type surfactants do not dissociate or ionizes in aqueous system due to their hydrophilic part has a non-dissociable functionality such as alcohol, phenol, ether, ester or amide. The hydrophilic part carries noncharged polyethylene oxide (PEO) or polyglycerin chains. There important application in drugs, cosmetic as personal care products.

*Examples*: Polyoxyethylene 20 cetyl ether (Brij 58), Triton X-100, Tween 20 etc **(Figure 1.10)**.



**Figure 1.10 Examples of non-ionic surfactant**

**II) Bio-surfactant-microbial surfactant:**

Surface active biomolecules are produced from microorganisms, plants and animal materials known as biosurfactant. These types of surfactants are anionic or neutral in behaviour due to hydrophilic groups are carbohydrate, amino acid, peptide, phosphate etc. while hydrocarbon chain is hydrophobic tail. Biosurfactants are better than synthetic or chemical surfactants owing to their lower toxicity, easy biodegradability, specific activity, effectiveness at extreme temperatures as well as at pH, lower surface tension, and lower interfacial tension.

**Classification of biosurfactant:** Classification of biosurfactant on the basis of their chemical composition and source of origin.

**Based on chemical composition**

**1. Glycolipids:** Glycolipids are the most common type of biosurfactant found in the environment, consisting of a combination of carbohydrates and long-chain aliphatic or hydroxyl acids linked by an ester or ether portion. Ex. Rhamnolipids, Trehalose lipids, Sophorolipids **(Figure 1.11)**.

**Figure 1.11 Examples of glycolipids**

**2. Lipopeptides and Lipoprotiens:** In lipopeptides lipid acts as hydrophobic head and peptide is hydrophilic tail that lipid is attached to the polypeptide chain.Along with antimicrobial properties they are also excellent surfactant.

*Examples.* Surfactin, Lichenysin, Viscosin **(Figure 1.12)**.



**Figure 1.12 Structure of Surfactin**

**3. Fatty acids, phospholipids, and neutral lipids:** These types of surfactants are produced by several bacteria and yeast during the microbial oxidation of n-alkanes. The equilibrium between hydrophilic and lipophilic groups is directly proportional to the length of the hydrocarbon chain in their structural frameworks. Ex. Acinetobacter sp., corynomicolic acids.

**4. Polymeric Microbial Surfactants:** Most commonly used polymeric microbial surfactant are polymeric heterosaccharides containing proteins. The researcher interested in studied of polymeric biosurfactants are emulsan, liposan, alasan and lipomannan. Ex. Acinetobacter calcoaceticus **(Figure 1.13)**.



**Figure 1.13 Structure of Acinetobacter calcoaceticus**

**5. Particulate biosurfactant:** The creation of microemulsion and the presence of extracellular membrane vesicles that partition hydrocarbons play significant roles in alkane intake by microbial cells. Ex. vesicles of Acinetobacter sp. strain HO1-N.

***Based on origin:***

**1. Microbially-based Surfactants:**

These surfactants are produced by variety of microorganisms or by microbial fermentation processes using cheaper agro-based materials. They are divided into two groups depending on molecular weight. First group contains low molecular weight surfactant such as glycolipids, lipopeptides and phospholipids shows effectiveness in reducing surface and interfacial tension. High molecular weight surfactant contains polysaccharides, proteins, lipopolysaccharides, lipoproteins or complex mixtures of these biopolymers which stabilizes newly created surfaces.

**2. Plant-based surfactant:**

In environmentally conscious days demand increases for the natural sourced surfactant. Plant derived surfactants are good source of biosurfactant. Saponin is excellent class of plant having characteristic surface-active properties due to those plants are rich in saponin class used as biosurfactant. Plant-based saponins are largely distributed in nature offering large potential replacement for the hazardous synthetic surfactant which exhibits excellent surface and biological activities. Biological activities include antimicrobial activity, antidiabetic activity, adjuvant potentials, anticancer activity, and others are reported. They can be extracted from various parts of plants such as roots, stem, leaves, bark, seeds and fruits. Commonly found dietary based saponins are legumes: soybeans, chickpeas, peanuts, sapindus mukorossi, *Accacia concinna* pods.

