INTRODUCTION

The worldwide demand and requirement for environmentally friendly chemical processes and products has led to the development of novel and cost-effective approaches towards pollution prevention. One of the most attractive concepts of pollution prevention is ‘GREEN CHEMISTRY’ which is best defined as utilization of a set of principles that reduces or eliminates the use or regeneration of hazardous substances in the design, manufacture and applications of chemical products. Advances in green chemistry address both obvious hazards and those associated with such global issues as climate change, energy production, availability of a safe and adequate water supply, food production and the presence of toxic substances in the environment.

Rapid development of green chemistry is due to the simple recognition that environmentally friendly products and processes are economical in the long term. Since its inception in the last decade, green chemistry has grown into a significant area within chemistry. The main issues taken up in ‘Green Chemistry’ include alternative reagents, environmentally benign solvents, novel energy sources and design of new technologies that provide safer and better routes in chemical research.

The design of environmentally benign solvents and solvent free systems has been one of the most active areas of green chemistry. Solvents are highly regulated and used in large quantities. Organic solvents pose a particular concern to the chemical industry because of the sheer volume used in synthesis, processing and separation. Many of the solvents are classified as volatile organic compounds (VOCs) or hazardous air pollutants (HAPs) and are flammable, toxic or carcinogenic. Breakthroughs in the use of supercritical fluids such as CO$_2$ have met with success in the research laboratory as well as commercially. The use of an obviously benign and inexpensive solvent like water could yield significant green chemistry benefits if challenges of energy and separations can be met.

The area of ‘catalysis’ is sometimes referred to as a ‘fundamental pillar’ of green chemistry. Catalytic reactions often reduce energy requirements and permits use of less toxic reagents. The utilization of benign, renewable feedstocks is a needed component of addressing...
the global depletion of resources. Synthetic methodologies are being designed in both academic and industry that are more environmentally benign and more atom efficient.10

Design for reduced hazard is a green chemistry principle that is being achieved in classes of chemicals ranging from pesticides to surfactants, from polymers to dyes.11 Methods are being designed to synthesize safer chemicals like more selective and less persistent pesticides and dyes without heavy metals.

The design of environmentally benign products and processes are guided by the following principles12 of ‘Green Chemistry’.

- It is better to prevent waste than to treat or clean waste after it is formed (source reduction).
- Synthetic methods should be designed to maximize the incorporation of all materials used in the process into final product.
- Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- Chemical products should be designed such that their efficiency is preserved but with reduced toxicity.
- The use of auxiliary substances (e.g. solvent, co-solvent additives, etc.) should be made unnecessary wherever possible and innocuous when used.
- Energy requirements should be recognized for their environmental and economical impacts and their use should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
- Reactions should be designed in such a way to regenerate the excessive raw materials used rather than depleting wherever technically and economically practicable.
- Unnecessary derivatization (blocking group, protection/deprotection) should be avoided whenever possible.
- Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
- Chemical products should be so designed that at the end of their function, they do not persist in the environment but should breakdown into innocuous degradation substances.
- Analytical methodologies need to be further developed to allow for real time, in-process monitoring and control prior to the formation of hazardous substances.

Introduction
Substances and their forms used in the chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

Green chemistry methodologies make use of non-conventional techniques such as microwave, ultrasound, solid state, ionic liquids and aqueous media and their applications in organic chemistry. Of all the existing areas of chemistry, medicinal and pharmaceutical chemistry with their traditionally large volume of waste/product ratio, are perhaps the most ripe for greening.

When all the principles of green chemistry are simply incorporated as an integral part of everyday chemistry, there will be no longer be a need for the focusing, highlighting, and moniker of green chemistry. And when that day comes, the challenges that chemistry will meet cannot be imagined.

‘Natural products’ in the broadest sense should connote all the chemical compounds which occur in nature or are derived from natural sources. Natural product chemistry in its different aspects is an ancient science. It covers the chemistry of naturally occurring compounds, their biosynthesis, function in their own environment, metabolism and more conventional branches of chemistry such as structure elucidation and synthesis. The preparation of foodstuffs, colouring matter, medicines or stimulants are examples of activities as old as mankind.

The chemistry of natural products has undergone an explosive growth during the latter half of the 20th century. Investigations in the chemistry of natural products have attracted scientists to unravel the mysteries of the living world and to understand new chemistry. Another reason is to explore new and less expensive pathways to synthesize compounds found in nature without disturbing the ecological balance. The important reason being the growing number of substances from natural sources which display interesting pharmaceutical activities such as antibiotics, anti-tumor, juvenile hormones, insect sex attractants, alkaloids, terpenes, flavanoids, prostaglandins, etc. Natural products have played a key role in the development of medicinal chemistry. The majority of natural products have been isolated from plant origins, mainly due to ease of the isolation process. Greater emphasis is laid on the synthetic properties and functions of the organic molecules with recent improvements in techniques for isolation and determination of the structure of natural products.
Fatty acids are characteristic building block components of lipids. Typical fatty acids constitute of two parts: (i) a long hydrocarbon chain with length ranges from 4 to 30 carbons, most common chain length has 12-24 carbons. The chain is typically linear and usually contains an even number of carbons. (ii) a carboxylic acid group. Fatty acids can be saturated fatty acids (stearic acid, capric acid, palmitic acid, lauric acid), monounsaturated (oleic acid, palmitoleic acid), polyunsaturated acids (linoleic acid, linolenic acid arachidonic acid) and some cyclic fatty acids are also known (chaulmoogric acid).

Fatty acids are important intermediates in the synthesis of important compounds. Examples include phospholipids and leucotrienes which play a role in physiological regulation. Fatty acids are also important source of energy in human body.

Nature’s virtuosity of linking and tailoring simple carboxylic acid monomers to give a huge structural diversity of fatty acid metabolites has been a fascinating subject for interdisciplinary research since the early works of Collie. During the past few decades great knowledge has been established by using modern molecular biology methods for the processes employed in fatty acid biosynthesis.

Monounsaturated even chain fatty acids with $\Delta^6$ and $\Delta^8$ unsaturations are less common than their corresponding fatty acids with $\Delta^5$ and $\Delta^9$ double bonds. Normal chain $\Delta^6$ fatty acids with C$_{14}$-C$_{17}$ chain lengths have been identified in a variety of natural sources such as sponges, opisthobranchs, human skin and seed oil. On the other hand, $\Delta^8$ monounsaturated fatty acids such as the 8-octadecenoic acid, have also been identified in nature, for example, in the exocrinology of the queen humblebee Bombus terrestris (Hymenoptera).

 Branched chain $iso$-anteiso $\Delta^6$ and $\Delta^8$ monounsaturated fatty acids are less ubiquitous than their corresponding normal chain analogues. The best known example is

$$\text{HO} \quad \begin{array}{c} \text{O} \\ \text{14-Methyl-6(Z)-pentadecenoic Acid} \end{array}$$

the 14-methyl-6(Z)-pentadecenoic acid, which was identified in several marine organisms, for example, in the phospholipids of the sponge Tethya aurantium and in the freshwater mussel Unio tumidus.

Introduction
Isolation of natural products involve steam distillation or solvent extraction of the dead insects or their parts, followed by chromatographic separation of the different components. For structure elucidation, the modern synthetic chemist has at his disposal excellent physical techniques as IR, UV NMR spectroscopy and mass spectrometry. More recently, different sophisticated methods and techniques are being utilized, giving precise information regarding the component ratios and stereochemistry, such as GC (gas chromatography) retention time, use of achiral and chiral GLC, optical rotation, GC-US analyser, dual column GC-EAD (electro-antennog detector), SPME (solid-phase microextraction)-GC and HPLC etc. However, the ultimate and final proof of the proposed structure of a compound is rendered by its synthesis. Synthesis also provides sufficient amount of the compound compared to the trace amounts in which it is obtained in nature.

Keeping in view the principles of ‘Green Chemistry’, we have made use of non-conventional techniques such as microwave, ultrasound, solid support in certain organic transformations and in the synthesis of a few natural products.

Microwave activation, as a non-conventional energy source has become a very popular and useful technology in organic chemistry. As we approach the sixth decade of microwave oven, it is interesting to reflect that although microwaves have been used in the preparation of food for around forty years, it is only in the past decade that these have been exploited in the chemical laboratory. Microwave radiation is a non-conventional energy source whose popularity and synthetic utility in organic chemistry have increased considerably in recent years. Application of the microwave heating techniques to the preparation of samples for analysis, the most developed chemical area to date, began in the mid 1980’s, the first reports of which appeared in 1986. Before that its use was limited to moisture analysis, dissolution of biological samples in mineral acid for subsequent analysis and spectroscopy. Unlike other non-conventional energy sources (such as ultrasound, high pressure or vacuum flash thermolysis), microwaves lend themselves easily to industrial use, where they provide many advantages in certain production processes. The rapid heating effect associated with the microwave technology is also very successful for the application of waste treatment, drug release and targeting, ceramics, alkane decomposition, polymer technology, hydrolysis of proteins and peptides inorganic and solid-state synthesis and others. Industrial application of microwave heating
included tempering meat, curing and vulcanizing rubber, curing bacon, proofing doughnuts, curing wood and drying polymers.

Synergy of this methodology with reactions performed on support media and/or in the absence of solvent constitutes an environmentally clean technique, which allows the attainment of high yields of products at reduced energy costs. Rate enhancements upto 1200 times have been achieved in microwave induced reactions as compared to conventional procedures. Lately this technique has come to be known as ‘Microwave Oven-Induced Reaction Enhancement’ (M.O.R.E.) technique.\(^{52}\)

The microwave region of the electromagnetic spectrum lies between infrared and radiofrequency corresponding to wavelengths from 1 cm to 1 m and frequency 30 GHz to 300 MHz. Wavelengths between 1 cm and 25 cm are used in RADAR transmissions and the remaining range is used in telecommunications, microwave ovens are restricted to 12.2 cm or 33.3 cm (2450 MHz or 900 MHz). Domestic microwave ovens usually operate at 2450 MHz.

A schematic diagram of a domestic microwave oven, a multimode applicator is shown in the figure 1. Some of the components and features of a microwave are as follows.

Figure 1 Schematic Diagram of a Microwave Oven
The device responsible for generating microwaves is **magnetron**, which generally operates at a frequency of 2450 MHz (wavelength 33.2 cm), was first designed by Randell and Booth at the University of Birmingham during the Second World War as a part of development of RADAR. It is a vacuum device that converts DC electrical energy into microwaves. It comprises of a thermionic diode having an anode and a directly heated cathode. As the cathode is heated electrons are released and are attracted towards anode, which consists of a series of circuits timed to oscillate at a specific frequency or its overtones. **Waveguide** is a rectangular channel made of sheet metal. On generation the waves are guided into the cavity by waveguide and reflected off the walls of cavity (or oven interior). **Microwave cavity** is the internal space of the oven where samples can be placed for heating. The cavity has reflective walls to prevent leakage of radiation and to increase the efficiency of the oven.

When working with small loads, poorly absorbing loads or at high powers, a dummy load, for example a beaker of water (sink) should always be placed in cavity along with the sample to absorb the excess microwave energy waves, otherwise they may get reflected back into the waveguide and consequently damage the magnetron.

The most widely used equipment for organic synthesis on a laboratory scale is the domestic microwave oven, which is a multimode applicator. In this distribution of the electric field inside the cavity is heterogeneous, the temperature cannot be simply and accurately measured, the power is not tunable and moreover the reproducibility of experiments is very poor.

These drawbacks led to the development of monomode applicators, which focus the electromagnetic waves onto the sample using an accurately dimensioned waveguide. In this way, the interaction between the microwave field and the reaction mixture is well controlled and with effective control of the incident power.

In many cases the multimode cavity has been modified to attach a magnetic stirrer or to include a reflux condensor or modified with a source of inert gas which can be bubbled continuously into the reaction mixture. Figure 2 illustrates the basic set up of the two alternative microwave ovens.
Microwave radiation is an alternative to conventional heating for introducing energy into reactions. The microwave heating uses the ability of some compounds (liquids or solids) to transform electromagnetic energy into heat. This mode of heating has many attractions in chemistry because its magnitude depends on the dielectrical properties of the molecules. The mechanism of microwave heating of solvents is related to the existence of an electrical dipole in the molecule of the solution. For a molecule to be ‘microwave active’ that is capable of absorbing microwave energy, it should have a dipole moment permanent and/or induced. On exposure to microwaves, the molecules tend to align themselves parallel to this field. This new arrangement [2] of molecules is rather higher in energy than the random arrangement [1] found in the absence of field. The molecules can be thought of as storing potential energy due to application of the field. If the direction of the field is slowly changed, the molecules will rotate, keeping their alignment with the field.

