Bashir Ahmad Dar

Fundamentals of Green Chemistry

BASHIR AHMAD DAR

FUNDAMENTALS OF GREEN CHEMISTRY

Fundamentals of Green Chemistry
1st edition

ISBN 978-87-403-2936-0
Peer review by Dr Baldev Singh, retired faculty of Indian Institute of Integrative Medicine

CONTENTS

ABOUT THE AUTHOR

Dr Bashir is presently working as Assistant Professor at Govt. Degree College Sopore Kashmir. Previously he was lecturer at University of Kashmir, North campus Baramulla Kashmir. He has also worked as Assistant Professor at Maulana Azad College Aurangabad Maharastra India, Senior Project Fellow IIIM Jammu, Senior Research Fellow IIIM Jammu, Junior Research Fellow IIIM Jammu, Junior Research Fellow (IICT Hyderabad), Lecturer (Maulana Azad College, Aurangabad Maharastra India) and Visiting Lecturer (Post Graduate Department of Chemistry, Vasantroa Nayak College, of Science Aurangabad Maharastra India. He has 12 years of experience in teaching and research. Dr Bashir has published more than 50 research papers in highly reputed journal. He has also published some books on different topics of chemistry. He is editor and peer reviewer of many chemistry journals. He has participated in the scientific committee of several conferences and associations and has delivered many invited talks in India and abroad. His research interests involve Green Chemistry, Heterogeneous Catalysis, Organic Chemistry and Environmental Chemistry.

PREFACE

The need for a basic text dealing with **Fundamentals of Green Chemistry** inspired me to prepare his book for students of different Universities. There are some good extensive texts and valuable reference works dealing with Green Chemistry. But there was a need for a basic text of introductory material, sufficient to cover all important areas of the subject, yet limited in scope so that completion of the book in short time may be a reasonable goal. Although i have prepared this text strictly in accordance with the demand of students of different universities, it may also serve as an excellent resource and reference for persons working in the chemical and related industries.

The subject matter of this book has been presented in a simple, systematic, clear and comprehensive manner which is easy to understand.

To attempt to thank everyone who has helped me expand my knowledge of this subject would be an impossible task, but certain teachers and students deserve a special mention. I thank the students who have given me valuable feedback on the course and book. In particular, special acknowledgement to my student **Tehseen Mir** and my colleague **Dr. Fairoz Ahmad Khan** who have helped me directly or indirectly for the compilation of this manuscript. Thanks also to my friends and colleagues who inspired me to write this book.

I am extremely thankful to **Bookboon.com** for taking great pains to make this venture a success.

Suggestions for the improvement of this book will be gratefully acknowledged.

Dr. Bashir Ahmad Dar
Assistant Professor
Higher Education Department,
Govt. of Jammu and Kashmir India
Email: bdar181@gmail.com

1 GREEN CHEMISTRY THEORY

1.1 INTRODUCTION

The term “green chemistry” was introduced by Paul Anastas in 1991. There can be no denying that in years past, and even at present, chemistry has been misused in many respects, such as the release of pollutants and toxic substances and the production of non-biodegradable materials, resulting in harm to the environment and living things, including humans. It is now obvious that chemical science must be turned away from emphasis upon the exploitation of limited resources and the production of increasing amounts of products that ultimately end up as waste and toward the application of chemistry in ways that provide for human needs without damaging the Earth support system upon which all living things depend. Fortunately, the practice of chemical science and industry is moving steadily in the direction of environmental friendliness and resource sustainability. The practice of chemistry in a manner that maximizes its benefits while eliminating or at least greatly reducing its adverse impacts has come to be known as **green chemistry**.

There may be a confusion that green chemical pathway is almost benign, but it is not a perfectly true statement because there cannot be any chemical, which is perfectly benign and therefore, green chemistry diverts use of chemicals from malign to benign manner. Common salt is necessary for life, but it may develop hypertension, if taken in excess; so is the case with carbohydrates (sugar), which are required for providing energy for daily routine life but if given in excess, it may be harmful to humans.

Therefore, shifting from less benign (more malign) to more benign (less malign) process may be considered as a green chemical approach. Someone has well said that “A matter may act as poison if given in large amount, and a poison if given in very small amount may act as nectar”.

This is the basic concept of homoeopathy, which deals with very small concentrations of toxic chemicals and surprisingly enough, it may cure many dreadful diseases. The efficiency of these homoeopathic medicines increases on dilutions.

1.2 DEFINITION OF GREEN CHEMISTRY

The term green chemistry is defined as: The invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances. While this short definition appears straightforward, it marks a significant departure from the manner in which environmental issues have been considered or ignored in the up-front design of the molecules and molecular transformations that are at the heart of the chemical enterprise. Looking at the definition of green chemistry, the first thing one sees is the concept of invention and design. By requiring that the impacts of chemical products and chemical processes are included as design criteria, the definition of green chemistry inextricably links hazard considerations to performance criteria.

Another aspect of the definition of green chemistry is found in the phrase “use and generation”. Rather than focusing only on those undesirable substances that might be inadvertently produced in a process, green chemistry also includes all substances that are part of the process. Therefore, green chemistry is a tool not only for minimizing the negative impact of those procedures aimed at optimizing efficiency, although clearly both impact minimization and process optimization are legitimate and complementary objectives of the subject. Green chemistry, however, also recognizes that there are significant consequences to the use of hazardous substances, ranging from regulatory, handling and transport, and liability issues, to name a few. To limit the definition to deal with waste only would be to address only part of the problem. As will be seen later, green chemistry is applicable to all aspects of the product life cycle as well.

Finally, the definition of green chemistry includes the term “hazardous”. It is important to note that green chemistry is a way of dealing with risk reduction and pollution prevention by addressing the intrinsic hazards of the substances rather than those circumstances and conditions of their use that might increase their risk. Why is it important for green chemistry to adopt a hazard-based approach? To understand this, we have to revisit the concept of risk. Risk, in its most fundamental terms, is the product of hazard and exposure:

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

A substance manifesting some quantifiable hazard, together with a quantifiable exposure to that hazard, will allow us to calculate the risk associated with that substance. Virtually all common approaches to risk reduction focus on reducing exposure to hazardous substances. Regulations often require increases in control technologies and treatment technology, and in personal protective equipment such as respirators, gloves, etc., in order to reduce risk by restricting exposure.

By achieving risk reduction through hazard reduction, green chemistry addresses concerns about the cost and potential for failure of exposure controls. Regardless of the type of exposure control, ranging from engineering controls through personal protective gear, there is always going to be an upfront capital cost; to what degree this cost can be recouped will be situation-specific, but it will always be there. In contrast, there is no additional up-front capital cost necessarily associated with green chemistry. While some green chemistry options may require capital investment, others may actually lower total cost of operations from the outset. This result is frequently the case in some of the easiest ways of implementing green chemistry technologies.

Exposure controls, because they rely on either equipment or human activity to accomplish their goals, are capable of failing. Respirators can rupture; air scrubbers can break down, and so forth. When failure occurs, risk is maximized because the resultant exposure is to a constant hazard. Green chemistry, in contrast, does not rely on equipment, human activity, or circumstances of use but, instead, changes the intrinsic hazard properties of the chemical products and transformations. Consequently, green chemistry is not as vulnerable to failure, as are the traditional approaches to hazard control.

The definition of green chemistry also illustrates another important point about the use of the term “hazard”. This term is not restricted to physical hazards such as explosiveness, flammability, and corrodibility, but certainly also includes acute and chronic toxicity, carcinogenicity, and ecological toxicity. Furthermore, for the purposes of this definition, hazards must include global threats such as global warming, stratospheric ozone depletion, resource depletion and bioaccumulation, and persistent chemicals. To include this broad perspective is both philosophically and pragmatically consistent. It would certainly be unreasonable to address only some subset of hazards while ignoring or not addressing others. But more importantly, intrinsically hazardous properties constitute those issues that can be addressed through the proper design or redesign of chemistry and chemicals.

1.3 THE ROLE OF CHEMISTRY

Chemistry plays an integral part in our lives and is everywhere around us: the air we breathe, the water we drink, the plastics we use, clothes we wear, food we eat, buildings we live in, etc. Chemistry is the heart of science, which is the foundation on which technology for development of any nation is based and built. The chemist is increasingly engaged in the health sector, research for recycling of waste matters and sewage, production of agrochemicals and fertilizers for forestation, production of renewable energy to replace the fossil fuels and other non-renewable energies, production and application of water treatment and sanitation chemicals, environmental chemical control, monitoring of environmental degradation, and much more.

The role of chemistry is essential in ensuring that our next generation of chemicals, materials, and energy is sustainable. Worldwide demand for environment-friendly chemical processes and products requires the development of novel and cost-effective approaches for preventing pollution.

Developments in water treatment, waste disposal methods, agricultural pesticides and fungicides, polymers, materials sciences, detergents, petroleum additives, and so forth, have all contributed to the improvement in our quality of life. But unfortunately all these advances come with a price tag of pollution. Gone are the days when better living through chemistry was a promise; now it is a bitter irony that nearly everything we use depends on the petrochemical industry. If substantial damage to the environment has resulted from the actions of the chemists and chemical technologists in the 20th century, then the responsibility of global improvement will also be on them as now they are realizing the importance of preserving the natural resources, Today, with growing awareness, in industry, academia and the general public, of the need for sustainable development, the international scientific community is under increasing pressure to change current working practices and to find greener alternatives. In fact, present day chemistry is driven by an unparalleled social demand for better products and services with a growing sentiment that undue exploitations of resources must be minimized.

Scientists and engineers from both the chemical industry and the academic world have made efforts to correct pollution problems by the more extensive use of "green chemistry" concepts, i.e., development of methodologies and products that are environmentally friendly. Green chemistry has essentially two parts. The first, and the most fundamental part, is the development of a principled and environmentally conscious approach to chemistry.

The other is the innovative buildup of greener strategies in the chemists' tools kit. The former aspect is not new, although it has found more support only recently.

The increasing importance of green chemistry is seen in the awards and honors bestowed on achievements in this field. Professor Walter Kohn was awarded the Nobel Prize in Chemistry in 1998 jointly with Prof. J. Pople for metathesis. The Royal Swedish Academy of Sciences has rewarded efforts to make the world more habitable and encouraged good and environment-friendly chemical practices. Yves Chauvin (France), Robert Grubbs (USA), and Richard Schrock (USA) shared the prize for their contribution to the development of metathesis (meaning "change places"), an energetically favored and less hazardous method in organic synthesis, which has immense industrial applications. Metathesis is an example of how important basic science has been exploited for the benefit of man, society, and environment. Apart from its applications in the polymer industry (for making stronger plastics), metathesis has also found an important role in biotechnology in recent years.

It represents a great step forward for green chemistry, reducing potentially hazardous waste through smarter production. The field of chemistry has undergone revolutionary changes and development in light of increasing awareness for environment protection. Industries and scientific organizations have put clean technology as an important research and development (R&D) concern.

It is indeed a challenge before the chemists to develop synthetic methods that are less polluting, i.e., to design clean or "green" chemical transformations. Chemistry is here to stay whether to cause environmental problems or to maintain and develop our quality of life and save humanity from the doomsday. It is important for chemists to use their creativity and innovation to develop environment-friendly routes for the betterment of the world. With proper foresight and planning, the chemist can design reactions that are economically sound, environmentally compatible and socially acceptable, that is adopting greener route to chemical transformations. Green chemistry is no doubt a special contribution of chemists to the conditions for sustainable development.

1.4 TOOLS FOR GREEN CHEMISTRY

The list of tools to help companies start the process of changing to safer chemicals in their products and processes is growing rapidly, and it can sometimes be challenging to know which among the many available options will prove the most useful.

Equally important, especially for those with a limited background in chemistry who are looking for ways to use tools which integrate the principles of green chemistry into engineering applications, some tools require less technical knowledge of toxicology and chemistry than others, and are more applicable for technical assistance providers seeking to introduce companies to the concepts of green chemistry.

Most tools require that the users know what chemicals are being used. The size of the company and their position in the supply chain may determine how much information they have about the products they are using and the processes involved. In some cases, companies may find it helpful or necessary to engage consultants for assistance in using these tools.

Other tools are proprietary, and require contractual services with the company that created the tool; typically in this case, it is the contractor who should have the expertise required in areas such as toxicology, chemistry, and/or chemical engineering. A key factor in looking at the tools and deciding on a contractor is determining the degree of transparency required. Often there is a trade-off between the degrees of involvement the consultant requires from the client versus the transparency of the process to the client.

Finally, there is another class of tools, which offer a label that identifies a product that has been determined to meet certain environmental standards. These usually require what is called "third party certification," that is, independent verification that the product meets the criteria for making the claim the labeling represents. Once again, the position of the business in the supply chain and, therefore, their customer expectations will usually drive the decision to pursue this type of certification.

A resource that is particularly helpful in understanding how to navigate the decision-making process, the different criteria, and matching the needs of the user to tool capabilities is a publication called *A Compendium of Methods and Tools for Chemical Hazard Assessment* that was written by The Lowell Center for Sustainable Production. The information about understanding the differences between the available tools and the criteria for choosing the tools that are best suited to the client's needs can be easily applied and are extremely useful across the board.

Two of the more well-known categories of tools using the principles of green chemistry are *hazard assessment* and *alternatives assessment*. A *hazard assessment* evaluates the health and environmental hazards of chemicals in use, as well as potential alternatives under consideration for substitution.

An *alternatives assessment* (AA) more fully evaluates the impacts of chemical hazards by including other assessment components, such as risk/exposure evaluation and social impact analysis. However, no standard presently exists that defines the components of an *alternatives assessment*, although there is consensus that a chemical hazard assessment is the foundation of any AA.

Various tools employ different frameworks for analysis, and it is important to choose the framework that will give the best information to suit the client's needs. The use of *alternatives assessments* in particular, is growing. An AA helps companies seeking to replace problematic chemicals determine what alternatives exist and assures that any substitute selected is not worse than what it is replacing. This is sometimes known as "regrettable substitution" (which is, unfortunately, more common than one would expect).

Many tools are available for performing a chemical hazard assessment. The U.S. EPA, for example, has a tool called TEST for estimating toxicity, and has developed tools to assist in the replacement of industrial solvents (PARIS III) and facilitate waste reduction (WAR). Other well-respected tools in this category include GreenScreen™ for Safer Chemicals, GreenWERCS®, and the Quick Chemical Assessment Tool, more commonly known as QCAT. In addition, organizations such as the Green Chemistry and Commerce Council (GC3), the state of California, and others have put together databases, which include tools across a spectrum of needs.

The excess of available tools makes navigating them challenging. There is also no standard definition for what comprises an effective alternatives assessment and/or accepted understanding of what differentiates it from other evaluation tools. Companies will often need assistance in matching their needs to the tools available.

A life-cycle analysis (LCA) is a procedure for evaluating environmental impacts through all stages of a product's life, and most of the tools available for LCA are proprietary. However, the U.S. EPA has an excellent webpage that covers many aspects of LCA and gives a good definition and grounding in what LCA is about. The California Department of Toxic Substance Control published a document, *Hazard Assessment Tools and Methods*, which includes an extensive review of LCA tools. Other resources include the Cradle to Cradle concept, and its not-for-profit institute, the Cradle to Cradle Products Innovation Institute.

Tool Selectors: Essenscia, the Belgian Federation for Chemistry and Life Sciences Industries, has developed an online tool selector for searching for appropriate sustainability tools, called SUSCHEM compass. The site contains an inventory of tools that "measure the ecological and/or economic impact of products and/or processes and that are useful in the chemical value chain" - "eco-efficiency measurement methods." However, this toolkit also contains some tools that would assist with a *hazard assessment*, including life cycle, economic, and other ecological evaluation tools that would be useful in conducting an *alternatives assessment.*

The green chemistry program facilitates the achievement of plan goals by establishing and maintaining specific objectives and targets to improve the risks associated with hazardous materials use. The objectives and targets are the most important tools for articulating the green chemistry planning goals. Although an organization has discretion with regard to its objectives and targets, they must be consistent with the organization's Green Chemistry Policy, which contains a commitment to toxics use reduction that helps reinforce source reduction goals and compliance with regulatory requirements. Also, green chemistry objectives and targets may be different for various levels of the organization and these should be documented.

The most important tools for green chemistry are: selection of starting material, catalysts, alternative solvents, appropriate reagents.

Use of sonication, microwave radiations, cascade and/or multi-component reactions can be useful tools for green chemistry, if they proceed in good yields with high atom economy and generate little waste.

1.5 SELECTION OF STARTING MATERIAL

It is very important to choose the appropriate starting materials. The synthetic pathway will depend on this. Also consider the hazards that may be faced by the workers (chemists carrying out the reaction and also the shippers who transport these) handling the starting materials.

Till now, most syntheses make use of petrochemicals (made from petroleum), which are non-renewable. Petroleum refining also requires considerable amounts of energy. It is therefore important to reduce the use of petrochemicals by using alternative starting materials, which may be of agricultural or biological origin. For example, some of the agricultural products such as corn, potatoes, soya and molasses are transformed through a variety of processes into products like textiles, nylon etc. Some of the materials that have biological origin (obtained from biomass) are: butadiene, pentane, pentene, benzene, toluene, xylene, phenolics, aldehydes, resorcinol, acetic acid, peracetic acid, acrylic acid, methyl aryl ethers, sorbitol, mannitol, glucose, gluconic acid, 5-hydroxymethyl furfural, furfural, levulinic acid, furan, tetrahydrofuran, furfuryl alcohol etc.

1.6 CHOICE OF CATALYSTS

Catalysts have played an important part in the development of more sustainable processes for the manufacture of chemicals. There are many advantages in developing and using catalysts for industrial reactions, some important ones being:

They affect the conditions that are needed, often reducing energy demand by lowering the temperature and pressure used.

They enable alternative reactions to be used which have better atom economy and thus reduce waste.

It is possible to control reaction pathways more precisely, reducing unwanted side products and making it easier to separate and purify the required product.

Certain reactions proceed much faster and at a lower temperature with the use of catalyst. Heavy metal catalysts should be avoided as they cause environmental problems and are toxic in nature. Following are some different types of catalysts used for green transformations.

a. **Acid catalyst:** Hydrogen fluoride, an extremely corrosive, hazardous and toxic chemical used in the preparation of linear alkyl benzenes has been replaced by a solid acid catalyst fluorided silica- alumina catalyst.
b. **Polymer supported catalyst**: Polymer super acid catalyst is obtained by binding aluminum chloride to sulfonated polystyrene. This is used for the cracking and isomerization of alkanes at 357 °C at atmospheric pressure.
c. **Photo catalysts:** Titanium- oxide based photo catalytic systems have been developed and are important for purification of polluted water, the decomposition of offensive odors, toxins, fixation of CO_2 and decomposition of chloro-flouro-carbons (CFCS).

d. **Phase transfer catalysts**: PTC"s are soluble in water as well as in the organic solvent. The PTC reaction is a methodology for accelerating the reaction between water insoluble organic compounds and water soluble reagents. In chemistry, a phase transfer catalyst or PTC is a catalyst that facilitates the migration of a reactant from one phase into another phase where reaction occurs. Ionic reactants are often soluble in an aqueous phase but insoluble in an organic phase in the absence of the phase transfer catalyst. By using a PTC process, one can achieve faster reactions, obtain higher yields, make fewer byproducts and eliminate dangerous solvents, eliminate the need for expensive raw materials or minimize waste problems.

e. **Bio catalysts:** The most important conversions in the context of green chemistry are with the help of enzymes. Enzymes are also referred to as biocatalysts and the transformations are referred to as biocatalyst conversions.

1.7 ALTERNATIVE SOLVENTS

In a very general sense, solvents are a class of chemical compounds that allow chemistry to occur.

We tend to think of a substance like "water" as a universal solvent because it is so useful in so many disciplines. Water cleans up everything, allows biochemical reactions to occur, is used in paints, coatings, and films, allows cooking to occur (or else everything would catch fire), and provides lubrication and ease of movement for a great many devices.

The ability of a compound to dissolve in some other (likely different) compound is termed "solubility". Miscibility is another term that characterizes the facility of compound to dissolve in compound. When the two compounds can completely dissolve or combine to form a homogeneous solution, the two liquids are said to be *miscible* and those, which can never blend well enough to form a solution are called *immiscible*.

Solvent Categories: There are a number of solvents that from a green chemistry perspective must be dealt with care. The following are representative solvent classes:

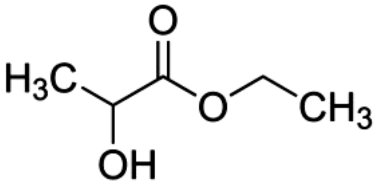
- Hydrocarbons
- Halogenated hydrocarbons
- Aromatic hydrocarbons
- Alcohols
- Ethers
- Aprotic Solvents

Each of the above has their pros & cons in terms of environmental benefit/issue, economics, and social justice. Each may do different things; for example, the aprotic solvent class is one where there is no chance for the solvent to provide a proton to a reaction it is hosting. Alcohols, on the other hand, can easily do that and should not be used in reactions where water/protons could quench a reaction or trigger a violent reaction.

Methyl Soyate: Methyl soyate is a biobased solvent that is a mixture of long-chain fatty acid methyl esters.

In general, it can be used to clean countertops, pretreat fabric stains, clean concrete, degreaser, graffiti remover (with ethyl lactate and surfactants), paint stripper, mastic remover, varnish remover, deinker, asphalt remover, and waterless hand cleaner.

Lactic acid ethyl ester: A representation of ethyl lactate, also known as lactic acid ethyl ester, which is a monobasic ester formed from lactic acid and ethanol, that can be used as a solvent. It is considered biodegradable and can be used as a water-rinse-able degreaser.



Supercritical Fluids: A supercritical fluid (sCF) is a substance at a temperature and pressure that are above the critical point, at which distinct liquid and gas phases do not exist. It is a very unique phase that can effuse through solids like a gas, and dissolve materials like a liquid.

sCFs are extremely useful in green chemistry because they can be derived from environmentally friendly materials such as water and carbon dioxide with little to no impact on the carbon footprint of the planet.

Water as a Solvent: Water can behave as an exquisite solvent in a host of typical organic reactions by virtue of its ability to encourage reactivity via the "hydrophobic effect".

Micro-emulsions: Micro-emulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and a surfactant that are frequently in combination with a co-surfactant. The aqueous phase likely contains salt(s) or other ingredients, whereas the "oil" may actually be a complex mixture of different hydrocarbons and olefins.

Another way to carry out the reaction is without the use of solvent (solvent free reactions). Following are some examples:

Gas Phase: The gas phase is a very useful modality to allow reactions to occur because (like the hydrophobic effect) it forces reactions or processes to occur through non-solvent-mediated channels. For example, the production of methanol can be done in the gas phase by reaction of "syn" gas (hydrogen and carbon monoxide) with ZnO as the solid catalyst for the reaction to occur.

No Solvents: It is altogether possible and highly desirable to use the starting materials themselves for the reaction of interest. This is doable if one of the reactants is a liquid that can allow the other(s) to dissolve into it.

Melt State: It is possible to combine two solids to provide a composition that can achieve a eutectic point, or melts/solidifies at a single temperature lower than the melting points of the separate constituents or of any other mixture of them.

Ball Milling: Ball milling works on the principle of impact and attrition; size reduction results from impact as the balls drop from near the top of the shell. A ball mill is made up of a hollow cylindrical shell rotating about its axis. The axis may be either horizontal or at an acute angle to the horizontal. The shell is partially filled with balls who is grinding by action of balls, made of steel (chrome steel), stainless steel, ceramic, or rubber, results in much finer particles. The inner surface of the cylindrical shell is usually lined with an abrasion-resistant material such as manganese steel or rubber whereas less wear takes place in a rubber-lined mill. One of the reactions that are done in this manner is polymerization of MMA (methylmethacrylic acid) to PMMA (poly- methylmethacrylate).

1.8 APPROPRIATE REAGENTS

As in the selection of a starting material, the selection of a reagent must include an evaluation to identify what the hazards associated with a particular reagent are. This evaluation should include an analysis of the reagent itself, as well as an analysis of the synthetic transformation associated with the use of that reagent (i.e., to determine product selectivity, reaction efficiency, separation needs, etc.). In addition, an investigation should be undertaken to determine if more alternative reagents are available that either are themselves more environmentally benign or are able to carrying out the necessary synthetic transformation in a more environmentally benign way.

As in the selection of a starting material, the selection of a reagent should start with an evaluation of the reagent itself to determine if it possesses any hazardous properties. Inherent in this analysis is the question: Is the transformation requiring the hazardous reagent necessary, or can the final target compound be obtained from an alternative pathway that uses a less hazardous reagent?

In order to answer this question, alternative reagents must be identified, and any hazardous properties that the alternatives possess must be compared with the hazardous properties associated with the reagent originally selected. One example of an innocuous reagent (which is produced from nontoxic intermediates) is dimethylcarbonate.

An important consideration and benefit associated with the use of a particular reagent is whether it is responsible for the generation of more or less waste than other reagents. The amount of waste either generated or eliminated, however, cannot be the only consideration. The type of any waste generated must also be assessed. Just as all chemical products are not equal in terms of their hazard, neither are chemical waste streams. Waste streams therefore must also be assessed for any hazard properties that they possess. In this regard, it is obvious that oxidation reactions involving oxygen and hydrogen peroxide will be of outstanding priority, as they produce water as a by-product.

Green oxidation reactions require the use of nontoxic solvents (water or CO_2) and mild reaction conditions. Oxidations using air as a reagent are difficult to control, being either too slow or too fast for industrial applications, and intrinsically nonselective when selectivity is very often a crucial parameter. Hydrogen peroxide is a clean reagent, with water the only by-product formed, and a very high selectivity can be obtained. However, the use of hydrogen peroxide for fine chemical production is currently limited by its poor reactivity and its ease to undergo radical decomposition. Therefore, there is a great effort to develop systems able to selectively activate oxygen and hydrogen peroxide for oxidative transformations. In this context, both homogeneous and heterogeneous catalysis play a key role. Oxidation reactions are critical to pharmaceutical, petrochemical, and agricultural industries.

Direct oxidation of isoprenol, b-picoline and benzene are chosen as examples for continuous gas-phase processes, and oxidation of cyclopentanone, limonene, pinene, and propylene as examples for semi continuous or batchwise processes in the liquid phase.

These examples illustrate that features known from the synthesis of bulk chemicals can successfully be applied to manufacturing intermediate and specialty chemicals by utilizing the phases associated with conventional industrial reactor systems.

Metal-peroxo systems, polyoxometallates and heteropolyanions, zeolitic and smectitic materials, and other titanium catalysts are also used. Recent research progress in catalytic systems for potential use with hydrogen peroxide in industrial chemical synthesis is reviewed in terms of the positive features identified to date, and the obstacles yet to be surmounted in order to become more widely adopted.

It is believed that fully inorganic systems have more scope for commercialization than those containing organic ligands or supports, however robust. Critical targets are larger-pore analogs of titanium silicalite (TS-1), more exploration of smectite-based materials, effective immobilization of activated metal-peroxo systems, and improvements in design and manipulation of polyoxometallate compounds. Cooperation between branches of chemistry that have not traditionally worked closely together is advocated.

Using a reagent that is more selective means; more of the starting material is going to be converted into the desired product. High product selectivity does not always translate into high product yield (and less waste generated), however. Both high selectivity and high conversion must be achieved in order for a synthetic transformation to generate little or no waste. Utilizing highly selective reagents can mean that separation, isolation, and purification of the product will be significantly less difficult. Since a substantial portion of the burden to the environment that chemical manufacturing processes incur often results from separation and purification processes, highly selective reagents are very desirable in green chemistry.

If a catalyst is necessary, it should be used in actually "catalytic amount". In fact, if a reagent can be utilized and yet not consumed in the process, it will require less material to continuously effect the transformation. This implies that catalysis has to be as efficient (not only effective) as possible, involving a high turnover number.

Other criteria that should be used in the selection of a reagent need to be balanced against each another in order to optimize the utility of the reagent and minimize the environmental impact.

A large number of industrial processes are based on the use of inorganic or minerals acids. While many of these processes are catalytic, some require (e.g., acylation using $AlCl_3$) stoichiometric amounts of Lewis acid. Final isolation of the product necessitates neutralization steps to remove the acid, resulting in enormous quantities of hazardous waste, with the cost of disposal of this waste often outweighing the value of the product.

The use of heteropolyacids as green catalysts for both acid-catalyzed and oxidation reactions are also reporting for examples, two industrial processes which were made greener by the use of such catalysts in liquid bi-phase systems. The first is the hydration of a mixture of butenes; only isobutylene reacts selectively and supplies the starting material for the twostep oxidation to methacrylic acid (1- and 2-butenes left after reaction are utilized as raw material in the production of low-density polyethylene).

The second example is the polymerization of tetrahydrofuran, which gives polyoxytetramethyleneglycol, used as an elastic fiber and elastomer.

Heteropolyacids can be active solid-acid catalysts, providing the unique reaction environment of a pseudoliquid (catalytically active solid solvent) and thus find many green applications in the future.

The use of heterogeneous catalysts in these processes may simplify catalyst removal, thus minimizing the amount of waste formed. Diffusion limitation of liquids within porous solids dictates that effective solid acids for liquid-phase reactions require the use of mesoporous materials <20-100Å.

In particular mesoporous solid acids which minimize diffusion limitation in liquid phase organic transformations and open up new possibilities in the preparation of solid acid catalysts for liquid-phase reactions are highly focused. Solid-acid catalysts in organic synthesis are discussed in terms of properties, preparation, and a few selected applications.

1.9 MICROWAVE CHEMISTRY

Microwave heating under controlled conditions is an invaluable technology because it not only dramatically reduces reaction times, typically from days or hours to minutes or even seconds, that is speed up the reaction, but it also fulfills the aim of green chemistry by reducing side reactions increasing yields and improves reproducibility. This approach has now become a central tool in this rapid paced, time sensitive field and it has also blossomed into a useful technique for a variety of applications in organic synthesis, where high yielding protocols and facility of purification are highly desirable.

Furthermore, this technique is energy efficient and the possibilities for application in combinatorial, parallel and automated environmentally benign chemistry are obvious.

Microwaves as energy source: Microwave (MW) radiations are electromagnetic radiations, which are widely used as a source of heating in organic synthesis. Microwaves have enough momentum to activate reaction mixture to cross energy barrier and complete the reaction in lesser time.