**3. Animal-based surfactant:**

Animal derived surfactant take important position in medical field. Commonly known biosurfactants obtained from animals includes the lecithin, gelatin, casein, wool fat, cholesterol, and wax. This type of surfactant also contains low molecular weight surfactant includes lecithin and high molecular weight surfactant as like gelatin. Egg yolk provides the natural surfactant lecithin, which contains zwitterionic phosphatidylethanolamine (PE, ~18.1 %) as well as phosphatidylcholine (PC, ~78.7 %). Refined egg lecithin is good intravenous nutrition and an excipient for drug delivery. The commercially available source for gelatin is bovine skin, as well as bones and pigskin, which are applied as a stabiliser, thicker, and texturizer in food along with non-food products. It is an inadequate source of protein surfactant yet shows excellent emulsifying qualities, which might be enhanced with enzyme-catalysed attachment of hydrophobic side chains. Different protein-based biosurfactants are available from animal sources of origin, like casein, egg albumin, bovine serum albumin, and human serum albumin. Bile acids as well as pulmonary surfactants are two physiologically significant animal-based surfactants. Clinical usage and preclinical animal research both point to the superiority of animal-derived surfactants over synthetic formulations.

**Applications of Surfactants:**

**Figure 1.15 Applications of Surfactant**

The implementation of biosurfactants as a green replacement for chemical surfactants in organic transformations has been successfully analysed by scientists in recent years. In these circumstances, aqueous as well as natural extracts of various fruits, plants, seeds, leaf and juice from fruit were selected as the source of biosurfactants, including *Sapindus trifoliatus* fruit, chickpea leaf extract, *Balanites roxburghii,* and pods of *Accacia concinna.* The aqueous extracts of these fruits have an acidic pH and high surface activity due to the presence of several saponins; therefore, they show catalytic activity in various synthesises. Saponins are plant-based surfactants that contain the amphiphilic moieties in which sugars are connected to either the sterol or triterpene nonpolar groups.

Santosh Pore et al. [35] prepared a novel green catalyst from the pericarp of Sapindus trifoliatus fruits in 2010 and applied it to aldimine synthesis. The different derivatives of aldimines prepared from aromatic aldehydes and amines were catalysed by the natural extract. They observed the aromatic ketones and amines did not produce ketimines under similar reaction environments, which denotes the chemoselective nature of the extract **(Scheme 1.6).**



**Scheme 1.6**

Madhuri Barge and Rajashri Salunkhe [36] develop a protocol for C–C bond formation in an aqueous extract of Balanites roxburghii fruit. An aqueous extract of balanites roxburghii fruit is utilised as a biosurfactant for Knoevenagel condensation of 1,3-indanedione with aryl aldehydes, which acts as a biogenic green acidic catalyst **(Scheme 1.7).**



**Scheme 1.7**

An ecologically and economically affordable preparation of aryl-hydrazones in an aqueous extract of Acacia pods, which is a natural surfactant-type catalyst developed by Hemant V. Chavan and co-workers [37] **(Scheme 1.8).**



**Scheme 1.8**

Seema P. Patil and co-workers [38] reported a greener and ecologically benign protocol for ligand free Pd-catalysed Mizoroki–Heck cross coupling reactions by using biosurfactant. The biosurfactant used in this study was prepared from the seeds of the pericarps (pods) of the Acacia concinna plant, which are soaked in water. The resulting extract contains saponin, which acts as a natural biosurfactant **(Scheme 1.9)**.



**Scheme 1.9**

Chickpea leaf exudates: a green brønsted acid type biosurfactant reported by Rupesh C. Patil et al. [39] for the synthesis of bis(indole)methane and bis(pyrazolyl)methane **(Scheme 1.10)**.