Figure 2 Schematic Representation of Household Multimode Microwave Oven and Monomode Microwave Oven

Introduction
The sum of the potential energy over all directions does not change. If we change the direction of the field more quickly, some of the molecules may be unable to remain aligned with the field's direction. [3] The molecules may try to keep up with the field but they keep bumping into other molecules. The potential energy stored in the molecular arrangement no longer matches the applied field. In fact, the excess energy is transformed into kinetic energy on collisions between the molecules and it is this effect which gives rise to microwave heating. It is noteworthy that, if the electrical field changes direction very rapidly, the molecules do not have time to react to the applied field and they remain randomly oriented. At these frequencies they are unable to interact with the applied field and no heating occurs. The microwave frequencies commonly used for heating match the time domain for which polar molecules can no longer follow the changing direction of the field.

The propensity of a sample to generate heat from microwave irradiation at a given frequency and temperature their capability to absorb microwave energy and to convert the
absorbed energy into heat must be taken into account. These factors may be considered using the loss angle which is expressed in the form of its tangent.

$$\tan \delta = \frac{\varepsilon''}{\varepsilon'}$$

where $\delta$ = dissipation factor

$\varepsilon''$ = dielectric loss or efficiency of heat generated from electromagnetic radiation

$\varepsilon'$ = dielectric constant of the molecule i.e. the ability of molecule to be polarized by an electric field.

$\tan \delta = $ dielectric loss tangent

A reaction with a high tan $\delta$ is required for absorption and consequently for rapid heating. Compounds with high dielectric constants tend to heat under microwave irradiation while less polar substances and highly ordered crystalline materials are poorly absorbing.

Reactions can occur faster under microwave irradiation than on a hot plate. When a sample is heated on a hot plate, a convection process takes place. The heat is transformed from hot plate to the vessel and in turn from the vessel to the liquid inside it, an inefficient method of heating. If a liquid is exposed to microwave radiation, the microwaves induce rotation of dipoles within the liquid, causing polar molecules to align and relax in the field of oscillating electromagnetic radiation. Energy is dissipated from those dipole rotations, which causes the liquid to become hot. In such a way, the heat is produced within the liquid and not transferred from the vessel as in the hot plate system. In a microwave oven, the liquid is therefore often at high temperature than the vessel. This efficient heating has been reported to lead to the increases in reaction rates and yields.

![Microwave Heating vs Conventional Heating](image_url)
The shape and size of objects have much greater and completely different effect on temperature distribution than in classical heating. Materials of spherical appearance will concentrate on electromagnetic field at their center. The preferred reaction vessel for MORE chemistry, is an ordinary Erlenmeyer flask or a pyrex or PTFE beaker, loosely covered with a watch glass. Alternatively, teflon and polystyrene vessels can also be used. These materials are transparent to microwaves. No metallic container can be used as a reaction vessel as it gets heated soon due to preferential absorption and reflection of rays. For reactions carried out under pressure, sealed pyrex vials are used which are generally surrounded by vermiculite.

Reactions on the laboratory scale are carried out using a domestic microwave oven as they are easily accessible and economically priced. These ovens are effective for bringing about two types of reactions, non-solid state and solid state reactions.

The solid state reactions make use of a solid support and such microwave assisted ‘dry’ reactions are of two types, i.e. the microwave active reagent supported on an inactive material such as finely powdered alumina or silica or a microwave active support with reactants that may or may not be microwave active.

The non-solid state reactions are governed by the type of solvent used i.e. microwave active (DMF, DMSO, HCB etc.) or microwave inactive (n-hexane, toluene, CCl₄ etc.).

The choice of solvent in microwave oven-induced reaction enhancement (MORE) chemistry is most important. The solvent must have a dipole moment so as to absorb microwaves and a boiling point at least 20-30°C higher than the required reaction temperature. The solvents which can be effectively used for carrying out reactions are polar solvents such as water, methanol, ethanol, N,N-dimethylformamide, ethylene glycol, o-dichlorobenzene and 1,2-dichloroethane to name a few. It is well known that the larger the dielectric constant, greater is the coupling with microwaves. Non-polar solvents such as benzene, petroleum ether and carbon tetrachloride have negligible dielectric constant and therefore do not couple effectively with microwaves. Absorption of microwave irradiation by solvents causes them to attain their reflux temperature within a very small span of time (table 1).

*Introduction*
TABLE 1: The temperature of 50 mL of several solvents after heating for 1 min. at 560 W in an open vessel in microwave oven

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Raised Temperature (°) After 1 min.</th>
<th>Boiling Point (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>81</td>
<td>100</td>
</tr>
<tr>
<td>Methanol</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Hexane</td>
<td>25</td>
<td>69</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td>Methylene Chloride</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Carbon Tetrachloride</td>
<td>28</td>
<td>77</td>
</tr>
<tr>
<td>N,N-Dimethylformamide</td>
<td>131</td>
<td>153</td>
</tr>
</tbody>
</table>

It has also been observed that higher boiling point values could be observed when solvents are submitted to microwave conditions when compared with conventional heating. This effect called the ‘Superheating effect’ arises due to retardation of nucleation in microwave heating.

Table 2: Boiling points of solvents observed in microwave oven

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Normal Conditions</th>
<th>Microwave exposure</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>100</td>
<td>105</td>
<td>5</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>77</td>
<td>102</td>
<td>25</td>
</tr>
<tr>
<td>Methanol</td>
<td>65</td>
<td>84</td>
<td>19</td>
</tr>
<tr>
<td>Acetone</td>
<td>56</td>
<td>89</td>
<td>33</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>67</td>
<td>103</td>
<td>36</td>
</tr>
</tbody>
</table>

As is evident from table 2 the effect of superheating on water and aqueous solvents is generally small, in comparison to the effect on organic solvents. Polar solvents heated in a microwave oven almost always boil at temperature above their accepted boiling points. e.g. a solution of DMF (b.p. 153°) reaches a temperature of 280° under microwave irradiation in 9 min. at 500 W.

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In conventional heating, boiling begins at the surface of the reaction vessel where there are many tiny pits and scratches. The vessel walls are always significantly hotter than the refluxing solution itself and this encourages the formation of bubbles of solvent vapour in the pits. When bubble reaches some critical volume, it detaches from the surface and boiling is observed.

Figure 5 The Mechanism of Microwave Superheating

In microwave heating, the vessel walls are generally cooler than the solution itself since they are made from poorly microwave absorbing materials such as glass and teflon. The areas of solvent close to the vessel walls are too cold to encourage the formation of bubbles and as a result, the bulk of solvent can be heated to temperature much higher than the conventional boiling point before stable boiling is attained. Figure 5 accounts for the rather poor superheating of water compared with organic solvents since the later wet the surface of the vessel much more effectively flooding the majority of the nucleation sites.
Microwave technique has a major advantage over the conventional ones in offering reactions which can be carried out in the absence of solvents on solid supports. Such microwave assisted dry reaction are of two types, that is microwave active reagent supported on an inactive material such as finely powdered alumina or silica or a microwave active support with reactants that may or may not be microwave active. Various supports such as alumina, silica gel, K-10 and KSF montmorillonite clays and zeolites have been used for this purpose. The absorption of microwave by such supports can be either due to the presence of hydroxyl groups present on the surface of these inorganic solids or due to non-stiochiometric character of these materials. These reactions are very convenient to carry out.

Various potentialities of microwaves in chemistry are as follows.

- The rapid heating capability of the microwaves leads to a considerable saving in dissolution or reaction time.
- Use of microwave acceleration eliminated the need for heating baths, reaction flasks and reflux condensers with ground glass joints.
- Microwaves being more energy efficient can lead to improved isolated yields of products.
- MORE chemistry coupled with dry media provides clean and economic procedures, appreciable improvements in yield, purity of the products and easy work up procedures.
- It is an ecofriendly and green technique as solvent free reactions can be performed.
- Applications of this approach to combinatorial synthesis should provide a major impetus for further developments in this area.
- Some flammable solvents can be easily handled.
- The smaller volume of solvent required contributed to a savings in cost and diminished the waste disposal problem.
- This method provides rapid and relatively inexpensive access to high temperatures and pressures.

Offsetting the advantages of microwave assisted organic reactions are some detractions.

- The processing of large quantities of material by scaling up small, low volume single mode reactions is not always feasible.
- Reliable temperature monitoring and feedback power control during MWI is also of utmost importance for successful applications in synthetic chemistry.

Introduction
• The temperature feedback control should be capable of very rapid reduction of microwave power when exothermic reaction energy becomes significant, or when the dissipation factor increases rapidly, to avoid thermal runaways.

• It is unsafe to flash heat volatile and potentially flammable organic solvents in a contained space, and explosions of vessels are common in reported experiments with closed systems.

The microwave heating technique provides the chemist with a new way of heating chemical reactions. Owing to differences between the mechanism of microwave heating and those of conventional heating techniques such as the use of oil baths and furnaces, improvements to synthetic procedures have been discovered. Applications for microwave techniques have been identified in many diverse areas of chemistry, including analytical chemistry, organic and inorganic chemistry, ceramics, pharmaceutical chemistry and catalysis.

Over the last decade microwave assisted chemistry has matured into a highly useful technique and provides an interesting alternative for heating chemical reactions. A wide range of microwave induced reactions have been successfully accomplished, recent reviews are available in literature. Some important applications of the use of microwave heating in organic synthesis are described below in broad catagories.

1. Coupling Reactions

A microwave enhanced solvent free Glaser coupling reaction has been developed. Self-coupling of alkynes on KF-alumina in the presence of CuCl2 affords good yields of the corresponding diacetylenes.

\[
\text{RC≡CH} \quad \xrightarrow{\text{CuCl}_2/\text{KF}/\text{Al}_2\text{O}_3} \quad \text{MWI} \quad \xrightarrow{\text{RC≡C–C≡CR}} \quad 56-68\%
\]

\[
R = n-\text{C}_8\text{H}_{17}, n-\text{C}_6\text{H}_{13}, 4-\text{CH}_3\text{C}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, \text{C}_6\text{H}_5
\]

Wang and coworkers have reported palladium catalyzed Heck couplings of aryl halides in water without an organic solvent on MWI under phase transfer conditions to give the trans-stilbenes and substituted trans-cinnamic acids in good to high yields.
Schotten et al. reported Suzuki Cross coupling of poly(ethylene glycol)esters of bromo-, iodo- and triflates-para-substituted benzoates with any boronoc acids catalyzed by 'ligandless' Pd(OAc)$_2$ in water without organic cosolvent under MWI for 2-4 min.

Singh et al. demonstrated the selective conversion of benzylic alcohols in the presence of saturated alcohols into the corresponding iodides on solid support using NaI-KSF Clay under microwave irradiation.

Hallberg and coworkers have prepared aryl and vinyl nitriles from the corresponding bromides using palladium catalyzed reactions in very high yields with MWI employed as the energy source.

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Under the same reaction conditions, a simple procedure for one-pot transformation of aryl halides directly to the aryl tetrazoles has been described both in solution and on solid support.