A microwave oven consists of a magnetron, a wave guide feed and an oven cavity. A magnetron is a thermionic diode that works on the principle of dielectric heating by converting part of the electric power into electromagnetic energy and the rest of it into heat energy. Microwaves occupy a place in the electromagnetic spectrum between infrared waves and radio waves, ranging in wavelengths between 0.01 and 1m, and operate in a frequency range between 0.3 and 30 GHz. The typical bands for industrial applications are 915 ± 15 and 2450 ± 50MHz. The wavelength between 1 and 25cm are extensively used for RADAR transmissions and the remaining wavelength range is used for telecommunications. The entire microwave region is therefore not available for heating applications and the equipment operating at 2.45GHz, corresponding to a wavelength of 12.2cm, is quite commonly used. The energy carried by microwave at 2.45GHz is 1 joule per mole of quanta, which is relatively very small energy.

Microwaves as a tool for synthetic chemistry: The earliest description of the magnetron (the high-power generator of microwave power), a diode with a cylindrical anode was reported by Hull. The potential of microwave heating for organic synthesis has been explored in last two and half decades after the first reports appeared in 1986. Initially, reactions were performed in domestic microwave ovens using appropriate solvents. After that, several groups started investigating reactions in solvent free conditions including "dry media" usually with open vessels. The use of microwave units specially designed for synthesis, which are expensive and it becomes rather difficult at times to procure. Thus, unmodified home microwave units are suitable in some cases. However, simple modifications (for example, a reflux condenser) can enhance the safety factor. High-pressure chemistry should only be carried out in special reactors with a microwave oven specifically designed for this purpose. A further point in favor of using the more expensive apparatus is the question of reproducibility, since only these specialized machines can achieve good field homogeneity and in some cases, these can even be directed on the reaction vessel.

It has long been known that molecules undergo excitation with electromagnetic radiation. This effect is utilized in household microwave ovens to heat up food. However, chemists have been using microwaves only as a reaction methodology for a few years. Some of the first examples gave amazing results, which led to a flood of interest in microwave-accelerated synthesis. The MW heating has not been restricted to organic chemistry only, but its application to various aspects of inorganic chemistry and polymer chemistry has also been investigated with several advantage of an eco-friendly approach. In the past few decades, this technique has found a valuable place in the synthetic chemist's tool box, which is evident from a large number of publications, particularly acetylation reaction, addition reaction, elimination reaction, alkylation reaction, alkynes metathesis, allylation reaction, amination reaction, aromatic nucleophillic substitution reaction, arylation reaction, carbonylation reaction, combinatorial reaction, condensation reaction, coupling reaction, cyanation reaction, cyclization reaction, cyclo-addition reaction, deacetylation reaction, dehalogenation reaction, Diel's- Alder reaction, dimerization reaction , transesterifi cation reaction, enantioselective reaction, halogenation reaction, hydrolysis reaction, Mannich reaction, oxidation reaction, phosphorylation synthesis, polymerization reaction, rearrangement reaction and so on.

The initial slow development of this technology in the last 1980's and early 1990's has been attributed to lack of its controllability and reproducibility coupled with detail understanding of the basics of MW dielectric heating.

Principle: The basic principle behind heating by microwaves is the interaction of charged particle of the reaction material with electromagnetic wavelength of a particular frequency. The phenomenon of producing heat by electromagnetic irradiation involves either collision or conduction and some time both. Two basic principles are involved in heating the materials by microwaves.

Dipolar polarization: Dipolar polarization is the phenomenon responsible for the majority of microwave heating. It depends upon polarity of solvent and compound. In polar molecules, different electronegativities of individual atoms results in a permanent electric dipole, which is sensitive to external electric fields and will attempt to align with them by rotation. This realignment is rapid for a free molecule, but in liquid, the instantaneous alignment is prohibited by the presence of other molecules. A limit is, therefore, placed on the ability of the dipole to respond to an electric field, which affects the behavior of the molecule with different frequencies of electric field for example, under low frequency irradiation, the dipole may react by aligning itself in phase with the electric field. Molecules will polarize uniformly and thus, no random motion results.

Under high frequency irradiation, the polar molecule will attempt to follow the field, but intermolecular inertia stops any significant motion before the field has reversed, in this case, the dipole do not have sufficient time to respond the field, and it does not rotate. As no motion is induced in the molecules, no energy transfers will take place, and therefore, no heating results. In case of intermediate frequency, the field will be such that the molecule is almost (but not quite) able to keep in phase with the field polarity. The microwave frequency is low enough so that the dipoles have enough time to respond to the alternating field, and therefore to rotate, but high enough so that the rotation does not precisely follow the field. As the dipole reoriented to align itself with the field, the field is already changing, and a phase difference causes energy to be lost from the dipole in random collisions. Thus, giving rise to dielectric heating.

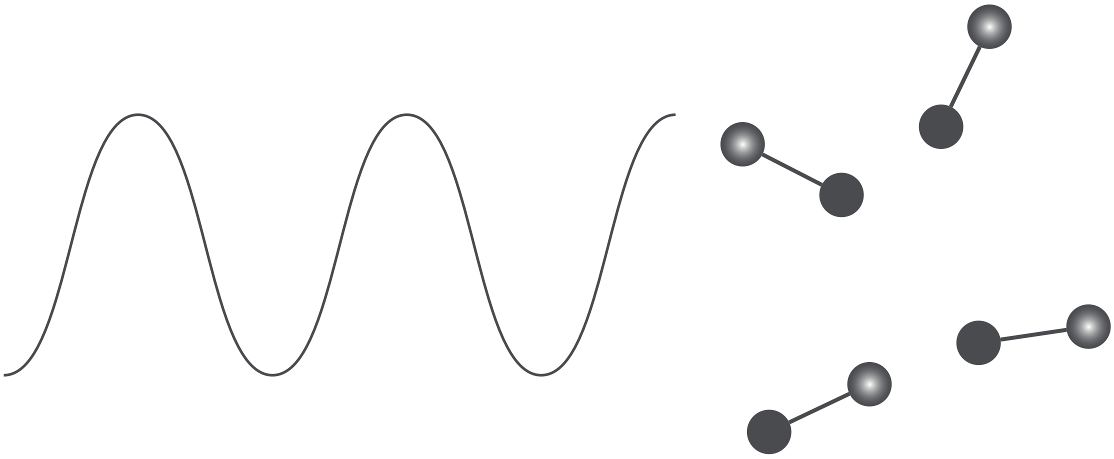


Fig 1.1: Microwave heating by dipolar polarization mechanism.

Conduction mechanism: The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor resulting in an electric current. This current faces internal resistance, which heats the conductor.

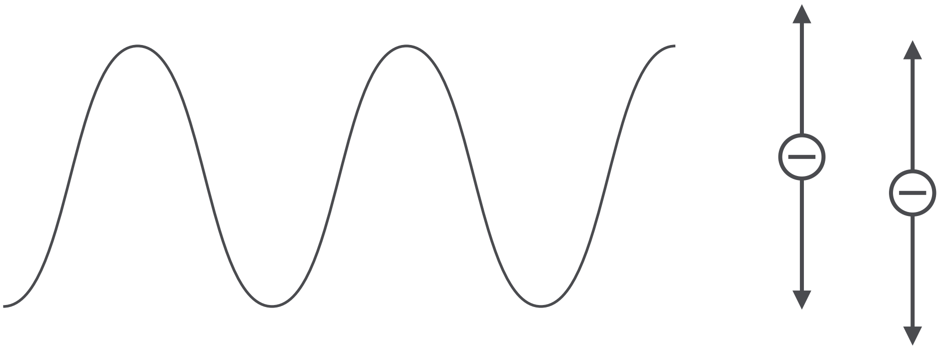
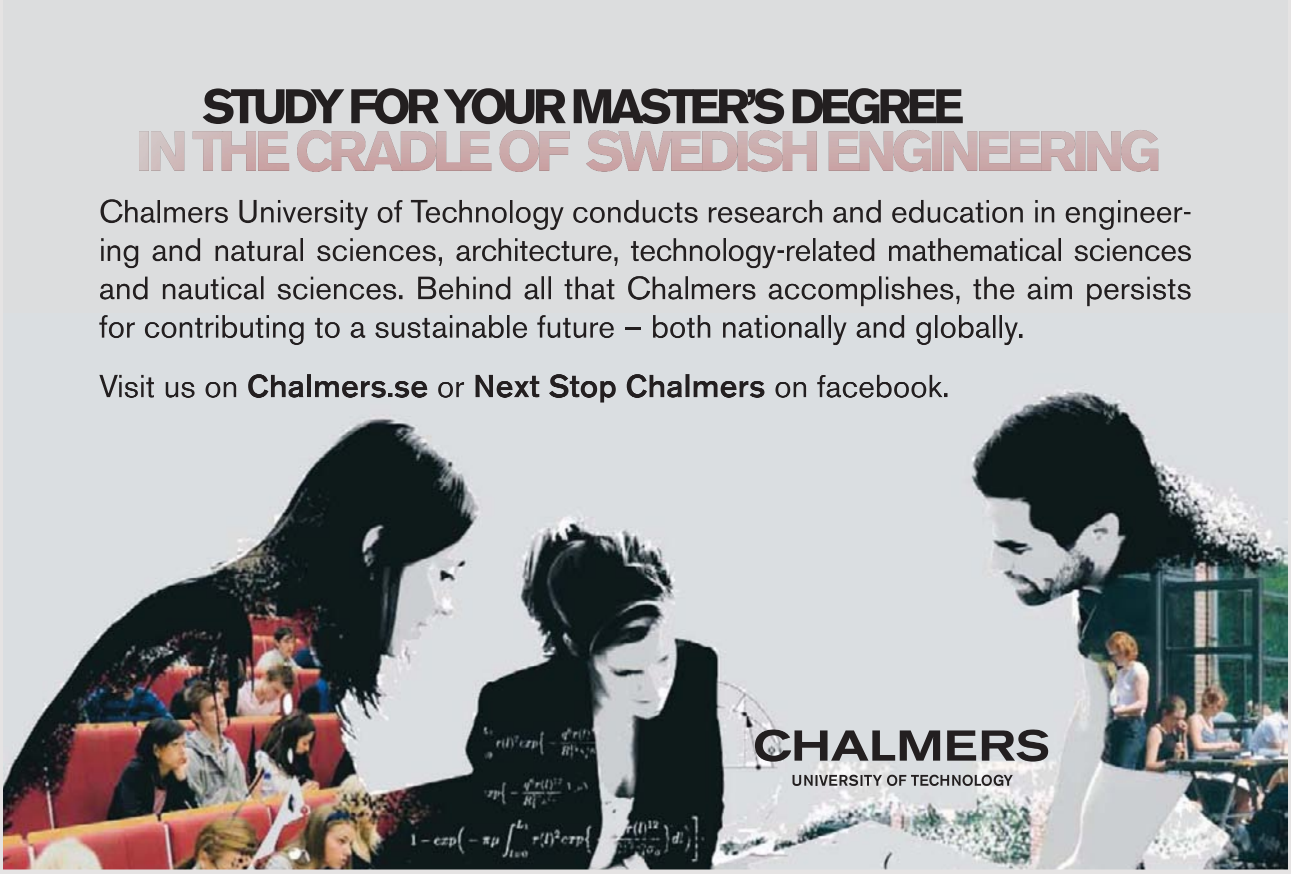


Fig 1.2: Conduction mechanism

When the irradiated sample is an electrical conductor, the charge carriers (electrons, ions etc.) are moved through the material under the influence of the electric field, resulting in a polarization. These induced currents will cause heating in the sample due to electrical resistance.

Reaction vessels and reaction medium: The reaction vessel must be transparent to the microwaves. These are preferably being made up of Teflon, polystyrene and glass. Metallic containers are not used as it gets heated soon due to preferential absorption and reflection of rays. For reactions in solvents, the solvent must have a dipole moment and a boiling point higher than the desired reaction temperature and a dielectric constant. Some of the



solvents used commonly as microwave absorber are N,N-dimethyl formamide or DMF (b.p.154°C, ε = 36.7), formamide (b.p. 216°C, ε = 111), methanol (b.p. 65°C, ε = 32.7), ethanol (b.p. 78°C, ε = 24.6), chlorobenzene (b.p.132°C, ε = 5.6), 1,2-dichlorobenzene (b.p. 180°C, ε = 10.5), 1,2-dichloroethane (b.p. 83°C), ethylene glycol (b.p. 196°C, ε = 37.7), dioxane (b.p. 101°C, ε = 2.25) and diglyme (b.p. 162°C, ε = 7.23). The presence of salts in polar solvents can frequently enhance microwave coupling. Hydrocarbon solvents such as toluene (ε = 2.4), hexane (ε = 1.9) and benzene (ε =2.3), because of less dipole moment, are unsuitable as they absorb microwave radiation poorly. For solid state reactions, mineral oxides such as zeolite, alumina, silica, montmorillonite K-10 clay and so on, are used as absorbents.

1.10 MICROWAVE EFFECT

The microwave effect applies to a range of observations in microwave chemistry. These may be classified in two categories: specific microwave and non-thermal microwave effects.

Specific microwave effects: These are those effects that cannot be easily done by conventional heating methods. Examples include (i) selective heating of specific reaction components, (ii) rapid heating rates and temperature gradients, (iii) the elimination of wall effects and (iv) superheating of solvents.

Non-thermal microwave effects: Excitation with microwave radiation results in the molecules aligning their dipoles within the external field. Strong agitation, provided by the reorientation of molecules, in phase with the electrical field excitation, causes an intense internal heating. The question of whether a non-thermal process is operating can be answered simply by comparing the reaction rates between the cases where the reaction is carried out under irradiation versus under conventional heating. In fact, no non-thermal effect has been found in the majority of reactions, and the acceleration is attributed to superheating alone. It is clear that non-thermal effects do play a role in some reactions.

1.11 COMPARISON BETWEEN MICROWAVE HEATING AND CONVENTIONAL HEATING

Microwave radiation provides rapid and homogeneous heating, which has certain advantages such as reaction rate acceleration, milder reaction conditions and higher chemical yields. In short, microwave enhanced chemical reactions are safer, faster, cleaner and more economical than conventional reactions. It helps in developing cleaner and greener synthetic routes.

Increased rate of reaction: Microwave heating enhances the rate of certain chemical reactions by 10 to 1,000 times compared to conventional heating. This is due to its ability to increase the temperature of a reaction. For instance, synthesis of fluorescein, which usually takes about 10hrs by conventional heating methods, can be completed in only 35min by means of microwave heating. The rate acceleration caused by microwaves has been attributed to superheating of solvents (liquid phase reactions) and high temperature on the surface of catalyst or other solid reactants. The water molecule is the target for microwave ovens in the home; like any other molecule with a dipole, it absorbs microwave radiation. Microwave radiation is converted into heat with high efficiency, so that "superheating" becomes possible at ambient pressure.

Enormous accelerations in reaction time can be achieved, if superheating is performed in closed vessels under high pressure; a reaction that takes several hours under conventional conditions can be completed over the course of minutes.

Efficient source of heating: Microwave assisted heating is a highly efficient process and results in a significant energy saving. This is because microwaves heat up just the sample and not the apparatus and therefore, energy consumption is less.

Higher yields: In certain chemical reactions, microwave radiation produces higher yields as compared to conventional heating methods. For example, microwave synthesis of fluorescein results in an increase in the yield of the product from 70 to 82%.

Uniform heating: Microwave radiation provides uniform heating throughout a reaction mixture unlike conventional heating methods. It is because in conventional heating, the walls of the oil bath gets heated first and then the solvent. As a result of this, there is always a temperature difference between the walls and the solvent. In the case of microwave heating, only the solvent and the solute particles are excited, which results in uniform heating of the solvent.

Selective heating: Selective heating is based on the principle that different materials absorb microwaves to different extent. Some materials are transparent where as others absorb microwaves. Therefore, microwaves can be used to heat a combination of such materials for example, the production of metal sulfide with conventional heating requires weeks because of the volatility of sulfur vapors while rapid heating of sulfur in a closed tube results in the generation of sulfur fumes, which can cause an explosion. However, in microwave heating, since sulfur is transparent to microwaves, only the metal gets heated. Therefore, reaction can be carried out at a much faster rate with rapid heating, without the threat of an explosion.

Environmental-friendly chemistry: Reactions conducted through microwaves are cleaner and more environment friendly than conventional heating methods. Microwaves heat the compounds directly and therefore, use of solvents in the chemical reaction can be reduced or eliminated. An approach was developed to carry out a solvent free chemical reaction on solid support like clay, alumina, zeolite and so on. The reactants adsorbed on solid support under microwave; react at a faster rate than conventional heating. The use of microwaves has also reduced the extent of purification required for the end products of chemical reactions involving toxic reagents.

Greater reproducibility of chemical reactions: Reactions under microwave irradiation show more reproducibility as compared to conventional heating because of uniform heating and better control of process parameters. The temperature of chemical reactions can also be easily monitored. This is of particular relevance in the lead optimization phase of the drug development process in pharmaceutical companies.

1.12 LIMITATIONS OF MICROWAVE CHEMISTRY

The limitations associated with microwave heating are its scalability, limited application and the hazards involved in its use.

Lack of scalability: The yield obtained by using domestic microwave apparatus is limited to a few grams. Although there have been developments in the recent past relating to the scalability of microwave equipment, still there is a gap that needs to be spelled to make this technology scalable.

Limited applicability: Microwaves can be used for heating only those materials, which absorb them. Microwaves cannot heat materials, which are transparent to these radiations.

Safety hazards relating to the use of microwave heating apparatus: Although manufacturers of microwave heating apparatus have directed their research to make microwaves a safe source of heating. Uncontrolled reaction conditions may result in undesirable results for example; chemical reactions involving volatile reactants under superheated conditions may result in explosive conditions. Moreover, improper use of microwave heating for rate enhancement of chemical reactions involving radioisotopes may result in uncontrolled radioactive decay.

Health hazards: Health hazards related to microwaves are caused by the penetration of microwaves. The microwaves operating at a low frequency range are only able to penetrate the human skin white, higher frequency range microwaves can reach body organs. Research has proved that prolonged exposure to microwaves may result in the complete degeneration of body tissues and cells. It has also been established that constant exposure of DNA to high frequency microwaves during a biochemical reaction may result in complete degeneration of the DNA strand.

1.13 ULTRASOUND CHEMISTRY

Different forms of energy, like heat, light, and so on can drive some chemical reactions. But in past few decades, ultrasound has emerged as a potential source to enhance the chemical reactivity, besides being used in nonchemical situations, such as the medical diagnosis, navigation bats, cleaning and drilling of teeth, SONAR, and material testing. It has been found that when ultrasound in low frequency range is passed through a chemical system, it influences its chemical reactivity. The study of effects of ultrasound on chemical reactivity is termed as sonochemistry.

The chemical effect of ultrasound was first reported by Richards and Loomis (1927). The basis for the present day generation of ultrasounds was established as far back as 1880 with the discovery of piezoelectric effect by the Curie brothers (1880, 1881). Crystalline materials showing this effect are known as piezoelectric materials. Ultrasonic devices consist transducers (energy converters), which are composed of these piezoelectric materials. An inverse piezoelectric effect is used in transducer that is a rapidly alternating potential is placed across the faces of piezoelectric crystal, which generates dimensional change and thus, converts electrical energy into sound energy. The first ultrasonic transducer was a whistle developed by Galton, (1883) who was then investigating the frequency of human hearing.

1.14 SONOCHEMICAL REACTIONS

Scientifically, sound is the transmission of energy through the generation of acoustic pressure waves in the medium. These are mechanical in nature that is, require a medium and the particles in the medium vibrate to transfer the waves. The frequency of the wave determines its regime and these are classified in different kinds:

Infrasound: Sound waves having frequency less than 20Hz.

Audible sound: Sound waves having frequency between 20 and 20 KHz.

Ultrasound: Sound waves with frequency more than 20 KHz.

Hypersound: Sound waves with frequency higher than 10GHz.

Principles of Sono-chemistry: Sonochemical effects are due to the phenomenon of acoustic cavitation that is, the creation, growth and implosive collapse of gas filled bubbles in a liquid in response to an applied ultrasonic field. Cavitation was first identified and reported by Thornycraft and Barnaby (1895). When a liquid is irradiated by ultrasound, micro bubbles will appear, grow, and oscillate extreme quickly and even collapse near a solid surface generating micro jets and shock waves. Moreover, in the liquid phase surrounding the particles, high micro mixing will increase the heat and mass transfer and even the diffusion of species inside the pores of the solid.

Phenomenon of cavitation: Sound waves are basically pressure waves. It consists of alternating compression and expansion cycles. When an acoustic field is applied to a liquid, the sonic vibrations create an acoustic pressure (Pa) at any time (t), which is given by the equation

$$Pa = PA \sin 2\pi\ f\ t$$

Where, PA is the maximum pressure amplitude of the wave and f is the frequency of the sound wave.

When ultrasound is passed through a liquid, the total pressure (P) in the liquid is given by

$$P = Pa - Ph$$

Where, Ph is the hydrostatic pressure

During the negative cycle of the wave, the distance between the molecules of the liquid will vary (oscillate) about a mean position. It the distance between the molecules exceeds the critical molecular distance, R (for example for water, the value of R is 10-8cm), then the liquid will breakdown and voids will be created; that is, formation of cavitation bubbles.

During the positive cycle of the wave, the bubbles grew in size due to the positive acoustic pressure and then finally collapse, leading to the formation of new nuclei for the next cavitation.

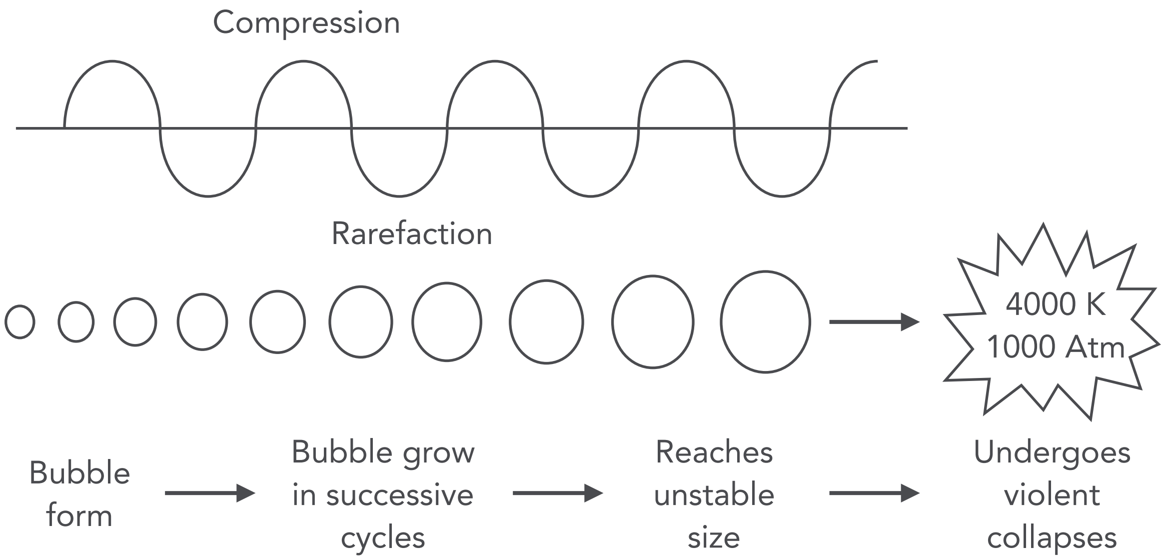


Fig 1.3: impulsive collapses of bubbles

This is the mechanism for a cavity formation. If attempts are made to remove contaminants, particulates, precipitates, and so on from a solution, there are generally small dust moles or crystalline materials present in it. These irregular surfaces allow gas to be trapped. Acoustic waves consist of alternating compression and rarefaction waves. Upon rarefaction, the gas, which is trapped in the dust molecule, is pulled out to become a freestanding bubble.

The occurrence of these collapses near a solid surface will generate microjets and shock wave. Moreover, in the liquid phase surrounding the particles, high micromixing will increase the heat and mass transfer and even the diffusion of species inside the pores of the solid.

1.15 FACTORS AFFECTING CAVITATION

1. **Ultrasound frequency:** Mostly sonochemical work involves frequencies between 20 and 50 KHz. It has been observed that sonochemical effect is limited at higher frequencies. It is due to the reason that the bubble has less time to grow and collapse at higher frequencies.
2. **Presence of gas:** Dissolved gases act as nucleation sites for cavitation. As gases are removed from the reaction mixture because of the implosion of the cavitation bubbles, initiation of new cavitational events becomes increasingly difficult. Bubbling gases through the mixture facilitate the production of cavitation bubbles.

3. **Effect of external pressure:** On increasing external pressure, Ph, it requires the application of greater acoustic pressure, Pa and hence, the system requires higher ultrasonic intensities, and so on to generate cavitation bubbles.
4. **Temperature:** Sonication proceeds more efficiently at lower temperatures.
   It is due to the effect on the solvent properties like densities, surface tensions, viscosities, and so on.

1.16 SOURCES OF ULTRASOUND IN SONOCHEMISTRY

Ultrasonic cleaning bath: The simple ultrasonic bath is economic and easily available source of ultrasonic irradiation in the chemical laboratories. It has several drawbacks like ultrasonic intensity is limited for every ultrasonic cleaning bath, temperature control is also difficult and reproducibility of results is relatively poor because inter-laboratory comparisons are difficult. Different baths have different frequencies and power outputs.

Ultrasonic probe system: In this type of system, a metal 'probe' is used, which is attached to the transducer introduced directly into a reaction system itself for increasing the amount of ultrasonic power.

The horn is part of an assembly which amplifies small vibrations of the piezoelecric crystal to larger amplitude. This probe system has several advantages over a cleaning bath.

The ultrasonic probe system is of two types:

1. Cup-horn system
2. Flow cell system

Submersible transducer: In this type of system, transducer is directly immersed into the reaction. It is an alternative to the cleaning bath and also used for batch sonication.

Whistle reactor: In this system, ultrasonic intensities are very low. Generally, this equipment is used for emulsification, polymerization, and phase transfer reactions. Liquids are pumped at a high rate through a narrow gap onto a thin metal blade. This sets the blade into vibration with a sufficiently high frequency to cause cavitation, which causes the reaction to proceed.

Tube reactor: Tube is surrounded by a radical transducer. Reaction mixture flows through this tube. The ultrasonic energy is focused toward the middle of the tube with much lower powers at the inner surface. In this way, erosion problems are reduced.

1.17 THE 12 PRINCIPLES OF GREEN CHEMISTRY

The green chemical approach is governed by 12 principles given by Anastas and Warner (1998). These principles are important in combating against environmental pollution and for the betterment of human health.

Principle 1: Waste prevention

This principle was formulated as follows: "It is better to prevent waste than to treat or clean up waste after it is formed." If chemical waste is hazardous, its separation from the desired product(s), any further treatment, and the final disposal may require special handling and protective gear and equipment.

If there was no hazardous and toxic waste to begin with, it would be the best in terms of health, environment, and economy. Even nonhazardous waste is undesirable, because its separation and removal from the desired product(s) still cost energy and time, and possibly require the use of solvents and other auxiliary substances, some of which may be hazardous.

In some cases, there may be limits to reducing waste, which are inherent to the chemical reaction itself. A simple example is preparion methyl *m*-nitrobenzoate from methyl benzoate via nitration with a mixture of concentrated HNO_3 and H_2SO_4.

This is a classical experiment that illustrates the principles of electrophilic aromatic substitution. The electrophile is NO_2^+ (nitronium ion). According to the theory, the predominant product should be the *m* (*meta*) isomer, rather than the other two possible isomers, namely, *o* (*ortho*) or *p* (*para*) isomers.

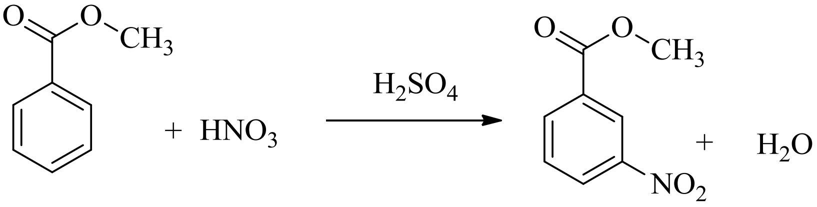


Fig 1.4: Nitration of methyl benzoate to give methyl *m*-nitrobenzoate

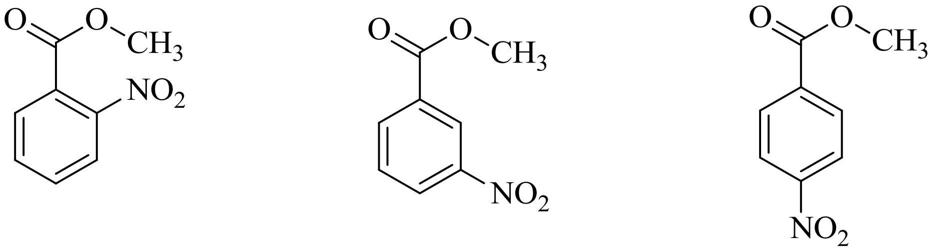


Fig 1.5: Three possible isomers of methyl nitrobenzoate

The reaction indeed gives the *meta* isomer as the predominant product. However, a closer look to the reaction outcome shows that the *meta* isomer is not the exclusive one but is obtained in ~68% yield. The other two isomers are also obtained: the *ortho* isomer in ~28% and the *para* isomer in only a minute amount of ~4%. These two isomers represent the undesired by-products and are the inevitable waste.

This type of waste cannot be controlled. Other possible organic waste would be the un-reacted starting material and di-nitrated product, but this can be controlled by following the experimental protocol carefully. Anastas and Warner point out that the waste that results from the un-reacted starting material is costly, because one pays for the substance twice: first as a feedstock and then for its disposal as a waste.

Principle 2: Atom economy

This principle is given as follows: “Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.”

The concept of "atom economy" is one of the major innovations in the analysis of synthetic efficiency of chemical reactions. It was invented by Barry M. Trost.

The atom economy (a measure of atom utilization or efficiency) is a measure of the amount of starting materials that end up as useful products. It is important for sustainable development and for good economic reasons to use reactions with high atom economy.

A chemical reaction may give, and often does, more than one product, but among the mixture of products, perhaps only one of them is the desired useful product.

The percentage atom economy of a reaction is readily calculated using the balanced equation for the reaction expressed in reacting masses.

Solvents, reagents or materials used in catalytic quantities are omitted from the analysis, as they do not contribute atoms to an intermediate and/or product.

