DIRECTORATE OF DISTANCE & CONTINUING EDUCATION

MANONMANIAM SUNDARANAR UNIVERSITY

TIRUNELVELI- 627 012

OPEN AND DISTANCE LEARNING (ODL) PROGRAMMES

(FOR THOSE WHO JOINED THE PROGRAMMES FROM THE ACADEMIC YEAR 2023–2024)

M. Sc. Chemistry Course Material
Elective - III
Green Chemistry
Course Code SCHE21

Prepared
by

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Green Chemistry

UNIT-I: Basic Principles of Green Chemistry: Introduction- Need for Green Chemistry. Goals of Green Chemistry. Limitations of Green Chemistry. Chemical accidents, terminologies, International green chemistry organizations and Twelve principles of Green Chemistry with examples.

UNIT-II: Green Synthesis: Choice of starting materials, reagents, catalysts and solvents in detail, Green chemistry in day today life. Designing green synthesis-Green reagents: dimethyl carbonate. Green solvents: Water, Ionic liquids - criteria, general methods of preparation, effect on organic reaction. Supercritical carbon dioxide- properties, advantages, drawbacks and a few examples of organic reactions in $scCO_2$. Green synthesis-adipic acid and catechol.

UNIT-III: Green Catalysis: Environmental pollution, Green Catalysis Acid catalysts, Oxidation catalysts, Basic catalysts, Polymer supported catalysts-Poly styrene aluminum chloride, polymeric super acid catalysts, Polymer supported photosensitizers.

UNIT-IV: Greener Reactions: Phase transfer catalysis in green synthesis-oxidation using hydrogen peroxide, crown ethers - esterification, saponification, anhydride formation, Elimination reaction, Displacement reaction. Applications in organic synthesis.

UNIT-V: Green Techniques: Micro wave induced green synthesis - Introduction, Instrumentation, Principle and applications. Sonochemistry – Instrumentation, Cavitation theory - Ultra sound assisted green synthesis and Applications

Recommended Text Books

1. Ahluwalia, V.K. and Kidwai, M.R. New Trends in Green Chemistry, Anamalaya Publishers, 2005.
2. W. L. McCabe, J.C. Smith and P. Harriott, Unit Operations of Chemical Engineering, 7th edition, McGraw-Hill, NewDelhi,2005.
3. J. M. Swan and D. St. C. Black, Organometallics in Organic Synthesis, Chapman Hall, 1974.
4. V. K. Ahluwalia and R. Aggarwal, Organic Synthesis: Special Techniques, Narosa Publishing House, New Delhi,2001.
5. A. K. De, Environmental Chemistry, New Age Publications, 2017.

Reference Books

1. Anastas, P.T. and Warner, J.K. Oxford Green Chemistry -Theory and Practical, University Press, 1998
2. Matlack, A.S. Introduction to Green Chemistry, Marcel Dekker, 2001
3. Cann, M.C. and Connely, M.E. Real-World Cases in Green Chemistry, American Chemical Society, Washington, 2000
4. Ryan, M.A. and Tinnesand, M., Introduction to Green Chemistry, American Chemical Society Washington, 2002.
5. Chandrakanta Bandyopadhyay, An Insight into Green Chemistry, Books and Allied (P) Ltd, 2019.

Unit- I
Basic Principles of Green Chemistry

Introduction

What Is Green Chemistry?

Green chemistry is defined1 as environmentally benign chemical synthesis with a view to minimize the environmental pollution. This is possible by using non-toxic starting materials from renewable sources and reduction in pollution by the prevention of hazardous by-products or substances. Chemists and research scientists all over the globe have been trying for the development of benign green synthesis of not only new products but also development of green synthesis for its existing chemicals.

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.

The definition of Green Chemistry includes the term "hazardous". It is important to note that Green Chemistry deals 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. 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. More importantly, intrinsically hazardous properties constitute those issues that can be addressed through the proper design or redesign of chemistry and chemicals.

Green Chemistry is often described within the context of new technologies But Green Chemistry is not beholden to ionic liquids, microwave chemistry, supercritical fluids, biotransformations, phase chemistry, or any other new technology. Green Chemistry is outside of techniques used but rather resides within the intent and the result of technical application.

Green Chemistry is neither a new type of chemistry nor an environmental movement, a condemnation of industry, new technology, or “what we do already”. Green Chemistry is simply a new environmental priority when accomplishing the science already being performed... regardless of the scientific discipline or the techniques applied. Green Chemistry is a concept driven by efficiency coupled to environmental responsibility

Green Chemistry is defined as environmentally benign chemical synthesis. Green Chemistry may also be defined as the invention, design, and application of chemical products and processes to reduce or eliminate the use and generation of hazardous substances. The synthetic schemes are designed in such a way that there is least pollution to the environment. As on today, maximum pollution to the environment is caused by numerous chemical industries. The cost involved in disposal of the waste products is also enormous. Therefore, attempts have been made to design synthesis for manufacturing processes in such a way that the waste products are minima, they have no effect on the environment and their disposal is convenient. For carrying out reactions it is necessary that the starting materials, solvents and catalysts should be carefully chosen. For example, use of benzene as a solvent must be avoided at any cost since it is carcinogenic in nature. If possible, it is best to carry out reactions in the aqueous phase. With this view in mind, synthetic methods should be designed in such a way that the starting materials are consumed to the maximum extent in the final product. The reaction should not generate any toxic by-products.

Need for Green Chemistry

Chemistry has changed the life style of the people. It has brought about (I) medical revolution (synthesis of drugs, medicines, etc.) (ii) manifold increase in food supply due to the discovery of hybrid varieties, improved method of farming, better seeds and use of agrochemicals like fertilizers, insecticides, herbicides, et.

Chemistry has proved the quality of life due to the discovery of dyes, plastics, cosmetics. All these development s increased the average life expectancy from 47 years in

1900 to 75 years in 1990's. But all these developments are responsible for various environmental problems at the local and global levels.

Some of the environmental problems are:

a) **Pesticides**: Chemicals that are used to kill unwanted insects, fungus, rodents, etc. Are called pesticides. Eg., DDT. They pose a health risk to humans and also damge the environment.

b) **CFC**: These are used in refrigerators. They create ozone holes which causes skin cancer.

c) **Acid Rain**: This is caused by discharge of pollutants like oxides of nitrogen and sulphus. This washes away the nutrients of the soil affects the plants and monuments made of marbles, eg: Taj mahal.

d) **Global warming**: The release of green house gases like CO2, CH4,N2O and CFC's have large effect on the climate due to increase in average temperature. This is called global warming.

e) **Dioxins:** Dioxins are environmental pollutants, which are often harmful to human health. They are sometimes called persistent organic pollutants (POPs) because they take many years to break down once they are in the environment. Serious problems related to childhood development and reproductive and immune system health are sometimes linked to dioxins. They can disrupt hormonal balances and are implicated in cancer.

f) **Thalidomide**: It is a drug used by pregnant women to lessen vomiting. Children of these women suffered acute birth defects.

g) **Photochemical Smog**: The photochemical smog of London during 1952 was responsible for the death of about 4000 people due to respiratory problem.

All the above stated problems are due to pollution. So, it is only green chemistry that can play a vital role in keeping the environment clean. Hence , it is necessary to bring green chemistry to the class room and laboratory to have the necessary changes at the grass root level. In a nut shell, "Green chemistry is a science based, non-regulatory and economically driven approach to achieve the goals of environmental protection and sustainable development.

Goals of Green Chemistry

Green Chemistry aims to eliminate or at least reduce the pollution by preventing it from happening as far as possible. In fact the goal of green chemistry or benign chemistry is to design synthetic methodologies that reduce or eliminate the use or generation of toxic products. In order to be eco-friendly, organic synthesis must meet all or some of the following requirements.

They are:

(i) avoid waste
(ii) avoid use and production of toxic and hazardous chemicals
(iii) avoid auxiliary substances
(iv) reduce energy requirements
(v) use catalysts like bio-catalysts
(vi) produce compounds which are biodegradable

In broad sense, green chemistry includes any chemical process or technology that improves the environment and thus enhances the quality of life.

Limitations of Green Chemistry

Environmental pollution can be eliminated or considerably reduced by following the principles of green chemistry. The most important principles (as we will see subsequently) include using renewable resources as starting materials in a chemical synthesis, using safer chemicals, economizing on atoms, using minimum energy for a process and discharging only the safe substances (or by-products) into the environment. However, a number of things that limit and there are constrains the goals of green chemistry.

Some of these include:

- It is not always possible to procure starting materials for a reaction from renewable resources.
- Use of benign or safer solvents is not always possible. If feasible, a particular reaction could be conducted without using any solvent, in solid state.
- It is not always possible to economise on atoms. This means that all the atoms of the starting materials cannot be incorporated into the final products. It is well known that only rearrangement reactions and addition reactions are 100% atom economical. All other reactions are not atom-economical.
- It is not always possible to discharge only the safer by-products into the environment.

It is very important to formulate guidelines and pass strict rules for the practising chemists. But the most important is to bring about changes at the grass root level, which can be achieved by bringing about necessary changes in the chemistry curriculum. A concerted and pervasive effort is needed to reach the widest audience. Bringing green chemistry to the classroom and the laboratory will have the desired effect in educating the students at various levels about green chemistry

Chemical accidents

A number of chemical accidents were reported from different parts of the world. They are:

Minamata disease

It is resulted due to the effects of mercury poisoning. It was reported in 1950, more than 50 people died and a number of people were affected in a sea coast village in Japan. The reason was consuming of fish contaminated with mercury. On investigation, it was found that the water of the Minamata Bay was polluted for more than 30 years (1932–1968) by approximately 27 tonnes of mercury compounds which were dumped by the Chisso Chemical Company, a company located in Kumamoto, Japan. On investigation, it was found that the Chisso Chemical Company used mercuric chloride as a catalyst for the manufacture of acetaldehyde, and only non-toxic mercury was released in the effluents. However, the sediments from the Minamata Bay were found to be rich in methyl mercury chloride. In the sediments of the lake, microorganisms help the biomethylation of mercury to form methyl mercury chloride. This is lipid soluble and found its way in the tissues of fish. Consumption of these fish caused birth defects and affected neural tissues, mainly the brain. This disease caused by mercury poisoning is called Minamata disease as it was found to occur in Minamata Bay in Japan.

Itai-Itai Disease

It is resulted due to the effects of cadmium poisoning. This disease occurred around 1912 in Japan due to consumption of rice affected by cadmium metal. The rice fields were found to be irrigated with effluents released by zinc smelters. On consumption of such rice, particularly the women suffered from acute pain in the entire body. In some cases, the women suffered from broken bones on trying to move. The clinical features were osteomalacia accompanied with osteoporosis and multiple renal tubular dysfunctions. Owing to acute pain, the victims cried “Itai-Itai” and so the disease was called “Itai-Itai”. On investigation it was found that the cause of the disease was cadmium poisoning. About 200 people were found to be having this disease. The disease cause cancer of liver and lungs.

Bhopal Gas Tragedy

On 3 December 1984, world’s worst air-pollution episode ccurred at Union Carbide in Bhopal. Approximately 33 tonnes of methyl isocyanate (MIC), a deadly poisonous gas used in the synthesis of a pesticide, leaked after midnight from a storage tank and spread mist and cloud over the city of Bhopal. A large number of people were exposed to MIC while in sleep. On an estimation about 22,000 people died and more than 120,000 people suffered from diseases. The survivors of Bhopal Gas Tragedy suffered from a number of problems, such as permanent respiratory illness, impairment of vision, damage to lungs, kidneys and muscles, gastrointestinal and reproductive problem combined with low response to the immune system. In a number of women,
menstrual abnormalities and abortion were reported.

Flixborough Disaster

An explosion occurred in a chemical plant near the village at Flixborough, North Lincolnshire, England, during 1974. This plant was used to oxidize cyclohexane into cyclohexanone by air at about 155 °C. About 28 people were killed due to the explosion and 36 were seriously injured out of a total of 72 people on the site at that time. It is believed that the explosion may be due to a hasty modification in the plant. Cyclohexanone (needed to produce caprolactam, which was used to produce nylon 6) was originally produced by the hydrogenation of phenol. Subsequently, additional capacity was added by using a DSM design in which hot liquid cyclohexane was oxidized partially by compressed air. In this process as many as six steel reactors were used. About two months before the explosion, reactor number 5 leaked due to developmental of a crack extending about six feet. It was decided to install a temporary pipe in order to bypass the leaking reactor so that there will be continued operation of the plant while the repairs were carried out. However, a massive release of hot cyclohexane occurred. This was followed by a release of hot cyclohexanone, which got ignited and a cloud of flammable vapor and a massive explosion occurred. The reason for the explosion was attributed to the change in the design of the original plant. Now, Cyclohexanone is prepared by the hydrogenation of phenol.

Seveso Disaster

In 1976, an explosion occurred at Seveso, Italy in a plant manufacturing herbicide. A dense white cloud of a poisonous gas consisting of 2, 3, 7, 8-tetra-chlorodibenzo-*p*-dioxan (TCDD) (Dioxan) was discharged in the atmosphere. Approximately an area of 150 km^2 with a population of about 40,000 was affected. This caused skin injuries to a large number of people who were exposed to the gas. The skin injuries, however, healed in about a month time. A large number of children suffered from chloracne, a condition characterized by skin blotches which disappeared in several months. A number of children born after the accident were premature and also deformed.

Manufacture of DDT

Dichlorodiphenyltrichloroethane (DDT) is a common insecticide insoluble in water, but easily soluble in ethanol and acetone. This insecticide is useful against agricultural pests, flies, lice and mosquitoes. Widespread use of DDT has resulted in pollution of crop lands, and a large number of pests have become resistant to it. When it enters the food chain, DDT accumulates in the fatty tissues of animals.

Manufacture of Adipic Acid

It is well known that adipic acid is used for manufacture of nylon, polyurethane, lubricants and plasticizers. Approximately 2 billion kg of adipic acid are needed each year. The normal standard way of making adipic acid involves the use of benzene, a carcinogen. The procedure has been changed by the development of a process aided by biocatalysts and replacing benzene by simple sugar glucose.

The above-mentioned accidents were responsible for environmental problems that are mostly caused by the discharge of harmful substances into the environment. All such incidents could be controlled by the use of basic principles of green chemistry.

Terminologies

In the decade of the 1990's, the notion of green chemistry was born out of the Environmental Protection Agency's efforts to prevent pollution. The United States Government, many industries, and many universities continued to work on the initiative until John Warner and Paul Anastas published their 12 Principles of Green Chemistry in 1998 (Anastas and Warner

1998). These principles have been the cornerstone of virtually all green chemistry endeavors worldwide.

Although the color green is often associated with the environment, throughout the millennia the color green has been associated with life, renewal, well-being, and even prosperity in some cultures.