3. Protection

Mitra et al.\textsuperscript{73} have reported a rapid and high yielding method of O-methylation of phenolic groups under MWI.

\[
\begin{align*}
\text{Ar—OH} & \xrightarrow{\text{Me}_2\text{SO}_4, \text{K}_2\text{CO}_3} \text{Ar—OMe} \\
\text{MWI, 3-15 min.} & 78-94\%
\end{align*}
\]

Sarma et al.\textsuperscript{74} have reported the selective protection of one hydroxyl group as its tetrahydropyranyl ether in 1,\textit{n}-symmetrical diol by iodine catalyzed reaction of the diol with DHP under MWI.

\[
\begin{align*}
\text{HO—(CH}_2\text{)}_{\text{n—OH}} & \xrightarrow{\text{DHP/}I_2} \text{HO—(CH}_2\text{)}_{\text{n—OTHP}} \\
\text{n = 2-6} & 75-78\%
\end{align*}
\]

Sarma and coworkers\textsuperscript{75} have reported a new method of acetalization of aldehydes and ketones with 1,2-diols or alcohols catalyzed by iodine under MWI in 1-2 min.
Khadilkar et al. have developed an easy, safe and simple method for protection of amino group in solvent free conditions using microwave.

\[ \text{H} \quad + \quad \text{RNH}_2 \quad \xrightarrow{\text{MWI} \sim 5 \text{ min.}} \quad \text{HNRR} \]

60-100%

R = 4-ClC₆H₄, 3-ClC₆H₄, 2-O₂NC₆H₄, 3-O₂NC₆H₄, 2-CH₃C₆H₄, 4-CH₃C₆H₄, C₆H₄, C₆H₅, HOCH₂CH₂

Varma et al. have shown an expeditious and environmentally friendlier approach to the synthesis of a variety of non-easily available hydrazones using MWI in the presence of any catalyst, solid support or solvent.

\[ \text{H} \quad + \quad \text{RNHNH}_2 \quad \xrightarrow{\text{MWI}} \quad \text{HNRR} \]

\[ R' = \text{Ph, 2,5-F₂C₆H₃, 3-CF₃C₆H₄, 4-O₂NC₆H₄} \]

4. Deprotection

Gajare et al. provided a useful alternative for deprotection of allyl esters by montmorillonite K-10 clay using MWI under solvent free conditions.

\[ \text{H} \quad + \quad \text{RNHNH}_2 \quad \xrightarrow{\text{MWI}} \quad \text{HNRR} \]

Introduction
An environmentally safe and facile solid state regeneration of carbonyl compounds from oximes by silica supported MnO$_2$ under MWI$^{79}$ has been developed.

\[
\begin{align*}
\text{NOH} & \quad \xrightarrow{\text{MnO}_2/\text{SiO}_2, \text{MWI}, 3 \text{ min.}} \quad \text{O} \\
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} & \quad 73\%
\end{align*}
\]

Bose and co-workers$^{80}$ have reported an environmentally benign, solvent free cleavage of acetals with peroxymonosulfate-alumina under MWI in 73- 95% yields.

\[
\begin{align*}
\text{EtO} & \quad \xrightarrow{\text{peroxymonosulfate, Al}_2\text{O}_3, \text{MWI}, 2-3.5 \text{ min}} \quad \text{HO} \\
\text{O} & \quad \text{R} \\
\text{R'} & \quad \text{OH} \\
\text{R} & \quad \text{R'} \\
\text{R} & \quad \text{R'}
\end{align*}
\]

5. Wittig Reaction

Cereda et al$^{81}$ have reported the Wittig reaction of a pool of stabilized ylides and aromatic aldehydes under MWI. Only a few minutes were needed for high conversion rates under microwave heating in comparison to hour time with traditional methods.

\[
\begin{align*}
\text{ArCHO} & \quad + \quad \xrightarrow{\text{MWI}, 280 \text{ W}, 5 \text{ min}} \quad \text{Ar} \\
\text{Ph}_3\text{P} & \quad \xrightarrow{\text{MWI}, 280 \text{ W}, 5 \text{ min}} \quad \text{R}_1 \\
\text{R}_2 & \quad \text{R}_1 \\
\text{Ph}_3\text{P} & \quad \text{R}_2 \\
\text{Ph}_3\text{PO} & \quad \text{R}_2 \\
\text{Ar} & = 4-\text{H}_3\text{COC}_6\text{H}_4, \; 3,4,5-\text{(H}_3\text{CO)C}_6\text{H}_3, \; 4-\text{ClC}_6\text{H}_4, \; 4-\text{O}_2\text{NC}_6\text{H}_4
\end{align*}
\]
Huang and coworkers\textsuperscript{82} have demonstrated a simple and rapid procedure for the tandem nucleophilic reaction synthesis of (Z)-heteroatom-\(\alpha,\beta\)-unsaturated enoates stereoselectively in moderate to high yields under MWI through the substitution of Wittig reaction of \(\alpha\)-hypervalent iodine functionalized phosphonium ylide.

\[
\begin{align*}
\text{Ph}_3\text{P} = \text{IPh} & \quad \text{BF}_4^- + \text{Bu}_4\text{N}^+\text{Br}^- \quad \text{MWI} \quad \text{DMF, 3 min.} \quad \text{Ph}_3\text{P} = \text{Br} \\
\text{Ph}_3\text{P} = \text{Br} & \quad \text{CO}_2\text{Et} + \text{PhCHO} \quad \text{MWI} \quad \text{DMF, 3 min.} \quad \text{Ph} = \text{Br} \\
\end{align*}
\]

6. Rearrangements

An expeditious solvent free Fries rearrangement\textsuperscript{83} is described which occurs under mild conditions on K-10 mont. using microwave irradiation.

\[
\begin{align*}
\text{O} & \quad \text{R} \quad \text{MWI} \quad \text{K-10 Clay} \quad 4-10 \text{ min.} \quad \text{OH} \\
\text{R} & = \text{CH}_3, \text{C}_6\text{H}_5 \\
\text{X} & = \text{H}, 2-\text{O}_2\text{N}, 3-\text{H}_3\text{C}, 4-\text{H}_3\text{C}, 2,5-(\text{H}_3\text{C})_2
\end{align*}
\]

Microwave irradiation of the \(\alpha\)-diazo ketones promoted efficient Wolf rearrangement\textsuperscript{84} of tremendous synthetic utility.

\[
\begin{align*}
\text{O} & \quad \text{N}_2 \quad \text{MWI} \quad \text{BnNH}_2 \quad \text{O} \\
\text{Bn} & \quad \text{N} \quad 75\% \\
\end{align*}
\]

\(\alpha\)-Allylsalicylic acids anchored to merrifield reaction are rapidly rearranged to the corresponding \(\alpha\)-allylsalicylic acids via Claisen rearrangement\textsuperscript{85} in high yields for the first time under MWI.

\textit{Introduction}
7. Cyclization

Tetrahydrocarbazole has been synthesized from phenylhydrazine and cyclohexanone over molecular sieve catalysts using Fischer cyclization\textsuperscript{86} in the presence of microwaves.

\[
\text{NHNNH}_2 + \text{O} \xrightarrow{\text{MWI, mol. sieves}} \begin{array}{c}
\text{R} \\
\text{mol. sieves}
\end{array}
\]

\[
\begin{array}{c}
\text{NHNNH} = \text{C} = \text{N} \\
\text{R}
\end{array}
\]

\[
\begin{array}{c}
\text{R} = -\text{H}, -\text{CH}_3 \\
\text{NHNNH} = \text{C} = \text{N} \\
\text{R}
\end{array}
\]

8. Esterification

Mitra and coworkers\textsuperscript{87} have reported a rapid and efficient method for the synthesis of \(\alpha,\beta\)-unsaturated esters from corresponding carboxylic acids using dry methanol in the presence of catalytic amount of conc. sulphuric acid under MWI.

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2
\end{array}
\xrightarrow{\text{dry MeOH, conc. H}_2\text{SO}_4, \text{MWI}} \begin{array}{c}
\text{R}_1 \\
\text{R}_2
\end{array}
\]

\[
\begin{array}{c}
\text{R}_1 = -\text{H, -OH, -NO}_2, -\text{OCH}_3, -\text{OBn} \\
\text{R}_2 = -\text{H, -OH, -OCH}_3
\end{array}
\]
Six-membered cyclic ketones on treatment with acetic anhydride and a catalytic amount of iodine\(^{88}\) under MWI give the corresponding enol acetates in good yields.

\[
\begin{array}{c}
\text{OAc} \\
\text{MWI, 5 min.} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Ac}_2\text{O}, \text{I}_2 \\
90\% \\
\end{array}
\]

9. Asymmetric Synthesis

MWI induced palladium catalyzed asymmetric allylic alkylation has been carried out by Hallberg \textit{et al.}\(^{89}\)

![Reaction scheme for asymmetric synthesis](image)

BSA = \(N,O\)-bis(trimethylsilyl)acetamide

10. Oxidation

Singh \textit{et al.}\(^{90}\) have reported selective allylic oxidation of allylic methyl groups to \(\text{trans-\(\alpha,\beta\)}\)-unsaturated alcohols using \(\text{SeO}_2/\text{t-BuOOH} \) adsorbed on \(\text{SiO}_2\) under MWI.

![Reaction scheme for oxidation](image)

\[83\%\]
A variety of alcohols were converted to their corresponding carbonyl compounds by using 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate as a useful reagent under MWI.

\[
\begin{align*}
\text{ArCHOH} & \xrightarrow{\text{MWI}} \text{ArCO} \\
\end{align*}
\]

The efficient use of microwave energy coupled with dry media technique for the oxidation of benzylic alcohols using catalytic CrO₃ and TBHP has been efficiently projected.

\[
\begin{align*}
\text{R'CH} & \xrightarrow{70\% \text{TBHP}, \text{CrO}_3 \text{, MWI, 640 W, 10 min.}} \text{R'C} \\
\end{align*}
\]

11. Reduction

Triethylsilane in the presence of catalytic amount of PdCl₂ is an efficient and selective system for reductive dehalogenation of aryl halides under MWI.

\[
\begin{align*}
\text{X} & + \text{Et₃SiH} \xrightarrow{\text{PdCl}_2 \text{, MWI}} \text{R} + \text{Et₃SiX} \\
\end{align*}
\]

\[X = \text{I, Br, Cl, F} \quad R = 4-\text{OMe}, 3-\text{COO Me}, 4-\text{OH}, 4-\text{NO}_2, 4-\text{COOH}\]

Meshram and coworkers have demonstrated a rapid and simple method for the reduction of nitro groups into amines using NaH₂PO₂/FeSO₄.7H₂O under MWI.

\[
\begin{align*}
\text{R'R'}\text{NO}_2 & \xrightarrow{\text{NaH}_2\text{PO}_2/\text{FeSO}_4.7\text{H}_2\text{O, MWI}} \text{R'RNH}_2 \\
\end{align*}
\]

\[R, R' = \text{H, CH}_3, \text{OH, CONH}_2, \text{C}_6\text{H}_5, \text{COOH, CN, NH}_2\]

Introduction
12. Catalytic Hydrogenation

Catalytic transfer hydrogenation has been conducted under MWI in open vessels using high boiling solvent such as ethylene glycol (b.p 198°C) as the microwave energy transfer agent. Reduction of double bond and hydrogenolysis of several functional groups was carried out safely and rapidly (3-5 min.) at about 110-130°C with 10% Pd/C as an efficient catalyst and ammonium formate\(^9\) as the hydrogen donor.

\[
\begin{align*}
\text{BnO} & \quad \text{CO}_2\text{Me} \\
\text{PhO} & \quad \text{Ph} \\
\text{HO} & \quad \text{Ph} \\
\end{align*}
\]

13. Condensation

Terminal alkynes react with secondary amines and \textit{para}-formaldehyde to afford Mannich adducts\(^9\) in the presence of cuprous iodide on alumina under microwave irradiation and solvent free conditions. The process is highly efficient, does not require pre-forming the iminium species and is not hampered by the heterogeneity of the reaction.

\[
\begin{align*}
\text{HC} = \text{CH} + \text{HCHO} + \text{HN} & \rightarrow \text{F} \\
\text{PhO} & \quad \text{OH} \\
\text{CO}_2\text{Me} & \quad \text{Ar} \\
\end{align*}
\]

Mogilaiah and coworkers\(^7\) have developed a facile and efficient method for the rapid synthesis of 1,8-napthyridines using Friedlander condensation of 2-amino nicotinaldehyde and active methylene compound in methanol in the presence of a catalytic amount of piperidine in unmodified domestic microwave oven.

\[
\begin{align*}
\text{F} & \quad \text{C} = \text{CH} \\
\text{HCHO} & \quad \text{HN} \\
\text{PhO} & \quad \text{CO}_2\text{Me} \\
\text{C} = \text{CH}_2\text{N} & \quad \text{O} \\
\text{F} & \quad \text{C} = \text{CH}_2\text{N} \\
\end{align*}
\]

\(63\%\)

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Hoel and Nielsen\textsuperscript{98} discussed Ugi four component condensation under microwave conditions in high yields.

\[
\text{R} = \text{CH}_3, \text{C}_6\text{H}_5, \text{CF}_3, \text{OH}, \text{NH}_2
\]

\[
\text{R'} = \text{COCH}_3, \text{COC}_6\text{H}_5, \text{CO}_2\text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{CN}, \text{CONH}_2
\]

14. Synthesis

Kad and coworkers\textsuperscript{99} have reported the synthesis of 9-oxo-2(\textit{E})-decenoic acid, the queen bee substance of \textit{apis mellifera} utilizing microwave irradiation.