The atom economy of a reaction is a theoretical percentage measure of the amount of starting materials that ends up as the 'desired' useful reaction products. It is sometimes referred to as atom utilization.

$$\textbf{Atom economy} = \frac{\textbf{Mass of desired useful product}}{\textbf{Total mass of all reactants or products}} \textbf{x100}$$

Solvents, reagents or materials used in catalytic quantities are omitted from the analysis, as they do not contribute atoms to an intermediate and/or product. Let us consider a general reaction in which C is desired product as given below

$$\mathbf{A + B} \xrightarrow[\text{Solvents}\\ \text{Catalysts}]{\text{Reagents}} \mathbf{C + D}$$

$$\textbf{Atom Economy} = \frac{\text{Mw of C}}{\text{Mw of (A+B)}} \textbf{ x 100}$$

Fig 1.6: Atom economy calculation for the synthesis of C

This is illustrated by using the blast furnace reaction as follows

$$\mathbf{Fe_2O_{3(s)} + 3CO_{(g)} \rightarrow 2Fe_{(l)} + 3CO_{2(g)}}$$

Using the atomic masses of Fe = 56, C = 12, O = 16, we can calculate the atom economy for extracting iron.

The reaction equation can be expressed in terms of theoretical reacting mass units

$$\mathbf{[(2 \times 56) + (3 \times 16)] + [3 \times (12 + 16)] \rightarrow [2 \times 56] + [3 \times (12 + 16 + 16)]}$$

$$\mathbf{[160 \text{ of } Fe_2O_3] + [84 \text{ of } CO] \rightarrow [112 \text{ of } Fe] + [132 \text{ of } CO_2]}$$

so there are a total of 112 mass units of the useful/desired product iron, Fe out of a total mass of reactants **or** products of 160 + 84 = 112 + 132 = 244.

Therefore the **atom economy** = 100 x 112 / 244 = **45.9%**

Similarly fermentation of sugar to make ethanol (‘alcohol’)

glucose (sugar) +enzyme → ethanol + carbon dioxide

$$C_6H_{12}O_{6(aq)} \rightarrow 2C_2H_5OH_{(aq)} + 2CO_{2(g)}$$

Atomic masses: C = 12, H = 1 and O = 16

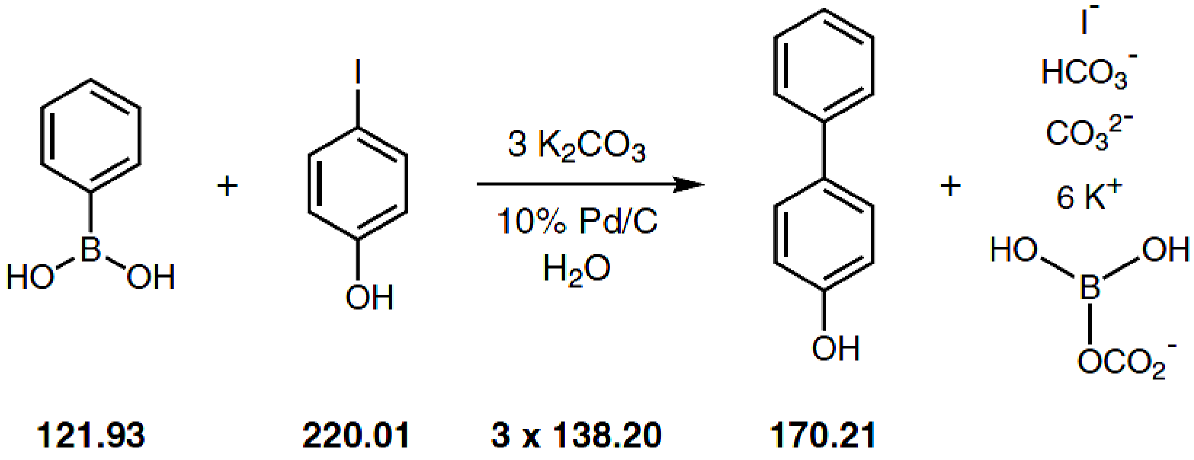
Formula mass of glucose reactant = 180 (6x12 + 12x1 + 6x16)

Formula mass of ethanol product = 46 (2x12 + 5x1 + 1x16 + 1x1)

Relative mass of desired useful product in the equation = 2 x 46 = 92

Atom economy = 100 x 92/180 = 51.1%

Atom economy of balanced Suzuki reaction can be calculated as



$$\% \textbf{ Atom Economy} = \frac{170.21}{121.93 + 220.01 + 3 \times 138.20} \times 100\% = 22.5\%$$

Fig 1.7: Atom economy of a balanced Suzuki reaction

The reactions that only give one product, have the maximum atom economy of 100% and these are the most economic reactions e.g. synthesis of ammonia and reacting ethene with water to make ethanol.

$N_2 + 3H_2 \rightarrow 2NH_3$

$CH_2{=}CH_2 + H_2O \rightarrow CH_3CH_2OH$

These are simple addition reactions where two reactants give one product e.g. synthesis of ammonia from nitrogen and hydrogen and the synthesis of ethanol from ethene and water.

100 minus the atom economy gives you the % waste, but reactions with only one product will always give the highest atom economy.

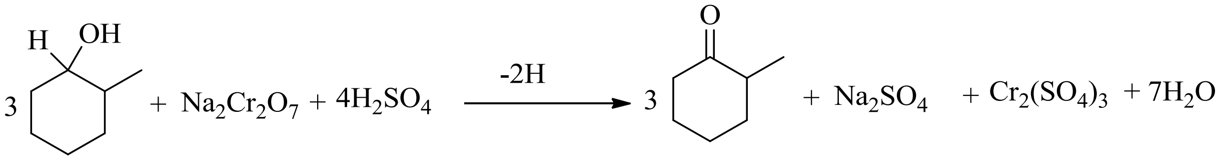
If a reaction gives more than one product it may be possible to use and sell these other products, thereby making the process more economic overall.

Reactions with a low atom economy are very wasteful and use up resources at faster rate than high atom economy reactions.

Principle 3: Safer syntheses

The full description of this principle is given as follows: "Whenever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and environment."

Let us take Jones oxidation of a secondary alcohol as an example.



The usual pedagogical emphasis is on learning the functional group transformations, in this case oxidation of secondary alcohols to ketones. This approach is not sufficient for green chemistry. One must always consider reagents and their potential hazards. In this case, the chromium reagent is toxic.

A complete, balanced equation, which includes all the reagents, needs to be considered. This is necessary not only for calculations of atom economy, which was shown previously, but also for hazard evaluation. Additional green chemistry metrics exist, which include solvents and environmental factors.

Before the students begin laboratory experiments, they should also make a list of solvents and other substances that they will use during the workup, isolation, and purification of products. These also need to be evaluated for toxicity.

Once all the hazards are evaluated, a brand new design for the reaction, which considers all the elements above, may be proposed by the student, or at least some hazard should be diminished via the appropriate "greening." Thus, the exercise on new design and greening is real, and not just a make-work project.

Principle 4: Safer Products

The full description of this principle is given as follows: "Chemical products should be designed to preserve efficacy of function while reducing toxicity." Implementation of this principle requires additional knowledge about toxicity, which the chemistry students typically do not get from their regular chemistry courses.

Thanks to the advances in chemistry and related sciences, we now understand better the relationship between the chemical structure and the resulting properties of the products. Examples include color (of dyes and paints), amphiphilicity (property required for detergent-type action), tensile strength (of various fibers), and non-flammability (of various fabrics).

To design chemicals that are not toxic, we need to learn as much as possible about the reasons why some chemicals are toxic and some others are not, and why some species are affected more by a particular toxic chemical than some others. We need to be able to predict in advance, as much as we can, if the chemical we intend to make will be toxic or not. Further, the dose of chemicals to which a living entity is exposed matters to the toxic effect. Something may not be toxic in small amounts, but, just like in a case of a drug overdose, may be quite toxic if the amount is above some limit. Some chemicals accumulate in the fatty tissues in the body, and the knowledge of partition coefficient (distribution between lipid and water) will be needed. We also need to be able to sort out all of these factors, and there are many more. This may appear to be a difficult task, but we shall overcome it gradually.

Principle 5: Safer solvents/ auxiliaries

This principle is given as follows: "The use of auxiliary substances (e.g. solvents, separation agents) should be made unnecessary whenever possible and harmless when used." Auxiliary substances are not the starting materials, reagents, catalysts, or products, and thus are not a part of the chemical equations. Instead, these are substances that are used during the workup, separation, isolation, and purification of the products. They are routinely used in syntheses in the laboratory, manufacturing, and processing or chemicals for various uses.

Various solvents are notorious for being harmful, especially halogenated solvents. Many of them are hazardous to health or environment. CH_2Cl_2 (methylene chloride), $CHCl_3$ (chloroform) CCl_4 (carbon tetrachloride) are suspected carcinogen (among other adverse effects on health). CFCs (chlorofluorocarbons) deplete the stratospheric ozone layer, thus are hazardous for environment.

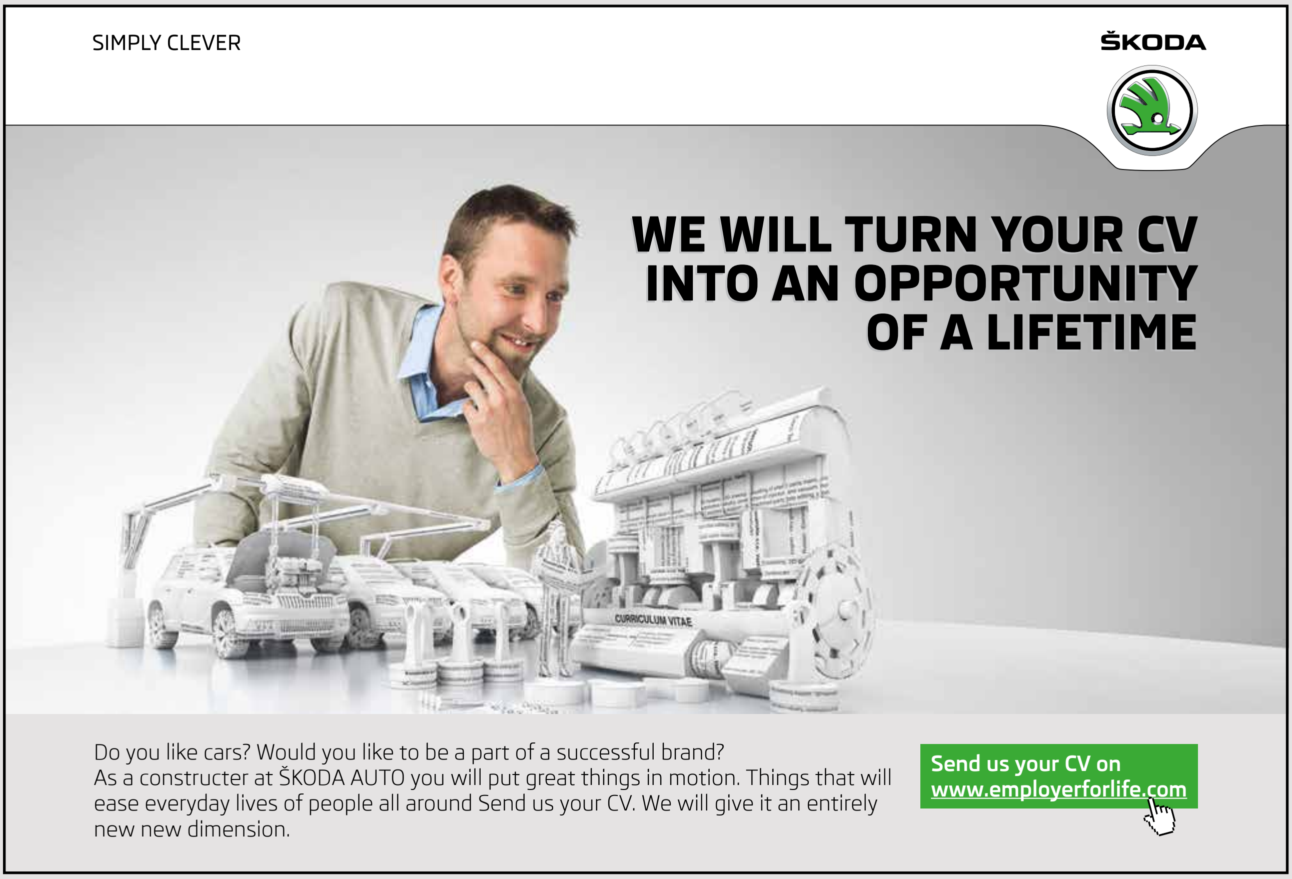
One of the desired properties of solvents that are used for isolation of products, their purification, and manipulation is low volatility. This property makes them easy to remove at the end of these procedures. However, the low volatility may carry other hazards, which are in common with all volatile organic compounds. Volatile compounds in general can escape easier from their containers, and this potentiates their health hazards, flammability, and negative effect on the environment such as smog formation.

The green chemistry initiatives are to either eliminate solvents altogether in the so-called solventless reactions or use benign solvents, such as water. These initiatives will be discussed in detail throughout other chapters.

Principle 6: Energy efficiency

Anastas and Warner (1998) gave the full description of this principle as follows:

“Energy requirements should be recognized for their environmental and economic impacts and should be minimized.”



Energy consumption is involved in virtually all stages of chemical experiments, manufacturing, and processing. Examples that students can relate to are heating or cooling of the reaction mixtures, heating required for distillation of products and solvents, melting, sublimation, and re-crystallization processes, among others. On the industrial scale, energy requirements are amplified and often require costly equipment to safely dissipate heat to avoid overheating and runaway reactions. Many energy uses are assumed to be necessary, but they may not be, and thus, the greening can often be done by saving energy. One example is heating under reflux. It is a common laboratory procedure, which is almost universally used, because it results in heating at a constant temperature. As the reaction mixture boils, its vapors are returned to the reaction flask by using a vertical cooled condenser. This is shown in Figure below

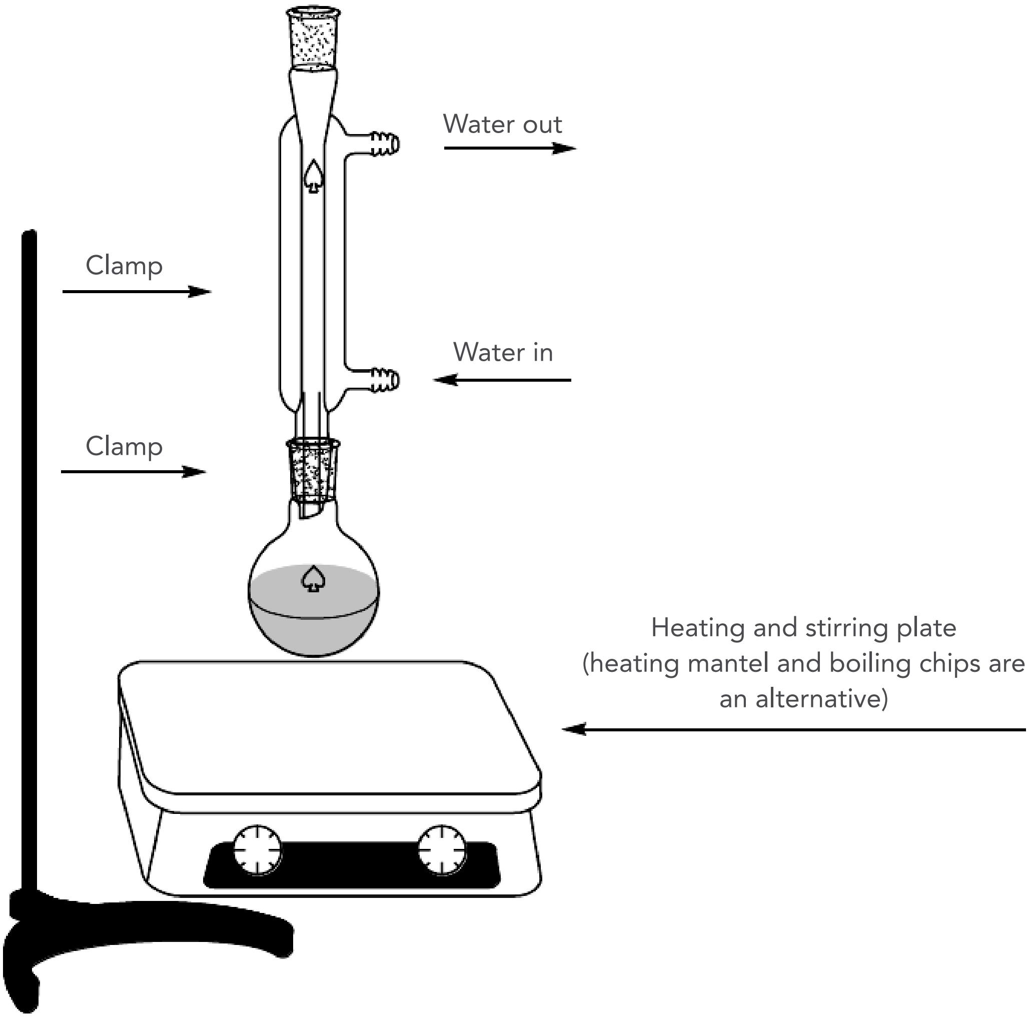


Fig 1.8: A setup for heating under reflux

In most of the cases, the heating requirements have not been determined. Thus, the energy requirement has not been optimized. It is possible that in many cases, comparable results could be achieved at temperatures that are lower than the reflux one. A reasonable compromise about the reaction time, which would perhaps need to be longer at lower temperature, needs to be considered. One could use a setup shown in Figure below, for heating at a constant temperature.

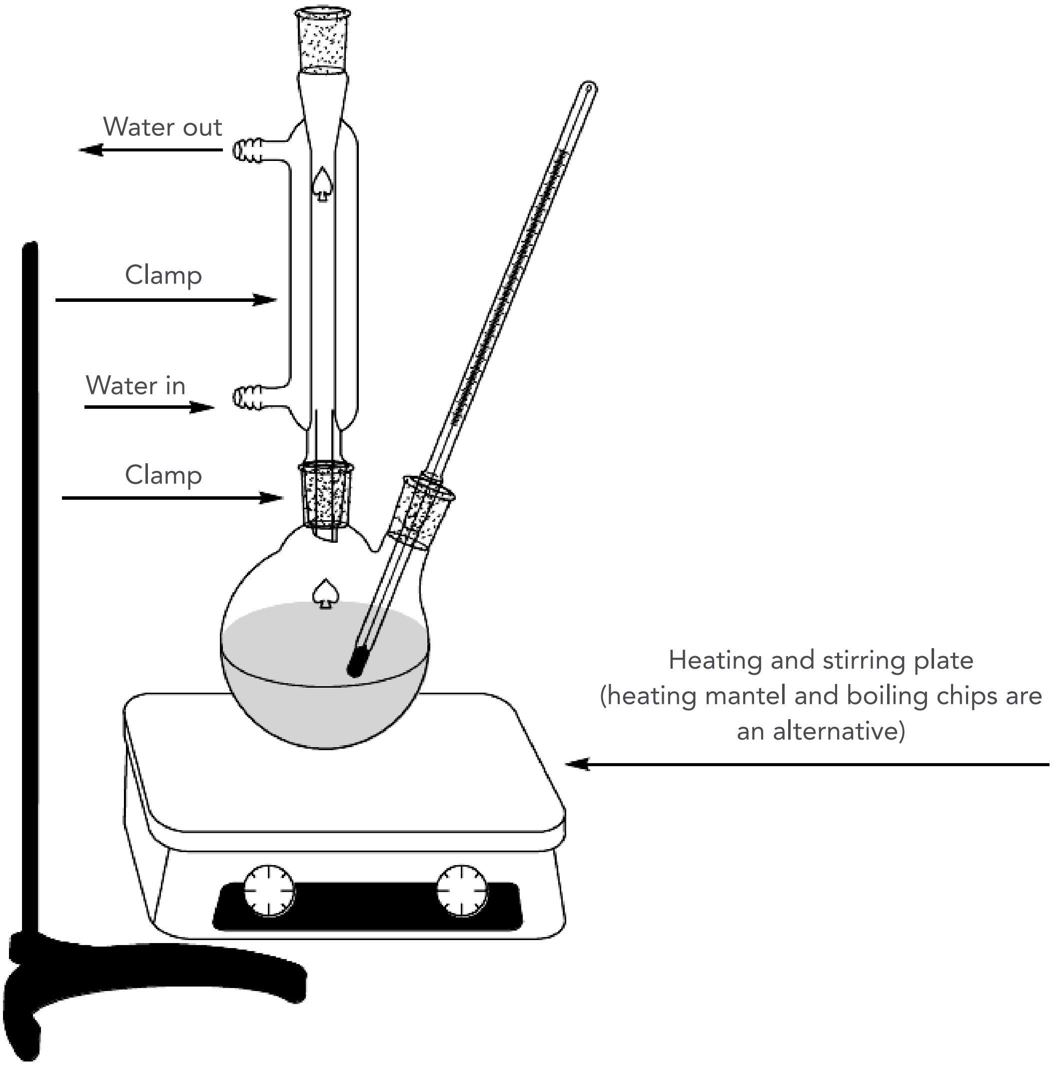


Fig 1.9: A setup for heating at constant temperature

Energy saving may also be accomplished by using microwave heating, when feasible.

Principle 7: Renewable Feed-stocks

The full definition of this principle is as follows: "A raw material or feedstock should be renewable rather than depleting, wherever technically and economically practicable."

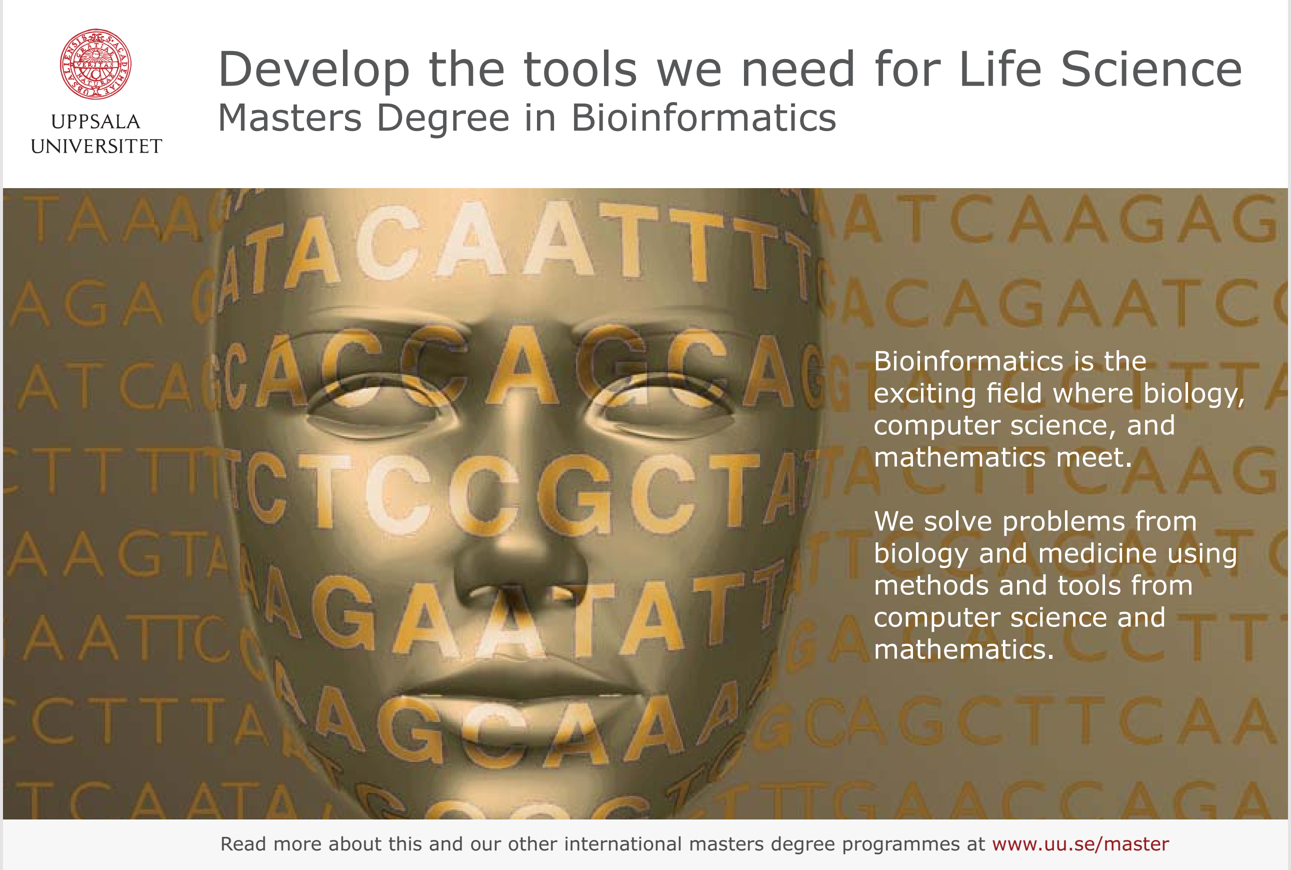
Fossil fuels belong to the resources that can be depleted, whereas renewable feed-stocks are typically associated with biological materials, such as plant-based materials.

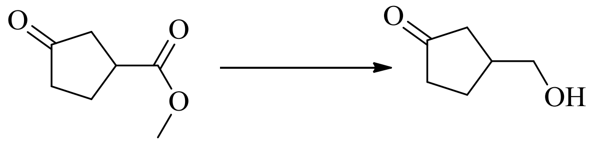
This principle is strongly correlated with sustainability. As we utilize the resources that are available to us, we need to find a way to have such resources available also for future generations. We need to switch from petroleum hydrocarbon resources to other resources, because they are not green in many respects. As one example, petroleum hydrocarbons are converted to other useful products typically by oxidation, which often requires catalysis by metals, such as chromium, which are toxic. We see in this example that the principles of green chemistry are often intertwined and are difficult to be looked at in isolation. The use of biological feedstock is promising. It also has a requirement to be renewable. Much of the green chemistry innovation is in this area (discussed ahead).

Principle 8: Derivative reduction

The definition of this principle as follows: “Unnecessary derivatization (blocking group, protection/deprotection, and temporary modification of physical/chemical processes) should be avoided whenever possible.”

The derivatization principle is illustrated on an example from the beginning of organic chemistry. Starting from compound **1**, which has a keto and ester groups, we need to make compound **2**, in which the ester group is converted to an alcohol, whereas the keto group is preserved. This desired transformation is shown in Figure below.





1 a keto ester 2 a keto alcohol

Fig 1.10: Transformation of a keto ester **1** to a keto alcohol **2**

The reaction requires a reduction of the ester group to an alcohol. Two reducing agents that students are generally familiar with are sodium borohydride, $NaBH_4$, and lithium aluminum hydride, $LiAlH_4$. $LiAlH_4$ will reduce the ester group, whereas the $NaBH_4$ will not. However, both reducing agents will reduce the keto group to an alcohol, because the keto function is more easily reduced than the ester. To solve this synthetic problem, one can react **1** with ethylene glycol, **3**, under the condition of acid catalysis, to give compound **4**, in which the keto group is transformed to the acetal **5**, whereas the ester group is unchanged (it does not react with **3**). One can then reduce the ester group in **5** with LiAlH4, which will convert it to the alcohol **6**, while leaving the acetal group intact. Finally, the acetal group is removed by an acid hydrolysis to give the desired product **2**. The terms chemists use are that the keto group is "protected" against reduction by "derivatization" into an acetal, which is later removed to "deprotect" the ketone. This sequence of protection, reduction, and deprotection is shown in Fig. below

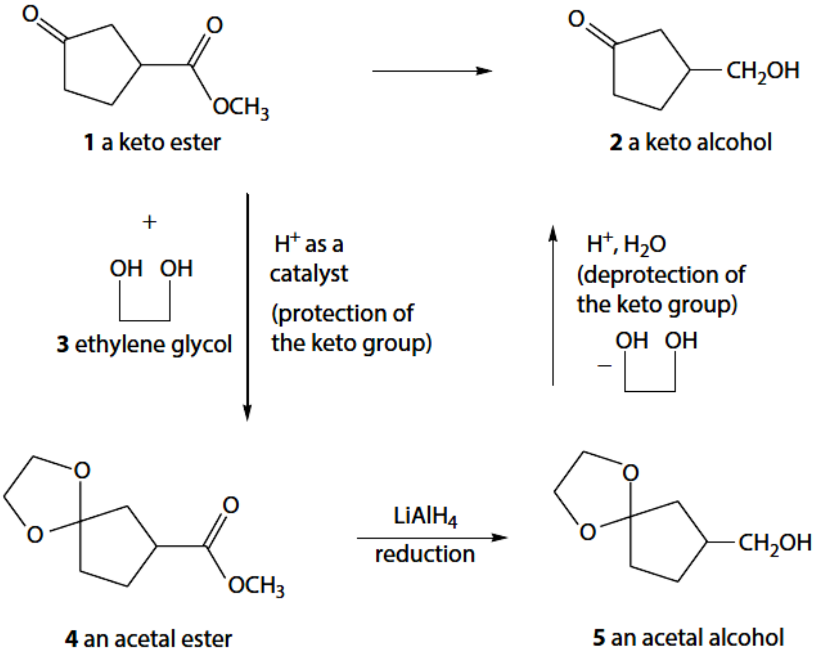


Fig 1.11: Transformation of a keto ester **1** to a keto alcohol **2** via a protection/deprotection scheme

In this example, and at the level of a beginning organic student, the protection/deprotection was necessary. A quick examination of the reaction sequence reveals a poor atom economy, because ethylene glycol will go to waste. Alternatively, a possible recycling of ethylene glycol would require extraction from the aqueous waste and purification for its reuse, which may not be economical.

Principle 9: Catalysis

The definition of this principle is given as follows: "Catalytic reagents (as selective as possible) are superior to stoichiometric reagents."

Catalysts typically lower the activation energy barrier for the reaction, thus enabling reactions to occur faster and become feasible at the lower temperatures.

This translates into the greener energy requirements.

Many catalysts have been developed to either enable or enhance selectivity of the reaction. Stereoselectivity and achievement of enantiomeric excess are necessary in the syntheses of fine chemicals, especially drugs. Enantiomers exhibit the opposite handedness, like the left and the right hand. Often only one of the enantiomers has the desired biological properties, and the other one may either be toxic or place burden on the organism's detoxification system. The production of the undesired enantiomers creates waste, but the more serious problem is the required separation of enantiomers for the purpose of isolating the biologically active one. This process is often difficult, lengthy, and expensive. It is often a major factor that drives up the cost of drugs. It is therefore very important that the chemical synthesis yields the desired enantiomer either exclusively or in excess. This is often achieved with special catalysts.