The US Environmental Protection Agency, on its website, defines Green Chemistry, also known as “sustainable chemistry,” as “the design of chemical products and processes that reduce or eliminate the use or generations of hazardous substances. Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, and use.” (Green Chemistry 2013).

This glossary of green chemistry vocabulary was developed from a chemist’s point of view to be a desktop companion for everyone active in the field. While there are seemingly countless words to choose from, the vocabulary contains 70 commonly used terms, including specialized words pertaining to green chemical applications and processes.

Glossary of Green Chemistry Terminology

Additionality

The environmental benefit realized from a particular project in comparison to the absence of the same project and its benefits.

Anthrosphere

The portion of the environment made or modified by man for human activities.

Benign solvent

An innocuous liquid utilized in chemical reactions or processes.

Bioaccumulation

The increase in the concentration of a substance within an organism over time. Biofuel An energy source derived from renewable plant and/or animal organic matter.

Bio-innovation

A novel process, product, or implementable idea contributing to sustainability or even a sustainable development.

Biomass

The sum of all living, non-living and other organic matter in a given area.

Black water

Waste water containing fecal matter and urine.

Carbon capture

Trapping carbon dioxide gas from its source for subsequent storage or other usage.

Carbon credit

A voluntary or compulsory credit purchase signifying that a company will offset or reduce carbon dioxide emissions by one ton.

Carbon footprint

All greenhouse gases emitted by processes, products, persons, and factories into the atmosphere.

Carbon neutral

An activity or process which does not generate atmospheric carbon dioxide and may be achieved by a variety of means, i.e., sequestrating and offsetting.

Carbon offsetting

Employing renewable energy projects, technological enhancements in production, and sequestration to counter balance carbon emissions in a given area.

Carbon pool

A reservoir for carbon storage including forests, soils, layers of the atmosphere, biomasses, or marine zones.

Carbon rationing

A credit system (mainly personal) for carbon-based activities whose goal is to reduce one's carbon footprint. In concept, credits can be bought, sold, redeemed, or traded.

Carbon sequestration

Literally, carbon removal from the atmosphere, i.e., carbon dioxide.

Carbon sink

A natural carbon storage depot, e.g., an ocean or forest.

Carbon tax

A tax on fossil fuel usage that emits carbon dioxide into the atmosphere.

Carrying capacity

The maximum number of organisms a given ecosystem can support indefinitely.

Climatic relevance

The importance and interaction of emissions within the earth's different atmospheric layers.

Cradle to cradle, C2C

An approach aimed at keeping materials, products, and systems in a continuous, waste-free loop by reutilizing and monitoring final materials, plus modifying the ongoing process.

Cradle to gate

A partial-product life cycle which begins with raw materials and ends in a pre-consumer product requiring final fabrication. Examples: wood products, certain metals (jewelry), or polymers for plastics.

Cradle to grave

A product life cycle leading to final waste disposal with little or no material recycling.

Deflagration

The extreme, rapid burning of a material without detonation which is often important in waste storage facilities.

Degradation

An active or even passive process in which a product or material is broken down into usable components.

Dematerialization

Producing a product or material, as well as running a process, with fewer resources, while not compromising the outcome in terms of quality, performance, appeal, or functionality.

Downcycling

Reclaiming a material for reuse in another product of lesser value, however, the original product cannot be remanufactured.

Ecological assessment

An evaluation done to examine the condition of life forms in a given area, and the human activities which influence the ecology of the area under consideration.

Eco-friendly

A product, building, process, factory, etc. having a minimal environmental impact.

Electrosmog

Electromagnetic radiation over various frequency ranges resulting from wireless technologies.

Embodied energy

The sum of all energies required for a process or product in a cradle to grave scenario. Does not include a reference to the molecular nature of product or material.

Environmental impact factor, E Factor

A calculation done for chemical processes where the E Factor equals the mass of the waste(s) divided by the mass of the product(s). Water is excluded in the calculations done in kilograms. An ideal E Factor is zero, and typical values range from 1 to 100. The calculation dates back some 15 years and does not consider waste toxicity.

Feedstock

Raw materials used in manufacturing processes, chiefly petroleum products.

Flue gas

A gas rising into the atmosphere from a flue stack.

Fuel cell

A device generating electricity using hydrogen, or hydrocarbons, and oxygen via chemical reactions.

Gold standard

A global certification standard for carbon mitigation projects incorporating mandatory, demonstrable achievements in energy efficiencies, additionality, carbon offsets, and renewable energy.

Gray or Grey water

Waste water free of fecal and urine contamination which may be used for irrigating fields, laundering clothes, or flushing toilet bowls. Note, although gray is used for the color gray in standard American English both gray and grey are often used interchangeably (Gerba et al 1995; Surendran S. and Wheatley 1998). Green design.

Although initially an architectural term referring to construction having a minimal environment impact, it can also refer to objects produced from sustainable materials, made from non-hazardous materials, or fabricated in a more energy efficient way.

Green project

One adhering to the 12 Principles of Green Chemistry and the concept of green design.

Green water

Precipitation, which remains within the soil for crop and plant growth, i.e., the water does not run off, or is not channeled away for any purpose.

Greenapsis

The processes a corporation or company utilizes to become chemically green.

Harvester

Individuals gathering human consumable products from the environment while observing the principles of sustainability.

Hydrocarbon

A compound consisting only of carbon and hydrogen atoms in various proportions.

LEED program [Leadership in Energy and Environmental Design]

Rates commercial and residential developments on a scale to achieve LEED Certification, which signifies compliance with many green initiatives, such as, stewardship, carbon footprint reduction, waste reduction, and energy efficiency.

Life cycle assessment

The evaluation and investigation of a product life-cycle from raw materials to ultimate disposal done from both an environmental and health perspective.

Low carbon project

A project in which there is a planned, purposeful reduction in greenhouse gases on a corporate scale.

Nanotechnology

The molecular-scale development of systems capable of performing specific tasks.

Non-renewable resources

Oil, natural gas, coal, and some radioactive materials collected in nature which are unable to be replenished.

Organic chemistry

A branch of chemistry dealing with compounds containing carbon as their framework or base.

Persistent substance

A substance which remains in a given area or environment in spite of removal efforts, time, treatment, or other suitable measures.

Post-consumer waste

Generally paper and plastics recovered from the consumer waste stream that are then recycled.

Potable water

Water suitable for human consumption.

Recyclable

Spent material able to be collected, processed, and purified into other usable raw materials or products.

Regenerative design

Broadly known as cradle to cradle design, however, also includes important concepts of nature as a model and biomimicry. Regenerative design has its own 12 strategies for compliance and adherence to its philosophy.

Renewable resources

Fully reusable and generally free environmental resources, e.g., biomass, water.

Responsible care

Begun in Canada in 1985, now a global initiative by chemical manufacturers who comply with the movements' own ethic and principles for sustainability.

Sequestration

Typically refers to capturing carbon dioxide from industrial processes, then storing the CO2 in sinks, reservoirs, or aquifers.

Stewardship

Maintaining, protecting, safeguarding, and managing environmental resources. Includes all those interacting with nature and the environment.

Sullage

Synonymous with gray water, primarily generated from households and human activities.

Supercritical fluid

A substance forced to exist as a liquid, beyond its critical temperature and critical pressure, used for industrial extraction and purification.

Sustainability

Meeting current needs of all kinds without compromising, endangering, or impairing the needs of future generations of mankind.

Sustainable chemistry

Innovating chemical processes and products leading to the reduction and/or elimination of using hazardous materials [a life cycle approach]. Green chemistry is synonymous with sustainable chemistry.

Sustainable solutions

Those methodologies providing relief from past practices of unchecked waste disposal, the rapid consumption of non-renewable resources and pollution control.

Symbiotic approach

A mutually benefiting, shared-value methodology aimed at sustainability.

Synergism

A toxicological term indicating the effect two chemicals have together, which is greater than either chemical considered alone.

Technical nutrients

Materials that are not able to be broken down in the natural environment yet are stable and essential to a particular industry who then retrieves and reuses them in a closed-loop cycle.

Toxic release inventory

An EPA report citing the release of designated toxic substances in the air, water, and land.

VOC, volatile organic compound

A compound, which easily evaporates into the air causing pollution directly, or indirectly by chemical and/or photochemical reactions that produce secondary pollutants.

Waste stream

The output of problematic substances from manufacturing processes, construction, farming, commerce, and households into the environment.

Zero waste process

One in which traditional waste is considered a resource and is reused or recycled back into the marketplace or environment for suitable usage.

International Green Chemistry Organizations

Advancing Green Chemistry, American Chemical Society Green Chemistry Institute (ACS-GCI), ACS-GCI Chemical Manufacturer's Roundtable, ACS-GCI Chemical Manufacturer's Roundtable, ACS-GCI Formulator's Roundtable, ACS-GCI Formulator's Roundtable, ACS-GCI Pharmaceutical Roundtable, American Institute of Chemical Engineers (AIChE): Institute for Sustainability, American Institute of Chemical Engineers (AIChE): Sustainable Engineering Forum, AIChE Sustainable Engineering Forum, Berkeley Center for Green Chemistry, Beyond Benign, Bioeconomy Institute (Michigan State University), Blue Green Alliance, Business-NGO Working Group for Safer Chemicals and Sustainable Materials, California Green Chemistry Initiative, Canadian Green Chemistry Network, Center for Green Chemistry at University of Massachusetts Boston, Center for Green Chemistry (Monash University) – Australia, Center for Green Chemistry and Green Engineering at Yale University etc.

Twelve principles of Green chemistry

The term “green chemistry” was coined by Professor Paul T. Anastas who is known as the Father of Green Chemistry. He along with the Professor John C. Warner formulated the twelve principles of green chemistry.

1.Prevention It is better to prevent waste than to treat or clean up waste after it is formed.

- carry out a synthesis in such a way so thatformation of waste (by-roducts) is minimumor absent
- cost involved in the treatment and disposal of waste adds to the overallproductioncost.
- the unreacted starting materials alsoform part of the waste, if discharged causes pollution and requires expenditure for cleaning-up

2. **Atom Economy** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

It is a method of expressing how efficiently a particular reaction makes use of the reactant atoms.

Calculation of Atom Economy

$$\text{Atom Economy} = \frac{\text{mass of atoms in desired products}}{\text{mass of atoms in reactants}} \times 100$$

Thisapproach does not take yield into account. According to this calculation, it is implied that if one mole of the reactant produces one mole of the product, the yield is 100%.

If one mole of the starting material produces one mole of the product, the yield is 100 %. However, such a synthesis may generate significant amount of waste or by product which is not visible in the above calculation. Such a synthesis, even though gives 100% yield, is not considered to be green synthesis.

Example: Consider the synthesis of ibuprofen.

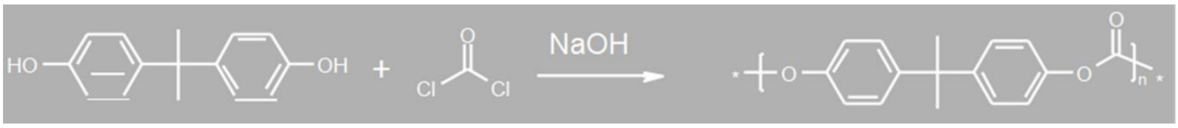
In the former process, developed in the 1960s, only 40% of the reactant atoms were incorporated into the desired ibuprofen product; the remaining 60% of the reactant atoms found their way into unwanted by-products or waste that required disposal. The new method requires fewer reaction steps and recovers 77% of the reactant atoms in the desired product. This 'green' process eliminates millions of pounds of waste chemical by-products every year, and it reduces by millions of pounds the amount of reactants needed to prepare this widely used analgesic.

3. **Less Hazardous Chemical Synthesis** Whenever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

Redesigning existing transformations to incorporate less hazardous materials is at the heart of Green Chemistry.

With the advancement of technology, the designing and production of safer chemicals has become possible.

Example: Synthesis of Polycarbonate: Phosgene Process



Disadvantages:

1. Phosgene is highly toxic and corrosive
2. It requires large amount of $COCl_2$
3. Polycarbonate

4. **Designing Safer Chemicals** Chemical products should be designed to preserve efficacy of the function while reducing toxicity.

The designing of safer chemical is now possible since there have been great advances in the understanding of chemical toxicity. It is now fairly understood that a correlation exist between chemical structure e.g. presence of functional groups and the existence of toxic effects. The idea is to avoid the functionality related to the toxic effect. Chemical properties of a molecule, such as water solubility, polarity etc. so that they can manipulate molecules to the desired effects.

5. **Safer Solvents and Auxiliaries.** The use of auxiliary substances (solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous (harmless)

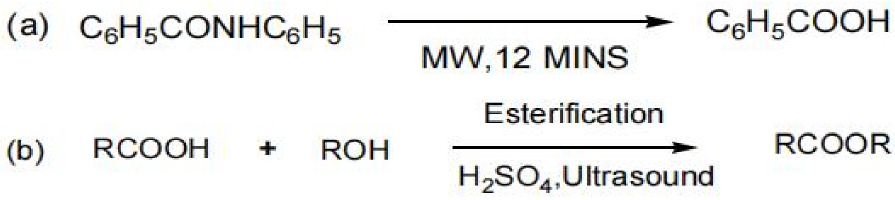
An auxiliary substance is one that helps in manufacture of a substance, but does not become an integral part of the chemical. Such substances are used in the manufacture, processing at every step. Major problem with many solvents is their volatility that may damage human health and the environment. Even processes like recrystalisation require energy and substances to change the solubility. The problem of solvents has been overcome by using such solvents which do not pollute the environment. Such solvents are known as green solvents. Examples include liquid carbon dioxide (supercritical CO_2), ionic liquid water. Even reactions have been conducted in solid state. For example the condensation reaction of ortho esters with o-phenylenediamines in presence of KSF clay under solvent free conditions using microwave.

6. **Design for Energy Efficiency** Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

Energy generation, as we know has a major environmental effect. 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.

$$\underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} + \text{aq } KCN \longrightarrow \underset{\text{Benzyl cyanide}}{C_6H_5CH_2CN} + KCl$$

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,



$$\text{(a)}\quad C_6H_5CONHC_6H_5 \xrightarrow[\text{MW, 12 MINS}]{} C_6H_5COOH$$

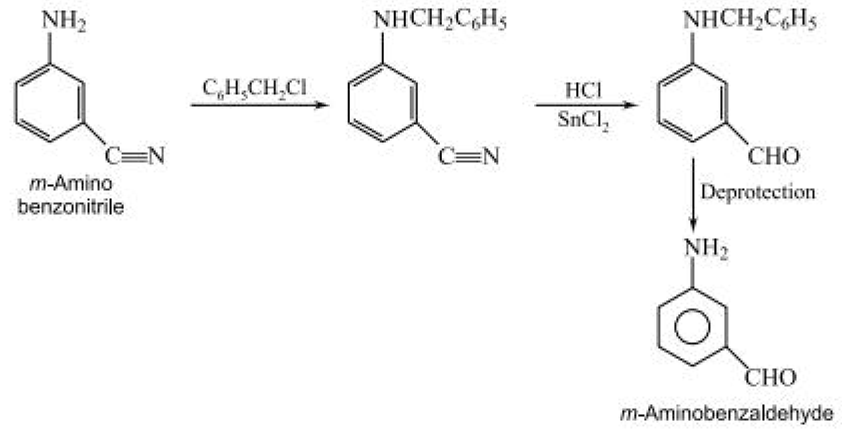
$$\text{(b)}\quad RCOOH + ROH \xrightarrow[H_2SO_4\text{, Ultrasound}]{\text{Esterification}} RCOOR$$

7. **Use of Renewable Feedstocks** A raw material or feedstock should be renewable rather than depleting whenever technically and economically practical.