A single step Gould-Jacob reaction\textsuperscript{100} between aromatic amines and diethyl ethoxymethylene malonates (EMME) for the synthesis of 4-quinolones under solvent free MWI has been carried out in excellent yields with decrease in the reaction period.
In addition to above-mentioned reactions microwave technique has been proved to be invaluable in the Diels-Alder reaction, radical cyclization reaction, Mannich reaction, Beckmann rearrangement, reductive amination and many other reactions. This technique has also proved to be invaluable in the synthesis of fungicidal pyrazoles, metal catalyzed reactions and bromination of aromatic compounds. Thus it can be seen that microwave assisted rapid organic reactions constitute an emerging technology that could make industrially important organic syntheses more eco-friendly than conventional reactions.

The growing awareness of the unacceptability of many conventional reagents and catalysts (often as a result of hazardous waste resulting from their use) and resulting legislation will give a major impetus in the search for 'cleaner technology' including new synthetic methods. Development of organic solid state reactions has emerged as a frontier area of research in synthetic organic chemistry. Solid state chemistry is a fast developing science enhanced by its numerous application in the high technology industries. Since the eighties, solid support chemistry has come into prominence as it provides numerous potential advantages but the most important are:

- Time effectiveness of setting up and carrying out the reactions.
- The constraints of the (molecular dimension) pores and the characteristics of surface adsorption can lead to useful improvements in reaction selectivity.
- Faster reaction rates as all the reagents are placed together on the 2-dimensional solid support as compared to the 3-dimensional conventional reactions. Thus the probability of a reactive encounter is greatly increased.
- Employs a convenient product isolation by simple work up.
- Allows regeneration and recovery of the reagent or catalyst hence minimizing cross contamination between organic and inorganic components.
- A number of toxic and volatile chemicals can be handled safely after being deposited on these supports.
- Nature of the products obtained from heterogeneous reactions can be attempted by changes in the solid support.
- Good dispersion of active sites can lead to significant improvements in reactivity.
- Reduction in pollution and cost.

Introduction
- Solids are generally easier and safe to handle than liquids or gaseous reagents.
- Some supported reagents may be easily reused.

The single most important factor in favour of supported reagents and catalysis in particular is environmental. The supported reagent can be rendered with either bronsted acidity or basicity. The most common method of activation of supported reagent is thermal activation\(^\text{116}\) which is generally used to control the water content of the final material although it may also cause other changes such as decomposition of the reagent, reaction of the reagent with the support, or even structural changes in the case of less robust supports.

The removal of water from most supported reagents is not a simple task since both physisorbed and chemisorbed water is generally present. The removal of surface chemisorbed water is rarely required or desired. It is important to note that physisorbed water may play a significant role either positive or negative in the reaction of a supported reagent. In some cases the presence of small amounts of water in the supported reagent can be beneficial.\(^\text{116-118}\) The general profile for supported reagent dehydration is shown in figure 6. Temperature can of course be reduced by employing vacuum drying.

![Figure 6: Dehydration of a Supported Reagent](image)

The type of support material used is a critical factor in the performance of the resulting supported catalyst or reagent in an organic reaction system.\(^\text{119}\) The careful choice of a support material is important to achieve satisfactory results in a synthetic application. The main factors that should be considered when employing a material as a support are:

**Introduction**
Thermal and chemical stability during the reaction process and for batch reactions during the separation stage.

Accessibility and good dispersion of the active sites.

Methods of preparing supported reagent include impregnation, precipitation, adsorption from solution, mixing, ion-exchange etc. The most widely used method especially on laboratory scale is impregnation, which includes filling the pores of a support with a solution of the reagent followed by evaporation of the solvent. This method provides good control over dispersion and loading.

The commonly used solid supports are silica, alumina, zeolites (alumina silicates), celite, carbon, montmorillonite clays, ash, amberlyst, inorganic fluorides, nafion-H, ion exchange resins and modified reagents to name a few. The most important factors in determining the best support for a particular application are likely to include surface area, pore size and acidity-basicity. Solid acids have been the subject of the most detailed and extensive studies of all heterogeneous catalysts.

The development of supported zinc reagent catalysis has proven to be an important breakthrough in solid Lewis acids. The most promising and interesting supported reagents, Friedel-Crafts alkylation catalysts have been based on the use of supported zinc. More recently reported, supported Zn catalysts involve much milder and simpler method of preparation and subsequent reactions in the condensed phase.\textsuperscript{120,121}

A study which focussed on the benzyl chloride-benzene reaction, showed that of a wide range of K-10 supported metal salts, ZnCl\textsubscript{2} was the reagent of choice.\textsuperscript{120} Supported ZnCl\textsubscript{2} or 'clayzic' proved to be a remarkably reactive catalyst in this reaction giving complete conversion of the alkylating agent in 0.25h at r.t., a much faster reaction than what could be achieved with an ion-exchanged material. ZnCl\textsubscript{2} doped on the surface of alumina proves to be a better Lewis acid and this has been used to carry out important organic reactions like Michael addition\textsuperscript{122} for example of silyl enol ethers to methyl vinyl ketone as shown below.

\[ \text{OSiMe}_3 + \text{Acidic alumina doped with ZnCl}_2 \rightarrow \text{O}_3 \]
The notable changes of this procedure involving combinations of Al₂O₃ and Zn involve clean and fast additions, simple operations, no need of chromatographic separation (no side product formed), involvement of no toxic and expensive reagent, high yields and mild conditions.

Catalysts using supported reagents and related materials, notably zeolites and molecular sieves, is rapidly emerging as a new ‘enviro-technology’. Zeolites are widely used as selective catalysts especially in the petrochemical industry.\textsuperscript{123,124} Specific channel structures present in zeolites result in molecular activity where size and scope of a diffusing substrate or product are closely matched to a support pore diameter. However their use in liquid-phase organic reaction chemistry as acid catalysts has been limited primarily due to applications taking advantage of the molecular sieving abilities of the small pore zeolites in drying and selective absorption. New molecular sieve catalysts with increasing pore diameters are able to catalyze a broader spectrum of liquid-phase organic reactions relevant to the bulk and especially chemical industries.\textsuperscript{125} In particular, zeolite catalysts make reaction processes expedient, cost effective, environmentally benign, and act as both Bronsted and Lewis acids in their natural or ion-exchanged forms, enabling them to function as efficient catalysts for various organic transformations.

Organic reactions were found to occur efficiently in the solid state which shows that molecules of reactant and reagent can move in the solid state. In fact, host guest inclusion complexation occurs by mixing both crystals in the solid state. Organic solid state reactions are usually carried out by keeping a mixture of finely powdered reactant and reagent at r.t. In some cases, solid state reactions are accelerated by heating, shaking, and irradiation with ultrasound or grinding of the reaction mixture using a mortar and pestle. Generation of local heat by grinding of crystals of substrate and reagent by mortar and pestle is also helpful. Mechanical processing (pestle and mortar) of solids is a scaleable technique which is routinely used in materials science\textsuperscript{126,127} and in the pharmaceutical industry.\textsuperscript{128} Solvent free machanochemistry has a potential to become an alternative to conventional organic synthesis.

In recent years, reagents impregnated on mineral solid supports,\textsuperscript{129,130} which are efficient in ‘dry media’, and assisted by microwaves have gained popularity in organic synthesis because of their enhanced selectivity, ease of handling, simple work up, solvent free reaction conditions.

\textit{Introduction}
and improved reaction rates. A large number of reactions have been successfully implemented on the solid supports with or without using microwaves.

1. Catalysis

Tetrabutylammonium bromide\textsuperscript{131} (TBAB) in the molten state has been demonstrated to be a very efficient and recyclable catalyst for trans-thioacetalisation of \( O,O \)-acetals to \( S,S \)-acetals under solvent free conditions.

\[
\begin{align*}
R_1 & \quad \text{HS} - (\text{CH}_2)_{m} - \text{SH} \\
\text{TBAB} & \quad \text{R}_1R_2
\end{align*}
\]

\( n = 1,2 \)

\( m = 2,3 \)

\( R_1 = \text{Ph}, \text{4-}O_2\text{NC}_6\text{H}_4, \text{4-CH}_2\text{OC}_6\text{H}_4, \text{PhCH} = \text{CH}, \text{CH}_3(\text{CH}_2)_2\text{CH}_2 \)

\( R_2 = \text{H} \)

Direct 1,4-conjugate addition\textsuperscript{132} of naked aldehydes to vinyl ketones is catalyzed effectively by \( N \)-methyl-3-aminopropylated FSM-16 mesoporous silica, which can be regarded as a novel heterogeneous catalysis for a practical carbon-carbon bond formation reaction.

\[
\begin{align*}
\text{R}_1\text{CH}=\text{O} & \quad + \quad \text{O} = \text{R}_2 \\
\text{FSM-16} & \quad \text{R}_1\text{C}=\text{O}
\end{align*}
\]

2. Oxidation

The oxidation of benzylic alcohols to benzaldehydes by bismuth (III) nitrate\textsuperscript{133} was investigated in the presence of various acidic aluminosilicates.

\[
\begin{align*}
\text{PhOH} & \quad \text{Bi(NO}_3)_3\cdot 5\text{H}_2\text{O} \\
\text{Clay or Zeolite} & \quad \text{acetone} \\
\text{R} & \quad \text{H, OPh}
\end{align*}
\]
Lee et al.\textsuperscript{134} studied the oxidation of styrene and cinnamic acid derivatives to corresponding substituted benzaldehydes by using permanganate under heterogeneous conditions.

\[
\text{CH}=\text{CH} \rightarrow \text{CHO} \quad \text{K MnO}_4 \quad \text{Solid Support} \n\]

\text{Solid Support} = \text{Alumina, Amberlite 1200 (H), Amberlite 36, Amberlite RG 50 (H), SiO}_2, \text{Florisil}

Ley and coworkers\textsuperscript{135} have carried out the oxidation of \textsuperscript{18} alcohols to the corresponding acids using selected immobilised oxidizing reagents in a single reaction vessel.

\[
\text{R OH} \quad \xrightarrow{\text{PS-TEMPO}} \quad \text{R COH} \quad 76-98\%
\]

PS-TEMPO = 4-(polystyrylmethyloxy)-2,2,6,6-tetramethylpiperidin-1-yloxy

3. Rearrangement

Chandrasekhar and coworkers\textsuperscript{136} reported the solid state Beckmann rearrangement of several ketoximes upon heating below their melting point for 5-48 h in excellent yields in solvent free conditions.

\[
\text{NOH} \quad \xrightarrow{\text{HCl}, \text{70-130}^\circ \text{C}, 5-48 \text{~h}} \quad \text{R NHCOR'} \quad 83-96\%
\]

\(\text{R}_1, \text{R}_2 = \text{Ph, Me, \text{p-Tolyl}}\)

Clark et al.\textsuperscript{137} have reported the rearrangement of \(\alpha\)-pinene oxide to campholenic aldehyde using MTS-Zn triflate.