Selectivity of catalysts is useful for many basic chemical reactions that are familiar to students. One such example is shown in Figure below.

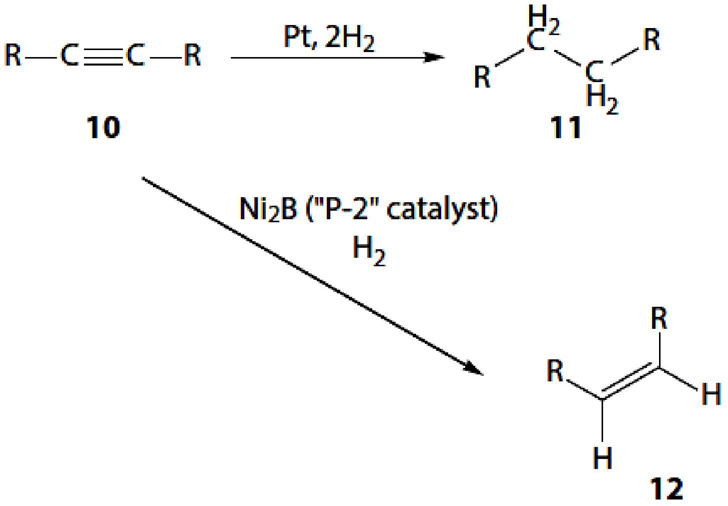


Fig 1.12: Selectivity in hydrogenation of unsaturated hydrocarbons.

When alkyne **10** reacts with H_2 in the presence of Pt, the reaction does not stop at the alkene stage, but gives the alkane **11**, a completely saturated product. If less than two equivalents of H_2 were used, one would still get the alkane, but would have some unreacted **11**. No alkene would be obtained. In contrast, when a less reactive catalyst is used, such as Ni_2B, the reaction stops at the alkene stage. In both cases, the hydrogenation takes place at the surface of the catalyst. This accounts for the *cis* stereochemistry of **12**.

Catalysis in general offers advantages over typical stoichiometric reactions, because many of them need to be facilitated, often by adding an excess of starting materials or additional reagents, which drive the cost up and typically end up in waste.

Principle 10: Degradability

The full description of this principle, as given as follows: "Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products."

Many useful products, such as various plastics, have been found to be persistent in the environment. This has created multiple problems, from overflowing landfills, to the danger for wild life, such as sea birds, which ingest these products, often with consequences that are detrimental for their health. For such reasons, chemists started creating plastics that can be degraded in the environment, often with the help of various microbes (thus the term "biodegradable").

Some other useful products, such as pesticides, tend to accumulate in living organisms (thus the term “bioaccumulation”), especially in the lipid tissues. The organisms are thus exposed to such chemicals over a prolonged period of time, which can exacerbate toxicity. It can also lead to the transfer of such chemicals from mothers to their nursing infants via milk. Degradability in cases of pesticides is therefore a desired property.

Degradation of chemical products should give benign end products. The design of chemical products needs to fulfill the degradability requirement. Green chemistry considers chemical degradation that often occurs in the environment via hydrolysis, photolysis, and oxidation, among other means. Also, various microbes and plants may be used to remove/degrade toxic chemicals.

Principle 11: Pollution prevention

The short definition of this principle was given by Sanderson (2011) and was further expanded on as follows: “Develop methods for real-time monitoring and control of chemical processes that might form hazardous substances.” Anastas and Warner (1998) give the definition of this principle as follows: “Analytical methodologies need to be further developed to allow for real-time, in-process monitoring, and control prior to the formation of hazardous substances.”

This principle focuses on the development of accurate and reliable analytical techniques that can be used to monitor the generation of hazardous by-products and occurrences of side reactions. Once these are observed, parameters of such reactions and processes can be adjusted to eliminate or reduce their formation. Especially important is the determination of the completion level of the chemical reactions, so that one can intervene before quenching them. One simple example, which is familiar to most of students, is to follow the reaction progress by thin-layer chromatography.

If the starting material is still present, the reaction time is increased to allow for all the materials to react. Modern analytical techniques are capable of detecting minute amounts of hazardous or undesirable chemicals. Technological capabilities exist for interfacing analytical sensors within process control, and thus minimizing hazards in an automated fashion.

Principle 12: Accident prevention

This principle is given by Anastas and Warner (1998) as follows: "Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires."

This is an important principle that broadens the scope of green chemistry to prevention/minimization of hazards above and beyond toxicity. Other hazardous properties, such as flammability and tendency to explode, are often responsible for injuries and large-scale releases of chemicals into the environment.

It is important to evaluate some other green chemistry principles in light of this one. For example, recycling of solvents is green according to principle 7, but solvents are often flammable and pose fire or explosion hazards.

One green technology is a rapid consumption of hazardous substances, so that they do not need to be stored.

2 DESIGNING A CHEMICAL SYNTHESIS

2.1 DESIGNING A GREEN SYNTHESIS

In any synthesis of a target molecule, the starting materials are made to react with a reagent under appropriate conditions. Before coming to a final decision, consider all the possible methods that can give the desired product.

The same product can also be obtained by modifying the conditions. The method of choice should not use toxic starting materials and should eliminate by-products and wastes. Following are some of the important considerations.

Choice of starting materials: It is very important to choose the appropriate starting materials. The synthetic pathway will depend on this. Also consider the hazards that may be faced by the workers (chemists carrying out the reaction and the shippers who transport these) handling the starting materials.

Choice of reagents: Selection of the right reagent for a reaction is made on the basis of efficiency, availability and its effect on environment. The selection of a particular reagent versus another reagent for the same transformation can affect the nature of by-products, percentage yield etc.

Choice of catalysts: Certain reactions proceed much faster and at a lower temperature with the use of catalysts. Heavy metal catalysts should be avoided as they cause environmental problems and are toxic in nature.

2.2 PREVENTION OF WASTE/BY-PRODUCTS

It is most advantageous to carry out a synthesis in such a way so that formation of waste (by-products) is minimum or absent. It is especially important because in most of the cases the cost involved in the treatment and disposal of waste adds to the overall production cost. Even the un-reacted starting materials (which may or may not be hazardous) form part of the waste. Hence, the next basic principle is important and should carefully be considered as “prevention is better than cure” applies in this case also. In other words, the formation of the waste (or by-products) should be avoided as far as possible. The waste (or by-products) if discharged (or disposed off) in the atmosphere, sea or land not only causes pollution but also requires expenditure for cleaning-up. The waste (or by-products) can be prevented or minimized by maximum Incorporation of the reactants into the final product.

2.3 MAXIMUM INCORPORATION OF THE REACTANTS (STARTING MATERIALS AND REAGENTS) INTO THE FINAL PRODUCT

Chemists globally consider that if the yield of a reaction is about 90%, the reaction is good. The percentage yield is calculated by

$$\%\ \text{yield} = \frac{\text{Actual yield of the product}}{\text{Theoritical yield of the product}} \text{x } 100$$

In other words, if one mole of a starting material produces one mole of the product, the yield is 100%. Such synthesis is deemed perfectly efficient by this calculation. A perfectly efficient synthesis according to the percentage yield calculations may, however, generate significant amount of waste (or byproducts) which is not visible in the above calculation. Such synthesis is not green synthesis. Typical examples like Wittig reaction and the Grignard reactions illustrate the above contention. Both these reactions may proceed with 100% yield but do not take into account the large amounts of by-products obtained.

The reaction or the synthesis is considered to be green if there is maximum incorporation of the starting materials and reagents in the final product. We should take into account the percentage atom utilization,

Percent atom utilization: The atom utilization of a particular process is calculated by dividing the molecular weight of the desired product by the sum total of all the materials (excluding solvents) used. It provides a simple way of assessing how 'clean' a particular process is with regard to the amount of waste that is formed, in the ideal case of 100% selective conversion of starting material.

$$\%\ \text{atom utilization} = \frac{\text{Mw of desired product}}{\text{Mw of (desired product+waste products)}} \times 100$$

The concept of atom economy developed by B.M. Trost is a consideration of how much of the reactants end up in the final product'. The same concept determined by R.A. Sheldon is given as

$$\text{Atom economy} = \frac{\text{Mass of desired useful product}}{\text{Total mass of all reactants or products}} \times 100$$

The two useful measures of the potential environmental impact of chemical processes are the E-factor, and the atom efficiency.

E factor

E factor is defined as the mass ratio of waste to desired product.

$$\text{E factor} = \frac{\text{mass of waste}}{\text{mass of desired product}}$$

It means the processes producing more waste have higher E Factor

A main cause of high E-factors is the use of stoichiometric inorganic reagents. Manufacture of fine chemicals and pharmaceuticals, through classic stoichiometric technologies generate large amounts of inorganic salt as waste. For example, stoichiometric reductions with metals (Zn, Fe) and metal hydrides ($NaBH_4$, $LiAlH_4$, and derivatives thereof) and stoichiometric oxidations with permanganate, dichromate, periodate, and so on. Similarly, processes using mineral acids (H_2SO_4, HF), Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3), or inorganic bases (NaOH, K_2CO_3), often in stoichiometric amounts, represent a major source of inorganic waste that cannot easily be recycled. Reactions of this type, widely used in the fine chemical industry also include Friedel–Crafts acylation mediated by Lewis acids such as $AlCl_3$, sulfonations, and diazotizations etc.

The workup for such reactions involves neutralization and concomitant generation of salts such as NaCl, Na_2SO_4, and $(NH_4)_2SO_4$. The elimination of such waste streams and a reduction in the dependence on the use of hazardous chemicals, such as phosgene, dimethyl sulfate, peracids, sodium azide, halogens, and HF, are primary goals in green chemistry.

Most of the processes for fine chemicals and pharmaceuticals, with a very large E-factor, use reagents in stoichiometric quantities, often in combination with environmentally unfriendly solvents. The E-factor is the actual amount of waste formed in the process and includes everything except the desired product. It includes not only the raw materials and reagents involved in the stoichiometric equation but also chemicals used in the workup, for example, acids and bases for neutralization, and solvent losses. Strictly speaking, it should also include the fuel used to generate the energy required to operate the process, but this is often difficult to quantify. Process water is not included, as this leads to E-factors that are not generally meaningful.

2.4 ATOM EFFICIENCY

The concept of atom efficiency has proven to be a popular tool in the evaluation of the "greenness" of a chemical process. It is also revealing to compare sectors of chemical manufacturing. Most people would associate oil refining more than pharmaceutical manufacturing with dirty processes and waste. Though the complete scale of the former leads to the largest volume of waste, the ratio of waste to product is greater for the latter by a factor of 102–103. In pharmaceutical and fine chemicals manufacturing, the high value of the product has been a particularly significant feature in the establishment of many highly (atom) inefficient processes. Stoichiometric reagents (e.g., chromate oxidants), catalysts that cannot easily be recovered and reused, and large volumes of volatile organic solvents are routinely used with all the consequential waste at the end of the reaction when the organic products need to be separated from the inorganic reagents, catalysts, and solvents (typically by an aqueous quench). Some of the biggest problem areas in synthetic methodology in this context are:

- Acid-catalyzed reactions
- Selective oxidations
- Halogenations
- Base-catalyzed reactions
- Reductions
- Metal-catalyzed reactions
- Phase-transfer-catalyzed reactions

In tackling these problem areas, we should not be afraid to strive toward the "ideal synthesis" which would be

- Atom efficient,
- Safe,
- One step,
- involving no wasted reagents,
- based on renewable resources, and
- Environmentally acceptable (including product fate considerations).

Step changes that move toward the ideal synthesis can be achieved with the application of several technologies including catalysis, process intensification, alternative energy sources, and supercritical fluids. Since the major source of waste from a chemical process is the reparation stage, it would seem sensible to focus heavily on that. The heterogenization of catalysts (and, where appropriate, reagents) so that they can easily be separated (and reused) at the end of a process, is a logical and versatile approach to simplifying the process, removing the need for an aqueous quench (or other destructive separation step) and reducing the demand for raw materials.

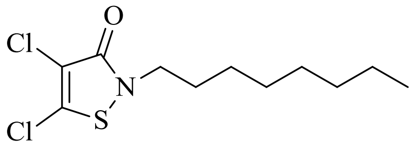
2.5 PREVENTION OR MINIMIZATION OF HAZARDOUS/TOXIC PRODUCTS

The most important principle of green chemistry is to prevent or at least minimize the formation of hazardous products, which may be toxic or environmentally harmful. The effect of hazardous substances if formed may be minimized for the workers by the use of protective clothing, engineering controls, respirator etc. This, however, adds to the cost of production. It is found that sometimes the controls can fail and so there is much more risk involved. Green chemistry, in fact, offers a scientific option to deal with such situations.

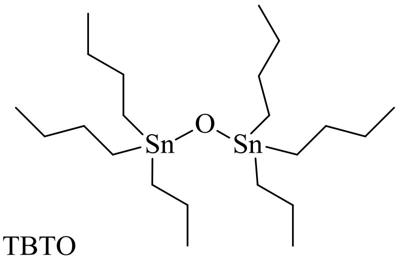
2.6 DESIGNING SAFER CHEMICALS

The concept of designing safer chemicals can be defined as: “The employment of structure - activity relationships (S AR) and molecular manipulation to achieve the optimum relationship between toxicological effects and the efficacy of intended use.” The key word in this definition is “optimum” since it is often not possible to achieve zero toxicity or to achieve a maximum level of efficacy, but rather some optimum combination of the two goals.

An understanding of the fundamental relationships between chemical properties and toxicity has enabled researchers to design safer substances. Underlying the concept of green chemistry is the desire to produce chemicals that are as useful as possible whilst also being both safe for us to use and safe for the environment. Safety refers to both flammability and toxicity. One example of designing safer chemicals is the compound 4,5-dichloro-2-*n*-octyl-4-isothiazoline-3-one (DCOI), which finds use as an antifouling agent to reduce the deposition of various microorganisms.This compound was developed by Rohm and Haas to replace the antifouling agent tributyltin oxide (TBTO), which has a tendency to bioaccumulate in the marine environment and is toxic to many organisms. In comparison, DCOI is found to exhibit less bioaccumulation and toxicity.

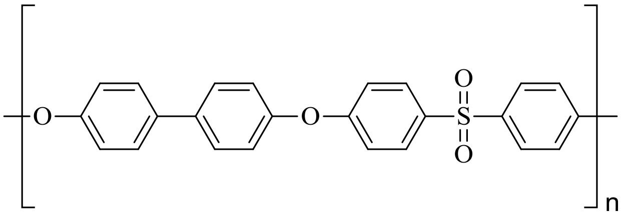


DCOI



TBTO

Polymers have been developed which are much less flammable than the more well known polymers but also retain properties such as toughness. They must be able to absorb severe impacts without cracking and breaking. One such polymer is polyphenylsulfone which has the formula:



polyphenylsulfone

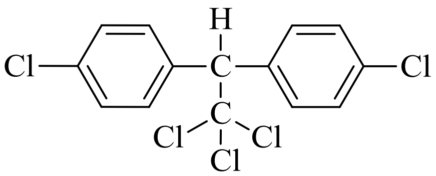
It is also important that chemicals that are produced are safe for the environment. Some products are specifically intended to be spread on soil, used in water, sprayed in the air or ingested by people; others, like washing detergents, may end up in water courses or in household waste for landfill. In both these cases, the material should degrade to harmless products. Detergents used to be based on the sodium salts of alkylbenzene sulfonic acids, and the alkyl group was branched. These were not degraded naturally in sewage works and caused foaming which made the sewage difficult to manage. Now these compounds have been replaced with sodium salts of linear alkylbenzene sulfonic acids, which are readily degraded. Their production is not simple and it took much research to develop it.

Another development to help the environment was the replacement of the compounds added to detergents to remove magnesium and calcium ions from hard water (known as builders. Sodium phosphates were used for this purpose but these caused considerable problems leading to eutrophication of water courses. Now zeolites (aluminosilicates) are used which are benign.

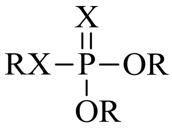
Further examples are the pyrethoid pesticides which have the duel benefits of breaking down in sunlight in 2-3 days and have much lower acute toxicity to humans than phosphorus, or chlorine-based pesticides.

Products designed should be biodegradable: The problem of products not being biodegradable is encountered particularly in insecticides and polymers.

It is well known that farmers use different types of insecticides to protect crops from insects. The more widely used insecticides are organophosphates, carbamates and organochlorides. Of these, organophosphates and carbamates are less persistent in the environment compared to the organochlorides (for example aldrin, dieldrin and DDT). Though the latter are definitely effective but they tend to bioaccumulate in many plant and animal species and incorporate into the food chain. Some of the insecticides are also responsible for the population decline of beneficial insects and animals, such as honeybees, lacewings, mites, bald eagles etc.

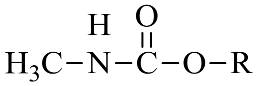


DDT



$\mathrm{RX{-}\overset{X}{\overset{\|}{\underset{\underset{OR}{|}}{P}}}{-}OR}$

Organophosphate
X=O or S
R = CH_3 or CH_3CH_2

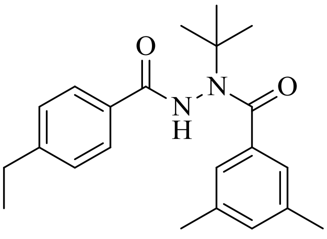


$\mathrm{H_3C{-}\overset{H}{N}{-}\overset{O}{\overset{\|}{C}}{-}O{-}R}$

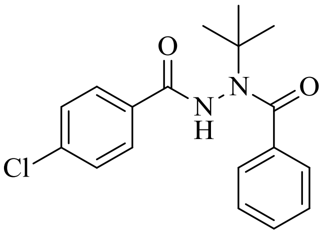
Carbamate

Considering the above, it is of utmost importance that any product (e.g. insecticides) synthesised must be biodegradable. It is also equally important that during degradation the products themselves should not possess any toxic effects or be harmful to human health. It is possible to have a molecule (e. g. insecticide) which may possess functional groups that facilitate its biodegradation. The functional groups should be susceptible to hydrolysis, photolysis or other cleavage.

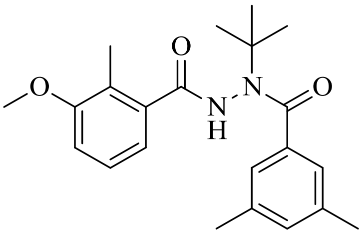
Some of the diacylhydrazines (developed by Rohm and Hass Company) which have been found to be useful as insecticides are:



Tebufenozide

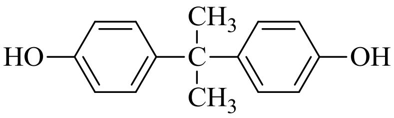


Halofenozide



Methoxyfenozide

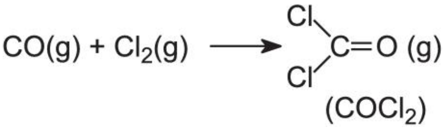
Less hazardous chemical synthetic routes: The family of polycarbonates contains very important polymers which are used where high optical properties combined with strength are needed. The polycarbonate most used is manufactured from bisphenol A, whose structure is:



4,4'-(propane-2,2-diyl)diphenol

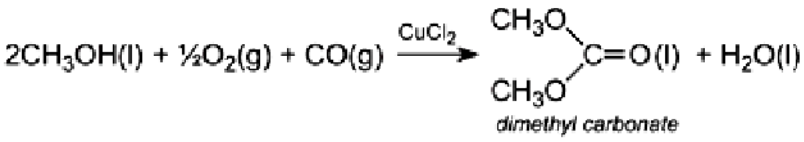
The polycarbonate is manufactured by a condensation reaction between bisphenol A and either carbonyl chloride or diphenyl carbonate.

Carbonyl chloride is a very poisonous gas, manufactured from other hazardous gases, carbon monoxide and chlorine:



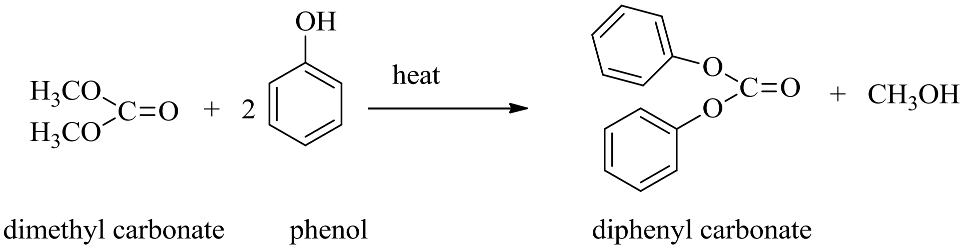
$$CO(g) + Cl_2(g) \longrightarrow Cl_2C{=}O\,(g) \quad (COCl_2)$$

On the other hand, diphenyl carbonate is produced from dimethyl carbonate, which is readily manufactured from methanol, carbon monoxide and oxygen in the liquid phase, in presence of copper(II) chloride, $CuCl_2$:



$$2CH_3OH(l) + \tfrac{1}{2}O_2(g) + CO(g) \xrightarrow{CuCl_2} (CH_3O)_2C{=}O(l) + H_2O(l)$$

Dimethyl carbonate, when heated with phenol in the liquid phase, forms the diphenyl carbonate:



Overall, the process for the production of polycarbonate that uses diphenyl carbonate is less hazardous than that using carbonyl chloride.

2.7 SELECTION OF APPROPRIATE AUXILIARY SUBSTANCE

Selection of appropriate auxiliary substance is a very important tool for green chemical synthesis. Let us discuss these auxiliaries one by one.

2.8 GREEN SOLVENTS

Solvents are extensively used in most of the syntheses. Widely used solvents in syntheses are toxic and volatile alcohol, benzene (known carcinogenic), CCl_4, $CHCl_3$, perchloroethylene, CH_2Cl_2. Purification steps also utilize and generate large amounts of solvent and other wastes (e.g., chromatography supports). These have now been replaced by safer green solvents like ionic liquids, supercritical CO_2 fluid, water or supercritical water and also solvent-free systems that utilize the surfaces or interiors of clays, zeolites, silica, and alumina. These are the basis of many of the cleaner chemical technologies that have reached commercial development.

It is known that the process efficiency is highly dependent on the solvent type. Owing to their special properties, green solvents improve chemical processes, lower the use of solvents and decrease the processing steps.

Water, supercritical fluids, ionic liquids, non-toxic liquid polymers, and their diverse combinations are part of the class of green solvents. They are characterized by low toxicity, convenient accessibility and the possibility of reuse as well as great efficiency. An ideal green solvent would also mediate reactions, separations or catalyst recycling.

An idea of green chemistry is aiming for replacement of commonly used solvent with ‘green’ ones, resulting in a reduced environmental impact. However, it leads to discussions about supremacy of one green solvent over another. Ionic liquids have been especially canceled for their complicated synthesis and toxicity although so has water. A choice of an optimal solvent for a reaction is crucial and it significantly affects the outcome.

Supercritical carbon dioxide and supercritical water: A supercritical liquid is a substance at a temperature and pressure above their respective critical levels, where is so distinct phase between gas and liquid. A supercritical liquid can act like a gas, pass trough solid materials or like liquids, dissolving other materials. Moreover, when both temperature and pressure are near the critical point, changing them even slightly can result in serious density alterations.

Supercritical liquids are suitable replacement of organic solvents for industrial and lab processes. In general, carbon dioxide ($scCO_2$- supercritical carbon dioxide) and water are most commonly used supercritical fluids. They are considered to be green solvents. Due to the great solubility in many polymers, $scCO_2$ is an irreplaceable component of polymer processing. What more, the choice of less harmful fluids ($scCO_2$) instead of conventional organic solvents is an advantage to the environment.

FOSS

Sharp Minds - Bright Ideas!

Employees at FOSS Analytical A/S are living proof of the company value - First - using new inventions to make dedicated solutions for our customers. With sharp minds and cross functional teamwork, we constantly strive to develop new unique products - Would you like to join our team?

FOSS works diligently with innovation and development as basis for its growth. It is reflected in the fact that more than 200 of the 1200 employees in FOSS work with Research & Development in Scandinavia and USA. Engineers at FOSS work in production, development and marketing, within a wide range of different fields, i.e. Chemistry, Electronics, Mechanics, Software, Optics, Microbiology, Chemometrics.

We offer
A challenging job in an international and innovative company that is leading in its field. You will get the opportunity to work with the most advanced technology together with highly skilled colleagues.

Read more about FOSS at www.foss.dk - or go directly to our student site www.foss.dk/sharpminds where you can learn more about your possibilities of working together with us on projects, your thesis etc.

The Family owned FOSS group is the world leader as supplier of dedicated, high-tech analytical solutions which measure and control the quality and production of agricultural, food, pharmaceutical and chemical products. Main activities are initiated from Denmark, Sweden and USA with headquarters domiciled in Hillerød, DK. The products are marketed globally by 23 sales companies and an extensive net of distributors. In line with the corevalue to be ‘First’, the company intends to expand its market position.

Dedicated Analytical Solutions
FOSS
Slangerupgade 69
3400 Hillerød
Tel. +45 70103370

www.foss.dk

Ionic liquids in organic synthesis: Lately, ionic liquids received a lot of attention from scientists due to their unique properties and abilities. Ionic liquids consist of a mixture of cations and anions, molten salts. Their melting points reach 100 °C which makes them a great alternative to convenient solvents in organic syntheses. Most often they possess quaternary ammonium cations and inorganic anions. Despite this fact, ionic liquids do not precisely meet all "green" conditions, they are still quite promising alternative solvents.

Non-toxic liquid polymers: Liquid polymers comprise a group of non-volatile solvents that gained the attention, because of a possibility of using them in combination with $scCO_2$ as media, for homogeneous catalysis with catalyst recovery. Their job as a solvent in reactions and a catalyst is like ionic liquids in biphasic catalysis. Liquid polymers are not as polar as ionic liquids, they should be considered as a supplement to ionic liquids, not a substitution.

PEG (polyethylene glycol) is called a green chemical, because it is inflammable, non-volatile, non-toxic to humans, animals and aqueous environment. Additionally, the polymer is biodegradable by bacteria found in sewage and soil. PPG (polypropylene glycol) is the next non-toxic liquid having similar properties as PEG, however it is slightly less biodegradable. There are some other polymers also and all these polymers have the potential to be extensively used as solvents, for various reactions and catalysis.

Reactions in solid phase: Large number of reactions occurs in solid state without the solvent. These reactions are simple to operate, economical and solvent-related pollution is avoided.

2.9 ALTERNATIVE SOLVENTS FOR SEPARATION PROCESSES

The application of organic solvents for the separation of organic substances and metal ions from different sources is well known. These separations are usually carried out by extracting the target compound into the organic phase for purification, enrichment, and pollution remediation. It is advantageous to replace the organic solvents used in liquid extractions with environmentally friendly solvents. In some cases it is helpful to employ new separation techniques to reduce the use of large volumes of organic solvents. Among these, liquid extraction techniques employing supercritical fluids and aqueous formulations containing surfactants or soluble polymers are most frequently considered. It is because of their environmentally friendly character and because they often afford increased extracting strength.

Recrystallization/cooling Solvents: The development of a successful crystallization process for purification and isolation of an organic compound requires the selection of a suitable solvent or solvent mixture. To this date, no logical method has been established for determining the best solvent combination. The process chemist or engineer often employs a trial-and-error procedure to identify an appropriate solvent system. A strategy for choosing crystallization solvents can be based upon equilibrium limits. The approach utilizes a group contribution method to predict a value for the activity coefficient of the solute in a given solvent system at the saturation point. Performance of this approach will reduce product cycle time, minimize solvent usage, and allow identification of cheaper solvent alternatives.

Supercritical fluid extraction: The characteristics of supercritical fluids make them ideal for the recovery of natural products. As a result, the food industry was among the first to implement supercritical fluid extraction using CO_2. This process is not only environmentally benign, it is also nontoxic.

Supercritical fluid extraction (SFE) has also replaced many regulated solvents in analytical chemistry applications in recent years. Because it provides a more reliable measure of the concentrations of environmental contaminants and can play an important role in pollution estimation and control. Advantages have been shown for using SFE compared to the conventional Soxhlet extraction with toluene for determining the presence of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans in ashes from a municipal incinerator. SFE allows the complete extraction of the analytes from the sample, whereas conventional extraction results in an incomplete, and hence, inferior extraction.

Analysis of agrochemical samples from soils after extraction by Soxhlet methods are now replaced by analysis following supercritical extractions.

Extraction of Pirimicarb (a pesticide present in sediments of rivers) using supercritical CO_2 modified with triethylamine shows better results as compared to the conventional Soxhlet method.

The supercritical fluid method offered increased precision, shorter analysis time, and a 10-fold reduction in solvent usage.

Use of CO_2 enhanced by the addition of methanol (co-solvent) to extract nitroaromatic and phenolics, environmental pollutants is also on records.

An attractive temporary option from an environmental standpoint is the use of HFCs or HCFCs.

At supercritical conditions these solvents effectively extract relatively polar compounds such as polychlorinated biphenyls, dibenzo-p-dioxins, and dibenzofurans without the use of a co-solvent.

Aqueous surfactant and macromolecular solutions: Removal of organic or heavy metal ion contaminants from aqueous streams can be achieved using a variety of different separation strategies, one of which is solvent extraction. Potential counter-contamination of the streams being treated with the extracting solvent can be avoided by eliminating the organic solvent altogether in favor aqueous-based solvent systems that rely for their effectiveness on the presence of dissolved surfactant micelles or polymers. These aggregates or polymers can solubilize organic solutes with the aqueous phase or form complexes with the metal ions to be removed.

A particularly important class of surfactants for the solubilization of organic compounds in aqueous solution is the polyethylene oxide-polypropylene oxide-polyethene oxide family of block copolymers. These polymers form polymeric micelles that have a high capacity for the solubilization of organic compounds.

An advantage of these polymeric micellar systems is that the micelles form only above a certain temperature, called the critical micelle temperature (CMT).

2.10 PROLIFERATION OF SOLVENT-LESS PROCESSES

Solvent-free reactions, has gained special attention from synthetic organic chemists. Many reactions are newly found to proceed cleanly and efficiently in the solid state or under solvent-free conditions. Less chemical pollution, lower expenses, and easier procedures are the main reasons for the recent increase in the popularity of solvent-free reactions.