Non reversible or depleting sources can exhausted by their continual use. So these are not regarded as sustainable from environmental point of view. The starting materials which are obtained agricultural or biological processes are referred to as renewable starting materials. Substances like carbon dioxide (generated from natural sources or synthetic routes like fermentation etc) and methane gas (obtained from natural sources such as marsh gas, natural gas etc) are available in reasonable amounts and so are considered as renewable starting material. Methane, a constituent of biogas and natural gas can easily be converted into acetylene by partial combustion. Acetylene is a potential source of number of chemicals such as ethyl alcohol, acetaldehyde, vinyl acetate etc

8. **Reduce Derivatives** Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.

In organic Synthesis, the commonly used technique is the use of protecting or blocking group. These groups are used to protect a sensitive moiety from the conditions of the reaction, which may lead the reaction to proceed in an unwanted way if it is left unprotected. A typical example of this type of transformation would be protection of amine by making benzyl ether in order to carry out a transformation of another group present in the molecule. After the reaction is complete, the NH_2 group can be regenerated through cleavage of the benzyl ether.



In this example, benzyl chloride (a known hazard) needs to be handled with care and used in the preparation of the desired material and then regenerated as waste upon deprotection. In this procedure, the protecting group is not incorporated into the final product, and their use makes a reaction less atom-economical. Thus, the use of protecting groups be avoided. Though atom economy is a valuable criterion in evaluating a particular synthesis as “green”, other aspects of efficiency must also be considered.

9. **Catalysis.** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

In some reactions, the reactants (A and B) react to form a product (C), in which all the atoms contained within A and B are incorporated in the product (C). In such cases, stoichiometric reactions are equally environmentally benign from the point of material usage as any other type of reactions. However, if one of the starting materials (A or B) is a limiting reagent, in such cases, even if the yield is 100%, some unreacted starting material will be left over as waste. In other cases, if the reagents A and B do not give 100% yield of the product (C), both the excess of unreacted reagents will form part of waste. It is found that because of the reason mentioned above, catalysts wherever available offer distinct advantages over typical stoichiometric reagents. The catalyst facilitates the transformations without being consumed or without being incorporated into the final product.

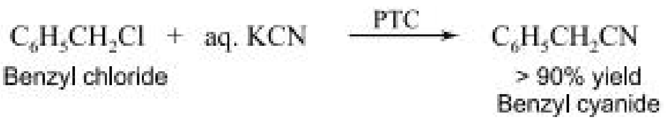
By using catalysts, both starting material utilization is enhanced and formation of waste is reduced. An additional advantage of the use of catalyst is that the activation energy of a reaction is reduced, so the temperature necessary for the reaction is also lowered. This results in saving the energy. It should be understood that in stoichiometric processes, the product obtained is one mole for every mole of the reagent used. However, a catalyst will carry out thousands of transformations before being exhausted.

Examples:

1. Hydrogenation of olefins in the presence of nickel catalyst gives much better yields

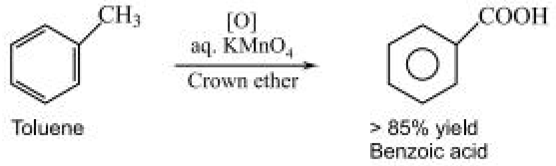
$$H_3C{-}CH{=}CH_2 + H_2 \xrightarrow{Ni} H_3C{-}CH_2{-}CH_3$$

2. Conversion of benzyl chloride into benzyl cyanide results in much better yields on using phase transfer catalysts



$$C_6H_5CH_2Cl + aq.\ KCN \xrightarrow{PTC} C_6H_5CH_2CN$$

3. Oxidation of toluene with KMnO4 in the presence of crown ether gives much better yield



10. Design for Degradation Chemical products should be designed so that at the end of their function they do not persist in the environment and instead break down into innocuous degradation products.

It is of more important that the products that are synthesized should be biodegradable; they should not be “persistent chemicals” or “persistent bioaccumulators”. Such chemicals (which are non-biodegradable) remain in the same form in the environment or are taken up by various plants and animal species, and accumulate in their systems; this is detrimental to the concerned species. The problem of non-biodegradability is generally associated with pesticides, plastics and a host of other organic molecules.

Most of the pesticides in use are organohalogen-based compounds. These pesticides though effective tend to bioaccumulate in plants and animals. The pesticide DDT was one of the first pesticide which bioaccumulated in plants and animals. Whenever a chemical is being designed, it should be made sure that it will be biodegradable. It is now possible to place functional groups and other features in the molecule which will facilitate its degradation. Functional groups which are susceptible to hydrolysis, photolysis or other cleavage have been used to ensure that products will biodegrade. It is equally important to make sure that the degradation products should not possess any toxicity and be detrimental to the environment.

Plastics are known to remain persistent and are not biodegradable. The waste plastics were mostly used for landfills and so on. However, it now possible to make plastics (particularly for garbage bags etc.) that are biodegradable.

11.Real-time Analysis for Pollution Prevention Analytical methodologies need to be further developed to allow for real time in-process monitoring and control prior to the formation of hazardous substances.

Methods and technologies should be developed so that the prevention or minimization of generation of hazardous waste is achieved. It is necessary to have accurate and reliable reasons, monitors and other analytical methodologies to assess the hazardous that may be present in the process stream. These can prevent any accidents which may occur in chemical plants.

12. **Inherently Safer Chemistry for Accident Prevention** Substance 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.

The occurrence of accidents in chemical industry must be avoided. The accidents in Bhopal (India) and Seveso (Italy) and many others have resulted in the loss of thousands of lives. At times, it is possible to increase accident potential inadvertently in an attempt to minimize the generation of waste in order to prevent pollution. It has been noticed that in an attempt to recycle solvents from a process (in order to be economical and also prevent escape of solvent to the atmosphere) increases the potential for a chemical accident or fire. In fact, a process must balance the accident prevention with a desire for preventing pollution. A possible course is not to use volatile solvents, instead solids or low vapour pressure substance can be used.

Unit – II

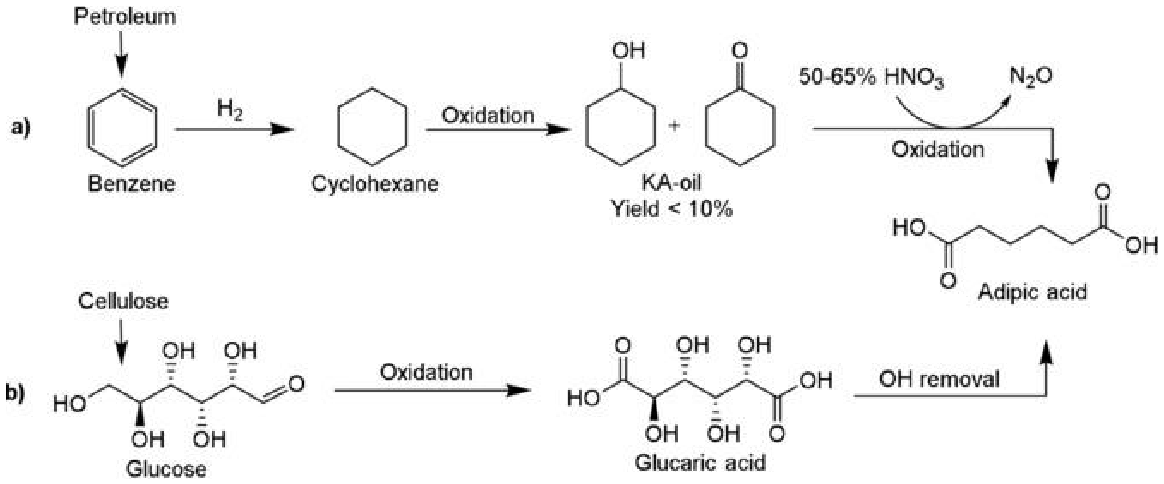
Designing a green synthesis

Designing a green synthesis

The starting materials are made to react with suitable reagents under appropriate conditions in all synthetic reactions. Consider all possible methods that can give the desired product before deciding the route to be followed for any synthesis. The method of choice should not use any toxic starting material and should eliminate the formation of by products and wastes. Following is some of the important considerations for designing green synthetic routes:

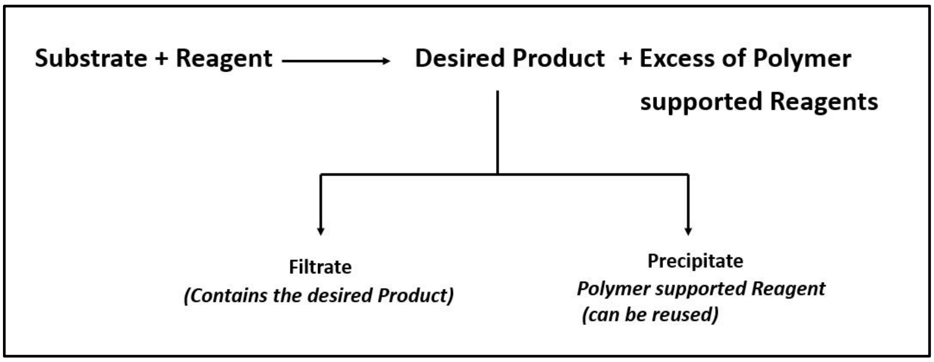
(i) **Choice of Starting Materials:** It is very important to choose the appropriate starting materials, since the synthetic pathway will depend on this. Also, it is essential to consider the hazards that may face by the workers handling the starting materials. Most of the synthesis make use of petrochemicals (Chemicals made from petroleum) which are non-renewable. It is therefore very 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, nylons, etc. Some of the chemicals that have biological origin (obtained from biomass) are butadiene, pentene, phenolics, aldehydes, resorcinol, acetic acid, peracetic acid, acrylic acid, methyl aryl ethers, sorbitol, mannitol, glucose, gluconic acid, 5-hydromethylfurfural, furan, tetrahydrofuran, furfuryl alcohol, etc.

A typical example using biomass materials is the manufacture of adipic acid from glucose using catalysts. By this newly developed process, the use of large quantities of benzene (a petrochemical and a suspect carcinogen) could be avoided.



In the above synthesis, benzene is the starting material which possess environmental and health hazards. Also, the above synthesis uses HNO_3 resulting in the production of nitrous oxide (N_2O) as by product. It is a green house gas and has adverse effect. The environmentally benign synthesis of adipic acid uses D-glucose as the starting material. Also, the synthesis is conducted in water instead of organic solvents.

(ii) **Choice of reagents (Green Reagents):** The selection of a suitable reagent is made on the basis of easy availability, efficiency and its effect on environment. Some of such reagents include triplet oxygen, singlet oxygen, ozone, hydrogen peroxide, dioxiranes, dimethylcarbonate and polymer supported reagents. The advantage of using polymer supported reagents is that the reagent is recovered (since polymer supported) and can be used again. The various steps involved are:



Polystyrene is the most widely used polymer. Some examples of polymer supported reagents include:

(a) Polymer supported peracids – p-C6H4- CO3H (p-polymer). This reagent is used for epoxidation of olefins.

(b) Polymer supported chromic acid – It is commercially available in the form of Amberlyst, A-26, $HCrO_4^-$ and is used to oxidise primary and secondary alcohols to carbonyl compounds and also allylic and benzylic aldehydes to aldehydes and ketones.

(iii) **Choice of Catalysts**: The catalysts facilitate reactions without being consumed or without being incorporated into the final product. They make the reactions to proceed in much short time, consume less energy and give good yields. They can be recycled. Even in those cases, where no reaction occurs usually, the reaction becomes feasible.

Advantages of Catalysts in Organic Synthesis

(a) Starting material utilization enhanced
(b) Formation of waste reduced
(c) Activation energy of the reaction is lowered, resulting in saving the energy.
(d) Focuses on selectivity
(e) Catalysts control site of reaction in the reactant

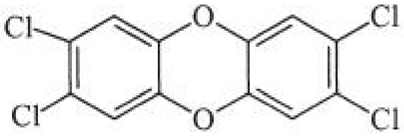
Green chemistry in day today life

Dry Cleaning of Clothes

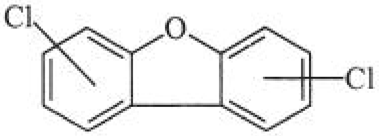
Perchloroethylene (PERC), $Cl_2C{=}CCl_2$ is commonly being used as a solvent for dry cleaning. It is now known that PERC contaminates ground water and is a suspected human carcinogen. A technology, known as Micell Technology developed by Joseph De Simons, Timothy Romack, and James McClain made use of liquid carbon dioxide and a surfactant for dry cleaning clothes, thereby replacing PERC. Dry cleaning machines have now been developed using this technique. Micell technology has also evolved a metal-cleaning system that uses carbon dioxide and a surfactant, thereby eliminating the need of halogenated solvents.

Versatile Bleaching Agent

It is common knowledge that paper is manufactured from wood (which contains about 70% polysaccharides and about 30% lignin). For good quality paper, the lignin must be completely removed. Initially, lignin is removed by placing small chipped pieces of wood into a bath of sodium hydroxide and sodium sulfide (that is how pulp is formed). By this process about 80-90% of lignin is decomposed. The remaining lignin was so far removed through reaction with chlorine gas. The use of chlorine removes all the lignin (to give good quality white paper) but causes environmental problems. Chlorine also reacts with aromatic rings of the lignin (by aromatic substitution) to produce dioxins, such as 2,3,7 ,8-tetrachloro-p-dioxin and chlorinated furans. These compounds are potential carcinogens and cause other health problems.



2,3,7,8-Tetrachloro-dibenzo-p-dioxin



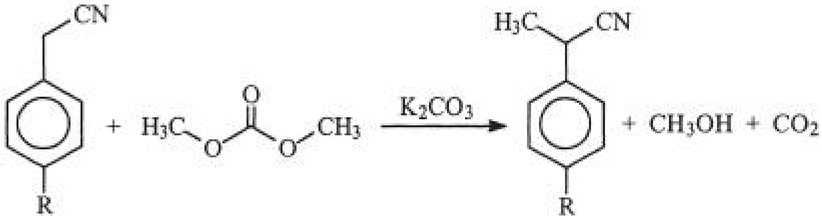
Chlorinated furans

These halogenated products find their way into the food chain and finally into products like dairy products, pork, beef and fish. In view of this, use of chlorine has been discouraged. Subsequently, chlorine dioxide was used. Other bleaching agents like hydrogen peroxide, ozone or oxygen also did not give the desired results.