**Scheme 1.10**

**1.3 Ionic liquid in organic transformation:**

Ionic liquids (ILs) have fascinated the interest of researchers in the last decade, due to their particular properties [40], [41] [42] and their use in organic synthesis as a catalyst [43]–[45], catalysis [46]–[48], biocatalysts [49], [50], processes of nanomaterial synthesis [51], [52], polymerization reactions [53], [54], and electrochemistry [55]. Ionic liquids are polar and ionic in nature, couple with microwave irradiations very expeditiously, and are therefore the best solvent for organic reactions that are assisted by MW irradiations [56], [57]. Ionic liquids are considered as green reaction medium by chemists due to its remarkable characteristic properties including thermal-chemical stability, lower vapour pressure, recyclability, stable at high temperature in liquid state, non-combustible, easily solvates organic, inorganic and polymeric materials. Ionic liquids are molten organic salts composed of ions and exist in liquid electrolytes at temperature below 100oC. Ionic liquids are mostly organic cations by combined with inorganic anions creating crystalline moieties with less lattice energies enabling these salts to be in liquid state at or near room temperature. Ionic liquids are replacement for regular organic solvents those are harmful to the nature. The most commonly used ionic liquids are heterocyclic imidazolium, pyridonium, pyrazolium molecules in addition to another non-heterocyclic cations like as ammonium and phosphonium **(Figure 1.15)**.



**Fig. 1.15 Structures of cations and anions used in ILs synthesis.**

**Applications of ILs in organic transformation**

solvent-free synthesis of 4H-pyrans and 4H-pyrano-pyrazoles reported by Jitender M. Khurana et al. [58] in basic ionic liquid 1-butyl-3-methyl imidazolium hydroxide {[bmim]OH}. [bmim]OH is a reusable, cost effective, reduces the time, and enhances yield of reaction **(Scheme 1.11)**.

 **Scheme 1.11**

One pot synthesis of pyrazoles carried out by Manashjyoti Konwar et al. [59] at room temperature in ionic liquid. Ionic liquid prepared from transition metal which is magnetic and acts as catalyst therefore, such ionic liquids are known as task-specific ionic liquids (TSIL). For screening the reaction condition different metal-based ionic liquids are used such as [AlxCly]-, [FeCl4]-, [MnCl4]2- [CuCl4]2-, [NiCl4]2-, [PdCl4]2-, etc. but out if which only [FeCl4]- gives excellent result **(Scheme 1.12)**.



**Scheme 1.12**

Bronsted acidic-SO3H ionic liquid used by Shirin Safaei et al.[60] to synthesize pyrazoles derivatives in water. For the synthesis of pyrazoles the reaction between various 1,3-diketones and hydrazines or hydrazides in the presence of multi-SO3H brønsted ionic liquid at ambient temperature within five minutes produces regioselective derivatives of pyrazoles in excellent yield **(Scheme1.13)**.



**Scheme 1.13**

By grinding in the presence of water, Srivastava et al. [61] synthesize functionally diverse pyrazole moieties, which were catalysed in an ionic liquid. Preparation takes place between malononitrile, phenyl hydrazine, and diversified aldehydes in ionic liquid1-butyl-3-methyl imidazolium hydroxide [(Bim)OH] in aqueous media, producing the desired product in good to excellent yield without any by-product generation **(Scheme 1.14)**.

 **Scheme 1.14**

**1.4 Microwave assisted organic transformations (MAOT):**

Microwave irradiation is one of the prominent non-conventional as well as non-traditional energy resources whose usefulness in synthetic chemistry have increased considerably in recent years [62]. During the second world war, Randall and Booth at the university of Birmingham, as part of the development of RADAR, devised a device for creating fixed-frequency microwaves, the magnetron [63]. Initially, it was established that microwaves warmed up water; after that, microwaves were used in household and commercial devices for heating and cooking purposes, which started in the 1950s. Tappan introduced first kitchen microwave oven in 1955 but its domestic use increases during the 1970's and 1980, s. Then scientists wonder why it is only used for domestic purposes and begin using microwave ovens for synthesis in the laboratory [64], but both household as well as laboratory ovens operate at 2.45 GHz. The scale of electromagnetic spectra shows microwaves are placed between infrared radiation and radio waves **(Figure 1.16)**. Researcher first proposed the mechanisms of dielectric heating and search the significances of the microwave irradiation technique in the chemical synthesis.