From Green Chemistry point of view a reaction should ideally, be conducted under solvent-free conditions with minimal or no side-product formation and with utmost atom-economy. Solvent-free techniques hold a strategic position as solvents are very often toxic, expensive, and problematic to use and to remove. It is the main reason for the development of such modern technologies. These approaches can also enable experiments to be run without strong mineral acids (i.e. HCl, H_2SO_4 for instance) that can in turn cause corrosion, safety, manipulation and pollution problems as wastes. These acids can be replaced advantageously by solid, re-cyclable acids such as clays.

The main reasons for the proliferation of solvent-less reactions are:

Reactivity: Under solvent free conditions reactivity is increased and only *mild conditions* are required. This is due to increasing concentrations in reactants when a diluting agent such as a solvent is avoided. In several cases, difficult reactions (even impossible) using solvents are easily achieved under solvent-free conditions. Another unquestionable advantage lies in the fact that *higher temperatures*, when compared to classical conditions, can be used without the limitation imposed by solvent boiling points.

One more benefit is the possibility of using solvent-free techniques coupled with *microwave irradiation*. This new type of activation is now more frequently used but often the presence of solvents prevents its use for safety reasons. This difficulty can be overcome by solvent-free processes.

Selectivity: The layout of reacting systems can be increased when high concentrations and/or aggregation of charged species are involved. It can lead to some modifications in mechanisms resulting in a decrease in molecular dynamics and induce subsequent *special selectivities* (stereo-, regio- or enantioselectivity).Weak interactions can, for instance, appear (such as *p*-stacking) which are usually masked by solvents, inducing further consequences on selectivity.

Simplification of experimental procedures: Firstly, complex apparatus is not needed and, for instance, reflux condensers are not required, which in turn allows the handling of a smaller quantity of material as there is no solvent. It also allows an operation to be carried out *with increased amounts of products in the same vessels*.

Washing and extraction steps are made easier or even suppressed. In the case of equilibrated reactions leading to light polar molecules (MeOH,EtOH or H_2O), equilibrium can be easily shifted by a simple heating just above the boiling points or under reduced pressure. With the usual procedure this operation is delayed by the presence of solvent required an azeotropic distillation using a Dean–Stark apparatus.

Overall Benefits: Solvent-free techniques represent a clean, economical, efficient and safe procedure which can lead to substantial savings in money, time and products. They can be efficiently coupled to non-classical methods of activation that include ultrasound and microwaves.

2.11 SOLVENT-FREE TECHNIQUES

Three types of experimental conditions without solvents can be considered.

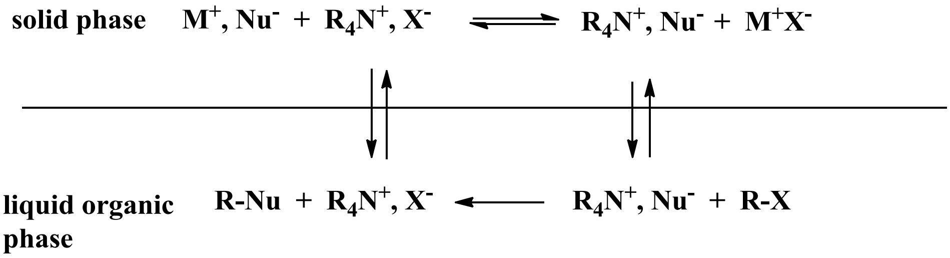
Reactions on solid mineral supports: Reactants are first impregnated as neat liquids onto solid supports such as aluminas, silicas and clays or via their solutions in an adequate organic solvent and further solvent removal in the case of solids. Reaction in “dry media” is performed between individually impregnated reactants, followed by a possible heating. At the end of the reaction, organic products are simply removed by elution with diethyl ether or dichloromethane.

Reactions without any solvent, support, or catalyst: These heterogeneous reactions are performed between neat reactants in quasi-equivalent amounts without any adduct. In the case of solid-liquid mixtures, the reaction implies either solublization of solid in the liquid phase or adsorption of liquid on the solid surface as an *interfacial* reaction.

Solid-liquid phase transfer catalysis (PTC): Reactions occur between neat reactants in quasi-equivalent amounts in the presence of a catalytic quantity of tetraalkylammonium salts or cation complexing agents. When performed in the absence of solvent, the liquid organic phase consists of the electrophilic reagent then possibly the reaction product.

$$K^+OH^- + R_4N^+Br^- \rightleftharpoons R_4N^+OH^- + K^+Br^-$$

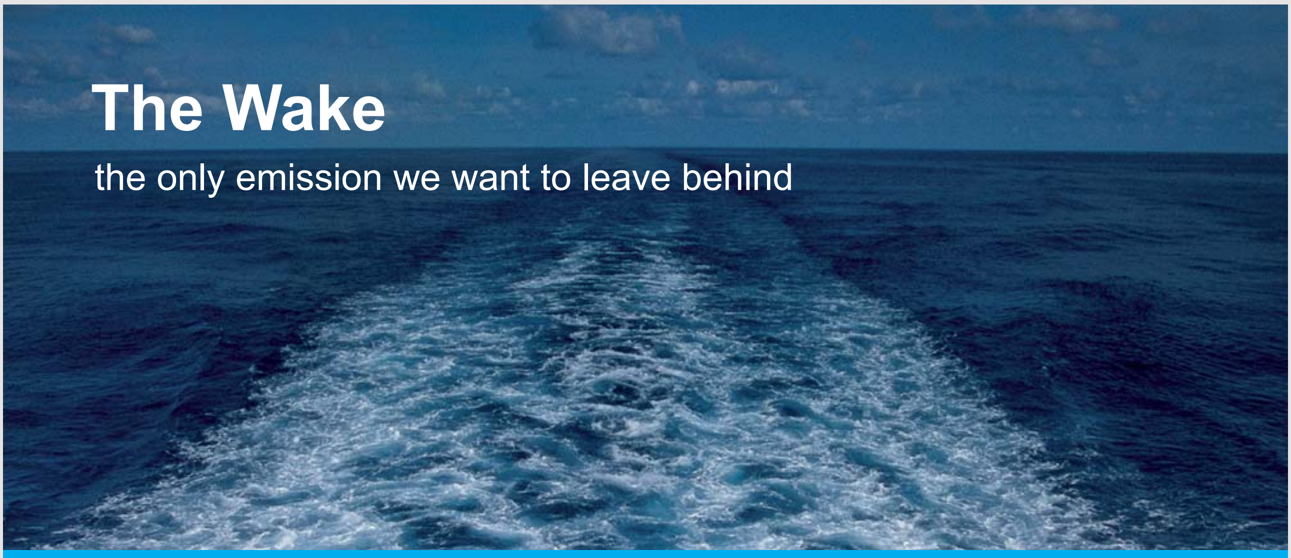
$$R_4N^+OH^- + NuH \rightleftharpoons R_4N^+Nu^- + H_2O$$



Nucleophilic anionic species can be generated *in situ* by reacting their conjugated acids with solid bases of increased strength due to ion-pair exchange with $R_4N^+X^-$.

2.12 REACTIONS ON MINERAL SOLID SUPPORTS

The different types of supports: Solvents are replaced by solid supports which can simply act as an inert phase towards reactants or as a catalyst according to their active sites.



Amorphous Supports (Aluminas, Silicas): Aluminas: Non-activated aluminas (chromatographic grade) are basic supports in comparison to carbonic acids and are able to abstract hydrogen and to subsequently react. When the alumina is calcinated up to 400–600°C, it behaves as Lewis acid due to liberation of the surface hydroxyl groups.

Silicas: Silicas are acidic with a large number of silanol groups on their surfaces. Quartz and Fontainebleau sand are particular cases, very pure nonhydrated silicas.

Layered Supports (Clays): Clay minerals consist of a large family of fine-grained crystalline silicate sheets with arrangements of tetrahedral and octahedral layers. Interlamellar cations can be exchanged (for instance, with H^+, leading to K10 and KSF montmorillonites which are very strong solid acids).

Microporous Supports (Zeolites): Zeolites are crystalline, microporous aluminosilicates with molecular-sized intracrystalline channels and cages. Guest molecules with molecular diameters smaller than zeolites (from 3 to 15 Å) can enter the interior of zeolite crystals (*Intercalation*) giving rise to shape and size selective sorption and, consequently, highly selective reactions.

2.13 IMMOBILIZED SOLVENTS

Immobilized solvents are solvent molecules that are bound to a low-molecular-weight polymer, for reducing its volatility. The immobilization of solvents helps in reduction of hazards. Immobilized solvents or solvent molecules joined to a polymeric backbone follow the same logic as the ionic liquids. By creating a system where a known solvent, e.g., THF, is joined properly, it can still maintain its solvency.

At present there are two main techniques to prepare immobilized solvents. In both these techniques liquid solvents are immobilized inside high surface area solids. In one of the methods solvent is trapped inside a capsule a few hundred microns in diameter. The shell is composed of a thin, permeable polymer membrane, and the liquid solvent is held in the capsule core. These are called **microencapsulation of liquid solvents** (MECS). In another technique the solvent is trapped inside a polymer matrix, forming a gel that may be shaped into thin sheets or particles. Such solvents are termed as **solvent impregnated polymers** (SIPs). Immobilized solvents have 1-2 orders of magnitude greater surface area than the liquid in a traditional absorption column.

Possible pathways for up-scaling their manufacture are available, and the mass transfer enhancement such materials may provide are substantial. However the technology is still in its infancy and further work is required to identify the processes and solvents to which it is best suited, to refine manufacturing methods and material selection, and to quantify the thermodynamic enhancement that the use of otherwise impractical solvents may provide.

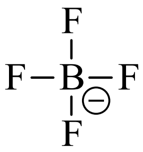
The main advantages of using immobilized solvents include reduced volatile organic compound emissions, negligible global warming potential, no ozone depletion, cleaner and easier separations from water, and reduced solvent contamination in aqueous waste streams. Immobilized solvent systems are a promising means of increasing gas uptake rates, and they may find application in a wide range of gas separations. The potential applications extend beyond synthesis to cleaning and separations processes.

Immobilized solvents are expensive to produce and difficult to handle. The life-cycle impact of using them has not been characterized. The recyclability of the solvents has not been characterized. Separations may be difficult in some cases.

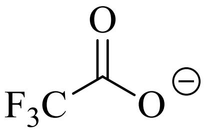
2.14 IONIC LIQUIDS (SHORT DESCRIPTION)

Ionic liquids (ILs) are attractive solvents due to their interesting advantages compared to the conventional organic solvents such as low volatility and low melting point (<100°C) and that is the reason why they were classified as “green solvents”. Other characteristics are: chemical and thermal stability, non-flammability, high ionic conductivity, high heat capacity, high thermal conductivity and wide electrochemical potential.

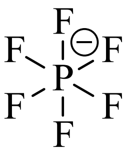
ILs are formed by combination of a cation and an anion which is very attractive in a way that an ionic liquid can be build with the aim of performing a specific application. For example, the anion bis(trifluoromethylsulfonyl)amide - $[NTf_2]$ has been shown to orginate thermally stable ionic liquids, Tetrafluoroborate $[BF_4]^-$, hexafluorophosphate$[PF_6]^-$, dicyanoamide $[DCA]^-$ and trifluoroacetate - [TFA], are other common anions.



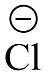
$[BF_4]$



[TFA]

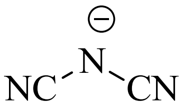


$[PF_6]$

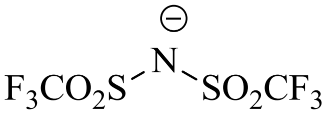


$\mathrm{Cl}^{\ominus}$

[Cl]



[DCA]

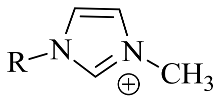


$[NTf_2]$

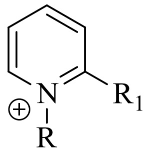
$\mathrm{Br}^{\ominus}$

[Br]

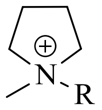
Typical cations are methylimidazolium - [MIM], pyridinium - [Py], pyrrolidinium - [Pyr], ammonium- and phosphonium- based cations.



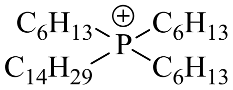
[1-alkyl-3-MIM]



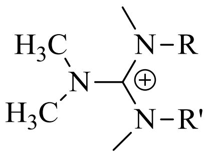
[1,2-dialkyl-Py]



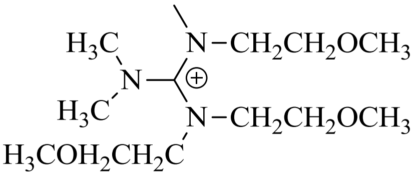
[alkyl-methyl-Pyl]



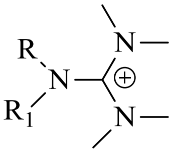
[P6,6,6,14]



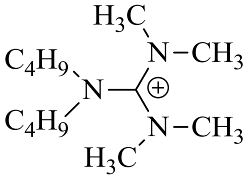
[DMG]



[$(C_3O)_4$DMG]



[TMG]



[(di-b)TMG]

There is a wide range of applications that ionic liquids are used for. They have been used for battery production, lubricants, plasticizers, solvents, mass spectrometry matrices, solvents for nanomaterials production, extraction reactions, gas absorption agents and among other things. ILs have been explored for synthesis and catalysis leading to interesting results.

They are non-volatile and non-flammable hence they could work in high-vacuum systems and exclude possible contaminants. Ionic liquids do not form a homogeneous mixture with many organic solvents and produce an anhydrous polar alternate option for two-phase systems. Additionally, they may provide immiscible polar phases with water, when they are hydrophobic.

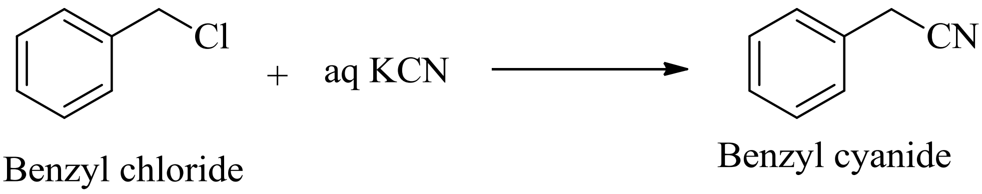
It is important to note that the use of ILs in chemistry has made possible in some situations to perform greener processes in a way that the use of other solvents was minimized or even eliminated. Some interesting bio-applications are biodiesel synthesis from free fatty acids and alcohols and the removal of water contaminants.

2.15 ENERGY REQUIREMENTS FOR SYNTHESIS

Energy generation, as we know has a major environmental effect. In any chemical synthesis, the energy requirements should be kept to a minimum. For example, if the starting material and the reagents are soluble in a particular solvent, the reaction mixture has to be heated to reflux for the required time or until the reaction is complete. In such a case, time required for completion should be minimum so that minimum amount of energy is required. Use of a catalyst has the great advantage of lowering the energy requirement of a reaction.

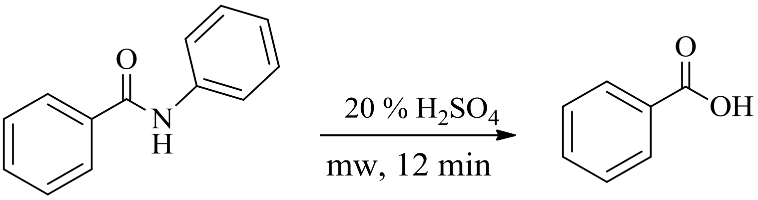
In case the reaction is exothermic, sometimes extensive cooling is required. This adds to the overall cost. If the final product is impure, it has to be purified by distillation, re-crystallization or ultra-filtration. All these steps involve the use of energy. By designing the process such that there is no need for separation or purification, the final energy requirements can be kept at the bare minimum. Energy to a reaction can be supplied by photochemical means, microwave or sonication.

The requirement of energy can be kept to a base minimum in certain cases by the use of a catalyst. For example in conversion of benzyl chloride into benzyl cyanide if we use phase transfer catalyst, the conversion goes to completion in a very short time.

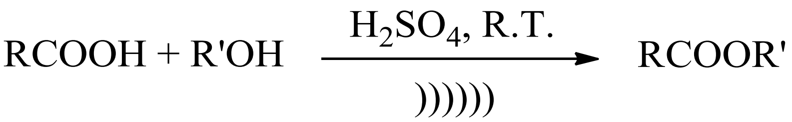


Conventionally, we have been carrying reaction by heating on wire gauze, in oil bath or heating mantels. It is now possible that the energy to a reaction can be supplied by using **microwaves,** by **sonication** or photo chemically. Simple examples are

a. Hydrolysis of benzamide under microwave irradiation.



b. Esterification of a variety of carboxylic acids with different alcohols at ambient temperature using ultrasound



$$RCOOH + R'OH \xrightarrow[))))))]{H_2SO_4,\ R.T.} RCOOR'$$

3 GREEN CHEMISTRY PRACTICE

3.1 MICROWAVE-ASSISTED REACTIONS IN ORGANIC SOLVENTS

This section includes that microwave induced reactions in which one or both the reactants (if liquid) act as a solvent and also those reactions in which organic solvent is used to assist the reaction.

3.2 ESTERIFICATION

Esterification is a chemical reaction that forms at least one ester. Esters are produced when acids are heated with alcohols. An ester can be made by an esterification reaction of a carboxylic acid and an alcohol.

Reaction of Carboxylic Acid and Alcohol: A mixture of benzoic acid and n-propanol on heating in a microwave oven for 6 min in presence of catalytic amount of cone. sulphuric acid gives propylbenzoate.

Technical training on
WHAT you need, *WHEN* you need it

At IDC Technologies we can tailor our technical and engineering training workshops to suit your needs. We have extensive experience in training technical and engineering staff and have trained people in organisations such as General Motors, Shell, Siemens, BHP and Honeywell to name a few.

Our onsite training is cost effective, convenient and completely customisable to the technical and engineering areas you want covered. Our workshops are all comprehensive hands-on learning experiences with ample time given to practical sessions and demonstrations. We communicate well to ensure that workshop content and timing match the knowledge, skills, and abilities of the participants.

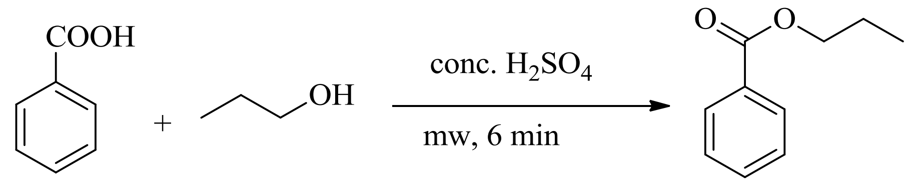
We run onsite training all year round and hold the workshops on your premises or a venue of your choice for your convenience.

For a no obligation proposal, contact us today at training@idc-online.com or visit our website for more information: www.idc-online.com/onsite/

OIL & GAS ENGINEERING
ELECTRONICS
AUTOMATION & PROCESS CONTROL
MECHANICAL ENGINEERING
INDUSTRIAL DATA COMMS
ELECTRICAL POWER

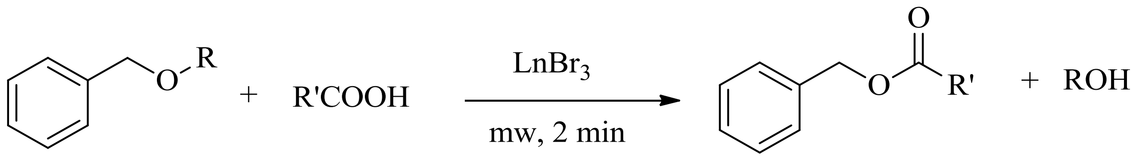
Phone: +61 8 9321 1702
Email: training@idc-online.com
Website: www.idc-online.com

IDC TECHNOLOGIES



benzoic acid propan-1-ol propyl benzoate

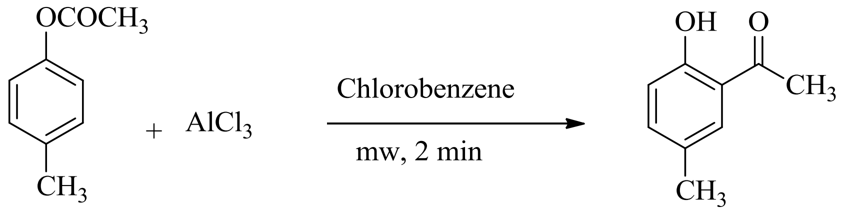
Reaction of Carboxylic Acids and Benzyl Ethers Using $LnBr_3$ (Ln = La, Nd, Sm, Dy, Er): A mixture of carboxylic acid and benzyl ether on heating in a microwave oven in the presence of $LnBr_3$ afforded the esters in 2 min.



3.3 FRIES REARRANGEMENT

Fries rearrangement is a useful method for the preparation of phenolic ketones and is usually carried out by heating a mixture of substrate and aluminium chloride.

There is considerable rate enhancement of Fries rearrangement by commercial microwave ovens over conventional methods. Thus, a mixture of p-cresyl acetate and anhydrous aluminium chloride are heated in dry chlorobenzene in a sealed tube in a microwave oven for 2 min to give 85% yield of the product.

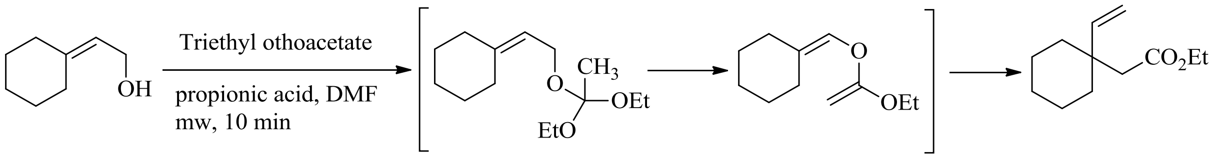


p-tolyl acetate

1-(2-hydroxy-5-methylphenyl)
ethanone

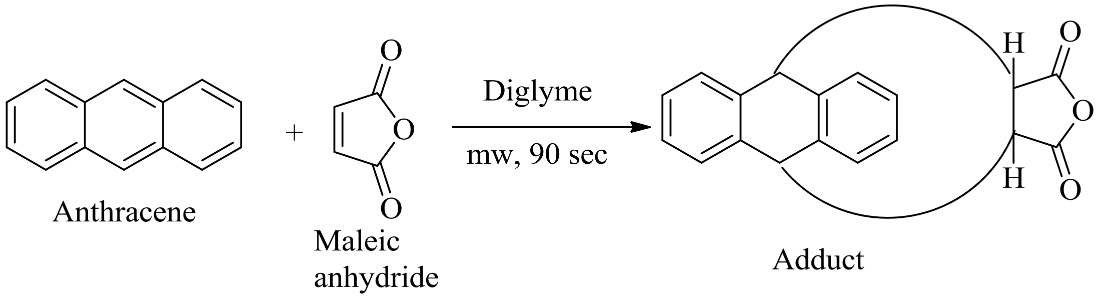
3.4 ORTHOESTER CLAISEN REARRANGEMENT

In the usual conventional procedure, a mixture of allyl alcohol, triethyl orthoacetate and propanoic acid is heated in a sealed tube for 48 hr. However, under microwave conditions a mixture of allyl alcohol, triethyl orthoacetate and propanoic acid in dry dimethylformamide is heated in microwave oven for 10 min. The product is obtained in 83% yield.



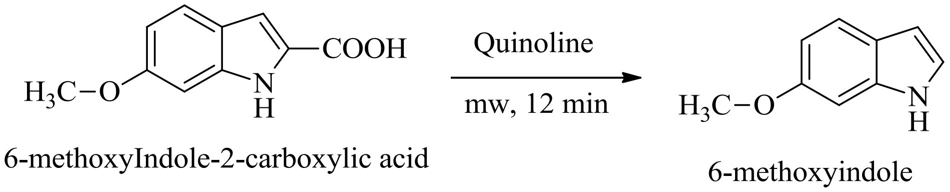
3.5 DIELS ALDER REACTION

The reaction involves 1,4-addition of an alkene (e.g., maleic anhydride) to a conjugated diene (e.g. anthracene) to form an adduct of six membered ring. Under usual conditions the reaction requires a reflux period of 90 min. However, under microwave conditions diglyme is used as a solvent and 80% yield of the product (called as adduct) is obtained in 90 sec.



3.6 DECARBOXYLATION

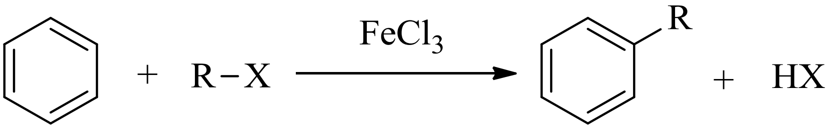
Decarboxylation is the reaction in which COO group is removed from a reactant molecule. Conventional decarboxylation of carboxylic acids involves refluxing in quinoline in presence of copper chromite and the yields are low. However, in the presence of microwaves, decarboxylation takes place in much shorter time as illustrated below.



3.7 ALKYLATION

Alkylation is the transfer of an alkyl group from one molecule to another. This group may be transferred as an alkyl carbocation, a free radical, a carbanion or a carbene (or their equivalents). Alkylating agents are quite commonly used in chemistry because the alkyl group is the most universal group encountered in organic molecules.

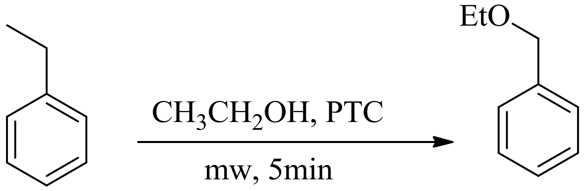
Alkylation is generally carried out by Friedel-Crafts reaction.



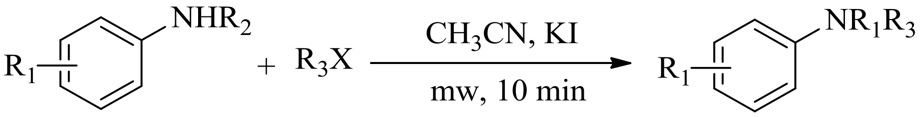
This Lewis acid catalyzed electrophilic aromatic substitution allows the synthesis of alkylated products via the reaction of arenes with alkyl halides or alkenes. Since alkyl substituents activate the arene substrate, polyalkylation may occur. A valuable, two-step alternative is Friedel-Crafts acylation followed by a carbonyl reduction.

Alkylation is an important modification that regularly uses toxic and hazardous reagents such as alkyl iodide or dialkyl sulfate. But green chemistry has given us microwave assisted environment friendly alkylation method. A few examples of these methods are given as follows:

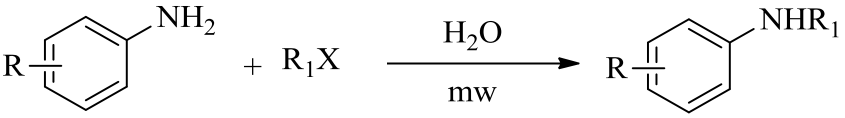
Ethanol can be alkylated under microwave irradiation in presence of phase transfer catalyst (PTC) within 5 min. Under conventional heating this reaction takes hours to complete.



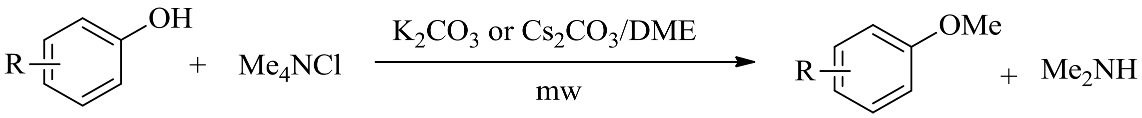
Similarly, direct monobenzylation of aniline can be carried out under microwave conditions using potassium iodide as catalyst.



A greener process for direct mono-N-alkylation of aromatic amines by alkyl halides can be done under microwave irradiation in water without any catalyst.



Tetramethylammonium chloride (Me_4NCl) has been used as a methylating agent for phenols under microwave-assisted conditions. This method needs heterogeneous conditions and 1,2-dimethoxyethane (DME) or toluene as a solvent. A number of simple phenols can be methylated in the presence of K_2CO_3, while some other less-reactive phenols need the presence of the more reactive Cs_2CO_3.

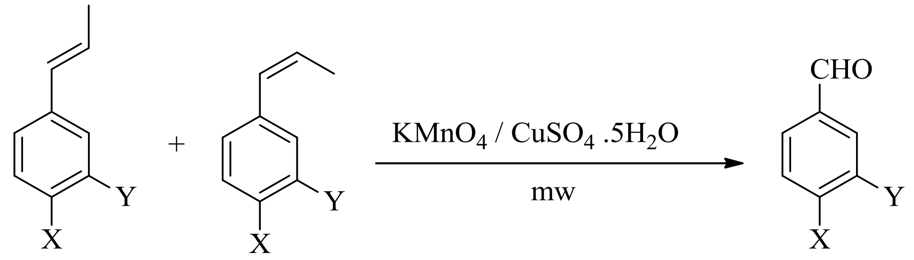


3.8 OXIDATION

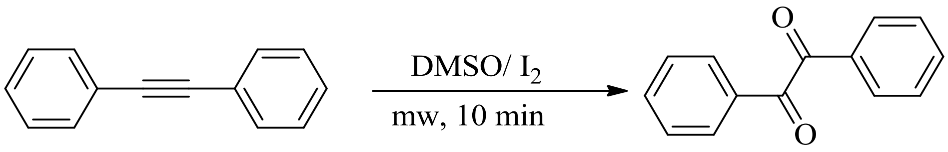
Oxidation is a chemical reaction that involves the transfer of electrons. Oxidation involves the loss of electrons or hydrogen or gain of oxygen or increase in oxidation state. Any chemical reaction, in which the oxidation numbers (oxidation states) of the atoms are increased, is termed as an oxidation reaction. Oxidation-reduction reactions (or redox) reactions are chemical reactions that involve a transfer of electrons between two species.

Microwave-assisted organic synthesis (MAOS) is a new and rapidly developing area in synthetic organic chemistry. This synthetic technique has been based on the empirical observations that some organic reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating.

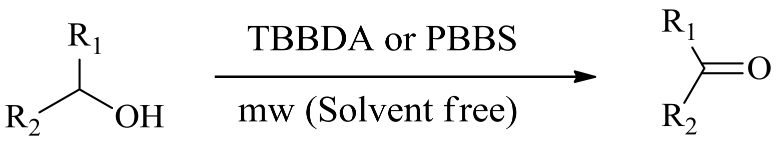
Oxidation of hydrocarbons: Solvent-less oxidation of a mixture of 1-arylpropene to the corresponding benzaldehyde by $KMnO_4/CuSO_4.5H_2O$ can be done under microwave irradiation in very short reaction times (<15 min).