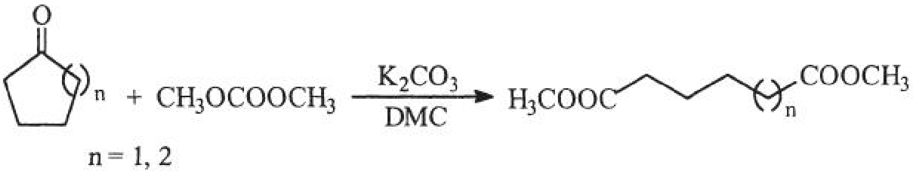
A versatile bleaching agent has been developed by Terrence Collins of Carnegie Mellon University. It involves the use of hydrogen peroxide as a bleaching agent in the presence of some activators known as TAML activators that act as catalysts which promote the conversion of H_2O_2 into hydroxyl radicals that are involved in oxidation bleaching. The catalytic activity of TAML activators allows H_2O_2 to break down more lignin in a shorter time and at much lower temperature. These bleaching agents also find use in laundry and result in lesser use of water.

Green Reagent – Dimethyl Carbonate

Conventional methylation reactions employ methyl halides or methyl sulfate. The toxicity ofthese compounds and their environmental consequences render these syntheses somewhat undesirable. Tundo developed a method to methylate active methylene compounds selectively using dimethy1carbonate (DMC) in which no inorganic salts are produced.



Dimethy1carbonate (DMC) can also act as an organic oxidant. Cyclopentanone and cyclohexanone react with DMC and a base K_2CO_3 to yield adipic and pimelic methyl (or ethyl) esters, respectively.

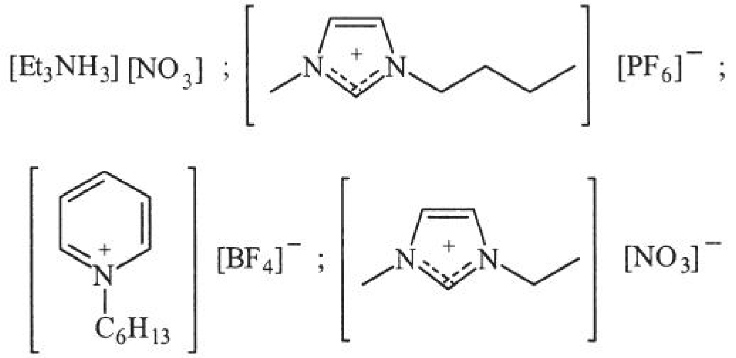


Green Solvents – Ionic Liquids

The commonly used solvents like benzene, toluene, methylene chloride etc. for organic synthesis, particularly in industrial production, are known to cause health and environmental problems. In view of this, the search for alternatives to the damaging solvent is of highest priority. This is particularly important as solvents are used.in huge amounts (in industrial production) and these are mostly volatile liquids, which are difficult to contain.

The ionic liquids, comprising entirely of ions were and mainly of interest to the electrochemists. It is possible, by careful choice of starting materials, to prepare ionic liquids that are liquid at and below room temperature. Different aspects of ionic liquids have been reviewed by a number of authors. The first ionic liquid $[EtNH_3]$ $[NO_3]$ (m.p. 12°C) was discovered in 1914.

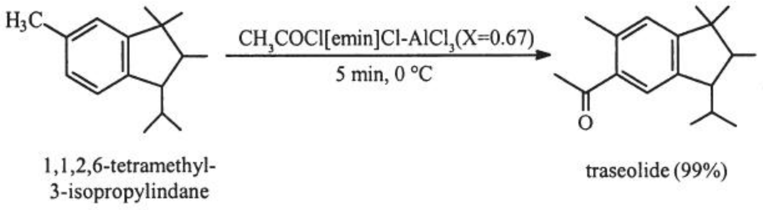
Broadly speaking, ionic liquids are of two types: simple salts (made up of a single anion and cation) and binary ionic liquids; the latter are salts where an equilibrium is involved. It is the binary ionic liquids that are used as green solvents. Some examples of simple salt are given.

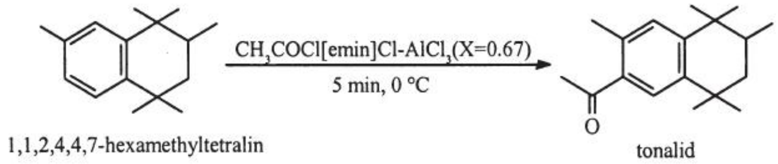


Reactions in Acidic Ionic Liquids

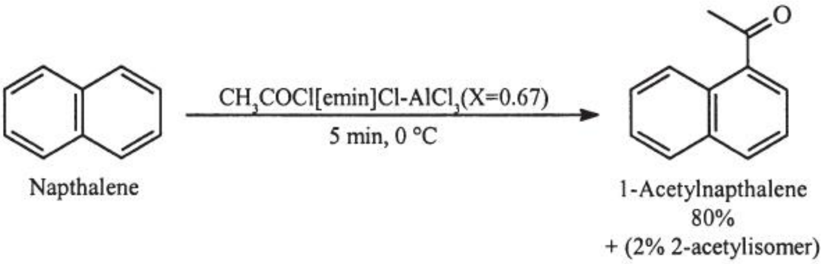
The chloroaluminate (III) ionic liquids (where X(AICI) > 0.50) behave like powerful Lewis acid and promote reactions that are usually promoted by $AlCl_3$. In fact, chloroaluminate ionic liquids are powerful solvents and can be prepared by mixing the appropriate organic halide salt with $AlCl_3$ and heating to form the ionic liquid. This synthesis should be performed in inert atmosphere.

The well known Friedel-Crafts reaction works very well with the chloroaluminate (III) ionic liquids. Thus, using this methodology, traseolide (5-acyl-1,1,2,6-tetramethyl-3-isopropylindane) and tonalid (6-acetyl- 1,1,2,4,4,7 -heaxmethyltetralin have been synthesised in high yield in the ionic liquid [emin]Cl- $AlCl_3$ (X = 0.67).

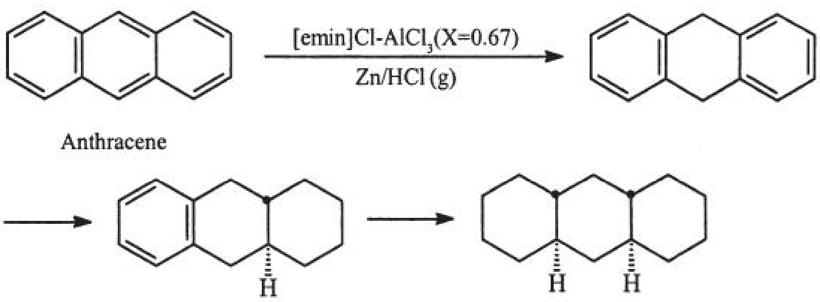




Similarly Friedel-Crafts reaction of naphthalene gives 1-acetyl derivative as the major product.



Another interesting application in the use of ionic liquids is in the hydrogenation of polycyclic aromatic hydrocarbons, which are soluble in chloroaluminate (III) ionic liquids to form highly coloured paramagnetic solutions, which on treatment with a reducing agent such as an electropositive metal and a proton source results in selective hydrogenation of the aromatic compound. Using this method, the anthracene can be reduced to perhydroanthracene at normal temperature and pressure to give the most stable isomer.



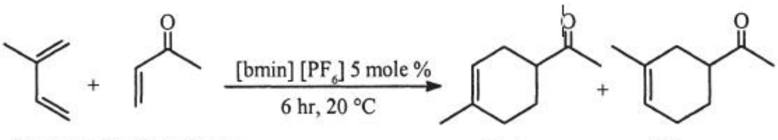
Perhydroanthracene
90% (single product)

Reactions in Neutral Ionic Liquids

As already stated, chloroaluminate (III) ionic liquids are excellent solvents in many reactions. The main problem arises due to their moisture sensitivity and difficulty in separation of products (containing heteroatoms) from the ionic liquid. In view of this, water-stable ionic liquids have been developed. One example of this is the ionic liquid [bmin][PF_6] [$(bmin)^+$ = 1-butyl-3-methylimidazolium)]. The ionic liquid [bmin][PF_6] forms triphasic mixture with water and alkanes, which makes it useful for clean synthesis. Such ionic liquids can be used without any special conditions needed to exclude moisture and the isolation of the reaction products is convenient. Some applications in the use of neutral ionic liquids are discussed here.

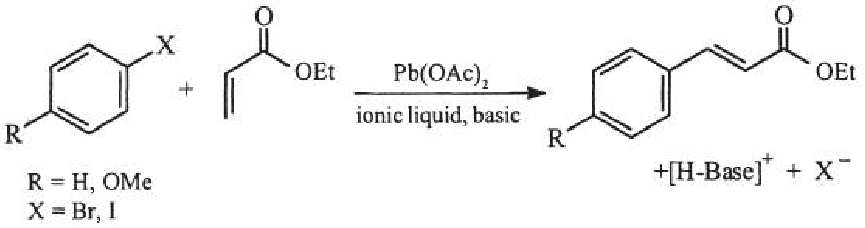
Diel's-Alder Reaction

The neutral ionic liquids are excellent solvents for the Diels-Alder reaction. and are better than the conventional solvents and even water. Addition of a mild Lewis acid like ZnI_2 increases the selectivities in this reaction. A special advantage of this system is that the ionic liquid and catalyst can be recycled and reused after extraction or direct distillation of the product from the ionic liquid. A typical Diel's-Alder reaction is given.



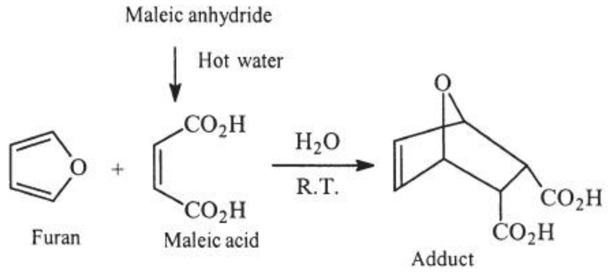
The Heck Reaction

Neutral ionic liquids are excellent solvents for the palladium catalysed coupling of alkyl halides with alkenes (Heck reaction). The special advantage of using neutral ionic liquids is that many palladium complexes are soluble in ionic liquids and that the products or product of the reaction can be extracted with water or alkane solvents. So the expensive catalyst can be recycled compared to the routine Heck reaction in which the catalyst is lost at the end of the reaction.



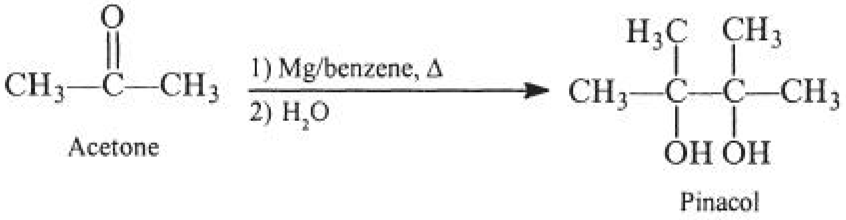
Water as a Solvent

Diel’s Alder reaction



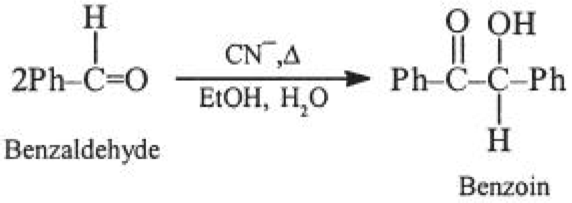
Pinacol Coupling

Ketones are known to react with Mg/benzene to give 1 ,2-diols by heating with magnesium in benzene followed by treatment with water. Thus, under these conditions acetone give pinacol.



Benzoin condensation

It consists in the treatment of aromatic aldehydes with sodium or potassium cyanide, usually in an aqueous ethanolic solution to give α-hydroxy ketones (benzoins).



Super critical Carbon dioxide

A versatile solvent, carbon dioxide is used as liquid CO_2 or supercritical CO_2 fluid (the states of CO_2 most commonly used for solvent use). A gas is normally converted to a liquid state by increasing the pressure exerted upon it. However, if the substance is placed at a temperature above its critical temperature *Tc* (31°C for CO_2) and critical pressure *Pc* (72.8 atm for CO_2), a supercritical fluid is obtained. The *Tc* of a substance is the temperature above which a distinct liquid phase of the substance cannot exist, regardless of the pressure applied. *Pc* is the pressure at which a substance can no longer exist in gaseous state. In a supercritical liquid, the individual molecules are pressed so close together (due to high pressure) that they are almost in liquid state. Supercritical liquids have density close to that of the liquid state and viscosity close to that of gaseous state.

Advantages and Drawbacks

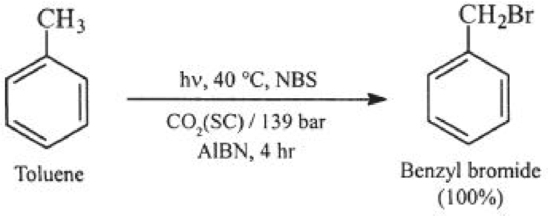
Carbon dioxide has the advantage of being non-flammable and non-toxic, which is not generally true of other common solvents. The disadvantage of this solvent is that it requires relatively high pressure compared to hydrocarbon solvents. A good quality supercritical CO_2 extraction machine, for example, will operate at 3800 psi or higher. High-pressure machinery can operate at 15000 psi or greater. A lot of engineering and expensive machinery is needed to generate and control these high pressures. The benefit is that the solvent cost is a fraction of hydrocarbon solvents and there is no need to operate in a hazardous location rated environment.

In addition to being GRAS (Generally Regarded as Safe) as well as it being so inexpensive, supercritical CO_2 has many advantages with regards to its ‘tunability’, meaning that incremental changes to temperature and/or pressure, the ‘behavior’ of the solvent can be highly selective when used for extractions and separations. One particular challenge with Supercritical CO_2 is that, due to its relatively high operating pressures, there may be some ‘unwanted’ extraction/separation results. For example, with botanical extractions, Supercritical CO_2 extracts many fats & lipids from botanical matter, which, in general, are not desirable.