\textit{Introduction}
4. Aza Diels-Alder reaction

The montmorillonite K-10 catalysed Aza Diels-Alder reaction\(^\text{138}\) of Danishefsky’s diene with aldimines, generated in situ from aliphatic aldehydes and \(p\)-anisidine proceeded smoothly in water or in aq. CH\(_2\text{CN}\) to afford 2-substituted 2,3-dihydro-4-pyridones in excellent yields.

\[
\begin{align*}
\text{N} & \text{C}_6\text{H}_4-p\text{-OMe} + \text{TMSO} + \text{OMe} & \text{Mont. K-10} \\
\text{r.t.} & \rightarrow & \text{PMP} \\
\end{align*}
\]

5. Protection

Kad \textit{et al}\(^\text{139}\) have developed two effective methodologies for the preparation of oximes from aldehydes and ketones which has the advantage of being eco-friendly, easy to handle, and solventless conditions using in one method microwave irradiation and in another pestle and mortar.

\[
\begin{align*}
\text{R} & \text{R'} + \text{NH}_2\text{OH.HCl} & \text{(i) Al}_2\text{O}_3 \text{(wet), MWI} \\
& & \text{(ii) Pestle and mortar} \\
& & \text{Molecular Sieves} \\
\end{align*}
\]

R = Aliphatic
R’ = -H, Aliphatic

Kad \textit{et al}\(^\text{140}\) have developed an efficient solvent free methodology for microwave assisted preparation of 1,3-dithiolanes from ketones under MWI.

\[
\begin{align*}
\text{KH} & \rightarrow \text{SH} \\
\text{K-10 Clay, MWI} & \text{640W, 7 min.} \\
\end{align*}
\]
Silica-gel supported metallic sulphates are found to be efficient catalysts for the protection of both aromatic and aliphatic aldehydes as 1,3-dioxolanes under MWI in solvent free conditions.

![Chemical structure](image)

6. Deprotection

An effective, eco-friendly and simplistic approach towards the regeneration of aldehydes and ketones from the corresponding oximes has been described using QCC\textsuperscript{142} in combination to MWI and also with a pestle and mortar.

\[ \text{CH}=\text{NOH} + \text{QCC} \rightarrow \text{CHO} \]

(i) MWI, 1 min.

(ii) p/m

Yadav \textit{et al}\textsuperscript{143} have achieved a mild and selective hydrolysis of \textit{t}-butyl esters to their parent carboxylic acids in high yields using reusable solid acid KSF clay in refluxing acetonitrile thereby leaving solid acid- and base-labile protecting groups intact.

![Chemical structure](image)

Bose and coworkers\textsuperscript{144} has studied silica gel adsorbed ferric chloride induced catalytic cleavage of oximes and hydrazones to parent carbonyl compounds under solvent free conditions in excellent yields.

\[ \text{R} \text{N-X} \xrightarrow{\text{FeCl}_3, \text{SiO}_2} \text{R} \text{R'} \text{X} \]

\( X = \text{OH, NMe}_2, \text{NHTs, NHPh} \)

\( \text{R, R'} = \text{Aryl, Cyclic} \)

\textit{Introduction}
7. Cyclization

Facile synthesis of cyclic ethers from dihalo compounds on alumina has been accomplished in high yields.\textsuperscript{145}

\[
\begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\end{array} \xrightarrow{\text{Al}_2\text{O}_3/\text{Hexane}} \begin{array}{c}
\begin{array}{c}
\text{O}
\end{array}
\end{array} \\
\text{92%}
\]

8. Condensation

An efficient and convenient procedure for the preparation of 3-cinnamoyl-2-methyl-1,8-napthyridines has been achieved by the Claisen-Schmidt condensation\textsuperscript{146} of 3-acetyl-2-methyl-1,8-napthyridines with aromatic aldehyde in the presence of KOH in the solid state in good yields.

\[
\begin{array}{c}
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3
\end{array}
\end{array} \xrightarrow{\text{ArCHO/KOH}} \begin{array}{c}
\begin{array}{c}
\text{Ar}
\end{array}
\end{array} \\
\text{84-94%}
\]

Kabalka and coworkers\textsuperscript{147} have reported a microwave enhanced, solvent free Mannich condensation-cyclization sequence involving the reaction of o-ethynylphenol with secondary amines and \textit{para}-formaldehyde on cuprous iodide doped alumina in the absence of solvent to generate 2-(dialkylaminomethyl)benzo[\textit{b}] furans in good yields.

\[
\begin{array}{c}
\begin{array}{c}
\text{R}
\end{array}
\end{array} + (\text{CH}_2\text{O})_n + \text{HNR}_1\text{R}_2 \xrightarrow{\text{Cul/Al}_2\text{O}_3/\text{MWI}} \begin{array}{c}
\begin{array}{c}
\text{NR}_1\text{R}_2
\end{array}
\end{array} \\
\text{R = H, CH}_3, \text{CH}_3\text{CO} \\
\text{R}_1, \text{R}_2 = \text{Aliphatic, Cyclic}
\]

9. Functional Group Transformation

Zolfigol and coworkers\textsuperscript{148} have utilized combination of silica sulphuric acid and sodium nitrite in the presence of wet silica for effective nitrosating agent for the chemoselective N-
nitrosation of secondary amines to their corresponding nitroso derivatives under mild and heterogeneous conditions in effective yields.

$$\text{SiO}_2\text{OH} + \text{CISO}_3\text{H (neat) } \xrightarrow{r.t.} \text{SiO}_2\text{OSiO}_3\text{H} + \text{HCl}$$

Neat chlorosulphonic acid reacts with silica gel to give silica sulphuric acid is immobilized on the surface of silica gel via a covalent bond.

$$\text{R}_1\text{R}_2\text{NH} \xrightarrow{\text{NaNO}_2, \text{Wet SiO}_2\text{DCM, r.t.}} \text{R}_1\text{R}_2\text{N} = \text{N}$$

$$\text{R}_1, \text{R}_2 = \text{Aliphatic, Cyclic, Benzyl}$$

Ley et al.\textsuperscript{49} have reported the conversion of a range of aldehydes to nitriles by using a polymer supported reagents in high yields. This methodology provides a clean and efficient route to more diverse blocks for combinatorial programs.

$$\text{R} = \text{O} \xrightarrow{\text{NMe}_3 \text{RuO}_4} \text{R} = \text{O} \xrightarrow{(i) \text{mCPBA}} \text{R} = \text{C=N}$$

A new and practical method for the conversion of nitriles to amides\textsuperscript{50} by employing the $$\text{Al}_2\text{O}_3/\text{CH}_3\text{SO}_3\text{H}$$ is described.

$$\text{Al}_2\text{O}_3 \xrightarrow{\text{CH}_3\text{SO}_3\text{H}} \text{O} \xrightarrow{\text{NH}_2} \text{95\%}$$

10. Wittig Reaction

The mechanically induced solid-state generation of ylides and the solvent free Wittig reaction\textsuperscript{51} can be successfully carried out as a ‘one-pot’ process starting with triphenylphosphine, an organic halide and an organic carbonyl compound in the presence of $$\text{K}_2\text{CO}_3$$.
11. Esterification

Kappe and Staler\textsuperscript{152} investigated the Cs\textsubscript{2}CO\textsubscript{3}-mediated ester formation with Wang resin-bound benzoyl chloride.

12. Synthesis

Singh and coworkers\textsuperscript{153} have reported a short, simple and elegant synthesis of Elvirol, Curcuphenol using Mont. K-10 clay in dry media.

\textit{Introduction}
Organic synthesis on solid support is a rapidly developing methodology, which offers several advantages if compared to traditional synthesis in solution. Toda et al.$^{109,110,129}$ have also introduced ‘solid-state chemistry’ which in most cases does not make use of any solvent, these reactions are also termed as ‘dry-media’ reactions. These have been used for a wide variety of reactions as reported in reviews.$^{154}$

Another very efficient and popular non-conventional methodology for organic synthesis in recent times involves the use of ultrasonic waves. Ultrasound$^{155}$ can be defined as sound of frequency beyond that to which human ear can respond that is greater than 16 kHz. Ultrasound encompasses frequencies ranging from 20 kHz to 10 MHz, which corresponds to wavelengths of 7.6 to 0.015 cm. The broad classification of ultrasound can be subdivided into three distinct regions (Figure 7).

![Figure 7 Classification of Sound Frequency](image)

- Conventional power ultrasound (20 to 100 kHz) generally used for industrial processing and sonochemistry.
- Extended frequency range for sonochemistry (100 kHz to 2 MHz).
- Low power high frequency ultrasound (5 to 10 MHz) used for diagnostic purposes.

The term ‘Sonochemistry’ is used to describe the effect of sound waves to chemical reactivity. The name is derived from the prefix *sono* indicating sound paralleling the longer established techniques that uses light (*photochemistry*) and electricity (*electrochemistry*) to

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*Introduction*
achieve chemical activation. Its application to chemistry began in 1927 with investigations by Richards and Loomis.\textsuperscript{156} Since 1980, the synthetic potential has attracted the attention of researchers.

Ultrasound is more familiar in context to animal communications (bats, dog whistles, etc.), medical diagnosis (foetal scanning), materials testing (flow detection), underwater ranging (depth gauges) or SONAR (SOund Navigation And Ranging), flow detection in metals and other materials, cleaning ultrasonic baths, cleaning and drilling of teeth, plastics and metals welding. There are two distinct ranges of ultrasound: diagnostic (for physical measurements) and power (to influence chemical reactivity).

Sir John Thornycroft and Sidney Barnaby\textsuperscript{157} characterized an effect called ‘Cavitation’ through which power ultrasound influences the chemical reactivity of a system. Cavitation is the production of microbubbles in a liquid that are formed when a large negative pressure is applied to it. There are two basic methods\textsuperscript{158} to induce cavitation in liquids that are outlined in figure 8.

On the one hand, cavitation occurs if a sufficiently high tension is generated in a liquid. This can be achieved by fluid flow (hydrodynamic cavitation) or by ultrasound (acoustic cavitation). On the other hand, cavitation can occur if a sufficiently high amount of energy is deposited locally in a liquid e.g. with a laser. Acoustic cavitation is responsible for the chemical effects in the following manner.

Ultrasound like sound and infrasound is made up of pressure waves, i.e. mechanical waves which require an elastic medium to propagate and they do so in the form of longitudinal

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waves. When high frequency sound waves pass through a liquid, the particles of the liquid vibrate in the same direction as the waves propagate and alternating rarefactions and compressions cycles are set up that cause low and high pressure areas respectively and result in acoustic cavitation. The rarefactions exert a negative pressure which when strong enough will cause the distance between the molecules to exceed the critical molecular distance necessary to hold the liquid intact. When this occurs the liquid will break down and voids will be created i.e. cavitation bubbles will be formed. This point is called the cavitation threshold, which is detected by the onset of a ‘Fizzing noise’. These bubbles are filled with liquids with pressure below its vapour pressure thus forming a series of gas and vapour filled cavities. It is only at powers above the cavitation threshold that sonochemistry can occur because only then can the great energies associated with cavitation collapse be released into the fluid. There are two forms of cavitation, stable and transient.

The larger bubbles or ‘stable cavitations’ have a longer lifetime relative to the acoustic cycle and can oscillate non-linearly (radially) with the sound wave not causing any chemical affect. They have an existence of many cycles. The smaller bubbles or ‘transient cavitations’ exist for no more than a few acoustic cycles (figure 9).

Figure 9 Lifetime Of An ‘Acoustic Transient Caviation Bubble

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Under proper conditions, these bubbles undergo a cycle of generation (I), growth (II) and subsequent implosive collapse (III) known as ‘transient cavitation’ as shown in figure. These bubbles can expand to at least two or three times their initial size before collapsing violently into smaller bubbles generating high energies in the bubbles involving pressures of thousands of atmospheres (10⁹ Pa or approx. 1000 atm.) and temperatures of thousands of degrees (10³ to 5x10³ K) at the point of collapse.

Important factors controlling the effectiveness of an ultrasound mediated reaction involve:
- The frequency of the waves, its optimum range being from 10 Hz to 10 MHz, when the ultrasonic frequency is increased into the MHz region it becomes more and more difficult to produce cavitation in liquids.
- Changes in the power input to the transducer.
- An ambient temperature of the bulk.
- Presence of ambient gases, such as the monoatomic noble gas, neon, argon, etc.
- Solvents with low vapour pressures are preferred as their sonication results in the formation of micro-bubbles that are more or less void and whose collapse produce highly energetic shock waves, such as in ethereal solvents, water and ethanol.

Four different types of devices are available for producing ultrasound for chemical synthesis namely whistle reactor which is a mechanical transducer device and is predominantly used for homogenization and emulsification. However problems can arise when using abrasive suspensions and coarse powder. Ultrasonic cleaning bath is most accessible, convenient and simplest instrument available. It comprises of water filled stainless steel bath with ultrasonic transducers firmly attached underneath the flat base of the bath (figure 10).