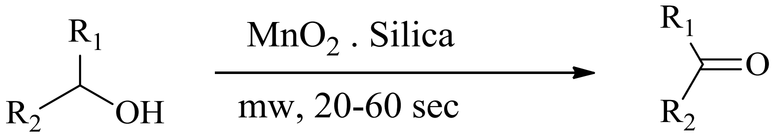
Oxidation of internal alkynes can be carried out with DMSO in the presence of iodine (I_2) gives 1,2-diaryldiketones under microwave irradiation with good yields. The most attractive feature of this method is the short reaction times, good yields, low-cost and easy preparation.



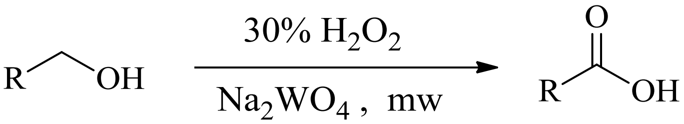
Oxidation of alcohols: An efficient rapid and mild methodology for the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds in presence of N,N,N′,N′-tetrabromobenzene-1,3-disulfonamide (TBBDA) or poly(N-bromobenzene-1,3-disulfonamide) (PBBS) using microwave irradiation under solvent-free conditions.



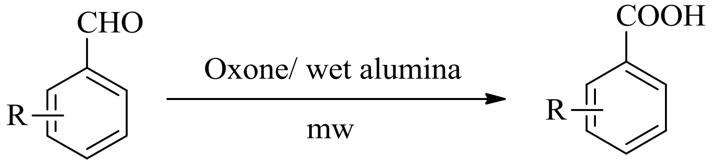
Microwave irradiation of alcohols with silica supported active manganese dioxide in solvent-free condition provides rapid and selective oxidation of alcohols to the corresponding carbonyl compounds.



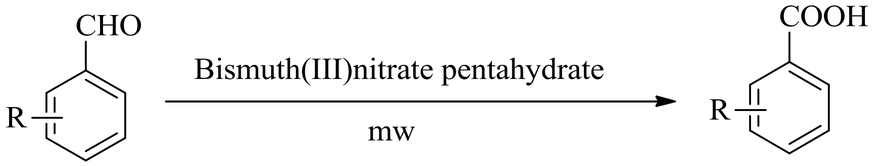
Use of sodium tungstate as catalyst in 30% aqueous hydrogen peroxide oxidizes primary alcohols to the corresponding carboxylic acids under microwave irradiation.



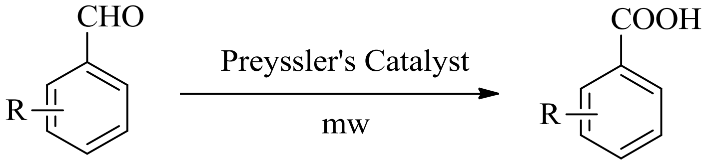
Oxidation of aldehydes: The oxidation of aldehydes to carboxylic acids is an important transformation in organic synthesis and several methods have been developed to accomplish this conversion. Oxidation of benzaldehydes with oxone ($2KHSO_5$, $KHSO_4$, K_2SO_4)/wet-alumina under microwave irradiation in solventless system is a rapid, manipulatively simple, inexpensive and selective protocol.



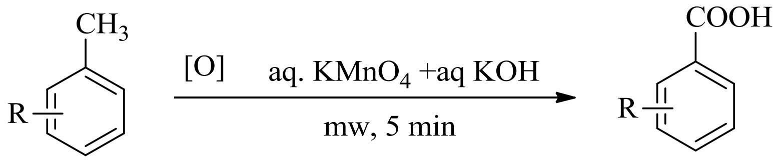
Aromatic aldehydes possessing a wide variety of substituents can be smoothly converted to carboxylic acids in excellent yields by stoichiometric bismuth (III) nitrate pentahydrate in presence of aerial oxygen in a microwave-oven under solventfree conditions.



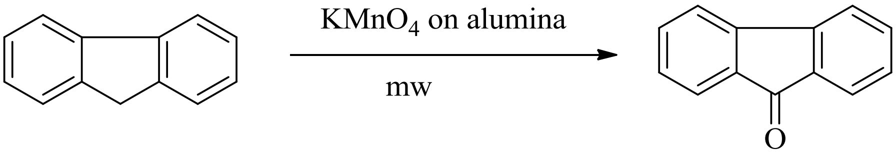
Preyssler's anion, $[NaP_5W_{30}O_{110}]^{14-}$, can be used as catalyst for the oxidation of aromatic aldehydes to related carboxylic acids using hydrogen peroxide as an oxidizing agent, under microwave irradiation. Oxidation of aldehydes is a surface type reaction and with Preyssler's anion, it produces the highest yields.



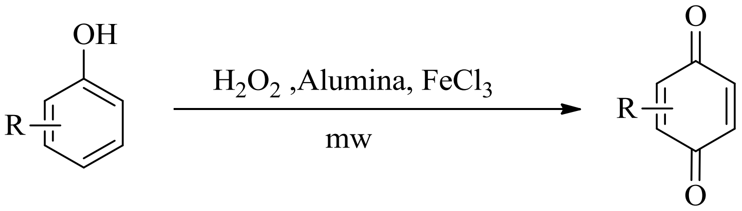
Oxidation of arenes: The oxidation of toluene to the benzoic acid with $KMnO_4$ under normal conditions takes 10–12 h reflux, which takes only 5 min under microwave irradiation and the yield is 40%.



Use of $KMnO_4$ impregnated on alumina under microwave activation in dry media oxidizes arenes into ketones within 10–30 min instead of several days under conventional conditions.



Oxidation of phenols: Phenols are readily oxidized to corresponding quinones by hydrogen peroxide, in the presence of catalyst Fe (III) supported on alumina. The reaction is carried out under microwave irradiation and it reduces the time of reaction and the yield of product was also improved.

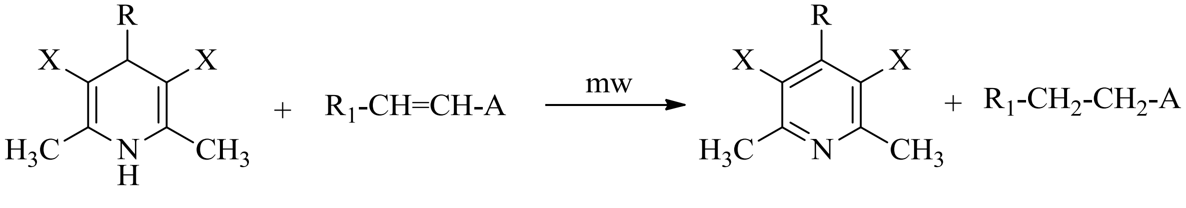


3.9 REDUCTION

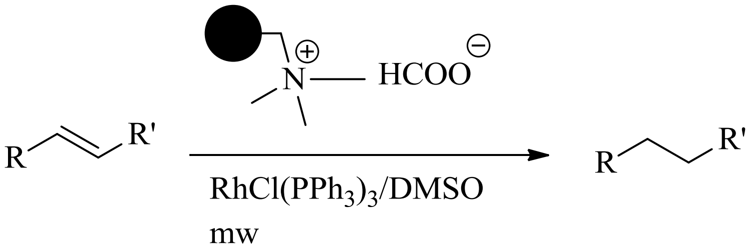
Reduction is a process, which either involves the gain of electrons/hydrogen or loss of oxygen/ decrease in oxidation state. An oxidation-reduction reaction occurs in our everyday life and is very vital for some of the basic functions of life. Some examples include photosynthesis, respiration, combustion, corrosion and rusting.

The application of microwave heating has been shown to have a strong beneficial impact on a large variety of synthetic procedures involving reduction. Reaction times can be drastically reduced with an overall milder reaction conditions, higher yields and pure products. In numerous examples, the application of microwave irradiation has also allowed the use of milder and more environmentally acceptable reagents. The use of microwave irradiation is thus expected to improve reductions of number of functional groups.

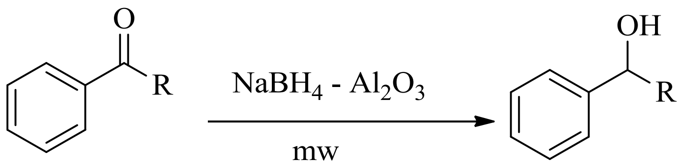
Multiple bond reduction: 1,4-Dihydropyridines have been used in the reduction of carbon-carbon double bond without solvent under microwave irradiation.



A combination of formate bound to an ion- exchange resin and Wilkinson's catalyst can be used in the transfer hydrogenation of electron deficient alkene. Reactions are completed upon microwave irradiation in 30 sec and the products were obtained in quantitative yields (80–95%).

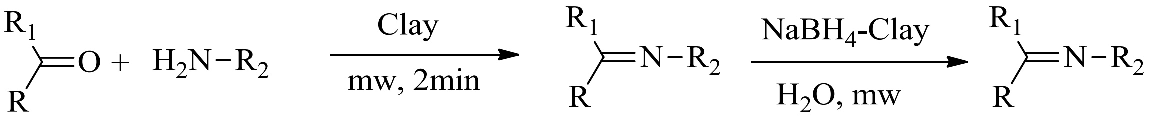


Carbonyl group reduction: Alumina supported sodium borohydride can be used for the reduction of carbonyl compounds to corresponding alcohols under microwave irradiation, using solvent-less conditions.

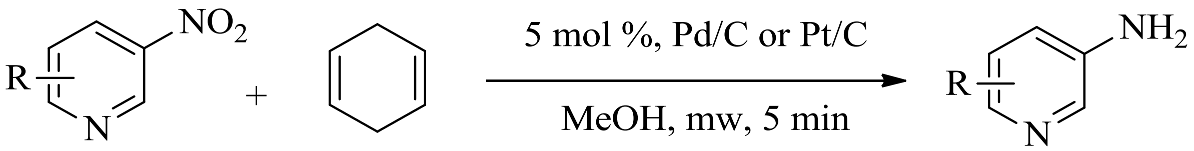


Reductive amination: The reductive amination of carbonyl compounds can be carried out using sodium cyanoborohydride, sodium triacetoxyborohydride or $NaBH_4$ coupled with sulfuric acid. These reagents involve the use of corrosive acids and/or produce waste stream.

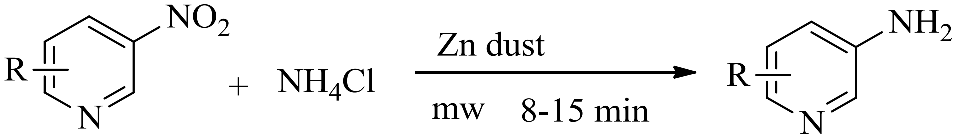
The environmentally benign methods using wet montmorillonite K10 clay supported sodium borohydride facilitated by microwave irradiation has been developed. Clay montmorillonite K10 not only behaves as a Lewis acid but it also provides water from its interlayers that increase the reducing ability of $NaBH_4$.



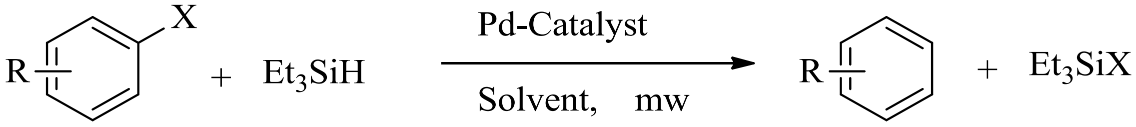
Nitro group reduction: Reduction of heteroaromatic and aromatic nitro groups to amines can be carried out using Pd/C or Pt/C catalyst, which is extremely effective with 1,4-cyclohexadiene as the hydrogen transfer source. In general, the reactions are completed within 5 min at 120 °C. Pt/C is effective and it gives little or no dehalogenation in case substrate contains labile aromatic halogens.



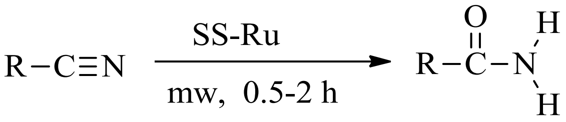
The reduction of aromatic nitro compound to corresponding amine can also be carried out in the presence of zinc dust-ammonium chloride and solvent-free condition by using microwave irradiation. The time of the reaction was generally 8–15 min and the product is obtained in good to excellent yields.



Aryl halide reduction: The reductive dehalogenation of aryl halide by triethylsilane with catalytic amount of palladium chloride under microwave irradiation is a simple, efficient and selective method. The silicon hydrides are nontoxic and stable and hence, these are effective reducing agents.



Nitrile group reduction: Solid supported ruthenium can be used as a heterogeneous catalyst for the reduction of aromatic, α,β-unsaturated and aliphatic nitriles to primary amides at 130–150 °C for 0.5–2 h in microwave. The catalyst is very stable under moisture and microwave irradiation, easily separable from the reaction mixture and recyclable up to ten times without any loss of catalytic activity.



3.10 COUPLING REACTIONS

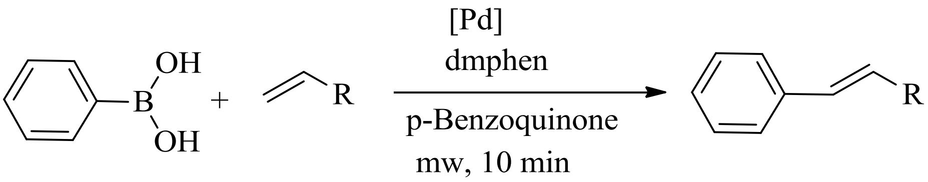
Coupling reaction in organic chemistry is a term for a variety of reactions, where two hydrocarbon fragments are coupled with the help of a metal, it salts or complexes as a catalyst.

Two types of coupling reactions have been recognized:

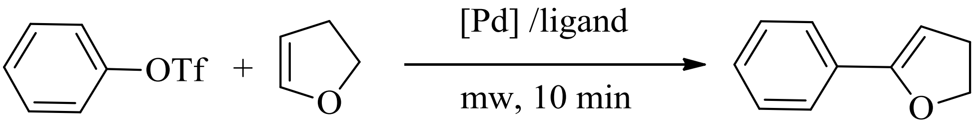
1. Homo couplings: when coupling of two identical partners occurs, for example, the conversion of iodobenzene (PhI) to biphenyl (Ph-Ph) and
2. Cross couplings: when reactions between two different partners occurs, for example, bromobenzene (PhBr) and vinyl chloride (CH_2=CH-Cl) to give styrene (PhCH=CH_2).

Some of the microwave assisted coupling reactions are discussed below:

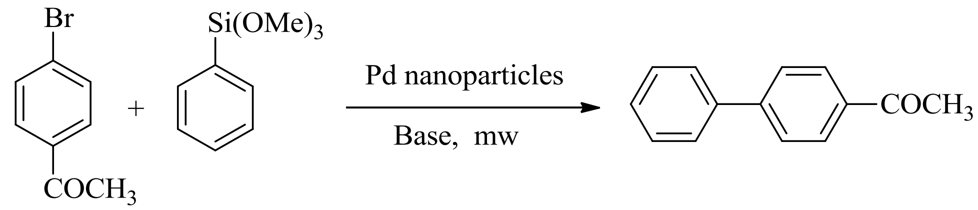
Heck reaction: High temperature and microwave heating appear to be beneficial for Heck-type coupling of simple alkenes in water. Heck reaction between aryl halides and alkenes are well established under microwave irradiation. Coupling employing different arylboronic acids with both electron rich and electron poor olefins can be done under ontrolled microwave to reduce reaction time from hours to minutes.



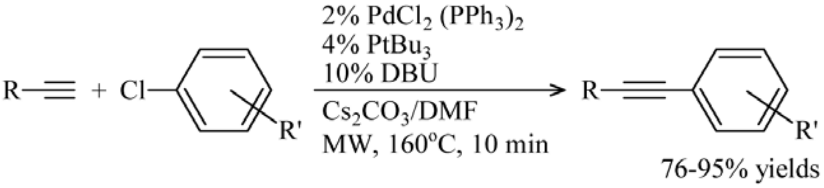
Another example is heck reactions of olfinic substrate and triflate under microwave conditions is give as

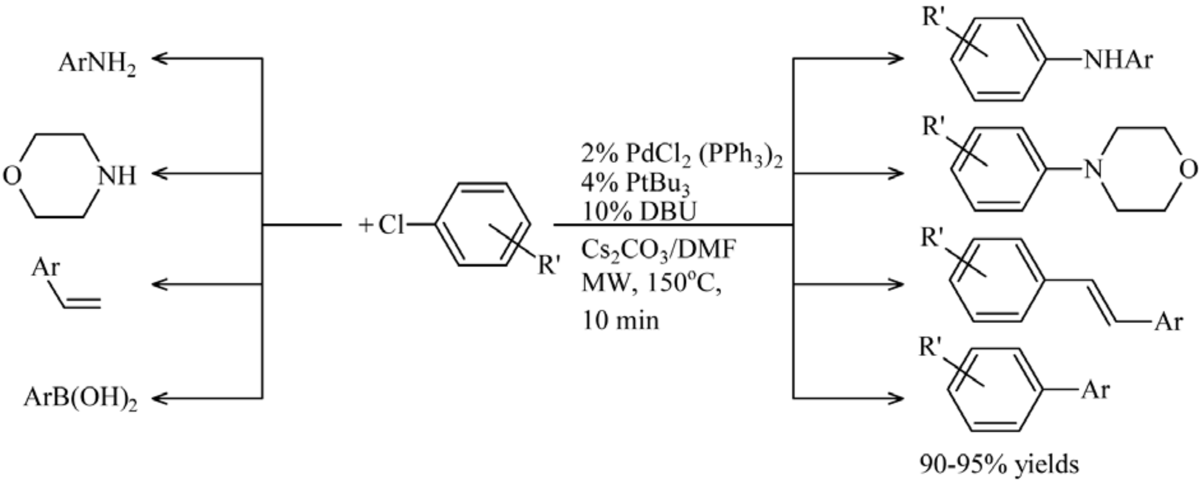


Hiyama reaction: Amberlite XAD-4, impregnated with palladium nanoparticles (PdNPs) arere used to catalyze the sodium hydroxide activated Hiyama cross-coupling reaction of phenyltrimethoxysilane with a variety of bromo and chloroarenes under microwave heating.

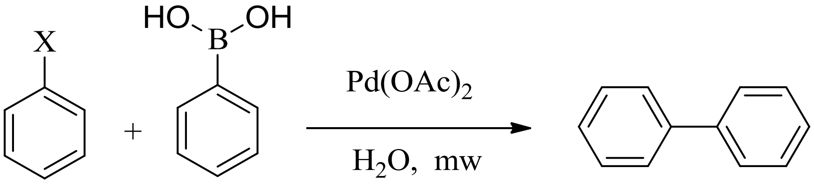


Sonogashira coupling: This microwave-assisted method offered shorter reaction times, higher yields and it was also applicable to a large set of substrates.





Suzuki coupling: Carbon-carbon bond formation via Suzuki coupling of organoborane compounds with organic halides provides a mild method for synthesis of various compounds, especially biaryls. An example of Suzuki coupling reaction using microwave irradiation with Pd catalyst is to give biaryl product in water.

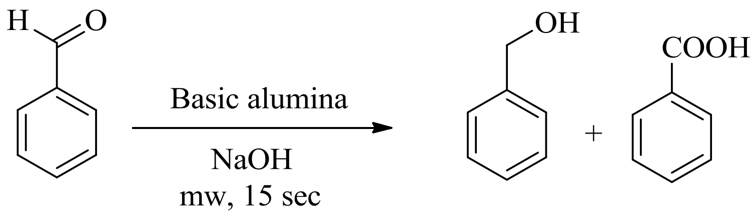


3.11 CANNIZZARO REACTION

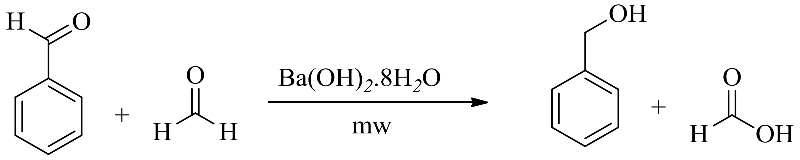
Cannizzaro reaction is the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt. It is restricted to aldehydes that donot have α-hydrogens and therefore cannot undergo aldol condensation. This reaction is usually carried out in homogeneous and strongly basic conditions.

Similarly the crossed Cannizzaro reaction, using an inexpensive paraformaldehyde to produce alcohol is also carried out.

Cannizzaro reaction can be carried out more efficiently under microwave-irradiations. The reaction is done using a mixture of an aldehyde, sodium hydroxide, and basic alumina. Microwave irradiation of only 15 sec gives quantitative yield of both; alcohol and the carboxylic acid.

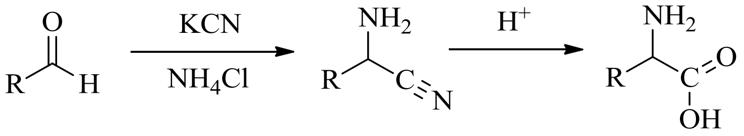


Crossed Cannizzaro reaction: Here, aldehydes react with 2 eq. paraformaldehyde and 2 eq. barium hydroxide, $Ba(OH)_2.8H_2O$ under microwave irradiation for 0.25–2 min at 900 W. In this reaction high yield of product is obtained along with very small amount of carboxylic acid as a byproduct.

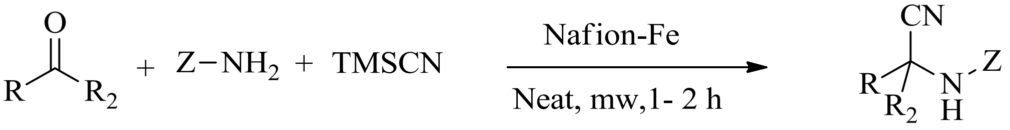


3.12 STRECKER SYNTHESIS

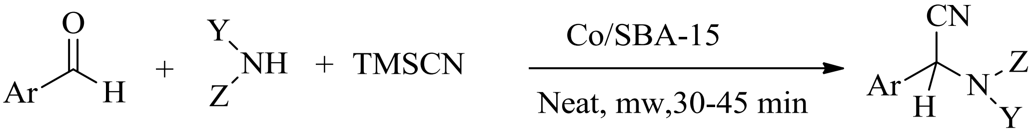
The Strecker synthesis is a term used for a series of chemical reactions that synthesize an amino acid from an aldehyde or ketone. The aldehyde is condensed with ammonium chloride in the presence of potassium cyanide to form α-aminonitrile, which is subsequently hydrolyzed to give the desired amino acid.



The Nafion-Fe-catalyzed Strecker reaction of various aldehydes or ketones with amines and trimethylsilyl cyanide were investigated, and the corresponding α-aminonitriles were obtained in good yields under solvent-free MW conditions.



A series of α-aminonitriles were synthesized via a catalytic Strecker-type reaction of aldehydes, amines and trimethylsilyl cyanide.The reactions were carried out at low temperature in the presence of Co(II) complex supported on mesoporous SBA 15 under solvent-free MW-assisted conditions.



3.13 REFORMATSKY REACTION

It is a reaction in which a carbonyl compound is reacted with an α-haloester in the presence of zinc metal to furnish the corresponding β-hydroxyester, is regarded as one of the most fundamental reactions for carbon–carbon bondformation. β-Hydroxyesters are widely utilised as one of the most important intermediates in organic synthesis.

This reaction can be done within 50 to 60 seconds under microwaves using activated Zn dust, ethyl bromoacetate and NH_4Cl

3.14 MICROWAVE-ASSISTED REACTIONS IN WATER

It was noted earlier that, despite microwave energy being targeted at polar molecules, a reaction mixture usually rapidly reaches temperature equilibrium through molecular collisions, etc. An exception to this rule has led to a high-yielding synthesis of a thermally unstable Hofmann elimination product. In this example a poorly mixed two-phase water/

chloroform system was used. Being polar the starting quaternary ammonium compound was water-soluble. Microwave irradiation quickly heated the water phase to over 100 °C, causing rapid elimination (reaction time 1 min). The less polar product rapidly partitioned into the chloroform phase, which being less polar had only reached a temperature of 48 °C. This low temperature enabled the product to be isolated in 97% yield, twice that using conventional heating.

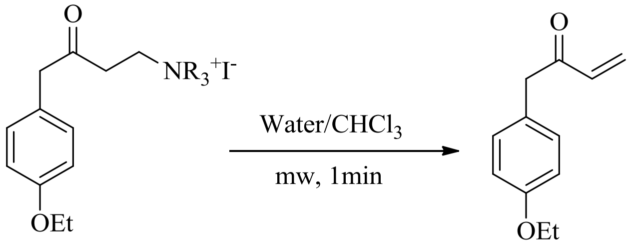
Water-based microwave reactions have been relatively well studied for hydrolysis and hydrogen peroxide oxidation reactions, where the natural solvent of choice would be water. In the hydrolysis of benzamide with sulfuric acid, quantitative conversion was achieved in 7 min under microwave irradiation at 140 °C, compared to a 90% conversion after a 1-h reflux using a conventional heating source. The difference in reaction time can be accounted for by the difference in reaction temperature coupled with the very rapid heating of the microwave reactor. A range of primary alcohols have been oxidized to the corresponding carboxylic acids using sodium tungstate as catalyst in 30% aqueous hydrogen peroxide. Yields, although variable, of up to 85% have been achieved in a rapid, clean, safe and atom efficient reaction.

3.15 ELIMINATION REACTION

Elimination reactions are the reactions in which a pair of atoms or group of atoms is removed from a molecule, usually through the action of acids, bases, or metals and in some cases, by heating to a high temperature. It is the principal process by which organic compounds containing only single carbon-carbon bonds (saturated compounds) are converted to compounds containing double or triple carbon-carbon bonds (unsaturated compounds).

Elimination reactions are commonly known by the kind of atoms or groups of atoms leaving the molecule. The removal of a hydrogen atom and a halogen atom, for example, is known as dehydrohalogenation; when both leaving atoms are halogens, the reaction is known as dehalogenation. Similarly, the elimination of a water molecule, usually from an alcohol, is known as dehydration; when both leaving atoms are hydrogen atoms, the reaction is known as dehydrogenation. Elimination reactions are also classified as E1 or E2, depending on the reaction kinetics. In an E1 reaction, the reaction rate is proportional to the concentration of the substance to be transformed; in an E2 reaction, the reaction rate is proportional to the concentrations of both the substrate and the eliminating agent.

Hofmann Elimination: In this method, normally quaternary ammonium salts are heated at high temperature and the yield of the product is low. Use of microwave irradiation has led to high-yielding synthesis of a thermally unstable Hofmann elimination product. In this water-chloroform system is used.



3.16 HYDROLYSIS

Hydrolysis is a type of decomposition reaction where one reactant is water. Typically, water is used to break chemical bonds in the other reactant. The term comes from the Greek prefix *hydro-* (meaning water) with *lysis* (meaning to break apart).

Hydrolysis may be considered the reverse of a condensation reaction, in which two molecules combine with each other, producing water as one of the products.

The general formula of a hydrolysis reaction is:

$$AB + H_2O \rightarrow AH + BOH$$

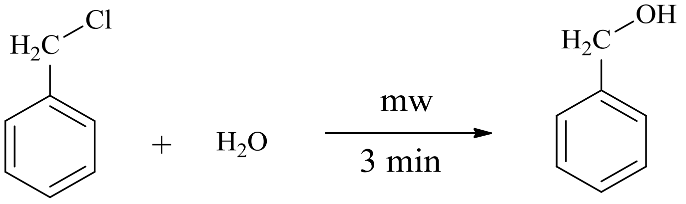
Organic hydrolysis reactions involve the reaction of water and an ester. This reaction follows the general formula:

$$RCO\text{-}OR' + H_2O \rightarrow RCO\text{-}OH + R'\text{-}OH$$

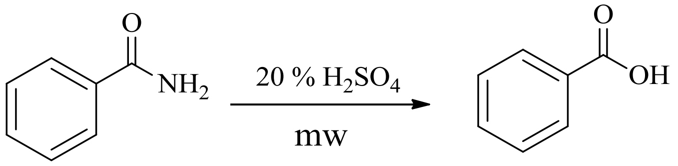
The hyphen on the left side denotes the covalent bond that is broken during the reaction.

Microwave reactions have been extensively used for hydrolysis.

Hydrolysis of Benzyl Chloride: Hydrolysis of benzyl chloride with water in microwave oven gives 97% yield of benzyl alcohol in 3 min. The usual hydrolysis in normal way takes about 35 min.

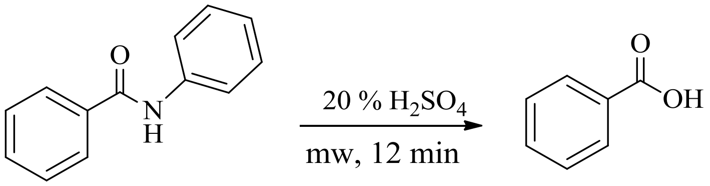


Hydrolysis of benzamide: The usual hydrolysis of benzamide takes 1 hr. However, under microwave conditions, the hydrolysis is completed in 7 min giving 99% yield of benzoic acid under acidic conditions

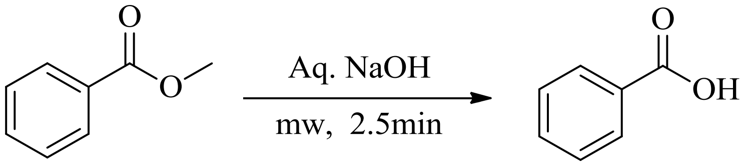


The rate increases considerably (5 - 1000 fold) when compared to classical thermal reflux conditions.

Hydrolysis of N-phenyl Benzamide: The acid hydrolysis of N-phenylbenzamide usually takes 18-20 hr. However, under microwave conditions the reaction is completed in 12 min giving6 74% of benzoic acid.

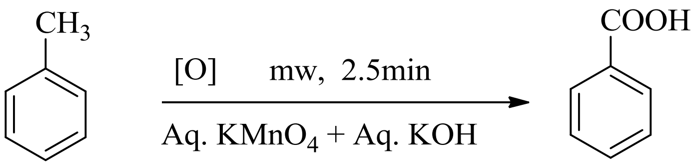


Hydrolysis of Methylbenzoate to Benzoic Acid (Saponification): Saponification of methylbenzoate in aqueous sodium hydroxide under microwave conditions (2.5 min) gives5 84% yield of the benzoic acid.