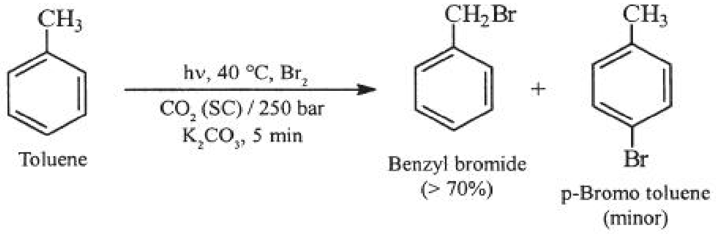
Examples of organic reactions in $scCO_2$

Free Radical Bromination

The usual free radical bromination of toluene with N-bromosuccinimide gives benzyl bromide. This bromination is carried out in a solvent, e.g., CCl_4. It has been found that free radical bromination of toluene with NBS in supercritical carbon dioxide gave 100% yield of benzyl bromide.

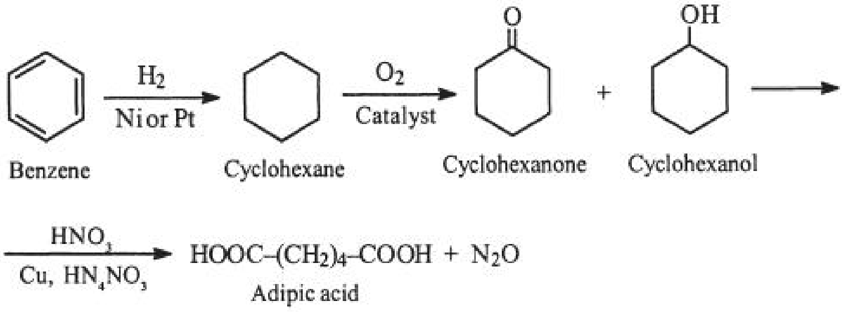


However, bromination oftoluene with bromine in supercritical CO_2 gave 70% benzyl bromide and minor amount of p-bromotoluene.



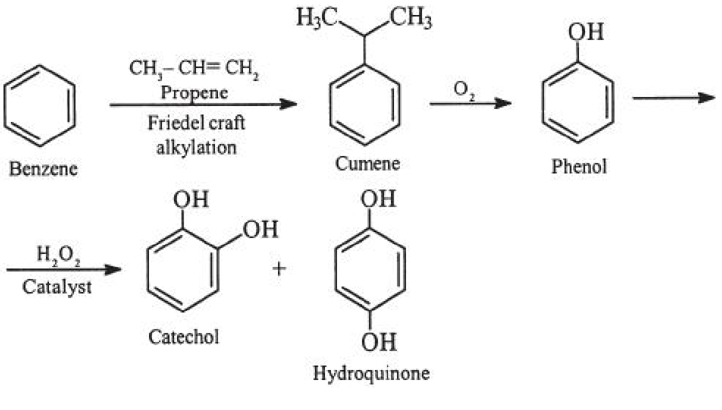
Green synthesis of Adipic Acid and Catechol

Adipic acid is required in large quantities (about 1 billion kg a year) for the synthesis of nylon, plasticizers and lubricants. Conventionally, adipic acid is made from benzene.



Conventional synthesis of Adipic acid

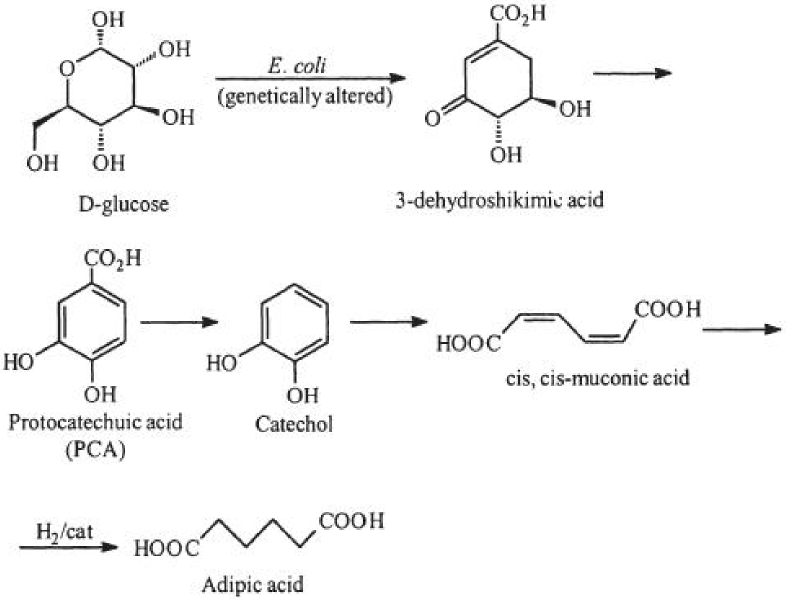
Like adipic acid, catechol is also manufactured using benzene as the starting material. The procedure is given.



Conventional synthesis of catechol

As seen, both adipic acid and catechol are obtained from benzene, which causes environmental and health problem. Also, benzene is produced from non-renewable source. In addition, in the synthesis of adipic acid, nitrous oxide is generated as a byproduct, which contributes to the greenhouse effect as well as destruction of the ozone layer.

An environmentally benign (or green) synthesis of adipic acid, catechol and BHT (a potential replacement for BHT) has been developed by John W. Frost and Karen M. Draths starting with glucose and using a biocatalyst (genetically altered *E. coli* bacteria).



Green synthesis of adipic acid and catechol

The above environmentally benign synthesis of catechol and adipic acid uses D-glucose (a non-toxic and a renuable resource) as the starting material. Also the synthesis is conducted in water instead of organic solvents. The reaction can also be used to stop at either catechol stage or at the adipic acid stage by using another genetically altered *E. coli.*

Unit – III

Green Catalysis

Environmental Pollution

The term pollution is used to describe the introduction of harmful substances into the environment as a result of domestic, agricultural or industrial activities. Substances which pollute the air include gases like oxides of carbon, sulphur and nitrogen and the hydrocarbons emitted by thermal plants, motor vehicles and chemical industries. The increase in the level of carbon dioxide produces greenhouse effect, while nitrogen and sulphur oxides come down as acid rain causing destruction of vegetation and aquatic life. Water is normally polluted by effluents from industries, pesticides and fertilizers washed down from agricultural fields and city sewage. The greatest release of hazardous waste to the environment is from industries. Toxic chemicals flowing into rivers often kill fish. People who eat the contaminated fish have been known to develop health related problems, at times even fatal. Oil spills are also a major cause of water pollution which, if happens near the shore may seriously affect coastal flora and fauna. The increasing level of noise is also another cause of pollution which effects the environment. Pollution in any form is harmful to human life, and unless checked in time may threaten our very survival.

As already stated, environmental pollution results in a variety of ways. Presently, only the environmental pollution caused by the use of solvents, reagents and products will be dealt with. The solvents that are mostly employed include volatile organic solvents (VOCs) like methylene chloride, chloroform, perchloroethylene (PERC) and carbon tetrachloride. Some VOCs like, isopropyl alcohols, xylenes, toluenes and ethylenes have been used as cleaning fluids because of their ability to dissolve oils, waxes and greases. Also, they readily evaporate from the items that they are being used to clean (VOCs readily evaporate or vaporise at room temperature). When VOCs come in contact with sun light and nitrogen oxides (by-products from the combustion of fossil fuels), these are transformed into ozone, nitric acid and partially oxidised organic compounds.

$$\text{VOCs} + \text{NO} + \text{Sunlight} \rightarrow\rightarrow\rightarrow O_3 + HNO_3 + \text{Organic compounds (Partially oxidised)}$$

This product mixture (consisting of ozone, nitric acid and partially oxidised organic compound) is formed at the ground level and is commonly called smog. Continued exposure to smog may result in aggravating asthma and may induce respiratory problems) and can also cause lung cancer.

This phenomenon leads to elevated levels of tropospheric ozone (one of the components of smog) and may cause damage to crops, discolour fabrics and harden rubber. The use of chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs) as solvents creates environmental problems. When CFCs are released into the atmosphere, these being inert, rise through the troposphere into the stratosphere (the CFCs are also released to the atmosphere from refrigeration industries), where they are photochemically decomposed by high-energy ultraviolet radiation from the sun. In fact the ozone layer present in the stratosphere prevents the harmful ultraviolet radiations from reaching the earth.

On photochemical decomposition, the CFCs result in the formation of atomic chlorine (chlorine radical), which destroys the ozone by abstracting an oxygen atom from an ozone molecule and converting it into oxygen. The ClO radical formed, can react with an oxygen atom to form an oxygen molecule and regenerate a chlorine radical.

$$CF_2Cl_2 + UV \longrightarrow CF_2Cl + Cl^{\bullet}$$

$$O_3 + Cl^{\bullet} \longrightarrow O_2 + ClO^{\bullet}$$

$$ClO^{\bullet} + O \longrightarrow Cl^{\bullet} + O_2$$

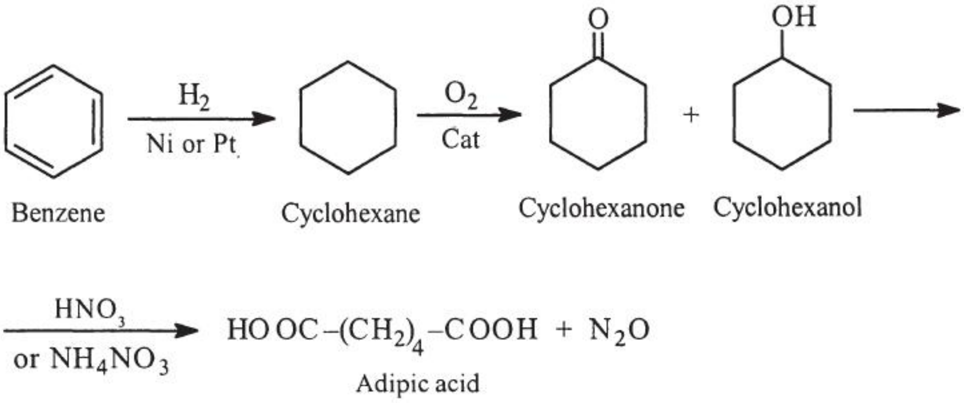
The overall reaction is the conversion of ozone into oxygen.

$$O_3 + O \longrightarrow 2O_2$$

This results in depletion of the ozone layer and so the harmful ultraviolet radiations reach the surface of the earth. These ultraviolet radiations are responsible for causing skin cancer and cataract among humans. Due to above reasons, the governments around the world have forbidden the use of CFCs. The Montreal Protocol, signed in Canada in 1987 and 1989, and subsequently in London in 1990 decided to speed up the phasing out of CFCs. It has already been stated that liquid and supercritical carbon dioxide has replaced CFCs which were also used as blowing agents for polystyrene. Subsequently in place of CFCs, aliphatic hydrocarbons (e.g., pentane) were used as blowing agents for polystyrene. Though aliphatic hydrocarbons are not ozone depleting, they can lead to the formation of ground level smog (a mixture of ozone, nitric acid and partially oxidised organic compounds) if their emissions are not captured. A harmless blowing agent viz. carbon dioxide has been developed. The advantage of CO_2 is that it does not deplete the ozone layer, does not form smog, is economical, handling is easier and is nonflammable.

However, carbon dioxide is a greenhouse gas. It is commonly known that in the atmosphere, CO_2 allows UV and visible radiations to reach the earth's surface but reflects the IR radiations (heat) coming from the earth's surface and directing it back to the earth. Thus, excess levels of CO2 in the atmosphere can significantly raise the temperature of the earth's atmosphere, which is responsible for global warming.

Nitrous oxide (NO), commonly known as laughing gas is also known to cause environment pollution. Nitrous oxide is obtained as a by-product during the manufacture of adipic acid as follows:



The production of N_2O as a by-product can cause 10% annual increase of N_2O levels. The N_2O is obtained as a by-product in a number of reactions involving oxidation with HNO_3. The N_2O formed rises into the stratosphere and plays a role in the destruction of the ozone layer. The first step in this process is the reaction of N_2O with atmospheric oxygen to produce NO·, which acts as a catalyst to deplete ozone (steps 2 and 3). Nitric oxide abstracts an oxygen atom from an ozone molecule, giving O_2 and NO; (step 2). The resulting NO_2· then reacts with an additional oxygen atom regenerating NO· and forming another molecule of O_2· The regenerated NO· (step 3) can react again (steps 2 and 3) resulting in significant loss of ozone or every molecule of N_2O.

$$N_2O + O^{\bullet} \longrightarrow 2NO^{\bullet} \qquad (1)$$

$$NO^{\bullet} + O_3 \longrightarrow NO_2^{\bullet} + O_2 \qquad (2)$$

$$NO_2^{\bullet} + O^{\bullet} \longrightarrow NO^{\bullet} + O_2 \qquad (3)$$

The overall reaction is

$$O_3 + O \rightarrow 2O_2$$

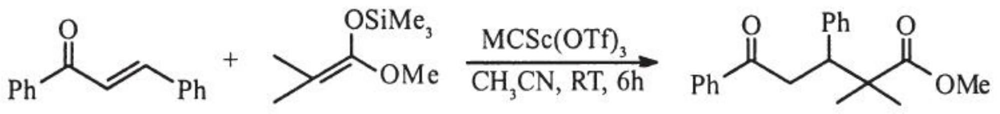
Green catalysts

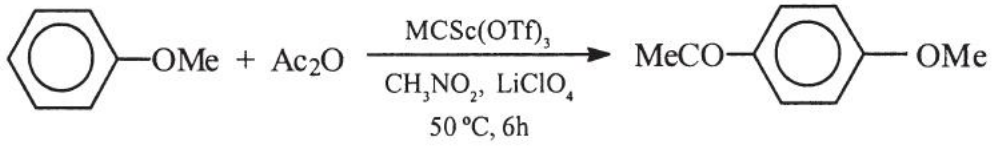
Some of the major advances in chemistry especially industrial chemistry, over the past decade have been in the area of catalysts. Through the use of catalyst, chemists have found ways of removing the need for large quantities of reagents that would otherwise have been needed to carry out the transformations and ultimately would have contributed to the waste stream.

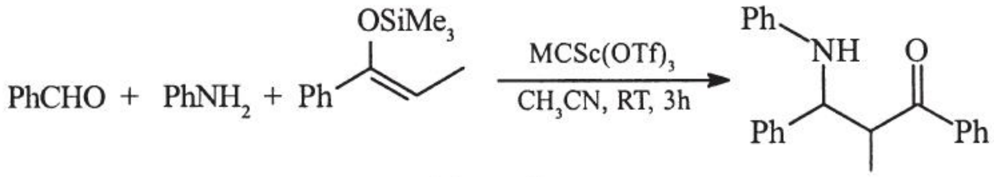
Catalysts play a major role in establishing the economic strength of the chemical industry and the clean technology revolution in the industry will provide new opportunities for catalysis and catalytic processes. Following are some different types of catalysts used.