![Image of Ultrasound Cleaning Bath](image-url)
The temperature control is generally poor in this system and so the system may require additional thermostatic control. A drawback in this system is that they don’t operate at the same frequency and so do not give reproducible results.

Direct immersion sonic horn or probe is the most effective method of transmitting ultrasonic energy into a reaction (figure 11). In this case, an ultrasonic probe is placed directly in the reacting system and such a equipment is used for biological cell disruption.

![Diagram of Ultrasonic Probe Apparatus with Modified 'Rossete' Cell]

Figure 11 Ultrasonic Probe Apparatus with Modified ‘Rossete’ Cell
The advantage of such a system is that it allows control over a wide range of frequencies, provides good reproducibility and allows the simultaneous placement of the reaction vessel into a cooling bath. But it is rather expensive, some specialized glassware and efficient cooling is required.

In the cup horn reactor, greater acoustic intensities can be obtained with easier control of temperature. Its disadvantages are similar to those of the cleaning bath in that it is very sensitive to liquid levels and the shape of the reaction vessel. The main difficulty with the cup horn is that it is only for only small scale reactions.

The ultrasonic waves in all these devices are produced by a piezoelectric ceramic, PET which is lead-zirconate-titanate ceramic.

Sonochemistry is an expanding field of study that continues to thrive on outstanding laboratory results. Some of the applications of this technique include the Michael and related conjugate additions\textsuperscript{165} carried out in aq. media.

The conjugate addition reaction under aq. sonochemical conditions of alkyl halides to $\alpha,\beta$-unsaturated carbonyl compounds in the presence of zinc-copper couple,\textsuperscript{166} is an attractive reaction due to its simplicity, ease of use, aq. media (ethanol-water) and compatibility. Sonication of zinc dust and copper iodide leads to the formation of a black suspension of Zn(Cu) couple within 3 min. to which the alkyl halide and $\alpha,\beta$-unsaturated carbonyl compounds are added. The reactivity of alkyl halide is found to be in the order $3^\circ$>$2^\circ$>$1^\circ$ and for the halide it is I > Br. Bromides or iodides can be used with $2^\circ$ and $3^\circ$ alkyl substrates, but for $1^\circ$ alkyl substrates only iodides are effective. Chlorides are however inert. The medium usually consists of a mixture of water, lower alcohols, acetone or even pyridine.

The reaction proceeds giving best results with water as the solvent and mechanism involved is believed to be a free radical\textsuperscript{167} one. It is proposed that a single electron transfer [SET] takes place from the metal surface to the alkyl halide bond.

The alkyl halide is associated to the solvent cage which is rigid and sensitive to cleavage under sonication. The later results in the acceleration of the SET and favours its addition to the Michael acceptor to result in the formation of the $\alpha$-keto radical. However whether this radical is reduced at the partial surface to the enolate followed by protonation is unclear, as this would result in an increase in the pH of the reaction mixture, Luche and co-workers\textsuperscript{166} however

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Observed that it was slightly acidic, that is ~6. So it is believed that the radical picks up the hydrogen free radical from the solvent cage surrounding it to furnish the alkylated product.

Various applications of this method have been reported. Kad et al\textsuperscript{168} have reported an efficient synthesis of many naturally occurring compounds e.g. 3,7-dimethyl-11-oxo-2(E),6(E)-dodecadienol (oxocrinol), 2-methylheptadecane, 6-oxo-1-nonanol and 2-tridecanone involving Zn-Cu couple catalysed conjugate addition of allylic halides to \(\alpha,\beta\)-unsaturated carbonyl compounds promoted by ultrasound waves in aq. media.

Ultrasound gives a way of energizing a chemical system along with more classical methods such as thermal, photochemical and electrochemical. In the last one and a half decades the use of ultrasound has been explored to cover many organic reactions and a number of reviews\textsuperscript{169} have been reported in the literature.

A few important reactions using ultrasound are given in broad categories as follows.
1. Alkylation

Cooper et al.\textsuperscript{170} have reported Friedal-Crafts alkylation reaction used for the synthesis of the anti-inflammatory agent ibuprofen under sonication.

\[
\begin{align*}
\text{CH}_2\text{CH}=&\text{COOH} & \text{CH}_2\text{CH}=\text{COOH} + \text{AlCl}_3 \\
\overset{\text{AlCl}_3}{\text{Sonication}} & \rightarrow & \text{COOH}
\end{align*}
\]

Jurczak and Ostaszewski\textsuperscript{171} reported an efficient alkylation reaction in the synthesis of diazacorand using ultrasonic conditions.

2. Oxidation

Jie and coworkers\textsuperscript{172} reported the oxidation of unsaturated fatty esters to the corresponding oxo derivatives on treatment of substrates with palladium (II) chloride and p-benzoquinone in aq. THF (THF:H$_2$O, 4:1 v/v) under ultrasound in moderate to high yields.

\[
\begin{align*}
\text{R}_1\text{=CH}=\text{CH}-\text{R}_2 & \overset{\text{PdCl}_2, \text{p-benzoquinone aq. THF}, \text{ripp})}{\longrightarrow} & \text{R}_1\text{=CH}_2\text{CO}=\text{R}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 = \text{H, CH}_3\text{(CH}_2\text{)}_{\gamma}, & \text{ CH}_3\text{(CH}_2\text{)}_{\gamma}, \text{ CH}_3\text{(CH}_2\text{)}_{\gamma}, \text{ CH}_3\text{(CH}_2\text{)}_{\gamma} \text{, CH}_3\text{(CH}_2\text{)}_{\gamma} \text{, CH}_3\text{(CH}_2\text{)}_{\gamma}, & \text{CH}_3\text{(CH}_2\text{)}_{\gamma} \text{, CH}_3\text{(CH}_2\text{)}_{\gamma}, \\
\text{R}_2 = \text{-}(\text{CH}_2\text{)}_3\text{COOMe, -}(\text{CH}_2\text{)}_3\text{COOMe, -CH}_2\text{COOMe & -CH}_2\text{COOMe}
\end{align*}
\]

3. Reduction

Chandrasekhar et al.\textsuperscript{173} reported for the first time an efficient ultrasound promoted novel direct conversion of nitro compounds to N-(tert-butoxycarbonyl) amines and N-(ethoxycarbonylamines) using Sn/NH$_4$Cl.

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Several aromatic and aliphatic sulfoxides are selectively deoxygenated to the corresponding thioethers in high to quantitative yields by samarium metal in methanolic NH₄Cl under sonication. Other functional groups such as halides, esters, ethers, olefins, nitriles and ketones are unaffected under the present reaction conditions.

Rama et al have applied ultrasound for the acceleration of reductive dehalogenation of α-haloketones with zinc-dust in presence of ammonium salts under aprotic conditions.

4. Coupling Reactions

Pinacol coupling of aromatic of aldehydes and ketones leading to pinacols has been carried out using Zn-ZnCl₂ in 50% aq. THF under ultrasound in 5-77% yield.

\[
\begin{align*}
\text{R} & \quad \text{CHO} \\
\text{R'} & \quad \text{CHO}
\end{align*}
\]

\[
\text{Zn-ZnCl}_2 \quad \text{HO} \quad \text{OH} \quad \text{R} \quad \text{R'} \\
\text{HO} \quad \text{OH} \quad \text{R} \quad \text{R'}
\]

\[
\begin{align*}
\text{R} & = \text{C}_6\text{H}_5, 4-\text{CH}_3\text{OC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4, \\
& \quad 4-\text{MeC}_6\text{H}_4, 2,4-\text{ClC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4 \\
\text{R'} & = \text{H}, \text{Me}
\end{align*}
\]
Among the carbon-carbon bond forming reactions, Suzuki cross coupling reaction is an extremely versatile methodology. Srinivasan et al\textsuperscript{177} demonstrated palladium catalyzed Suzuki cross coupling reactions of halobenzenes including chlorobenzenes with phenylboronic acid at ambient temperature (30°) in the absence of phosphic ligand using the ionic liquid 1,3-di-n-butylimidazolium tetrafluoroborate [bbim][BF\textsubscript{4}] with methanol as co-solvent under ultrasonic irradiation.

\[
\begin{align*}
\text{Ar-}X + (\text{HO})_2B\text{R}X = \text{I, Br, Cl} \\
\text{R} = \text{H, OCH}_3, \text{CH}_3, \text{Cl, NO}_2
\end{align*}
\]

Banic et al\textsuperscript{178} investigated ultrasound promoted Sm/NH\textsubscript{4}Cl mediated reductive coupling of aromatic ketones.

\[
\begin{align*}
\text{Ar} & \text{Ar'} \xrightarrow{\text{SmNH}_4\text{Cl}} \text{HO} \text{Ar} \text{Ar'} \xrightarrow{\text{OH}} \text{Ar(Ar')CHOH}
\end{align*}
\]

\[
\begin{align*}
\text{Ar} = \text{Aryl} \\
\text{Ar'} = \text{Aryl or Alkyl}
\end{align*}
\]

5. Reformatsky Reaction

The Reformatsky reaction\textsuperscript{179} when applied to Schiff bases leads to \(\beta\)-lactams under sonication in excellent yields.

\[
\begin{align*}
\text{Ar} = \text{Ph, 4-MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4
\end{align*}
\]

6. Rearrangement

Toma et al\textsuperscript{180} has studied the benzil-benzylic acid rearrangement under phase-transfer conditions. No rearrangement was observed using 50% KOH solution-toluene and benzyltriethylammonium chloride (TEBA) as the catalyst with or without sonication.
7. Cannizzaro reaction

Ultrasound accelerates the Cannizzaro reaction\textsuperscript{181} of p-chlorobenzaldehyde under phase transfer conditions. Of the three PTCs which were tested – benzyltriethylammonium chloride (TEBA), aliquat and 18-crown-6, TEBA was found to be the most effective.

\[
\text{RCHO} + \text{KOH} \xrightarrow{\text{Toluene, TEBA, PTC}} \text{RCOOH}
\]

8. Synthesis

A large variety of organic compounds have been synthesized through the use of sonochemistry.

Yadav \textit{et al}\textsuperscript{182} have reported ceric ammonium nitrate catalyzed three components condensation of an aldehyde, \(\beta\)-ketoester and urea in methanol to afford the corresponding dihydropyrimidinones in excellent yields under sonication.

\[
\text{RCHO} + \frac{O}{\text{R}_1 \quad \text{O}} + \text{CAN, Urea (3:3:2)}, \text{MeOH} \rightarrow \text{O} \quad \text{R}_2 \quad \text{NH} \quad \text{N}\text{O} \quad \text{O} \quad \text{R} \quad \text{R}.
\]

\( \text{R} = \text{C}_6\text{H}_5, 4\text{-CIC}_6\text{H}_5, \text{C}_6\text{H}_5\text{CH}_2, 3,4\text{-}(\text{MeO})_2\text{C}_6\text{H}_4, 3,4\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 4\text{-O}_2\text{NC}_6\text{H}_4, \text{Cyclohexyl, Cinnamyl, Thiethyl, Furfuryl, Hexyl} \)

\( \text{R}_1 = \text{CH}_3, \text{CF}_3 \)

\( \text{R}_2 = \text{C}_2\text{H}_4 \)

84-92%
Sonochemistry is a developing field with a number of such frontiers and a much wide range of applications will come out in the years to come. Recently the buckyball fullerene\textsuperscript{183} has also been synthesized utilizing ultrasound. Other synthetic applications of ultrasound include activation of metals,\textsuperscript{184} asymmetric synthesis,\textsuperscript{185} Diels-Alder reaction,\textsuperscript{186} Barbier reaction,\textsuperscript{187} waste water treatment\textsuperscript{188} and electrochemical reactions.\textsuperscript{189}

Over the past three decades, the high power techniques have seen a lot of growth, it makes use of high pressures to drive chemical reactions with the aid of simple equipment that can withstand pressures upto 20 kbar (2000 MPa) and with a capacity of 20-50 mL of the reaction mixture or solvent.\textsuperscript{190} Various reactions have been reported by this methodology.\textsuperscript{191-194}

From the ‘green’ aspect, water acts a very attractive solvent for the reaction medium. Water is safe, harmless, non-flammable, non toxic and extremely eco-friendly and has unique physical and chemical properties such as high dielectric constant and high cohesive energy density as compared with most organic solvents. Such inherent properties of water\textsuperscript{6} provide the driving force to the reactions, which cannot be attained in anhydrous organic solvents. Thus, work utilizing aqueous media as an alternative to the traditional non-aqueous organic solvents is rapidly gaining tremendous footholds.\textsuperscript{195} In the case of moisture sensitive reagents, a modification can be carried out in the form of an alternative reagent such as the use of late transition metals\textsuperscript{196} which are less moisture sensitive. Even variants of the Grignard reaction, notoriously sensitive to water, can be run in aqueous protic solvents using a variety of metals such as indium and zinc.\textsuperscript{196} The use of catalyst in aqueous media is considered to be ‘foundational pillars’ of green chemistry\textsuperscript{197} as water can hydrolyze the metal-alkyl bonds and block the coordination sites by binding as a ligand.