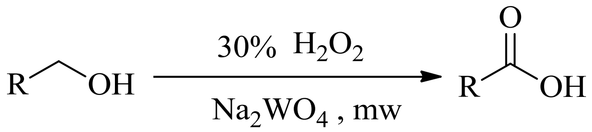
3.17 OXIDATION OF TOLUENE

Oxidation of toluene with $KMnO_4$ under normal conditions of refluxing takes 10-12 hr compared to reaction in microwave conditions, which takes only 5 min and the yield is 40%.



3.18 OXIDATION OF ALCOHOLS

A number of primary alcohols can be oxidised to the corresponding carboxylic acid using sodium tungstate as catalyst in 30% **aqueous** hydrogen peroxide.



4 TRENDS IN GREEN CHEMISTRY

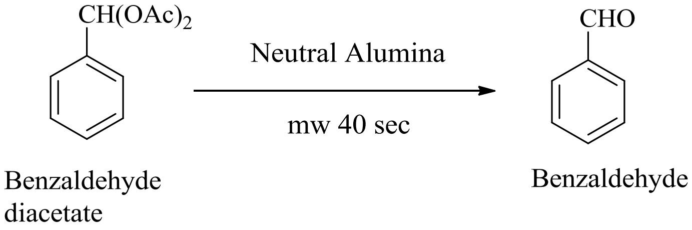
4.1 MICROWAVE ASSISTED SOLID STATE REACTIONS

Application of microwave irradiation in organic reactions has added a new dimension to solid phase synthesis. By the use of this technique, it is now possible to carry out reactions without the use of toxic or other solvents, which is one of the main problems associated with green synthesis. In these, the reactants are dissolved in a suitable solvent like water, alcohol, methylene chloride etc. and the solution stirred with a suitable adsorbent or solid support like silica gel, alumina or phyllosilicate (Mn^+ -montomorillonite). After stirring, the solvent is removed *in vacuo* and the dried solid supports on which the reactants have been adsorbed are used for carrying out the reaction under microwave irradiation. Following are some of the important applications of solid support synthesis.

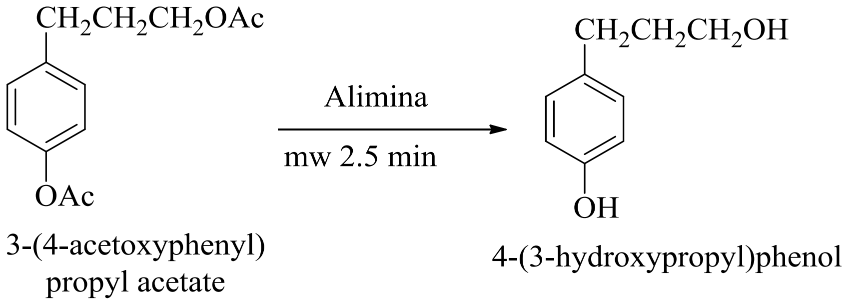
4.2 DEACETYLATION

Deactylation means removal of acetyl (Ac) group. Aldehydes, phenols and alcohols are protected by acetylation. After the reaction, the deacetylation of the product is carried out usually under acidic or basic conditions; the process takes long time and the yields are low. Use of microwave irradiation reduces the time of deacetylation and the yields are good. Some examples are as follows:

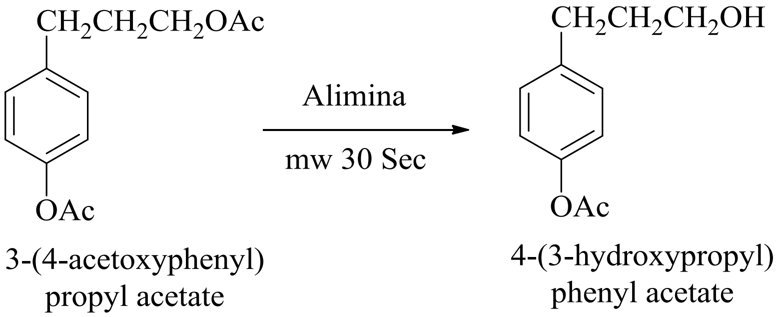
Benzalde diacetate can be deacetylated under microwave irradiation within 40 to 50 seconds. This reaction needs neutral alumina as catalyst and support. The product is obtained in good yield without using any liquid solvent.



Microwaves can also be used for selective deacetylation. For example if 3-(4-acetoxyphenyl) propyl acetate is microwave irradiated with alumina for 2.5 minutes it gives 3-(4-hydroxypropyl) phenol.



But the same reaction mixture gives 3-(4-hydroxypropyl)phenyl acetate if irradiated for only 30 seconds.



4.3 PROTECTION

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. This temporary blocking of a functional group is called protection.

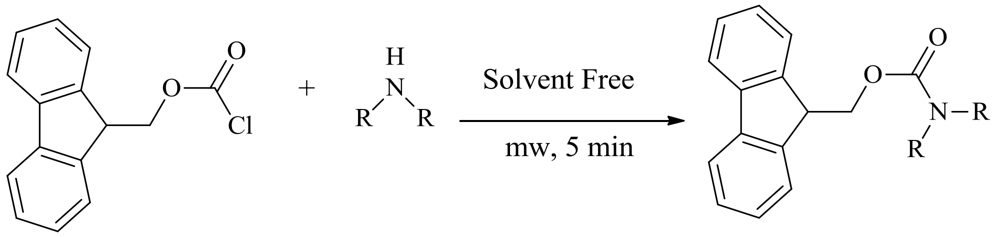
A protecting group must fulfill a number of requirements:

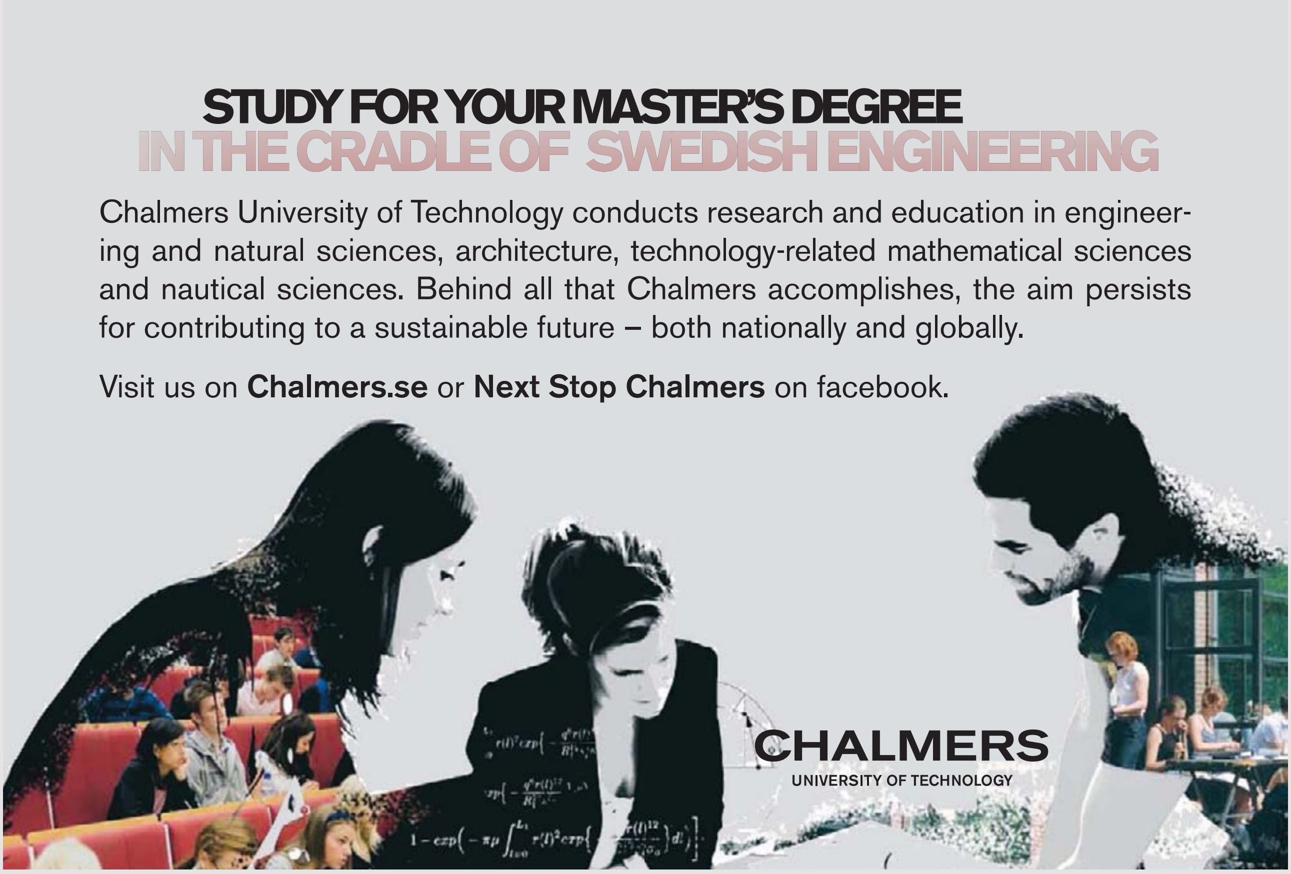
The protecting group reagent must react selectively (kinetic chemoselectivity) in good yield to give a protected substrate that is stable to the projected reactions.

The protecting group must be selectively removed in good yield by readily available reagents.

The protecting group should not have additional functionality that might provide additional sites of reaction.

Protection reactions are important when one needs to protect one of the functional group and wish to convert another functional group. Then certain protecting reagents are used for this purpose. In last few years, with the development of microwaves, protecting reactions are now being carried out with the help of microwave with the same or even better efficiency. For example efficient, quick, and sustainable method for the protection of amines is with a 9-fluorenylmethoxycarbonyl (Fmoc) group. It has been found that under microwave irradiation this solvent-free approach resulted in good to excellent isolated yields of the desired products within only 5 min.

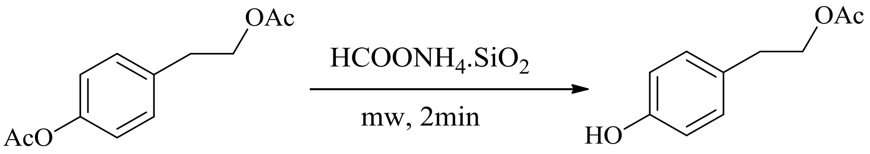




4.4 DEPROTECTION

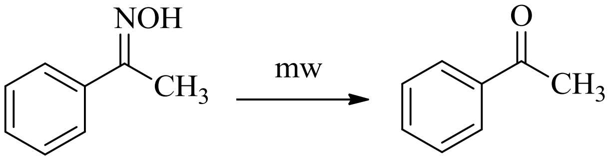
As the protection of a particular functional group is necessary along with the conversion of another functional group; similarly, deprotection process is equally important to get the actual functional group back in the product after completion of protecting reaction. Microwaves have been successfully employed for this purpose.

For example deprotection of several aryl acetates under microwave irradiation, which are rapidly and selectively deprotected to the corresponding phenols in excellent yields using silica gel supported ammonium formate.

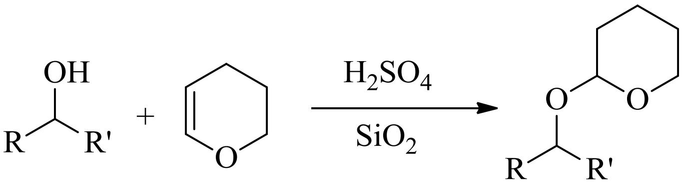


This process is environmentally benign in nature.

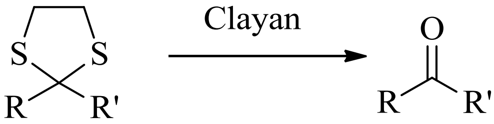
Cleavage of oximes to carbonyl compounds can be carried out by using readily available urea nitrate in acetonitrile–water (95: 5), under microwave irradiation. This reaction is not only completed within 2 min, but also with good yields of the products.



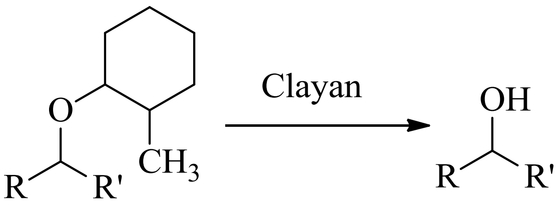
Alcohols and phenols are tetrahydropyranylated in the presence of sulfuric acid adsorbed on silica gel in high to excellent yields in solvent-free conditions under microwave irradiation. Addition of methanol performs the complete deprotection.



A variety of thioacetals, dithiolanes and dithianes are deprotected into their carbonyl compounds using clay-supported ammonium nitrate (Clayan) under micro wave irradiation. This method avoids the use of toxic oxidants and excess of solvent.



A variety of tetrahydropyranyl ethers (THP), acetonides and acetals are deprotected into their parent compounds using clayan under microwave irradiation. The ecofriendly nature of the reagent and solvent-free conditions are the important features of the procedure.



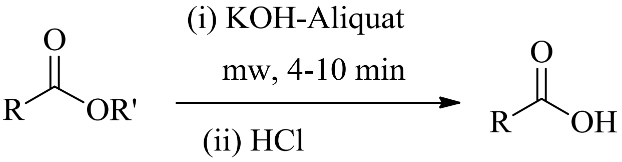
4.5 SAPONIFICATION OF ESTERS

Saponification is simply the process of making soaps. Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a base. The reaction is called a saponification from the Latin *sapo* which means soap. The name comes from the fact that soap used to be made by the ester hydrolysis of fats. Due to the basic conditions, a carboxylate ion is made rather than a carboxylic acid which on acid treatment produces carboxylic acid.

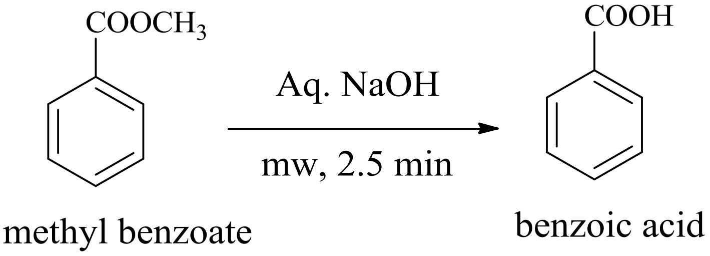
Ester + Base → Alcohol + Soap (salt of carboxylic acid)

Soap (salt of carboxylic acid) + HCl → carboxylic acid

Saponification of Esters under microwave: Hindered esters which take 5 hr under classical heating with alkali can be easily saponified under microwave irradiation using KOH-Aliquat.



Hydrolysis of Methylbenzoate to Benzoic Acid (Saponification): Saponification of methylbenzoate in sodium hydroxide under microwave conditions (2.5 min) gives 84% yield of the benzoic acid.



4.6 ULTRASOUND ASSISTED REACTIONS

Ultrasound assisted organic synthesis gives excellent yields compared to other reactions. It can dramatically affect the rates of chemical reactions and is helpful for a large number of organic transformations. In fact, a combination of sonication with other techniques, e.g., phase transfer techniques, reactions in aqueous media etc. give best results. Sonication has also been shown to stimulate microbiological reactions.

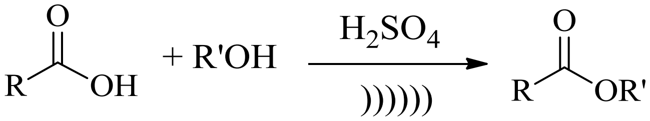
The term ‘sonochemistry’ is used to describe the effect of ultrasound waves on chemical reactivity.

Following are some of the important applications of ultrasound in chemical synthesis. Most of the reactions/syntheses reported are carried out at room temperature unless otherwise specified. The symbol))))) is used for reactions carried out on exposure to ultrasound.

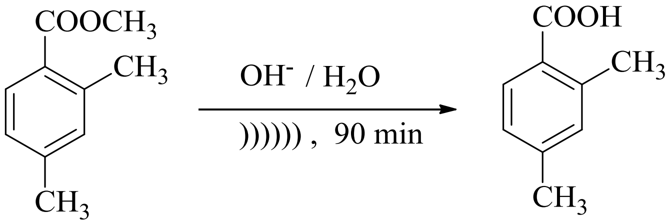
4.7 ESTERIFICATION BY UNDER ULTRASOUND IRRADIATION

This is generally carried out in presence of a catalyst like sulphuric acid, p-toluenesulphonic acid, tosylchloride, polyphosphoric acid, dicyclohexylcarbodiimide etc. The reaction takes longer time and yields are low.

A simple procedure for the esterification of a variety of carboxylic acids with different alcohols at ambient temperature using ultrasound has been reported.

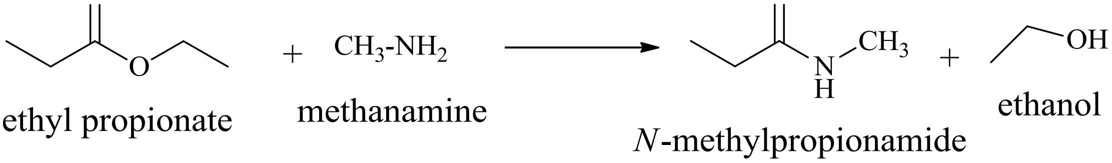


Saponification (ultrasound assisted): Saponification can be carried out under milder conditions using sonification. Thus, methyl- 2,4-dimethylbenzoate on saponification (20 KHz) gives the corresponding acid in 94% yield, compared to 15% yield by the usual process of heating with aqueous alkali (90 min).



4.8 SUBSTITUTION REACTIONS

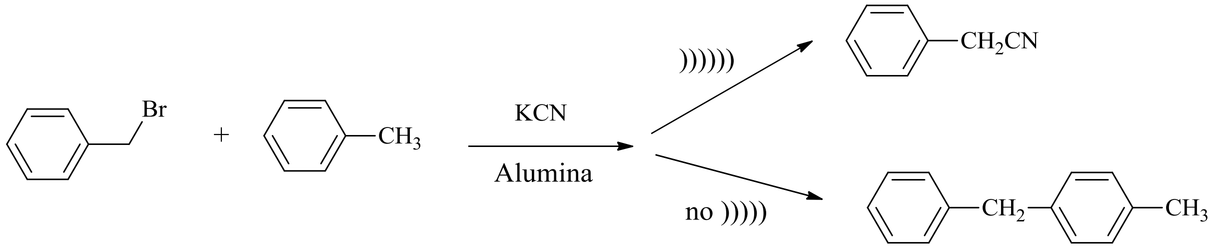
In substitution reactions, one atom (or group of atoms) is replaced by another atom (or group of atoms). The atom or group that is replaced is not utilized in the final product. Consider the substitution reaction of ethyl propionate with methyl amine.



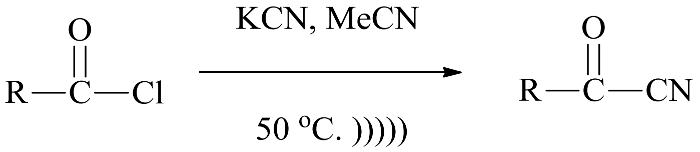
In this reaction, the leaving group (OC_2H_5) is replaced by $NHCH_3$.

4.9 ULTRASOUND PROMOTED SUBSTITUTION REACTIONS

Halides can be converted into cyanides. The reaction of benzyl bromide in toluene with potassium cyanide, catalyzed by alumina, on sonication gives the substitution product, viz. benzyl cyanide in 76% yield. In the absence of ultrasound alkylation is the preferred pathway. The difference is because ultrasound forces cyanide into the surface of alumina, enhancing cyanide nucleophilicity and reducing the lewis acid character.

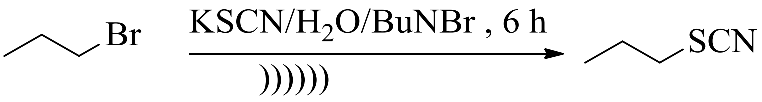


Sonication of acyl chloride and potassium cyanide in acetonitrile gave the corresponding acyl cyanides.



$$R-\overset{O}{\overset{\|}{C}}-Cl \xrightarrow[50\ ^{o}C.\ )))))]{KCN,\ MeCN} R-\overset{O}{\overset{\|}{C}}-CN$$

Similarly, alkyl bromides on sonication with KSCN in presence of a PTC catalyst gave the corresponding sulphocyanide in 62% yield.



4.10 OXIDIZING REAGENT AND CATALYSTS

Oxidizing Reagent: Numbers of oxidizing reagents have been used in organic chemistry for selective oxidation of various functional groups. No doubt that, many transition metals are efficient oxidizing agents; however, these metallic reagents are often required in stoichiometric amounts and may generate large amounts of hazardous metallic wastes. In addition to this some metals are very precious as well as some are toxic in nature. Therefore, alternative and cost effective oxidizing reagents are desirable. Non-metal catalysts have gained much attention in recent years. However, many traditional non-metal oxidants also associated with problems; many times they need in excess amount (more than stoichiometry), hazardous nature, and recovery is difficult or need regeneration by external additives.

Metal oxidant: The metal-based oxidants have the more potential to affect the oxidation reactions in a cleaner and efficient manner. They have also added benefits of easier product isolation and purification, increased reaction selectivity. In a number of cases the reagents/catalysts could be recovered and recycled.

Permanganate oxidations: Potassium permanganate is one of most classical oxidizing agent used widely in organic chemistry. The oxidation of alcohols to corresponding carbonyl compounds and alkylbenzenes to benzoic acids has been frequently performed using potassium permangate. It is slow in neutral conditions but faster in acidic and basic conditions. Under alkaline Potassium permangate is well known for the *cis*-diol synthesis from alkenes and tertiary amines to nitro compounds.

Chromic acid oxidations: Similar to permangate ion, chromic acid is also powerful oxidant. Chromic acid oxidizes the alcohols to carbonyl compounds, aldehydes to corresponding carboxylic acids. It oxidizes hydrocarbons, such as tertiary C-H groups in the hydrocarbons to produce tertiary alcohols whereas methylene group oxidizes to ketones. Chromic acid oxidation of olefins produces epoxides, glycols and cleavage products. Some modified reagents of chromium are also invented and are explored in the literature.

Jones reagent: The oxidation of alcohol with chromium trioxide acetate with sulphuric acid is known as Jones oxidation. This reagent is selective because it will oxidize alcohols in presence of alkenes, alkynes, benzylic and allylic functional groups.

Collins reagent: Chromium(VI) oxide pyridine complex is known as Collin's reagent. This reagent is useful for oxidation of alcohols containing acid sensitive functional groups.

Non-metal oxidant: Many non-metallic species are very good oxidizing agents. Polyvalent iodine is used for oxidation of alcohol to carbonyl compounds; HIO_4 in presence of catalyst reacts with olefins to give *syn*-diol, on the other hand HIO_3 is used for efficient oxidation of thiols to disulfides, sulfides to sulphoxide, anilines to quinones and thioacetals, thioketals to carbonyl compounds.

Miscellaneous oxidant: The various metallic and non-metallic reagents/catalysts are employed as oxidizing Agents.

From the green chemistry point of view, the ideal oxidants should be nonhazardous, cost effective, does not generate side products in the reaction, easily available and they can be regenerated and reused under simple reaction conditions in particularly under ambient conditions.

4.11 GREEN OXIDANTS

Oxygen and hydrogen peroxide are environmentally benign, cost effective and are efficient oxidants to achieve the required conversion and selectivity in the reactions under study; therefore both of these are the best suitable candidates to utilize them as oxidizing agents.

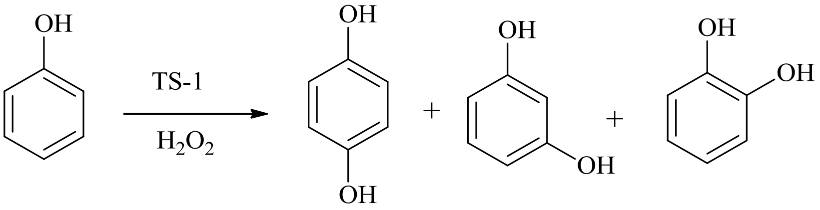
Molecular oxygen (O_2): Molecular oxygen received much attention as a green oxidant due to its safe use and green nature in presence of various metal catalysts. Molecular oxygen has many advantages in its use such as photosynthesis by plants produces little waste and it is inexpensive. Recently the direct synthesis of imines from amines in presence of aerial oxygen has reported. The direct synthesis of α–bromoketones from alkylarenes by aerobic photooxidation with hydrobromic acid is reported. There is large number of reports on oxidations using oxygen as oxidant in organic syntheses. The methods utilizing oxygen based on cobalt(II)-Schiff's base as catalysts are known. Inspite of these number of applications, moleculer oxygen is an ideal oxidant only if the process controls over oxidation and also if it utilizes both oxygen atom with 100% atom efficiency. Because, generally aerobic oxidation utilizes only one oxygen atom out of two and another atom requires reducing agent to capture it to give 50% atom economy.

Hydrogen peroxide (H_2O_2): It is another attractive terminal oxidant for liquid/aqueous phase oxidation reactions. Water is the only theoretical waste product in its use as an oxidant. Hydrogen peroxide is probably the best terminal oxidant after dioxygen with respect to environmental and economic considerations.

Hydrogen peroxide utilized for conversion of alkenes to epoxides. Under acidic condition, hydrogen peroxide oxidizes bromide ion to bromonium ion and this strategy is widely used in many oxybromination reactions. Under alkaline conditions hydrogen peroxide effect the conversion of carbonyl group (ortho or para hydroxyl substituted aldehyde or ketone) into hydroxyl group known as Dakins reaction.

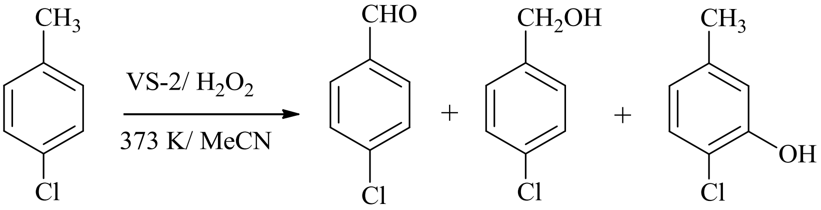
Hydrogen peroxide converts carboxylic acids to peracid, nitrile to amide, trialkyl boranes to alkyl borates in alkaline medium, primary/secondary amines to N-hydroxyl amine, tertiary amines to N-oxides, thiol to sulphonic acid and sulphide to sulphoxides etc.

Oxidation Catalysts: A large number of supported reagents have been used in the liquid phase partial oxidation of organic substrates. There has been considerable success in the use of molecular sieves (titanium and vanadium) in commercial units. The most important application oftitanium silicates (TS-I) is the hydroxylation of phenol, giving mixtures of hydroquinone and catechol.



The process is clean, giving excellent conversion to product with very little waste.

Vanadium silicate molecular sieves are capable of selectively oxidizing 4-chlorotoluene to 4-chlorobenzaldehyde using hydrogen peroxide as the source of oxygen in acetonitrile solvent.



Recent reports of oxidation catalysts based on chemically modified support materials include cobalt, copper and iron.

4.12 BIOMIMETIC, MULTIFUNCTIONAL REAGENTS

In the human system, there are thousands of reactions going on due to which the body survives. The scientists are trying to perceive the mechanism that the biological methods used to carry out their functions. The chemists are trying to mimic such reactions in the laboratory. In case of synthetic chemists, most of the transformations are sustained with the help of catalysts, e.g. oxidation, reduction and methylation. However, biological systems often carry out various manipulations with the same reagent. These collaborations may include activation, confirmation and other transformations. In the laboratory, it has now been feasible to carry out biochemical oxidations, biochemical reductions and enzyme catalyzed the hydrolytic process. Different types of proteins, e.g. hydrolase, Lyases, isomerases, Ligases, transferases, oxidoreductases are available.

The biocatalytic conversions have many advantages in relevance to green chemistry. Some of these are:

Most of the reactions are performed in an aqueous medium at ambient temperature and pressure.

The biocatalytic transformations usually involve only one step.

Protection and deprotection of functional group are not necessary.

The biocatalytic reactions are fast, and the conversion is stereospecific.

A biomimetic catalyst is a catalyst that carries out a reaction in a mode of action that resembles a natural enzyme. A generalized scheme for biomimetic reactions is shown in Fig. below.