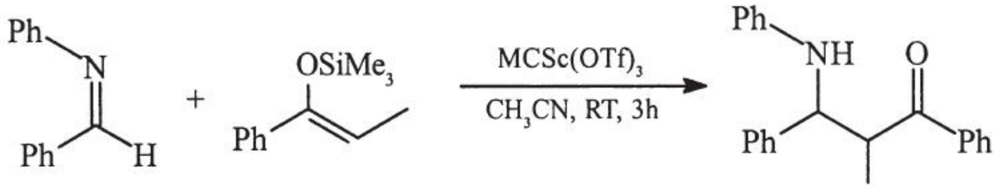
Acid catalysts

The traditional catalyst hydrogen fluoride, an extremely corrosive, hazardous and toxic chemical used in the production oflinear alkylbenzenes (LAB's), has been successfully replaced by a solid acid catalyst, viz. fluorided silica-alumina catalyst, which does not require special material of construction (of the container), involves lower operating costs and obviates the need for an acid scrubbing system and waste disposal of calcium fluoride.· Microencapsulated Lewis acids have replaced traditional corrosive monomeric Lewis acids in the reactions like Michael, Friedel Craft3, Mannich, Iminoaldol reactions.

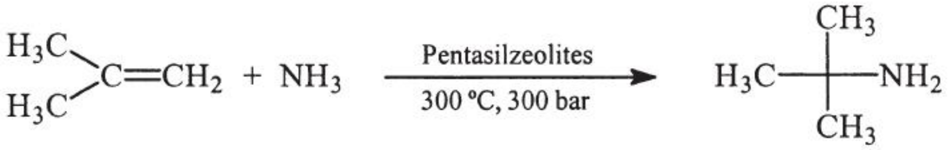


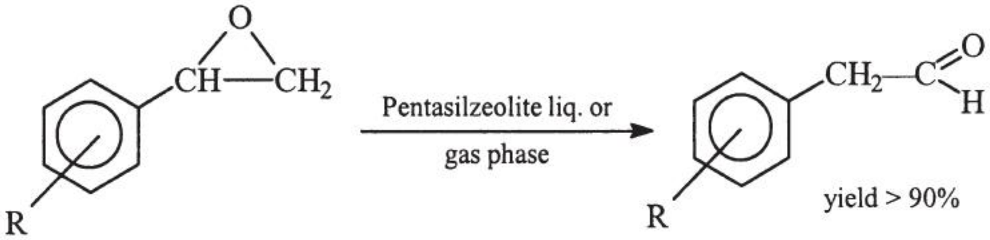






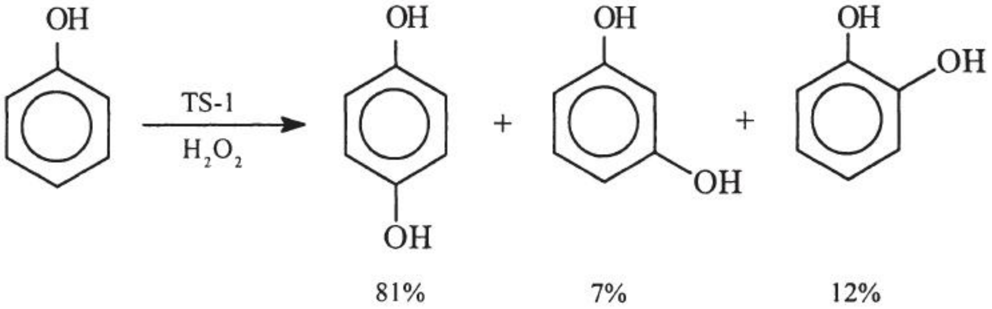
Several large-scale industrial processes utilizing heteropolyacids (HPA) catalysts exist. The two examples are hydration of the isobutylene and the polymerization of the tetrahydrofuran. Zeolites are widely used in the petrochemical industry in acid catalyzed processes and there are several reviews concerning recent developments in their use in the synthesis of fine and speciality chemicals.



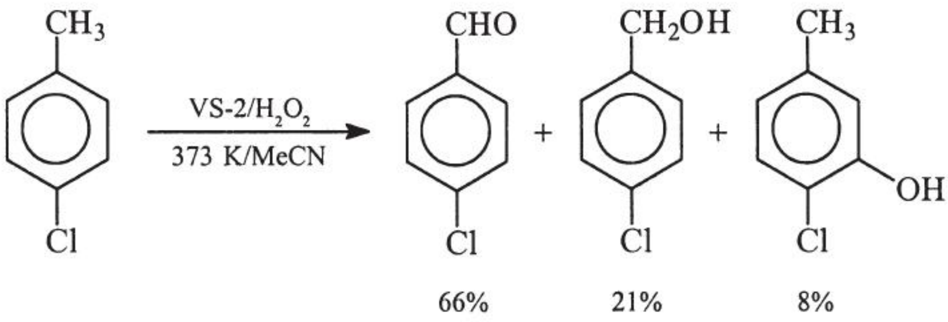


Oxidation Catalysts

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 of titanium silicates (TS-1) is the hydroxylation of phenol, giving mixtures of hydroquinone and catechol. The process is clean, giving excellent conversion to product with very little waste.

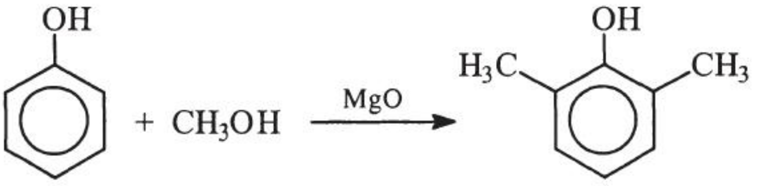


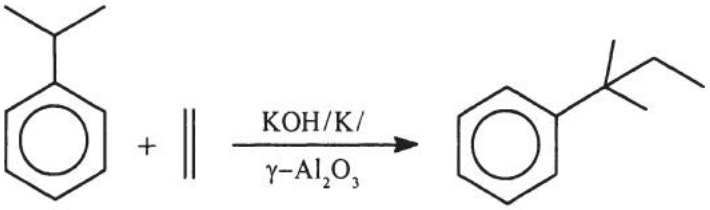
Vanadium silicate molecular sieves are capable of selectively oxidising 4-chlorotoluene to 4-chlorobenzaldehyde using hydrogen peroxide as the source of oxygen in acetonitrile solvent.

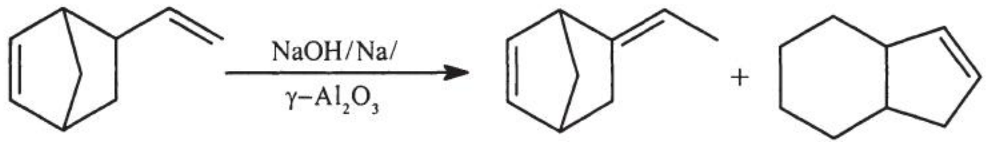


Basic Catalysts

In contrast to the areas of heterogeneous oxidation catalysis and solid acid catalysis, the use of solid base catalysis in liquid phase reactions has not met the same level of breakthrough. The industrial applications of basic catalysts are in the alkylation of phenol, side chain alkylation and isomerisation reactions.





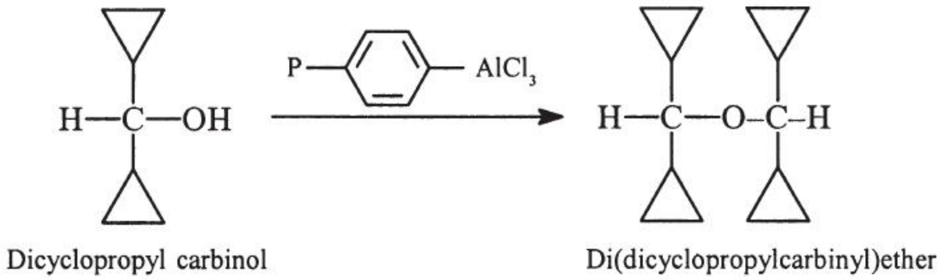


Polymer Supported Catalysts

The conventional catalyst which is normally used in the homogenous phase, is linked to a polymer backbone and is used in this form to catalyse different reactions. Following are some of the polymer supported catalysts and their applications.

Polystyrene-aluminium Chloride

It is used to prepare ethers from alcohols. Thus, dicyclopropyl carbinol on treatment with polystyrene-$AlCl_3$ produces die dicyclo-propylcarbinyl) ether in high yield.



Polystyrene-$AlCl_3$ is a useful catalyst for synthetic reactions, which require both a dehydrating agent and a Lewis acid. Thus, acetals are obtained in good yield by the reaction of aldehyde, alcohol and polymeric $AlCl_3$ in an organic inert solvent.

Polystyrene- $AlCl_3$ is also an effective catalyst for hydrolysis of acetals, e.g., heating the diethyl acetal of o-chlorobenzaldehyde with polymeric- $AlCl_3$ in benzene-methanol-water (2:6:1) for 17.5 hr gave o-chlorobenzaldehyde in 60% yield. Without the use of catalyst, the yield of aldehyde is only 4%.

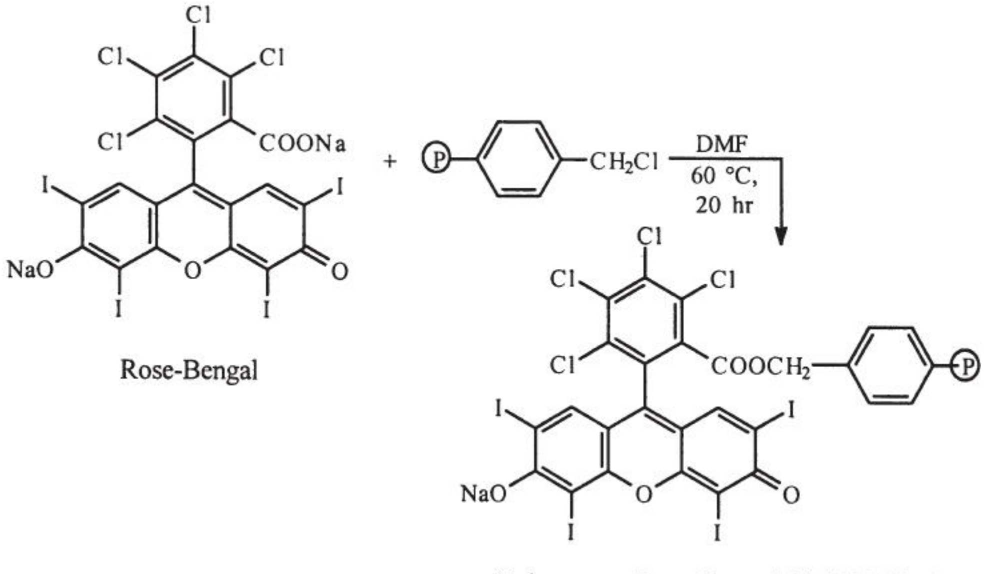
Polymeric Super Acid Catalysts

A polymeric super acid catalyst is obtained by binding aluminium chloride to sulfonated polystyrene. This polymeric super acid catalyst is used for the cracking and isomerisation of alkanes (e.g. n-hexane) at 357°C at atmospheric pressure. Normally the above cracking and isomerisation is carried out in the presence of Lewis acid at high temperature and high pressure.

Polymer Supported Photosensitizers

The photosensitizers supply molecular oxygen in a photochemical reaction. Examples of usual photo sensitizers are Rose-Bengal, eosin-y, fluorescein. The photo sensitizers are bound to Merifield type resin via ester bond.

A polymer-bound rose-bengal photosensitizer is commercially available. The efficiency of SENSITOX is about 65% of that of Rose-Bengal, but the high yields of the products and the ease of isolation more than compensate the slightly longer reaction periods.



Rose-Bengal

Polystyrene Rose-Bengal (SENSI TOX)

Unit – IV

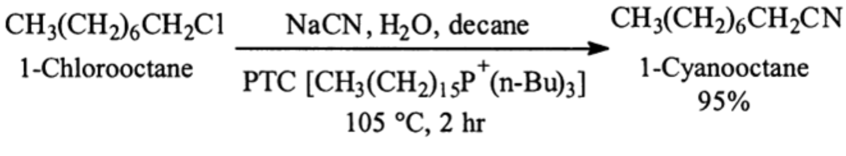
Phase-Transfer Catalysis in Green Synthesis

Introduction

Most of the pharmaceuticals or agricultural chemicals (insecticides, herbicides, plant growth regulators) are the result of organic synthesis. Most of the syntheses require a number of steps in which additional reagents, solvents and catalysts are used. In addition to the syntheses of the desired products, some waste material (by-products) is generated, the disposal of which causes problems and also environmental pollution. In view of this, attempts have been made to use procedures that minimise these problems. One of the most general and efficient methodologies that takes care of the above problems is to use a phase-transfer catalyst (PTC).

Difficulties are often encountered in organic synthesis if the organic compound is soluble in organic solvent and the reagent in water. In such cases, the two reactants will react very slowly and the reaction proceeds only at the interface where these two solutions are in contact. The rate of the reaction can, of course, be slightly increased by stirring the reaction mixture and by using aprotic polar solvents, which solvate the cations so that the anions are free. Such solvents (like dimethylsulfoxide, dimethylfonnamide) are expensive and their removal is difficult. Also the use of strong bases (which are necessary for the reactions like Wittig etc.) create other problems and many side reactions take place. These problems can be overcome by using a catalyst, which is soluble in water as well as in the organic solvent. Such catalysts are known as phase-transfer catalysts (PTC).

The PTC reaction, in fact, is a methodology for accelerating the reaction between water insoluble organic compounds and water soluble reactants (reagent). The basic function of PTC is to transfer the anion (from the reagent) from the aqueous phase to the organic phase. As a typical example, the reaction of I-chlorooctane with NaCN in water does not give I-cyanooctane even if the reaction mixture is stirred for several days. However, if a small quantity of an appropriate PTC is added the product is formed in about 2 hr giving 95% yield (Scheme 1).



Scheme 1

The mechanism of the PTC reaction is well known and is described in relevant literature.

Phase transfer catalysts used are the quaternary 'onium' salts, such as ammonium, phosphonium, antimonium and tertiary sulphonium salts. In practice, however, only a limited number of ammonium and phosphonium salts are widely used. Some of the PTCs normally used are:

(i) Aliquat 336: methyl trioctyl ammonium chloride, N^+CH_3 (C_8H173) Cl(ii) Benzyl trimethyl ammonium chloride or bromide (T MBA),

$N^+(CH_3)_3CH_2C_6H_5X^-$(X = Cl or Br)

(iii) Benzyl triethyl ammonium chloride or bromide (TEBA), $N^+(C_2H_5)_3$ $CH_2C_6H_5X^-$ (X = Cl or Br)

(iv) Tetra-n-butyl ammonium chloride, bromide, chlorate or hydroxide,

$\text{-Bu})_4X^-$(X = Cl, Br, 0104, OH)

(v) Cetyl trimethyl ammonium chloride or bromide (CTMAB for bromide),

$N+ (CH_3)_3 (CH_2)_{15}CH_3X^-$ (X = Cl or Br)

(vi) Benzyl tributyl ammonium chloride, $C_6H_5CH_2$ $(n\text{-}C_4H_9)_3$ N^+ Cl(vii) Benzyl triphenyl phosphonium iodide,$C_6H_5CH_2(C_6H_5)_3P^+I^-$

Besides the above, another catalyst, crown ether is also widely used as PTC.