It is obvious therefore that these new ‘green’ methodologies have outgrown some of the conventional methods, due to their milder conditions, reductions in time, increased reaction yields and at times the successful occurrence of the reaction not possible by conventional methods.

In addition to the above mentioned methodologies, a large variety of conventional procedures like Li$_2$CuCl$_4$ catalyzed coupling, Wittig reaction, Aldol condensation, conjugate
addition, oxidation, chemoselective reduction etc. have been efficiently utilized during these investigations.

Carbon-carbon bond formation is one of the most important reactions in the synthesis of natural products. Various methods have been used to increase carbon chain length which include alkylation of alkali metal salts of 1-alkyne using n-BuLi, Li/liq.NH₃, LiNH₂/liq.NH₃, Grignard reaction etc.

To increase the carbon chain length, the coupling of Grignard reagents and alkyl halides using transition metal catalysts has been used extensively in organic synthesis.

\[
\text{RMgX + R'Y} \rightarrow \text{R-R' + MgXY}
\]

Good yields of alkylated product are obtained in cases where the alkyl or aryl magnesium reagents do not contain a β-hydrogen atom, as pure products are formed without mixture of alkanes and alkenes due to disproportionation. Optimization of the coupling reaction relative to disproportionation depends mainly on

- The structure of the alkyl groups
- Transition metal catalyst
- The solvent used in the reaction

Tetrahydrofuran is a solvent of choice for these reactions as it offers a number of advantages over other solvents.

Copper (I) catalyses the cross coupling in THF at 0° or lower temperature. Cross coupling depends on the copper (I) assisted nucleophilic displacement of the halide ion from alkyl halide by Grignard moiety and as such is most facile with 1° alkyl halides because then the chances of disproportionation are minimum. It is not the case with 2° or 3° alkyl halides which thus give poor yields of coupled products.

Dilithium tetrachlorocuprate [Li₂CuCl₄] is a versatile copper (II) reagent, which catalyses cross coupling of Grignard reagents with a number of moieties such as alkyl halides, aryl halides, tosylates, mesylates, acetates, dihalides etc. under different conditions. Although the mechanism of the reaction is not clear as yet, a number of workers have exploited the potential of this reagent for elongating carbon chains in the synthesis of a variety of natural products. Some of these are [Z]-7-epoxy-2-methyloctadecene and royal gelly [10-hydroxy-(E)-

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2-decenoic acid\textsuperscript{217} Kad et al\textsuperscript{218} have synthesized phenolic terpene Alliodorin and a bisabolane sesquiterpene, Cucuhydroquinone utilizing this reaction procedure.

Use of trimethylsilyl enol ethers\textsuperscript{219} has been employed as excellent substrates for the acid-catalyzed alkylation of carbonyl compounds.

$\text{RCH}_2\text{COR'} \xrightarrow{\text{Me}_3\text{SiCl, DBU}} \text{RCH=CH}\text{OSiMe}_3$

The synthetic development of silyl enol ethers can be divided into three distinct phases. These separate phases involve:

- The use of silylation as a trap for equilibrium or kinetically generated enolate ions, with subsequent isolation, regeneration and reaction with electrophiles under basic conditions.
- Direct reaction of silyl enol ethers with suitable electrophiles, which are either good Lewis acids in their own right or can be made so by addition of Lewis acid catalyst.
- The uses of silyl enol ethers as synthons, which give reaction products that are different from those obtainable by either of the first two phases.

Triethylamine is the frequently used base for enol trimethylsilylation of carbonyl compounds\textsuperscript{220} under equilibrium conditions. However enol trimethylsilylation with this base in combination with chlorotrimethylsilane requires rather vigorous conditions (refluxing in $N,N'$-dimethylformamide for several hours)\textsuperscript{221}.

The use of 1,8-diazabicyclo[5.4.0]undec-7-ene\textsuperscript{222} as a base in combination with chlorotrimethylsilane provides a rapid, mild and efficient method of enol silylation of various carbonyl compounds.

The use of silyl enol ethers in organic synthesis is truly vast and this area of research has been well reviewed.\textsuperscript{219,223} These are important intermediates for the formation of C-C, C-N, C-S bonds. Some selected reactions of silyl enol ethers with electrophiles\textsuperscript{224} are discussed below.

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Primary and secondary alkyl groups can be introduced to the α-position of a carbonyl group by enolate alkylation with reasonable high regioselectivity, but attempted introduction of tertiary alkyl groups using enolate anions as nucleophile results in predominant 1,2-elimination processes occurring on the alkylation agent e.g. a tertiary alkyl halide. In the presence of Lewis acids (TiCl₄, SnCl₄, ZnX₂) they react with tertiary alkyl halides to give alkylated product in high yields.²⁰

It is supposed that the Lewis acid promotes ionization of the halide, RX, to form the cation, R⁺, which is trapped by the silyl enol ether to give the addition product which is rapidly desilylated.

This general method of activation of the electrophilic alkylation agent fails, as one might expect with simple 1° and 2° alkyl halides. It can, however be extended²² to a wide range of
S_N1 type alkylation moieties, such as benzylic, secondary, allylic and α-methoxy halides.

One of the important steps in the synthesis of natural products is the formation of a carbon-carbon double bond in specific position with a requisite stereochemistry. In this context, some of the important methods for obtaining cis- and trans-isomers are outlined in the following discussion.

Over the years, many methods for the generation of olefinic bond have been developed with varying degrees of success. These include dehydrogenation of alkyl halides, dehydrogenation of alcohols, Wittig reaction, Horner-Wittig reaction, catalytic hydrogenation of acetylenic bond, Aldol condensation, to name a few.

Since its development the ‘Wittig reaction’ has remained one of the most versatile, efficient and unambiguous routes utilized in synthetic organic chemistry for the stereoselective synthesis of olefins as reported by Wittig and Schollkopf. This reaction proceeds under mild conditions and is remarkably free from rearrangements and is regioselective. The steric course of the reaction can be controlled by appropriate experimental conditions and the structure of the reactants.

\[
\begin{align*}
\text{O} & \quad + \quad \text{Ph}_3\text{P} & - & \quad \text{R} \\
\text{C} & \quad \text{C} & \quad \text{C} & \quad \text{R} \\
\text{O} & \quad \text{R'} & \quad \text{R'} & \quad \text{Ph}_3\text{PO}
\end{align*}
\]

In the Wittig reaction an aldehyde or ketone is treated with phosphorus ylide (also called a phosphorane) to give an olefin. Phosphorus ylides (or phosphoranes) are resonance stabilized structures in which there is some overlap between the p-orbital and one of the d-orbital of the

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phosphorus atom. They are usually prepared by treatment of a phosphonium salt with a strong base such as BuLi, NaNH₂ NaH and phosphonium salts are usually prepared from quaternization of the phosphine with an alkyl halide. The phosphorus ylide may also contain double or triple bonds and certain functional groups.

\[
\text{Ph}_3\text{P} + \text{X—CH—R} \xrightarrow{\text{C}_6\text{H}_6 \Delta} \text{X—Ph}_3\text{P}^+—\text{CH—R}
\]

Phosphonium Salt

Base

\[
\begin{array}{c}
\text{Ph}_3\text{P}^+—\text{C—R} \\
\text{R'}
\end{array}
\quad \longleftrightarrow \quad
\begin{array}{c}
\text{Ph}_3\text{P}==\text{C—R} \\
\text{R'}
\end{array}
\]

Ylide

Reaction with a carbonyl compound takes place by attack of the carbanion carbon of the ylide form on the electrophilic carbon of the carbonyl group with the formation of a betaine intermediate which collapses to the products by way of a four-membered transition state, the driving force being provided by formation of the very strong P-O bonds. The reaction has been suggested to proceed according to the following mechanism.

\[
\text{R}_3\text{P}—\text{C}—\text{R}_1 \quad \longleftrightarrow \quad \text{R}_3\text{P}==\text{C—R}_1
\]

\[
\text{R}_3\text{P}==\text{O} + \text{R}_2\text{C}==\text{C—R}_3 \quad \longleftrightarrow \quad \text{R}_3\text{P}—\text{C}==\text{C—R}_3
\]

Recently, it has been argued that Wittig reaction proceeds not via betaines but through four-centered transition-state (quasi-betaine) leading directly to oxa-phosphetanes. This reaction is usually carried out in non-polar solvents in the absence of lithium salts or in dipolar solvents like DMF, DMSO or HMPA.

The stereochemistry of the Wittig reaction is also controlled by the structure of the ylide. The deficiency in the electron density at ylide carbon atom hinders electrophilic attack by the

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carbonyl carbon so that nucleophilic attack on ylide phosphorus by the carbonyl oxygen becomes more probable. Other factors which control stereochemistry are solvent, cation, temperature and type of aldehyde. Z-Stereoselectivity is maximized by polar aprotic solvents, exclusion of lithium salts and low reaction temperature.

The reaction of non-stabilized ylides with aldehydes can be induced to yield E-alkenes with high stereoselectivity by a procedure known as the Schlosser modification of the Wittig reaction.

Schlosser modification of the Wittig reaction has demonstrated how ω-hydroxyalkyltriphenylphosphonium bromides of varying lengths give high yields of (E)-isomer in a one-pot reaction with 99.5% isomeric purity. The (Z)-isomer with 97-98% stereoisomeric purity is attained by using ‘instant ylides’ with the inert base used being NaNH₂. The general reaction sequence to obtain the two isomers is as follows.

\[
\begin{align*}
\text{(C}_6\text{H}_5\text{)}_3\text{P}^-\text{CH}-(\text{CH}_2)_n^-\text{ONa} & \quad \text{R}_1\text{C}=\text{O} \quad \text{R}_2\text{C}=\text{CH}-(\text{CH}_2)_n^-\text{OH} \\
\text{cis} & \\
\text{[(C}_6\text{H}_5\text{)}_3\text{P}^-\text{CH}-(\text{CH}_2)_n^-\text{CH}_2\text{OH}]\text{Br}^- & \quad \text{2 LiC}_6\text{H}_5\text{LiBr} \quad \text{(C}_6\text{H}_5\text{)}_3\text{P}^-\text{CH}-(\text{CH}_2)_n^-\text{CH}_2\text{OLi} \quad \text{LiBr} \\
\text{RCHO} & \quad \text{LiC}_6\text{H}_5\text{LiBr} \quad \text{(C}_6\text{H}_5\text{)}_3\text{P}^-\text{CH}-(\text{CH}_2)_n^-\text{CH}_2\text{OLi} \quad \text{HCl} \quad \text{KOC(CH}_3\text{)}_3 \quad \text{R}=\text{C}-(\text{CH}_2)_n^-\text{CH}_2\text{OLi} \quad \text{trans}
\end{align*}
\]

The aldol condensation of an aldehyde and an aldehyde or a ketone is another important carbon-carbon bond forming reactions in organic synthesis.

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In this reaction $\alpha$-carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another. The reaction proceeds through the form of intermediate $\beta$-aldols or $\beta$-ketones which on dehydration yield the $\alpha,\beta$-unsaturated aldehydes or ketones.

Aldol condensation of aldehydes/ketones is catalyzed by acids and bases. Aldol condensation can be accomplished by using a variety of acid and base catalysts such as NaOH, KOH, potassium-t-butoxide, primary and secondary amines, piperidine, hydrochloric acid, POCI$_3$, to name a few. Many reviews have also appeared in literature regarding aldol condensation.