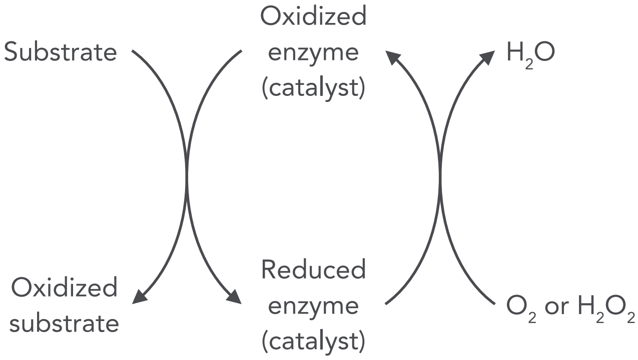


Fig 4.1: Biomimetic catalysis based on direct reoxidation of the enzyme (catalyst) by O_2 or H_2O_2

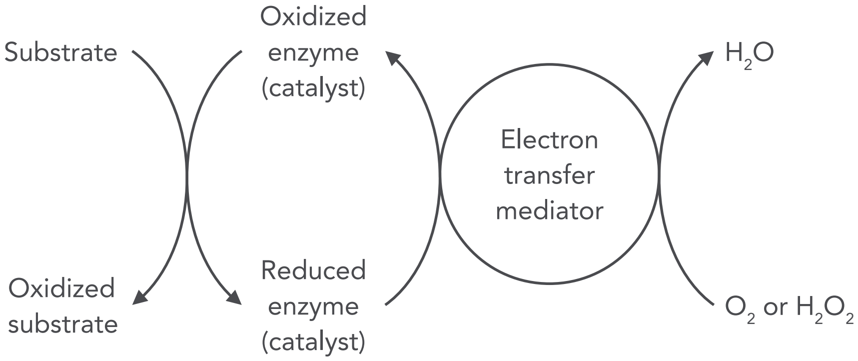
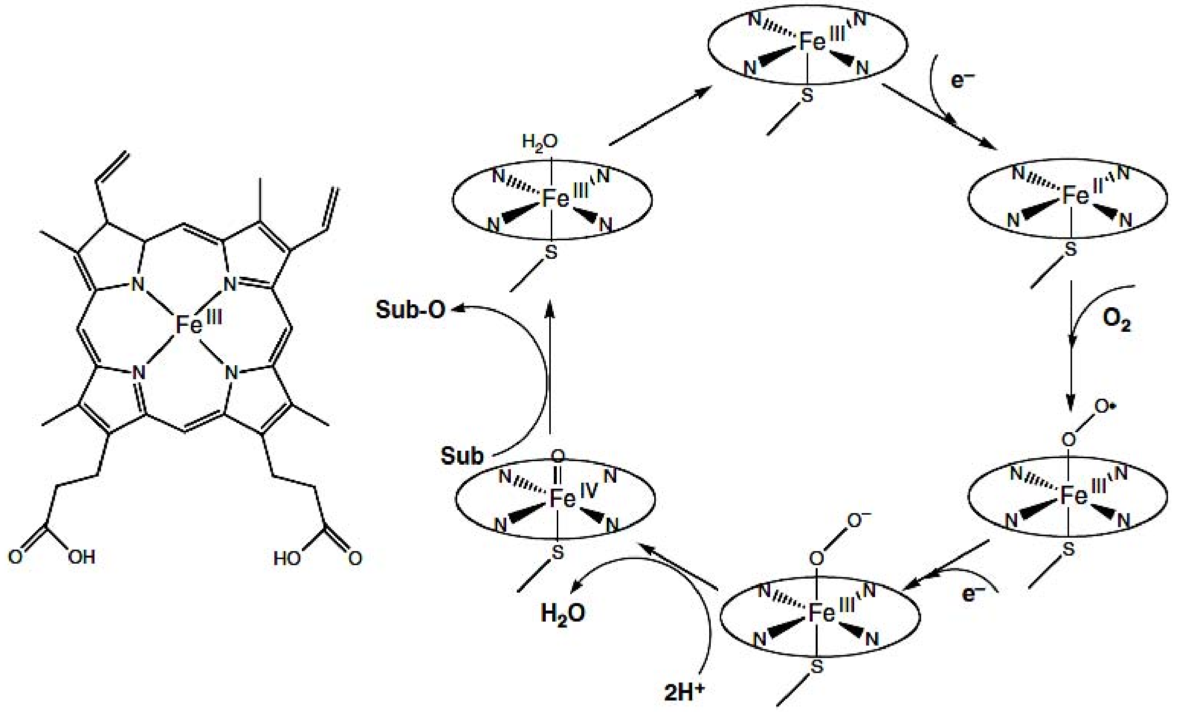


Fig 4.2: Biomimetic catalysis based on electron-transfer mediator reoxidation of the enzyme (catalyst) by O_2 or H_2O_2

Biomimetic oxidation reactions, especially those catalyzed by transition metal complexes, have provided a vast amount of scientific information with regard to structure, function, thermodynamics, kinetics, mechanism, synthesis, and enhanced or new analytical and spectroscopic methods.

The biomimetic chemist has the advantage in the design of a green catalyst as nature uses only those metals which are nontoxic and readily available in the geosphere. Manganese, iron, and copper probably are the dominant metals involved in biological oxidation processes, although vanadium and others play prominent roles as well. They are able to readily cycle through the electron-transfer steps that are needed for the oxidation process.

Nature's oxidations generally employ transition metals held in place by organic ligands. With few exceptions, the issue of ligand oxidation has hindered the development of highly successful commercial biomimetic oxidation catalysts. Nevertheless, even these less-than-ideal catalysts can be considered as green catalysts because they use nature's elements, and they can be useful under certain circumstances.



4.13 COMBINATORIAL CHEMISTRY

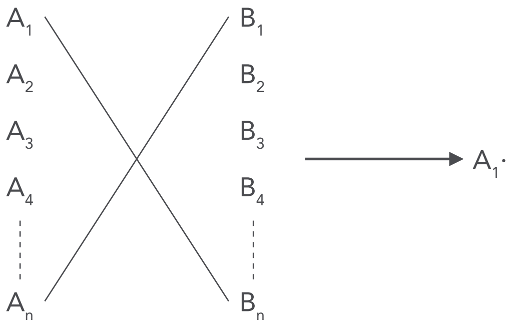
Combinatorial chemistry is a technique by which large numbers of structurally distinct molecules may be synthesized in a time and submitted for pharmacological assay. The key of combinatorial chemistry is that a large range of analogues is synthesized using the same reaction conditions, the same reaction vessels. In this way, the chemist can synthesize many hundreds or thousands of compounds in one time instead of preparing only a few by simple methodology.

In the past, chemists have traditionally made one compound at a time. For example compound A would have been reacted with compound B to give product AB, which would have been isolated after reaction work up and purification through crystallization, distillation, or chromatography.

A+B → AB

Orthodox

In contrast to this approach, combinatorial chemistry offers the potential to make every combination of compound A_1 to A_n with compound B_1 to B_n.

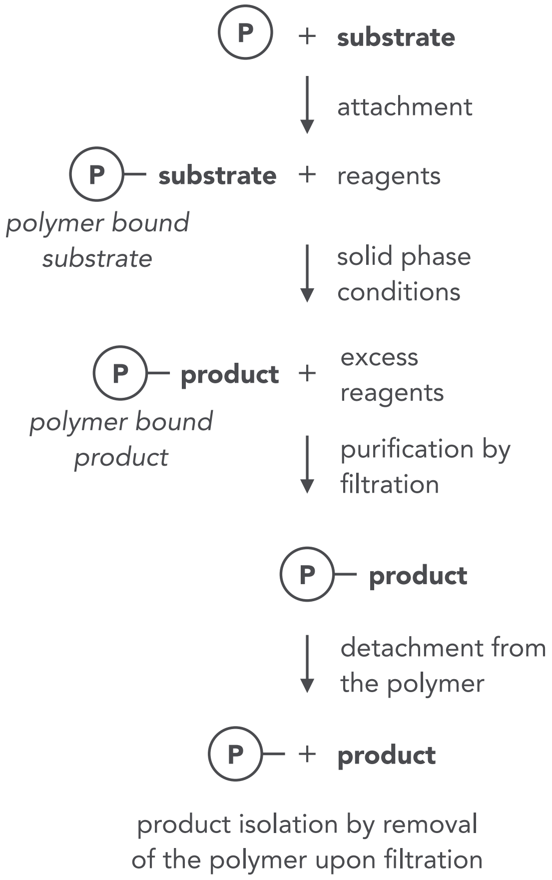


Combinatorial Synthesis

The range of combinatorial techniques is highly diverse, and these products could be made individually in a parallel or in mixtures, using either solution or solid phase techniques. Whatever the technique used the common denominator is that productivity has been amplified beyond the levels that have been routine for the last hundred years.

Merrifield pioneered solid phase synthesis in 1963, which earns him a Nobel Prize, since then the subject, has changed radically. Merrifield's Solid Phase synthesis concept first developed for biopolymer. It has spread in every field where organic synthesis is involved. Many laboratories and companies focused on the development of technologies and chemistry suitable to SPS. This resulted in the spectacular outburst of combinatorial chemistry, which profoundly changed the approach for new drugs, new catalyst or new natural discovery.

Solid Phase Chemistry



The use of solid support for organic synthesis relies on three interconnected requirements:

1. A cross linked, insoluble polymeric material that is inert to the condition of synthesis;
2. Some means of linking the substrate to this solid phase that permits selective cleavage of some or all of the product from the solid support during synthesis for analysis of the extent of reaction(s), and ultimately to give the final product of interest.
3. A chemical protection strategy to allow selective protection and deprotection of reactive groups.

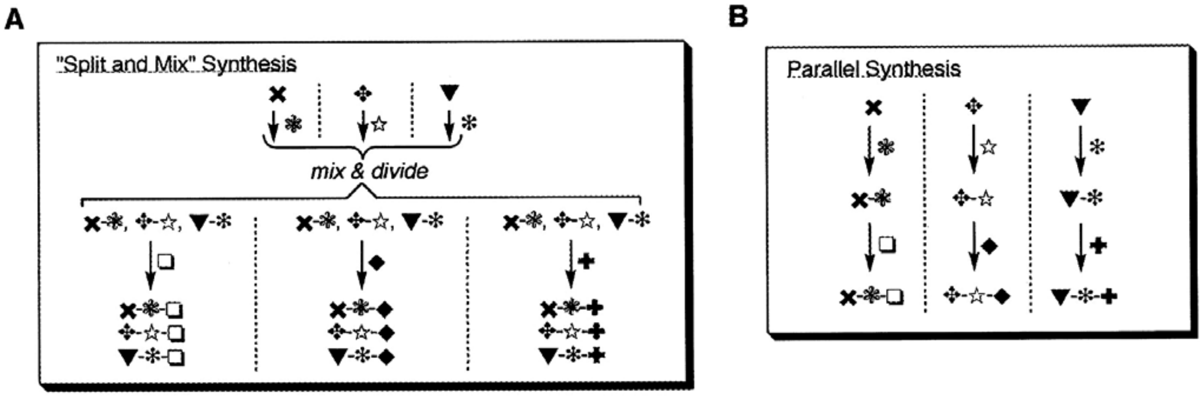
Over the years, many variations have been devised to perform the cleavages under milder conditions. The big advantage of the method is the ease of removal of un-reacted reagents and byproducts by simple washing. Large excesses of reagents can be used to speed up the reactions and ensure completion of reactions. In a study of the preparation of peptide guanidines, the solid-phase method offered several advantages. The reaction was seven times as fast as in solution. The yields were improved greatly.

Another recent innovation is the use of ultrasound to assist the coupling of zinc carboxylates with the Merrifield resin. Ultrasound also accelerated the cleavage of the final polypeptide from the resin by ethanolamines and aqueous sodium carbonate or sodium hydroxide. The process involves an initial transesterification, followed by hydrolysis of the new ester.

Combinatorial chemistry uses such methods to make mixtures of many possible compounds (called libraries) that can then be screened for the desired property to select those compounds that are active. The methods are suitable not only for polypeptides, but also for oligonucelotides, oligosaccharides, and a variety of small molecules, including many heterocyclic compounds.

The method can uncover new unnatural structures for biological targets. This is a shotgun method that works if there is a lead structure. Many leads are from natural products. The drug industry has been very disappointed by libraries made without leads.

A popular method is the split-and-mix one. The first reagent is attached to the support. The beads are then split into several batches, each of which receives a different building block. All the batches are recombined and again split into several lots, each of which receives a different added building block. This process is continued until the desired library of hundreds or thousands of compounds is complete.



Advantages

1. The creation of large libraries of molecules in a short time is the main advantage of combinatorial chemistry over traditional.
2. Compounds that cannot be synthesized using traditional methods of medicinal chemistry can be synthesized using combinatorial techniques.
3. The cost of combinatorial chemistry library generation and analysis of said library is very high, but when considered on a per compound basis the price is significantly lower when compared to the cost of individual synthesis.
4. More opportunities to generate lead compounds.
5. Combinatorial chemistry speeds up drug discovery.

Disadvantages

1. Though combinatorial chemistry would solve all the problems associated with drug discovery, one still needs to synthesize the right compound.
2. There is a limit to the chemistry you can do when using solid phase synthesis. The resin you use is often affected by the reaction types available and care must be taken so that the attachment of the reagent to the substrate and bead are unaffected. Each reaction step has to be carefully planned, and often a reaction isn't available because the chemistry affects the resin.
3. While a large number of compounds are created, the libraries created are often not focused enough to generate a sufficient number of hits (Library components whose activity exceeds a predefined, statistically relevant threshold) during an assay for biological activity. There is a great deal of diversity created, but not often a central synthetic idea in the libraries.

4.14 SOLVENT FREE REACTIONS

Solvent-free reactions, has gained special attention from synthetic organic chemists. Many reactions are newly found to proceed cleanly and efficiently in the solid state or under solvent-free conditions. Less chemical pollution, lower expenses, and easier procedures are the main reasons for the recent increase in the popularity of solvent-free reactions.

From Green Chemistry point of view a reaction should ideally, be conducted under solvent-free conditions with minimal or no side-product formation and with utmost atom-economy.

Examples of many solvent free reactions are discussed throughout this book.

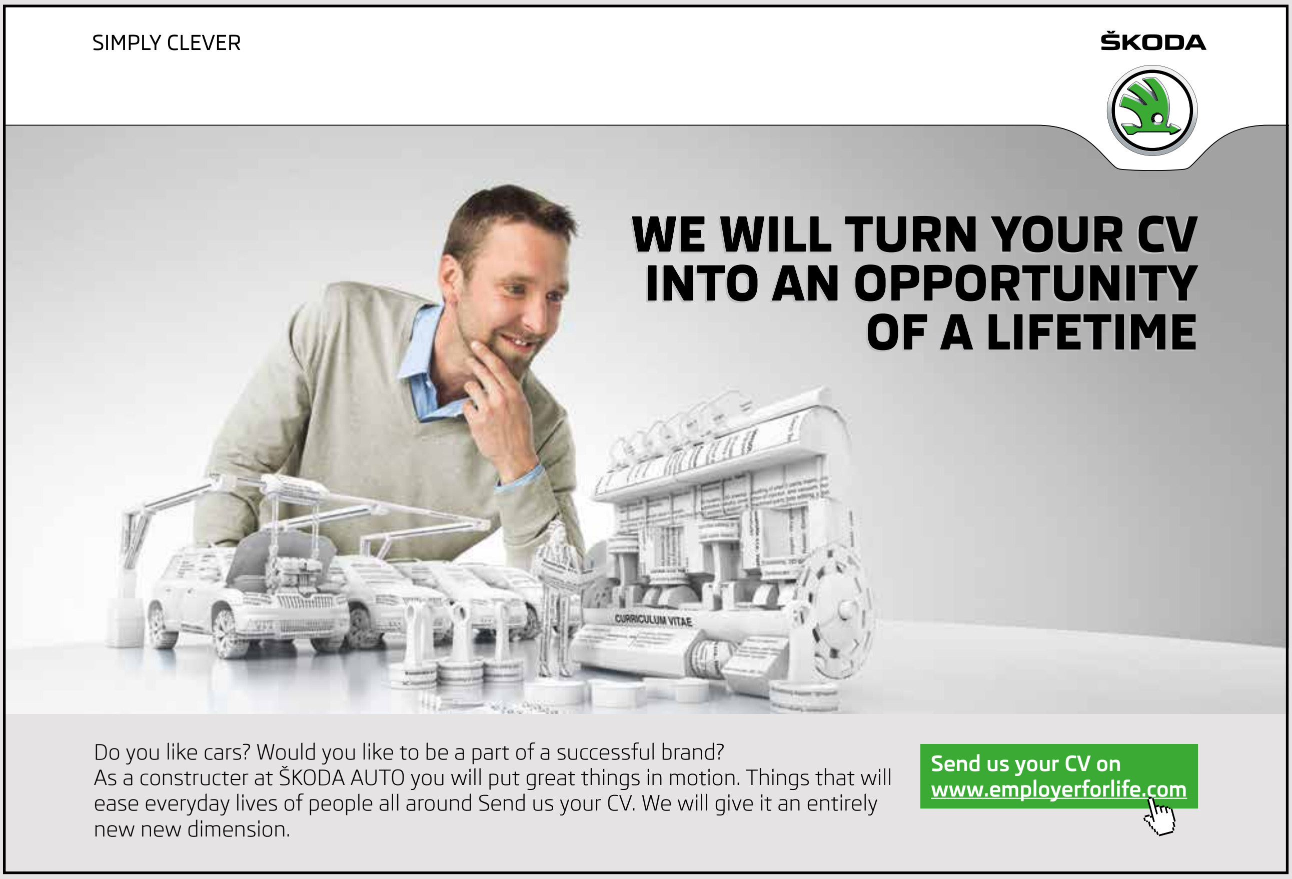
4.15 NON-COVALENT DERIVATIZATION

Chemistry is based on bond making and bond breaking, which are efficient but nonselective processes, leading to side and waste products. Through the utilization of dynamic complexation, or through non-bonded interaction, temporary modified chemical structures should be formed that would modify the properties of a molecule for the necessary period of time to carry out a particular function without all of the waste that would be generated if full derivatization is carried out.

Non-covalent derivatization is a process by which a material is formed when one co-former molecule or more is incorporated into the solid-state matrix of the target molecule by way of non-covalent forces. These forces can include ionic, Van der Waals forces, hydrogen bonding or pi-pi interactions. The resulting material (non-covalent derivative (NCD)) has properties that are distinctly different from those of the parent molecules.

There are two material forms that fall under the umbrella of NCDs: cocrystals and eutectics.

A cocrystal is s homogenous crystalline material that is made up of two or more molecules in definite stoichiometric amounts held together by non-covalent forces. The cocrystal is distinguished from a salt by the degree of proton sharing. A cocrystal is also differentiated



from a solvate by the state of matter of the starting material. If both the starting materials are solid then the NCD product is a cocrystal. If one of the materials is a liquid then the materials combine to form a solvate.

A eutectic can also be formed from two solids, but the resulting NCD is a homogenous material that is identifiable on a phase diagram as a single minimum point.

A non-covalent derivatization will result in a cocrystal or a eutectic depending on the main driving force. If the enthalpic advantage be more important than any entropy loss, then the system is enthalpically driven and the result is a cocrystal. On the other hand, if the entropy gain outweighs the enthalpy changes, then the eutectic predominates. The conditions for entropic versus enthalpic control can be credited in part to the topography of the parent molecules. In cases where the functional groups are compatible for effective non-covalent bonding and the size and shape of the parent molecules are similar enough for good crystal packing, cocrystals will result. In cases where only the non-covalent bonding is favored but there is poor packing shape compatibility of the parent molecules then only the binding forces predominate and a eutectic is formed.

Preparation of NCDs: Non-covalent derivatization can produce dramatic changes in the solubility, melting point, optical properties, bioavailability, or stability. The preparation of NCDs is an alternative that can be less toxic, produces less waste and is, in many cases, less labor-intensive.

NCDs can be prepared through a variety of solvent techniques, though the majority of these methods result in cocrystals. Traditional methods of precipitation cooling crystallization and slurry formation have been reported for the preparation of cocrystals. However, evaporation has emerged as the most common solvent-based method for cocrystal preparation. Solvent evaporation has also been reported in the preparation of eutectics. However, solvent preparation methods can be challenging because they not only require the target molecules to be compatible with each other for NCD formation, but also to have solubility relationships with the solvent that allow for concurrent precipitation as the solution cools or evaporates.

Eutectics can also be formed grinding the neat solids by mortar and pestle or automated grinders. Three mechanisms are recognized to be in effect with grinding in the solid state: grind molecular diffusion, eutectic formation, and cocrystallization mediated by amorphous phase. The grind molecular diffusion is described as a process by which the surface of the solid is made mobile either by vaporization or energy transfer to the surface of the solids. In the case of the eutectic, the eutectic liquid is first formed which then crystallizes to the final solid. Lastly, the cocrystals are described as combining out of the amorphous phase of the parent solids. In each of these cases, the intermediate bulk phase (gas liquid or amorphous solid) has a higher mobility and/or energy with respect to starting material forms. More importantly, grinding can produce cocrystals that are not available by solvent means.

Spray dry evaporation technique was also observed to produce different cocrystals forms from the same parent compounds. This was seen in the preparation of cocrystals formed from urea and succinic acid. With spray drying, a previously unidentified cocrystal structure was formed. It was found to have a 1 to 1 molar ratio and a laminar sheet form. With other preparation methods, the same materials produced a 2 to 1 urea to succinic acid structure with a complex three-dimensional structure that contains to ring-structure repeat units. The two forms had different stabilities and dissolution rates. This study is indicative of the versatility of NCD formation, not only in choice of coformer but also in method in order to produce NCDs with the desired properties.

Characterization of NCDs: The most direct and conclusive method for NCD characterization is through the analysis of cocrystals via crystal structure analysis. However in many cases, a cocrystal of the appropriate size for single crystal analysis is not achievable. In these cases, powder X-ray diffraction (PXRD) has been turned to as an alternative characterization technique. But PXRD alone cannot differentiate between hydrates, solvates, and cocrystals, the data is often considered in conjunction with another analysis method, for example, by combining PXRD, Nuclear Magnetic Resonance (NMR) and calculation theory. In addition to solid-state NMR (SS-NMR), other spectroscopic methods are often used for the identification of non-covalent derivatives. These methods are not generally predictive of the structure of the cocrystals or eutectic, but can indicate the presence of novel interactions (usually novel peaks) in the NCD that are not seen in the pure parent compounds. In some cases, especially those where the coformer has a carboxylic acid, infrared (IR) spectroscopy can be used because the frequency of some stretches will change when in a cocrystal environment. Raman spectroscopy has also proven to be an effective tool for NCD analysis as exemplified by the analysis of cocrystals prepared form salicylic acid and a series of coformers.Differential Scanning Calorimetry (DSC) can be used to identify the melting point NCDs.

Applications of NCDs

Pharmaceuticals: Much attention has been paid to the potential utility of cocrystals in the pharmaceutical industry. A variety of active pharmaceutical ingredients (APIs) have been incorporated into cocrystals and eutectics with the result of remarkable changes in physical properties without the loss of pharmaceutical activity.

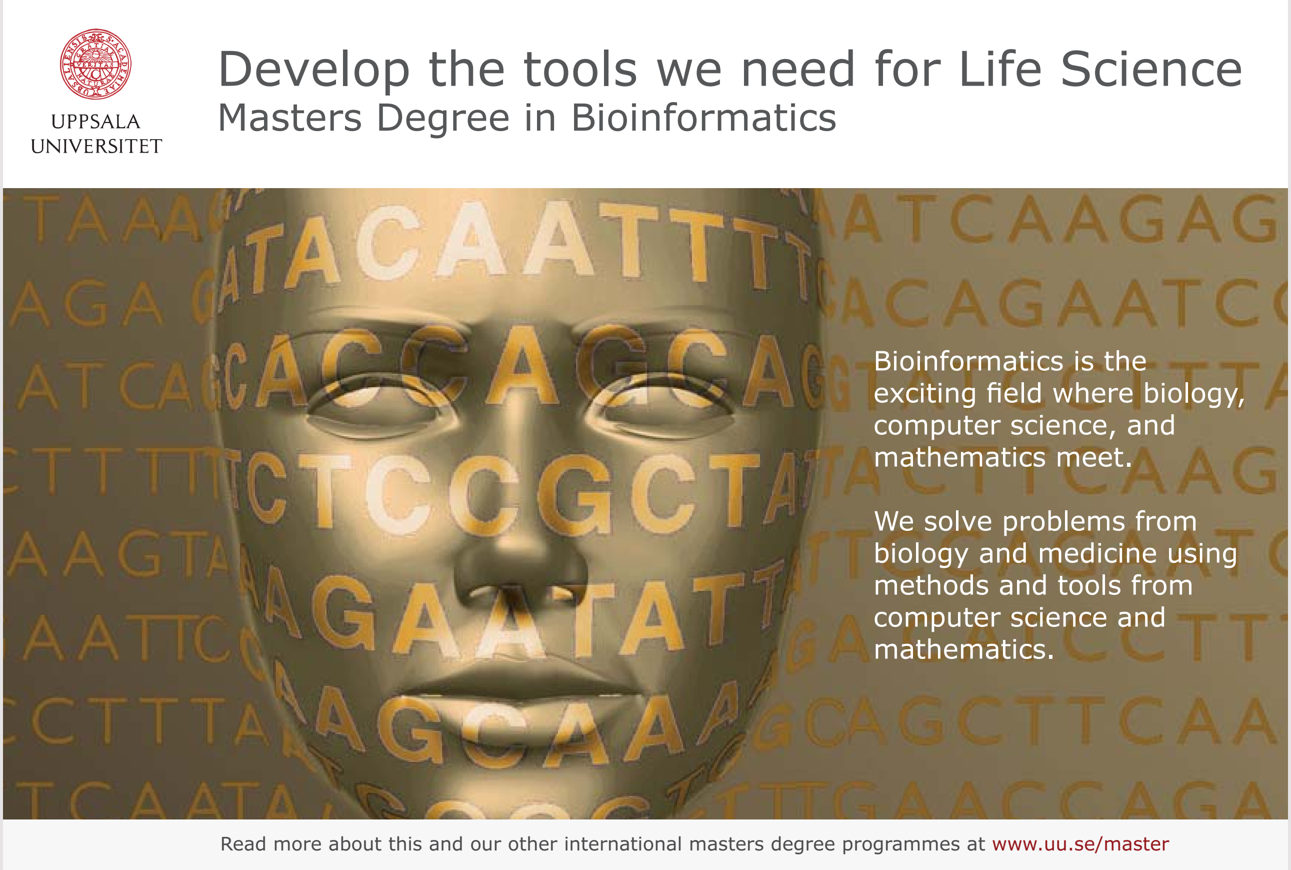
Cosmetics: Typical cosmetic formulation concerns involve preparing the active ingredient in a format that is both lends itself to easy application and is stable. Eutectic mixtures and cocrystals have been widely reported to facilitate this preparation. In one example, a eutectic mixture is utilized to incorporate solid fragrances into perfumes and colognes.

Agrochemicals: Numerous patents for cocrystals used for agricultural products, such as fungicides, fertilizers and insecticides have been filed. For example, cocrystals of metalaxyl, a fungicide, were prepared with prothioconazole, another broad spectrum fungicide, to produce a material with dramatically decreased water solubility than that of pure metalaxyl.

Chromophores: Pigments are a particularly interesting chromophore application of NCDs. Red textile pigments was prepared as two component dizao-based eutectics. These pigments were shown to have performance equal to those of more toxic dyes in terms of color fastness, heat resistance, acid resistance, alkali resistance and solubility.

Food Additives: NCDs have also found a place in food additives. Cocrystals prepared from the antioxidant yerba mate and sucrose resulted in powders with lowed hygroscopicity when compared to yerba mate and good flowability for processing. It was confirmed that the yerbe mate did not lose its antioxidant activity in the cocrystal form.

Other Potential Applications: NCDs have vast commercial potential in other less-developed areas as well. They are worth mentioning, despite limited patent activity, because the effects are notable.



Cocrystals have been used to alter electrical properties and shown to have potential as organic semi-conductor.

In another interesting application, hydroquinones were prepared with diamine coformers and used in instant photograph development.

Cocrystal reagents are also an interesting opportunity. By preparing cocrystals from olefins, solid-state reactions were run in high yield.

Unique photochemical reactions were possible with diarylethene due to the conformation induced by the cocrystal.

Cocrystals were also used to affect chiral resolution. Cocrystals were prepared from the racemic mixture DL-arginine. The difference in solubility between the D and L based cocrystals results in enantiomeric separation.

4.16 GREEN CHEMISTRY IN SUSTAINABLE DEVELOPMENT

According to the World Commission on Environment and development, Brundtland Commission 1987, sustainable development is the development *meeting the needs of the present generation without compromising the ability of future generations to meet their own needs*. We need greener chemistry, the chemistry that efficiently utilizes renewable raw materials, eliminates waste and avoids the use of toxic and or hazardous solvents and reagents in both products and processes in order to achieve this noble goal. Green chemistry represents two main components. First, it addresses the problem of efficient use of raw materials and the related elimination of waste. Second, it deals with the health, safety and environmental issues associated with the manufacture, use and disposal or reuse of chemicals.

Without green chemistry there is no path to sustainability. Green chemistry has attracted much attention. Green chemistry is a multidisciplinary field and covers areas such as synthesis, solvents, catalysis, raw materials, products and efficient processes.

Most current chemical production processes lack efficiency in using feedstocks and produce large amount of wastes. Increasing atom economy is crucial for reducing both the depletion of raw materials and the generation of waste. Another way to eliminate waste is integration of different reactions and processes, in which the by-product in one reaction is the feedstock of another. Huge amounts of toxic, flammable and volatile organic solvents are used in chemical processes to prepare chemicals and materials leading to solvent waste and environmental pollution. The use of greener solvents such as water, supercritical fluids, ionic liquids, nontoxic liquid polymers and their various combinations in chemical processes has become a major focus of research. Because of their special properties and functions, green solvents can be used to optimize chemical processes, decrease solvent usage and processing steps, and develop new routes and technologies that meet the requirements of sustainability.

Catalysis plays a key role in the chemical industry because most chemical processes need catalysts to accelerate reactions, enhance selectivity and lower energy requirements. Current catalysts are often based on expensive, toxic, harmful or noble metals. The design and use of green catalysts and catalytic systems to achieve the dual goals of environmental protection and economic benefits is an important task, and is essential for the sustainability of the chemical industry.

Currently, our energy supply and the feedstocks for producing organic chemicals and materials are mainly based on fossil resources, which are not renewable and are diminishing. The use of renewable carbon resources, i.e. biomass and CO_2, in the chemical and energy industries is extremely important, and different routes and processes have been developed. However, we face thermodynamic, kinetic and technical challenges in the conversion of biomass and CO_2 into fuels and chemicals. Many current routes are technically feasible, but economically prohibitive, and only very small proportions of the resources are currently used. The development of efficient methods for converting biomass and CO_2 into useful chemicals and liquid fuels through energetically and economically viable industrial processes is of great importance, but is challenging. Moreover, the use of greener, cheaper, safer reactants and sustainable energy sources, such as oxygen, hydrogen peroxide and solar energy, in chemical processes is also an interesting area.

It should be emphasized that green chemistry covers engineering aspects and green products. Chemicals and materials are produced by industrial chemical processes, and therefore, clean, energy-efficient and mass-efficient processes and technologies are essential tools for achieving the goal of maximizing efficiency and minimizing wastes. Many current pharmaceuticals, fine chemicals, commodity chemicals and polymers are harmful. Products that are benign to human health and the environment need be designed and produced to replace hazardous products. Clearly, the exploration of synthetic routes, design of sustainable products and solvents, and exploration of new catalysts and chemical processes are closely related, and should be integrated. In addition, economic benefits are the central driver for the development of green chemistry and technology.

Green chemistry will be one of the most important fields in the future. Although this field has developed rapidly in the last 20 years, it is still at an early stage. Promoting green chemistry is a long-term task, and many challenging scientific and technological issues need to be resolved; these are related to chemistry, material science, engineering, environmental science, physics and biology. Scientists, engineers and industrialists should work together to promote the development of this field. There is no doubt that the development and implementation of green chemistry will contribute greatly to the sustainable development of our society.