It is now well known that PTC reactions have considerable advantage over the conventional procedures. PTC reactions:

(i) Are fast and do not require vigorous conditions.
(ii) Do not require expensive aprotic solvents.
(iii) The reaction usually occurs at low temperature.
(iv) The reaction is conducted in water and hence does not require anhydrous conditions.
(v) With the help of PTC the anion is made available in the organic solvent and so the nucleophilicity increases.
(vi) The work-up procedure is simple.

(vii) Use of strong bases (like alkoxide, sodamide, sodium hydride) in the reactions is avoided. The reaction proceeds even with OH- as it becomes strong nucleophile in presence of PTC.

(viii) Except the reactions which are sensitive to water, all other reactions can be carried out by PTC.

(ix) The reactions which do not proceed in the normal way can be made to proceed in good yields.

Phase-Transfer Catalysis in Green Synthesis

A number of phase transfer catalysts are commercially available. However, these can be conveniently synthesised. Some of the advantages of phase-transfer catalysts which are relevant to green synthesis are as follows:

(i) As the reaction is in two phases, a benign solvent may be used since PTC devoids the solubility for all the reactants like dipolar aprotic solvent and dimethylcarbonate. Moreover, in some cases organic solvents may not be required at all, the substrate forming the second phase.

(ii) The procedures of separation are simple resulting in less waste as the organic layer is mainly free from water soluble compounds and can easily be decanted off. It is important to vigil the concentration of anion in organic phase as it should not exceed the concentration of catalyst (unless it is soluble in absence of a catalyst).

(iii) PTC catalysed reactions are very rapid as the anions in the organic phase have very few water molecules associated with them making them highly reactive because of less activation energy which causes higher productivity.

(iv) These reactions can be run at a lower temperature owing to reduced activation energy that causes greater selectivity and lesser by-product formation.

Applications of PTC in Organic Synthesis

PTC can be used in numerous types of organic reactions due to its advantages over conventional procedures. Some of the applications are as follows.

Nitriles from Alkyl or Acyl Halides

Reaction
$CH_3(CH_2)_6CH_2Cl \xrightarrow[\text{PTC; } C_{16}H_{33}P^+(n\text{-}C_4H_9)_3Br^-\text{; 2 hr, 105 °C}]{NaCN/H_2O} \underset{\text{94\% (purity 97\%)}}{CH_3(CH_2)_6CH_2CN}$
$C_6H_5CH_2CH_2Cl \xrightarrow[\text{PTC; } N^+(CH_3)_3CH_2C_6H_5Cl^-\text{; 3 hr, 90-95 °C}]{NaCN/H_2O} \underset{\text{91\%}}{C_6H_5CH_2CH_2CN}$
$C_6H_5COCl \xrightarrow[\text{PTC } Bu_4N^+X^-]{NaCN/H_2O} \underset{\text{60-70\%}}{C_6H_5COCN}$

Alkyl Fluorides from Alkyl Halides

The reaction of alkyl halides (chlorides or bromides) with KF in presence of a PTC give alkyl fluorides. Scheme 2 gives the preparation of I-fluorooctane.

$$\underset{\text{1-Chlorooctane}}{CH_3(CH_2)_6CH_2Cl} + KF \xrightarrow[C_{16}H_{33}P^+(C_4H_9)_3Br^-]{PTC} \underset{\text{1-Fluorooctane 77\%}}{CH_3(CH_2)_6CH_2F}$$

Scheme 2

The above procedure is far superior to the conventional methods and can also be used for the preparation of labelled alkyl halides having ^{36}01 by reacting the alkyl halide with labelled Na^{36}Cl. Scheme 3 illustrates [10] the synthesis of 1 -chlorooctane ^{36}Cl.

$$\underset{\text{1-Chlorooctane}}{CH_3(CH_2)_6CH_2Cl} + Na^{36}Cl \xrightarrow[C_{16}H_{33}P^+(C_4H_9)_3Br^-]{PTC} \underset{\text{1-Chlorooctane}^{36}\text{Cl}}{CH_3(CH_2)_6CH_2{}^{36}Cl}$$

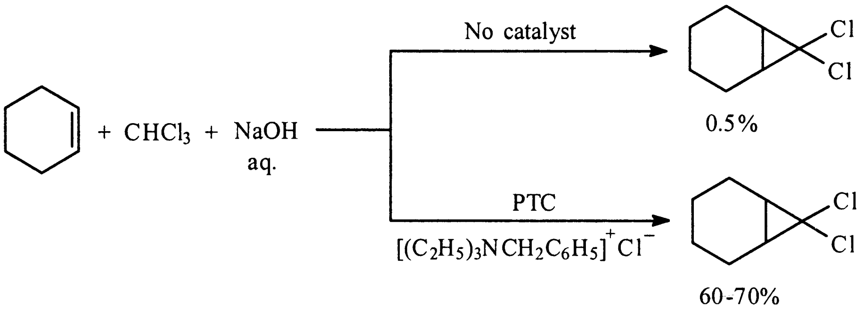
Scheme 3

Generation of Dihalocarbenes

Dihalocarbenes, synthetically useful intermediates, are normally generated by the action of a base on chloroform.

$$CHCl_3 + \text{Base} \longrightarrow CCl_3^- \xrightarrow{-Cl^-} \underset{\text{Dichlorocarbene}}{:CCl_2}$$

(a) The in situ generated carbene can add on to across the double bonds to give adducts. The use of PTC gives the adduct in 60-70% yield [il] (Scheme 4).



Scheme 4

Phase-Transfer Catalysis in Green Synthesis

(b)This method is used for making diazomethane (Scheme 5). The generated dichlorocarbene in situ is made to react with hydrazine to give diazomethane.

$$NH_2NH_2 + CHCl_3 + NaOH \xrightarrow[\text{ether or } CH_2Cl_2]{\text{PTC } (C_4H_9)N^+OH^-} \underset{\text{Diazomethane (35\%)}}{CH_2N_2 \text{ in ether or } CH_2Cl_2}$$

Scheme 5

However, use of crown ether gives better yield (48%).

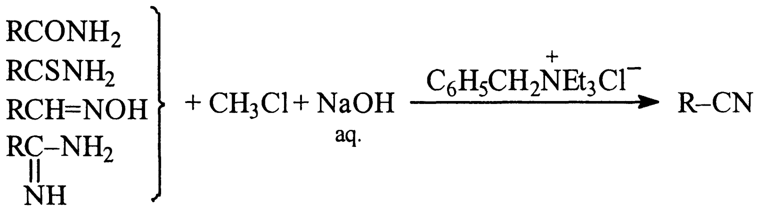
(C)The dichlorocarbene generated by the PTC method reacts with primary amines to yield isonitriles (Scheme-6).

$$RNH_2 + CHCl_3 + \underset{\text{aq.}}{NaOH} \xrightarrow{C_6H_5CH_2N^+Et_3Cl^-} \underset{\substack{\text{Isonitrile} \\ \text{40-60\%}}}{R{-}N{\equiv}C}$$

Scheme 6

This is a convenient method compared to the two step process.

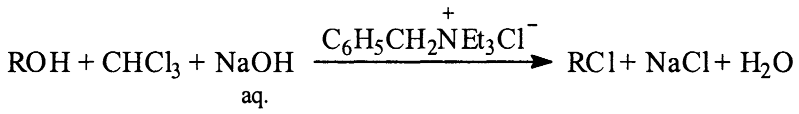
(d) The dichlorocarbene generated by PTC techniques reacts with amides, thioamides, aldoximes and amidines to give the corresponding nitriles (Scheme 7).



$$\left.\begin{matrix} RCONH_2 \\ RCSNH_2 \\ RCH{=}NOH \\ \underset{\substack{\| \\ NH}}{RC}{-}NH_2 \end{matrix}\right\} + CH_3Cl + \underset{\text{aq.}}{NaOH} \xrightarrow{C_6H_5CH_2\overset{+}{N}Et_3Cl^-} R{-}CN$$

Scheme 7

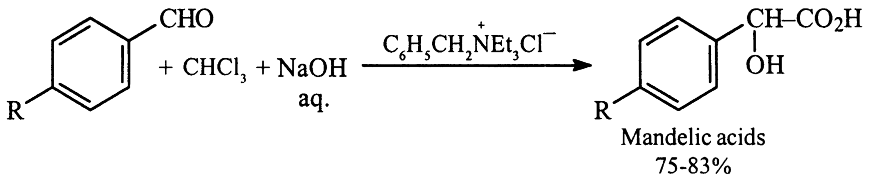
(e)Alcohols on reaction with dichlorocarbene generated in a PTC catalysed system gave good yield of chlorides (Scheme 8). In case of steroidal alcohols, the OH is replaced with Cl with retention of configuration.



$$ROH + CHCl_3 + \underset{\text{aq.}}{NaOH} \xrightarrow{C_6H_5CH_2\overset{+}{N}Et_3Cl^-} RCl + NaCl + H_2O$$

Scheme 8

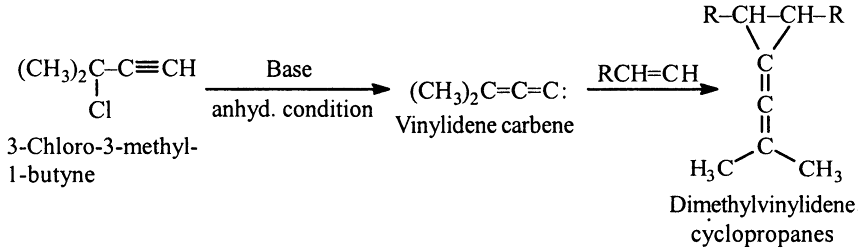
(f)Reaction with aromatic aldehydes. Dichlorocarbene generated by PTC method reacts with aromatic aldehydes to give mandelic acids (Scheme 9).



Scheme 9

Generation of Vinylidene Carbenes

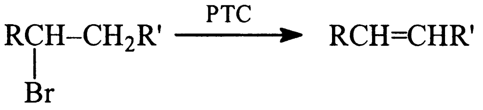
These can be generated from 3-chloro-3-methyl-1-butyne with base under vigorously anhydrous conditions. These add on to olefins in situ to give dimethyl vinylidinecyclopropanes (Scheme 10). Use of PTC technique with aqueous NaOH gives better yields and is more convenient.



Scheme 10

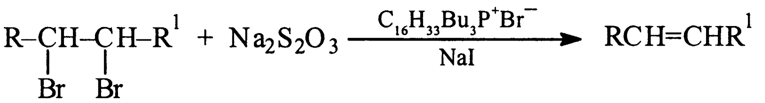
Elimination Reactions

(a) Dehydrohalogenation can be achieved by the reaction of alkyl halides with aq. NaOH in presence of PTC.



$$R\underset{\substack{|\\ Br}}{C}H{-}CH_2R' \xrightarrow{PTC} RCH{=}CHR'$$

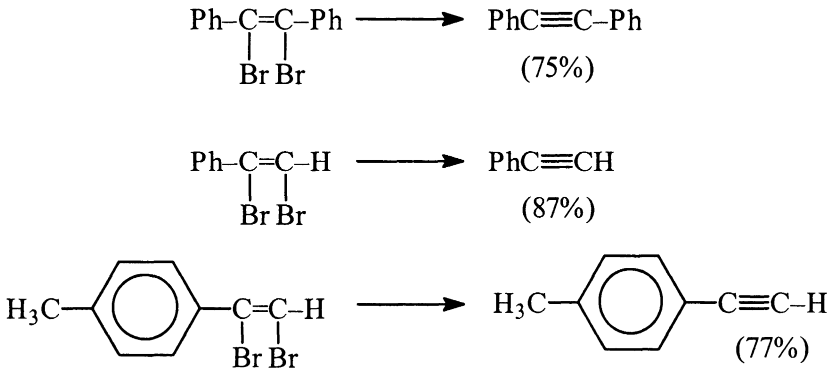
(b) The vic-dibromoalkanes can be neatly debrominated by the PTC process using sodium thiosulphate with a catalytic amount of sodium iodide (Scheme 11).



$$R{-}\underset{\substack{|\\ Br}}{C}H{-}\underset{\substack{|\\ Br}}{C}H{-}R^1 + Na_2S_2O_3 \xrightarrow[NaI]{C_{16}H_{33}Bu_3P^+Br^-} RCH{=}CHR^1$$

Scheme 11

Using this procedure the following compounds (Scheme 12) are obtained.

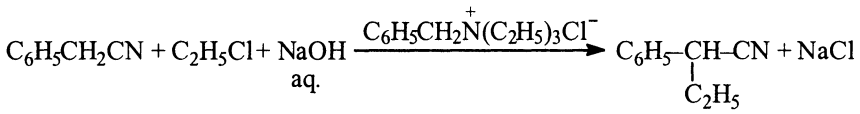


Scheme 12

C-Alkylations

C-Alkylations of Activated Nitrites

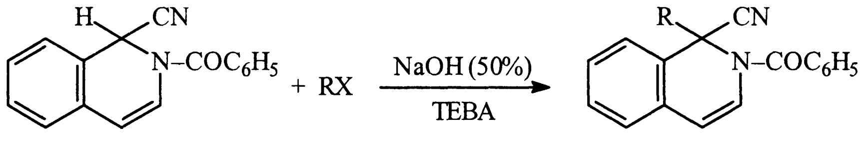
Normally C-alkylation involves the use of expensive condensing agents like sodamide, metal hydrides, potassium tertiary butoxide etc. and involves the use of anhydrous organic solvents. Due to the high selectivity of PTC, it is used for synthesis of mono alkyl derivatives of nitriles (Scheme 13).



$$C_6H_5CH_2CN + C_2H_5Cl + \underset{aq.}{NaOH} \xrightarrow{C_6H_5CH_2\overset{+}{N}(C_2H_5)_3Cl^-} C_6H_5-\underset{C_2H_5}{\underset{|}{CH}}-CN + NaCl$$

Scheme 13

The C-alkyl derivatives of activated nitriles are useful intermediates for the manufacture of various pharmaceuticals and are commonly used in industry. Similarly, N -benzoyl-l ,2-dihydroisoquinaldenitrile can be alkylated (Scheme 14) in presence of NaOH (aq.) and TEBA

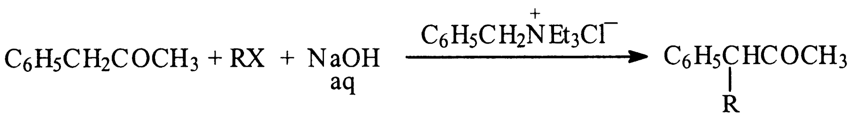


Scheme 14

Alkaline hydrolysis of the alkylated product gives isoquinoline derivatives which are starting materials for the synthesis of alkaloids.