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**Figure 1.16 Electromagnetic spectrum**

Selectivity is observed in the absorption of radiation and heating, such as when materials having high dielectric constant values have a tendency to consume microwave radiation, while less polar materials and highly ordered crystalline substances are inferior absorbers [65]. The microwaves transferred energy not only due to conduction but also due to dielectric loss. The affinity of a compound to come in contact with microwave heating is dependent on the dielectric properties, the dielectric loss factor (e"), and the dielectric constant (e'). Therefore, dielectric loss factor (e") indicates the effectiveness with which electromagnetic radiation is transformed into heat, while the dielectric constant (e') represents the efficiency of molecules to absorb microwaves. The ratio of tanδ = (e")/(e'), indicates the capability of these molecules to modify electromagnetic energy into heat at a given frequency and temperature. High values of dissipation factor(δ) of the sample means easy susceptibility to microwave energy [66]–[68]. Other important factors are ionic conduction, size, charge, conductivity of ions and their fundamental interaction with the solvent. In microwaves, heating starts from the inner side of the flask and radiates outside, in contrast to conventional heating, which initiate from the outside, and therefore microwave heating is less economical in terms of source energy used. Microwave radiation has some prominent microwave dielectric heating effects on organic reactions viz. thermal effect and non-thermal effect [69], [70]. Thermal effects are generated at the different temperatures which was due to microwave dielectric heating.

The aquatic emulsification and polymerization of butyl acrylate, acrylic acid, and methacrylic acid in the presence of pulsed electromagnetic radiation is the first documentated application of microwave irradiation in organic transformation [71]. The first successful application of microwave heating in organic transformation was made in 1986 by Gedye et al. [70] and Giguere et al. [72].  From the 19th to the 20th centuries, diverse organic reactions were successfully conducted in commercial as well as advanced microwave with a reduction in time and increasing yield.

**The microwave-assisted organic transformations have been carried out in two ways:**

1. Microwave assisted organic transformations in presence of solvents

2. Microwave assisted organic transformations without solvent

**1. Microwave assisted organic transformations in presence of solvents:**

To conduct the reaction under microwaves, choice of solvent depends on solubility of reagent in that solvent and whether the solvent which pairs efficiently with microwaves and functions as an energy-transferring medium.

Preparation of pyrazolo [1,5-a] pyrimidine demonstrated by Li Ming et al. [73] under MW irradiations. The reaction between enaminones and 5-amino-1H-pyrazoles in glacial acetic acid at 120oC, irradiates for 20 min under adjustable microwave range from 0 to 25 W gives good to excellent yield **(Scheme 1.15)**.

 **Scheme 1.15**

The greener protocol for the preparation of pyrazolo [3,4-b]quinolin-5-ones was proposed by Anastasiya Yu et al. [74] under microwave irradiations. It was multi-component reaction between 5-aminopyrazoles, aromatic aldehydes, and dimedone in hot-aqueous medium at 175οC (375W) within short period of time produces target compound in good yield **(Scheme 1.16)**.

 **Scheme 1.16**

The synthesis of 1,5 dihydropyrazolo[3′,4′:5,6] pyrano[3,4‑b]pyridines produced by Aaron T. Garrison et al. [75] under microwave irradiation. It was regioselective C−H arylation reaction catalysed by Pd(0) in between pyrazoles within five minute in the microwave generate 98% product **(Scheme 1.17)**.

**Scheme 1.18**

The new protocol for the synthesis of some novel pyrazole scaffolds was demonstrated by Sobhi M. Gomhal et al.[76] which are potent anticancer agents under controlled MW conditions. Multi-component condensation between acetyl pyrazole (a), dimethylformamide dimethylacetal (DMF–DMA) (b) and nitrile imine (c) in toluene under conventional heating as well as microwave irradiation at 150°C produces desired product. But time requirement is different, MW within 4-5 min. produces above 80% yield as compare to conventional heating that gives 60-70% yield in 10-15hr **(Scheme 1.19)**.

 **Scheme 1.20**

Preparation of tetrazolyl pyrazole amides proposed under microwaves by Jun Hu et al. [77]. They also study biological properties of tetrazole pyrazole amide which shows various remarkable biological activities such as, bactericidal, pesticidal, herbicidal and antimicrobial activities. Different molecules of tetrazolyl pyrazole were prepared by reacting various 3-methyl-1-phenyl-1H-pyrazole-5-carbonyl chlorides (a) and 1H-tetrazol-5-amine (b) under microwave irradiation at 400W (110oC) for 20 min produced desired product in 78-90% yield **(Scheme 1.21)**.