Kad et al$^{243}$ reported the aldol condensation of aromatic aldehydes and ketones in aqueous media using microwaves.

Toda et al$^{244}$ have successfully conducted aldol condensation of aromatic aldehydes and acetophenone using sodium hydroxide in the absence of solvent in pestle and mortar. Aldol condensation proceeds more efficiently and selectively in the absence of any solvent as compared to the reaction in solution as the former type of reaction has a high concentration of reagents that enhances the speed of the reaction. The molecules are arranged regularly in the crystals, so the reaction proceeds more selectively.

Organic synthesis is a highly potential field of reactions in which oxidation and reduction represent most fundamental type of reactions in organic synthesis. Oxidation in organic chemistry is apparently of great value as a fundamental process and has wide scope of chemical conversions.$^{245}$ It remains however of considerable interest to develop new reagents for oxidation reactions.

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Chromium based oxidants are probably the most widely used of all oxidizing agents. Chromium during oxidation is reduced from hexavalent to trivalent state. The transformation that is most often effected with CrO$_3$-based oxidants is the conversion of an alcohol to the corresponding ketone or aldehyde. The mechanism of alcohol oxidation is outlined below.

$$\ce{R_2CHOH + HO\ce{CrO_4}^- + H^+ \rightarrow R_2CHO\ce{CrO_3}H + H_2O}$$

Jones oxidation is one of the best known and most widely used methods of oxidation using Cr(VI). The procedure, which is amenable to large-scale preparation, uses a standard chromic acid/H$_2$SO$_4$ solution of the alcohol in acetone. Acetone performs a dual function: (a) it is an excellent solvent for a wide range of organic molecules (b) it protects the substrate from overoxidation or undesired side reactions by reacting with the excess oxidant itself. Among the other uses, the foremost use of Jones oxidation has been conversion of saturated alcohols to the corresponding acids. The progress of the oxidation is indicated by a colour change from the orange Cr(VI) oxidant to green colour of the hydrated Cr(III) ion product.

Pyridinium chlorochromate (PCC), first developed by Corey and coworkers in 1975, is a commercially available, stable, easily prepared which can be stored in air. PCC shows a high capability to convert 1° alcohols to aldehydes with great efficiency.

PCC has shown a slightly acidic character and it does not react with simple olefinic carbon-carbon double bond.

Another very useful Cr(VI) reagent is pyridinium dichromate (PDC), which has been used previously but it was Corey and coworkers who demonstrated the wide applicability.

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of this mild and selective oxidant in organic synthesis. 1° and 2° allylic alcohols and saturated 2° alcohols are oxidized to the corresponding carbonyl compounds quickly and in high yields at r.t. in DMF. There is no appreciable overoxidation of allylic alcohols in DMF, but 1° alcohols are readily oxidized to their corresponding acids. By using PDC as a suspension in DCM it becomes a selective oxidant for the preparation of saturated or unsaturated aldehydes.

QCC is a yellowish brown solid that possesses excellent selectivity for the oxidation of primary alcohols in the presence of secondary alcohols. Utility of QCC as an effective deprotecting agent for oximes to carbonyl compounds is also reported.

Another versatile oxidizing agent is QFC which has been used for the selective oxidation of aliphatic and aromatic alcohols and oxidative deoximation of oximes to corresponding carbonyl compounds.

Selective oxidation of allylic methyl groups of gem-dimethyl trisubstituted olefins to trans α,β-unsaturated alcohols and aldehydes remains a reaction of considerable value in organic synthesis. The presence of hydroxy, formyl or oxo groups α- to the double bond is an important feature in organic synthesis. Various reagents to bring about allylic oxidation are H2O2, CrO3-pyridine, SeO2 and recently employed cetyltrimethylammonium chlorochromate. SeO2 has proven to be a reliable reagent in the preparation of α,β-unsaturated aldehydes from corresponding substituted alkenes. A number of re-oxidants for selenium (IV) oxide have been examined, with best results from tert-butylhydroperoxide which serves to re-oxidize the spent catalyst. Oxidation of alcohols at allylic position with selenium dioxide in different solvents yields different compounds such as allylic alcohols and their dehydration products, esters, ethers and α,β-unsaturated carbonyl compounds. Commonly used solvents are dioxane, acetic acid, acetic anhydride, ethanol, DCM, water, benzene, methanol, ether and CC14.
It has been reported recently that allylic oxidation by \( \text{SeO}_2 \) in the presence of TBHP yields mainly allylic aldehydes with (\( E \))-geometry, in better yields and reaction went off neatly although removal of tert-butylhydroperoxide from the product is a little bit difficult.

Sharpless suggested the mechanism involving allylseleninic acid as the intermediate, that reacts via the [2,3]-sigmatropic rearrangement and final hydrolysis of the Se (II) ester to the allylic alcohol. Further oxidation of the alcohol gives \( \alpha,\beta \)-unsaturated carbonyl compound.

However this mechanism implies a higher regio- and stereocontrol than is actually observed. The alternative mechanism put forth by Woggon et al with reduced regio- and stereoselectivity, provides a more satisfactory explanation.
Selenium (IV) oxide has also been used supported on silica gel in combination with TBHP. SeO₂ supported on silica gel becomes extremely selective and attacks from one methyl group of iso-butenyl moiety. The cause of this selectivity may be that the reagent when supported on silica matrix attacks only those groups exposed maximally or in the least hindered position.

Singh et al. utilized SeO₂/t-BuOOH adsorbed on SiO₂ for oxidation of allylic methyl groups to trans-α,β-unsaturated aldehydes under MWI.

The reduction of the carbonyl group of aldehydes and ketones to the corresponding alcohol is ubiquitous in organic synthesis and has attracted considerable interest. Since the first report of reduction using diborane, more than half a century ago, metal hydride reagents have achieved prominence as the reagents of choice for performing this synthetic transformation.

A number of metal hydrides have been developed as reducing agents in organic chemistry, but the most commonly used are lithium aluminium hydride or sodium borohydride. These reagents carry reductions by the hydride transfer from boron or aluminium.

Sodium borohydride is a mild reducing agent which reacts slowly with water and most alcohols at room temperature NaBH₄ is more discriminating in its action as compared to LiAlH₄. It reduces aldehydes and ketones but does not attack esters, amides and isolated carbon-carbon double bond.

\[
\text{H} - \text{P} - \text{H} \quad \text{R} \quad \text{R} \\
\text{M}^+ \quad \text{O} \\
\text{H} \quad \text{H} \quad \text{H}
\]

The mechanism of reduction involves nucleophilic transfer of hydride to the carbonyl group. Activation of the carbonyl group by coordination with a metal cation is probably involved under most conditions.

Varma et al. reported a simple and rapid reduction of carbonyl compounds under solvent free ‘dry’ conditions using NaBH₄-alumina and MWI.

\[
\text{R} \quad \text{CHO} \quad \text{NaBH₄/Al₂O₃} \quad \text{MWI} \quad \text{R} \quad \text{OH}
\]
When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be chemoselective. A number of reagents have been known for chemoselective reduction of α,β-unsaturated carbonyl compounds.

A difficulty that occasionally arises when carrying out nucleophilic substitution reactions is that the reactants do not mix. For a reaction to take place the reacting molecules must collide. As an alternative to a homogeneous reaction, a two-phase reaction can be considered when the organic phase contains the substrate and the aqueous phase contains the nucleophile. Consequently, when two reactants are brought together, their concentration in the same phase is too low for convenient reaction rates.

One way to overcome this problem is 'phase transfer catalysis'. Phase transfer catalysis permits or accelerates reactions between ionic compounds and organic, water insoluble substrates in solvents of low polarity. The basic function of the catalyst is to transfer anions of the reacting species into the organic medium in the form of ion pairs. Phase transfer catalyst (PTC) offers significant advantages over conventional procedures such as no need for expensive anhydrous solvents, improved reaction rates, lower reaction temperature, easier work up and occurrence of reactions that would not otherwise proceed.

Common PTCs are tetrabutylammonium bromide, tetrabutylammonium iodide, tetrabutylammonium bisulfate, benzyltriethylammonium chloride (TEBA), cetyltrimethylammonium chloride, tricaprylmethylammonium chloride, aliquat 336, crown ethers etc.

The original PTC mechanism was proposed by Starks. The numerous carbon atoms give the catalyst organic character (lipophilic) and allow it to be soluble in the organic phase. At the same time, the catalyst also has ionic character (hydrophilic) and can therefore be soluble in aq. phase. Because of this dual nature, the large cation can cross the phase boundary efficiently and transport the nucleophile from the aq. phase to the organic phase.

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**Diagram:**

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\[ RX + [Q^+Y^-] \rightarrow_{\text{Organic Phase}} \rightarrow RY + [Q^-X^+] \]
\[ Na^+ \quad Y^- \quad Q^- \rightarrow_{\text{Interphase}} \rightarrow X^- \quad \text{Aqueous Phase} \]
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An ion pair formed by extraction of anion Y’ into the organic phase by the onium salt cation Q’, undergoes a rapid displacement with RX. The new salt [Q’X’] then returns to aq. phase where Q’ picks up a new Y’ ion for next cycle. As a result the substitution reaction proceeds under relatively mild conditions.

Conversion of tetrahydropyranyl ether directly into its bromide using carbon tetrabromide and triphenylphosphine in anhydrous DCM under nitrogen atmosphere has been recently reported.\textsuperscript{268}

Utilizing some of the above mentioned reactions and ‘green’ methodologies, some important organic transformations and synthesis of a few naturally occurring compounds have been accompanied. The work has been incorporated in two sections comprising of nine chapters. Section A describes the organic functional group transformations carried out during these investigations. It has been further subdivided into six chapters.

Chapter I deals with speedy and regioselective 1,2-reduction of conjugated $\alpha,\beta$-unsaturated aldehydes and ketones using sodium borohydride-iodine.

Oxidation of olefins has been studied by the use of quinolinium chlorochromate and iodine under microwave irradiation which has been introduced in the Chapter II.

Microwave assisted monobromination of diols, cyclic ethers and lactones using 48% aq. hydrogen bromide and phase transfer catalyst is the subject matter of Chapter III.

Chapter IV incorporates functional group transformation. Solid supported Finkelstein reaction for the conversion of mesylates into their corresponding iodides utilizing sodium iodide doped on alumina has been achieved in high yields by utilizing microwave energy.

Selective oxidation of functionalised benzylic and allylic alcohols has been studied by utilizing quinolinium fluorochromate under microwave irradiation in Chapter V.

Chapter VI innumerates with the conversion of aldehydes into imines which has been brought about through the combined use of microwave heating and grinding in a mortar along with molecular sieves.

Section B deals with synthesis of a few natural products and is divided into three chapters.

Chapter VII has been divided into two parts. Part A embodies the first synthesis of pentadecyl-7-hydroxy dodecanoate isolated by Mehta et al from the leaves of Arabotrys...
The key steps involved in the synthesis of this compound are microwave assisted monoprotection of symmetrical diols catalyzed by iodine, esterification using p-TSA and reduction using NaBH₄/Al₂O₃.

Part B includes the first syntheses of undecyl hexadecanoate and 12-hydroxy hentriacontane isolated by Agarwal et al from the leaves of plant Ziziphus mauritiana. The successful use of ‘green’ methodologies namely microwave and ultrasound in esterification, monoprotection, conjugate addition.

Chapter VIII deals with the first syntheses of two novel fatty acids 10-methyl-6(Z)-heptadecenoic acid and 16-methyl-8(Z)-heptadecenoic acid, isolated by Carballeira et al from bacterium Micrococcus from the lake Pomorie in Bulgaria. The syntheses have been accomplished by making use of microwave assisted monobromination of diols, protection of alcohols using DHP/I₂, oxidation and Wittig salt formation. It also includes ultrasonically mediated generation of ylide used in Schlosser-Wittig olefination.

Chapter IX includes the syntheses of three phenyl heptanes namely 1-phenylheptane-1, 5-dione, 7-phenylheptan-3-one and 7-phenylheptan-3-ol isolated from fungus Phellinus tremulus responsible for heart rot in Aspen tree. The key steps include surface mediated Michael addition using ZnCl₂ doped on alumina, aqueous sonochemically zinc couple catalyzed conjugate addition and microwave assisted reduction using NaBH₄ doped on alumina.