 **Scheme 1.21**

**2. Microwave assisted organic transformations without solvent:**

In these environmentally conscious days, the researchers develop solvent free procedures which involve simple workup, avoid toxic solvents, economically safe, clean and efficient.

A new methodology developed by Lilian Buriol et al. [78] develop for preparation of pyrazole derivatives under solvent-free-microwave irradiation conditions. In this synthesis they avoid use of organic solvent and conventional heating. To obtain 4,5-dihydro-1H-pyrazoles or pyrazoles there is cyclocondensation takes place between enones and hydrazine’s under MW irradiation under solvent free condition. They also perform same reaction by using domestic MW oven and also conventional heating but MW equipment for synthesis gives better yield as compare to others **(Scheme 1.22)**.

**Scheme 1.22**

Microwave assisted, preparation of pyrazoles derivatives developed by Kumkum Kumari et al. [79] under solvent free condition catalysed by [Sc(OTf)3]. Reaction mixture of phenyl hydrazine, aldehydes and ethyl acetoacetate is kept under microwave at 200W and 100οC within short period produces desired pyrazole molecules with good to excellent yield (74-92%) **(Scheme 1.23)**.

**Scheme 1.23**

The novel pyrazole and pyrazolo[3,4-d]pyridazine molecules synthesized by Mohamed F. Mady et al. [80] under microwaves. Synthetic talc was added in to the mixture of an enaminone derivative and hydrazonyl halides under microwaves and 98% -pyrazolo[3,4-d]pyridazine is obtained from pyrazole and hydrazine hydrate in ethanol which was irradiated by microwaves. Both preparations were carried out using different conditions such as conventional as well as MW heating but MW gives better result **(Scheme 1.24 and 1.25)**.



**Scheme 1.24**



**Scheme 1.25**

A new method under microwave conditions for the synthesis of 5-dihydro-1H-pyrazoles developed by Marcos A. P. Martins et al. [81] in absence of solvent. The desired product of 5-dihydro-1H-pyrazoles obtained by the reacting enones with methyl hydrazinocarboxylate in absence of solvent in microwave oven produces good to excellent yield (50–92%) **(Scheme 1.26)**.



**Scheme 1.26**

At microwave irradiation Buchi Reddy Vaddula et al. [82] synthesizes pyrazoles and diazepines in absence of catalyst and solvent. Pyrazole is obtained from condensation between hydrazine’s/hydrazides and 1,3-diketones in short period of time give excellent yield up to 99% which shows the full conversion of reactant in to desired product that eliminates generation of by products, reduce time, and energy **(Scheme 1.27)**.



**Scheme 1.27**

Advantages and disadvantages of microwave irradiations in organic synthesis is shows in following figure **(Figure 1.17).**

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**Figure 1.17 Advantages and disadvantages of MW irradiations**

**1.5 Organic Transformations Under Ultrasonic Irradiation:**

The usefulness of ultrasonic waves to assist reactions is now a well-established field of chemistry. The innovative ultrasonics era starts with Professor Paul Langevin's (1917) design of a quartz sandwich type transducer for underwater sound waves transmission in submarines for different purposes. Professor Alfred Lee Loomis modified the wartime acquaintance with Professor Robert Wood and provided for collaborative work and the writing of any joint research article. In 1926, Wood told Loomis of Langevin's experimental work and suggested that the topic provided a broad range of study in physics, chemistry, biology, along with in the medical field. It was this group start involvement of ultrasound into the chemistry in 1927. The actual use and application of sonochemistry took place in the 1980’s, soon after [83], [84].

The effect of ultrasound waves on chemical reactivity is known as sonochemistry. Sonochemistry is a chemical application of ultrasound. The best region for initiating chemical reactions is 20-100 kHz and 1-10 MHz is most appropriate for ultrasound imaging of different body parts in medical science **(Figure 1.18)**. The wavelength of ultrasound for 20 to 100 kHz range is from 7.5 to 0.015 cm. The phenomenon of cavitation seems to be the origin of the Sonochemical effect and the physical phenomenon, high temperatures or electrical fields, occurs during cavitation which breaks the many bonds, mostly homolytic cleavage occurs. The consequence of ultrasound waves because of direct interaction of ultrasonic beam with the reaction material but it is due to the phenomenon of cavitation created during the process of implosion of cavitating bubbles [85]. Ultrasound is in fact transferred through a media via pressured waves by causing vibrational motion of reacting molecules which alternately compressed and stretched the molecular structure of the medium which consequently, it breaks down and a cavity is formed [86]. This cavity is called cavitation bubble and the process "cavitation”. Many of these cavitation bubbles, generated in ultrasonic field which absorb energy from the propagating sound waves. The bubble then implodes creating very high temperature, pressure and mass transfer in a very small area of bubbles **(Figure 1.19)**. These tiny spaces act as micro reactors and due to which changes chemical reactivity of reactant molecule [87].

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**Figure 1.18 Ultrasound frequency range**

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**Figure 1.19 Bubble formation and collapsing.**

**There are two types of ultrasonic devices used in organic synthesis:**

1. Introducing ultrasound radiations directly into reaction mixture through the   
 ultrasonic probe.

2. Use of ultrasonic cleaning bath which radiates ultrasound radiations into the water   
 filled in the bath that propagates to the reaction mixture flask placed in the water of   
 ultrasonic bath.

In laboratory simple ultrasonic bath of 10-1liter capacities has been used   
 for synthesizing different organic compounds **(Figure 1.20)**. The reaction vessel   
 can be properly placed in water bath through which ultrasound propagates   
 and the wave passes through the reaction flask irradiating the reaction   
 mixture. The symbol **"))))))))"** is used for reaction carried out under   
 ultrasound irradiation.

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**Figure 1.20 Laboratory used ultrasonication bath.**

The ultrasound irradiations have applications in different fields with lots of advantages **(Figure 1.21)**. In literature survey, the variety of organic transformations that were carried out under ultrasound irradiation and studied by different researchers are given below:

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**Figure 1.21 Advantages and applications of ultrasound irradiations.**

M. Mishraa et al.[88] prepared pyrano [2, 3-c] pyrazoles by using magnetic nano- catalyst-[CoFe2O4] in presence of ultrasound waves. In presence of ultrasound waves reaction takes place between various aldehydes as well as dialdehydes, and ketones with malononitrile, followed by addition of ethyl acetoacetate along with hydrazine hydrate in the occurrence of magnetic nano-[CoFe2O4] catalyst in less time gives better result (90-96%) **(Scheme 1.28).**

**Scheme 1.28**

Firouzeh Nemati et al.[89] demonstrated eco-friendly, catalyst-free protocol for the synthesis of highly substituted pyrazole via ultrasonic irradiation. The reaction mixture of aldehyde, malononitrile, and phenyl hydrazine in PEG (polyethylene glycol): H2O (1:1) was irradiated under ultrasonic waves at room temperature within thirty minute, produces desired product in better yield (99%) **(Scheme 1.29)**.



**Scheme 1.29**

Greener and eco-friendly preparation of spiro[pyrano[2,3-c] pyrazoles] was developed by Anshu Dandia et al. [90]. The target product obtained by reacting isatin, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one in presence of CAN under ultrasound waves within 20 min gives 97% yield **(Scheme 1.30)**.

**Scheme 1.31**

Preparation of 4,5-dihydropyrazoles molecules carried out by Jorge Trilleras et al. [91] via ultrasound waves. Reaction between chalcones and hydrazine’s different solvents such as in ethanol or methanol or acetic acid in presence of sonication at room temperature produces good to excellent yield **(Scheme 1.32)**.

 **Scheme 1.33**

Sharad N. Shelke et. al. [92] prepared fluorinated pyrazoline molecules at room temperature within short period of time produces desired product in good yield. In the present protocol reaction carried out under ultrasonic irradiation is a ‘green’ alternative methodology for organic synthesis that serves many advantages over conventional synthesis **(Scheme 1.34)** .

**Scheme 1.34**

The present introductory topic represents the significance of various green approaches that enhance organic transformations through the utilisation of hydrotrope, biosurfactant, ionic liquid, and alternative energy sources including microwave and sonochemistry. These alternative ways minimise or eliminate the environmental issues caused due to traditional chemical productions carried out at the laboratory and industrial level.

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