C-Alkylation of Activated Ketones

Activated ketones (having an aromatic substituent at the a-CH2 group) can be activated using PTC system (Scheme 15).

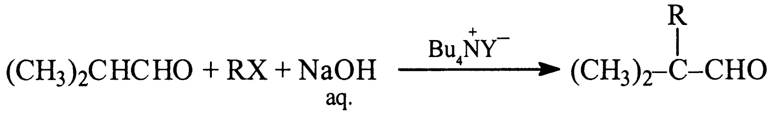


$$C_6H_5CH_2COCH_3 + RX + \underset{aq}{NaOH} \xrightarrow{C_6H_5CH_2\overset{+}{N}Et_3Cl^-} C_6H_5\underset{\substack{| \\ R}}{C}HCOCH_3$$

Scheme 15

C-Alkylation of Aldehydes

Aldehydes containing only an a-hydrogen atom, e.g. isobutyraldehyde, can be alkylated with alkyl halides in presence of 50% aq. NaOH and catalytic amount of tetrabutyl ammonium ions (Scheme 16).



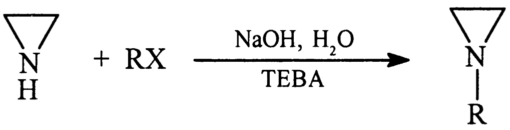
$$(CH_3)_2CHCHO + RX + \underset{aq.}{NaOH} \xrightarrow{Bu_4\overset{+}{N}Y^-} (CH_3)_2\text{–}\overset{\substack{R \\ |}}{C}\text{–}CHO$$

Scheme 16

N-Alkylations

N-Alkylation of Aziridines

Aziridines cannot be easily N-alkylated using conventional conditions due to rapid ring opening. However alkylation of aziridine can be achieved using PTC conditions (Scheme 17).

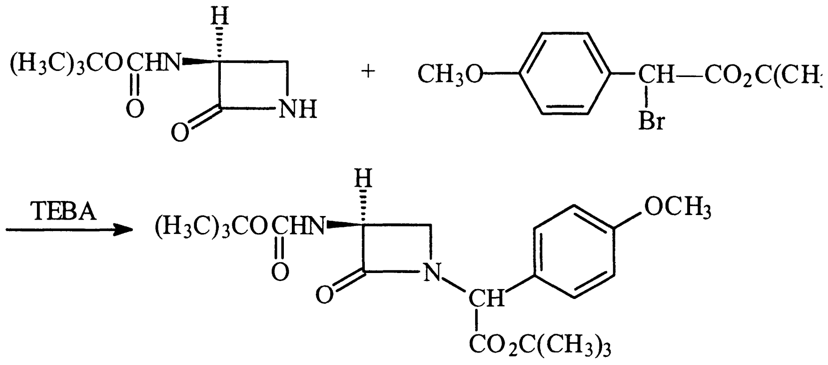


Scheme 17

In a similar way, N-alkylation ofpyrrole under PTC conditions gives the N-alkylated product as the major compound.28 However, under normal conditions C-alkylations also occur at positions 2 and 3.

N-Alkylation of J3 *-Lactams*

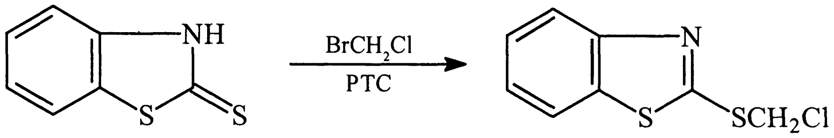
N-Alkylation of p-lactams has been carried out using PTC (Scheme 18). This is an important step in the synthesis of norcardicin.



Scheme 18

S-Alkylation

The reaction of benzothiazole-2-thione with chlorobromomethane and PTC conditions gave the corresponding 2-chloromethylthio-products (Scheme 19).

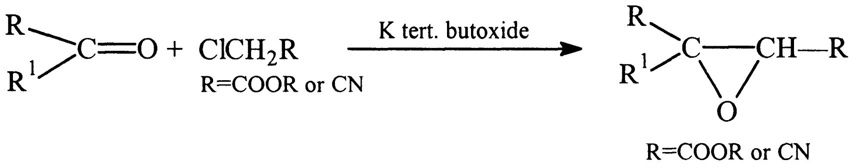


Scheme 19

S-Alkylation of 2-pyridinethiones, 2-quinolinethiones and pyrimidine derivatives has also been carried out.

Darzen's Reaction

The usual Darzen's reaction consists of the reaction of aldehydes or ketones with a-haloester or a-halonitriles in presence of a base like potassium tertiarybutoxide to give glycidic esters or nitriles, respectively (Scheme 20).



Scheme 20

This reaction has been found to occur in alkali solution in presence of PTC (benzyl triethylammonium chloride).

Williamson's Ether Synthesis

The PTC technique provides a simple method for conducting Williamson ether synthesis. Use of excess alcohol or alkyl halide, lower temperature and larger alcohol (e.g. CSH1PH) give higher yields of ethers (Scheme 21).

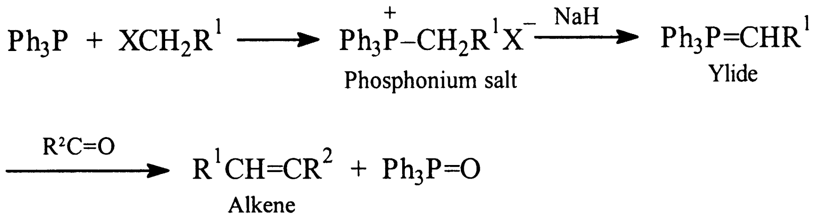
$$C_8H_{17}OH + C_4H_9Cl \xrightarrow[NaOH]{(Bu)_4N^+SO_4^-} C_8H_{17}OC_4H_9 + \underset{\text{Byproduct}}{C_8H_{17}OC_8H_{17}}$$

Scheme 21

Attempts to prepare ethers from alcohols by reacting with dimethyl sulphate in aq. NaOH or even by the use of alkali metal alkoxide have been unsuccessful. However, use of PTC (e.g. tetrabutyl ammonium salts) gives high yield of ethers.

Wittig Reaction

The usual Wittig reaction consists in the treatment of a phosphonium salt with a base (e.g. NaH) to give an ylide, which can react with aldehydes or ketones to give alkenes (Scheme 22).



$$Ph_3P + XCH_2R^1 \longrightarrow \underset{\text{Phosphonium salt}}{Ph_3\overset{+}{P}\text{–}CH_2R^1\overset{-}{X}} \xrightarrow{NaH} \underset{\text{Ylide}}{Ph_3P{=}CHR^1}$$

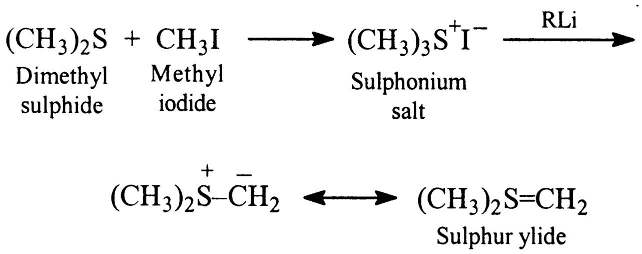
$$\xrightarrow{R^2C=O} \underset{\text{Alkene}}{R^1CH{=}CR^2} + Ph_3P{=}O$$

Scheme 22

It has been found that the formation of ylide from phosphonium salt (Scheme 22) can be very conveniently effected by using a PTC in aq. NaOH. In PTC method the yield of the olefin increases. However, this PTC method is applicable only to aldehydes; no olefin is obtained from ketones. Even with this limitation, this method is very convenient for the preparation of a number of olefins of the type RCH=CHRI.

Sulphur Ylides

The sulphur ylides are generally prepared by the treatment of a sulphonium salt with a base like alkyl lithium (Scheme 23).



$$\underset{\substack{\text{Dimethyl}\\\text{sulphide}}}{(CH_3)_2S} + \underset{\substack{\text{Methyl}\\\text{iodide}}}{CH_3I} \longrightarrow \underset{\substack{\text{Sulphonium}\\\text{salt}}}{(CH_3)_3\overset{+}{S}\overset{-}{I}} \xrightarrow{RLi}$$

$$(CH_3)_2\overset{+}{S}\text{–}\overset{-}{C}H_2 \longleftrightarrow \underset{\text{Sulphur ylide}}{(CH_3)_2S{=}CH_2}$$

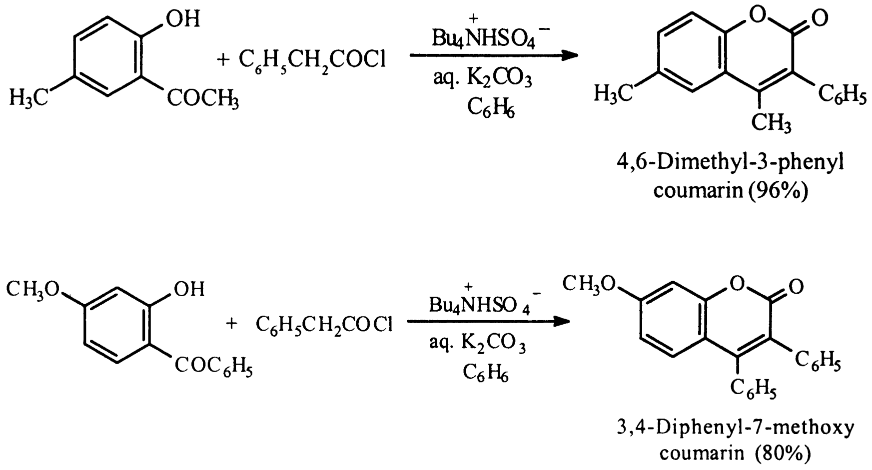
Scheme 23

It has now been found that in place of strong base (like alkyl lithium), a PTC like $(C_6H_s)_4N^+I^-$ in presence of aq. NaOH can be used.

Heterocyclic Compounds

3-Alkyl Coumarins

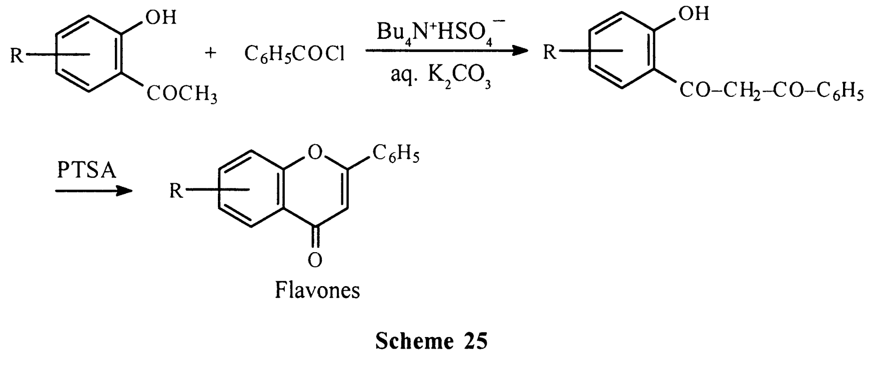
3-Alkyl Coumarins are increasingly being used as optical brightners and were obtained in low yields using anhydrous conditions. These have now been obtained (Scheme 24) in excellent yield and purity by the use of PTC in presence of aq. K2C03 by the reaction of o-hydroxycarbonyl compounds with phenyl acetyl chlorides.



Scheme 24

Flavones

Flavones are an important class of natural products. These were synthesised in low yields by a number of methods.39 These have now been obtained in excellent yields by the reaction of an appropriate o-hydroxyacetophenone with an appropriately substituted benzoyl chloride in benzene solution with a PTC in presence of NaOH or Na2C03 followed by cyclisation of the formed o-hydroxydibenzoyl methane with p-toluene sulphonic acid (Scheme 25).

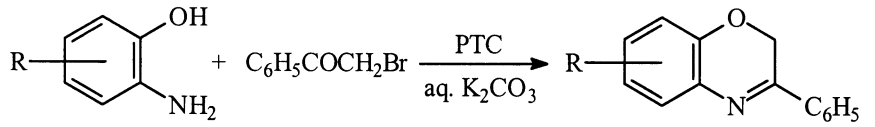


Scheme 25

3-Aryl-2H-1,4-Benzoxazines

The title compounds known for their anti-inflammatory activity were prepared earlier in low yields.41 Polymer supported phase transfer catalysts have also been used (for details see sec

7.4.5) for various reactions. These have now been prepared42 by the condensation of2-aminophenols with phenacyl bromide in presence of a PTC in aq. K2C03 (Scheme 26).

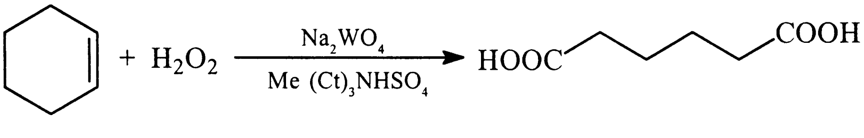


Scheme 26

In addition to the above, a number of other heterocyclic compounds, for example, 2-aroylbenzofurans, 1,3-benzoxathioles, dihydropyrans, 1,4-benzoxazines, hydantoin derivatives, piperazine-2,5-diones, thioethenes, l-arylbenzimidazoles, benzofuran-l-oxides, piperazinones, thiazoles, 5-thiacyclohexanecarboxaldehyde, pyrroles, triazines, fused napthoquinone derivatives and ~-lactams have been synthesised using PTC technique.

Oxidation Using Hydrogen Peroxide Under PTC Condition

Hydrogen peroxide is an excellent environmentally benign oxidant that produces water as the only by-product. It is used in relatively dilute form (30 volume). Hydrogen peroxide could be used in place of higher waste generating peroxides such as peracetic acid or tertiary butyl hydrogen peroxide. There are two possible mechanisms for transferring peroxide to the organic phase. First transporting the H02- ion. This anion is strongly hydrophilic and has a high hydration energy that does not exchange readily with other anions. It shows that the classical mechanism is followed. The second mechanistic approach seems to involve extraction via complexes of the type R+X--HP2' Hydrophobic quaternary salts such as $(C_6H_{13})_4$ NBr are most widely used. In some cases hydrogen peroxide is not involved in direct oxidation, the main oxidant in these cases are metal complexes of W or Mo. In this case the role of hydrogen peroxide is to reoxidize the metal complexes *in situ* that make the process a catalytic one with respect to metal. The major environmental benefit for the usage of hydrogen peroxide is exemplified in alkene cleavage. Thus, cyclohexene on treating with 30% hydrogen peroxide in presence of catalytic amount of sodium tungstate and methyltricetylammonium hydrogen sulphate at 90°C gives adipic acid in excellent yield. The commercial viability of this route holds obviously high potential (Scheme 27).



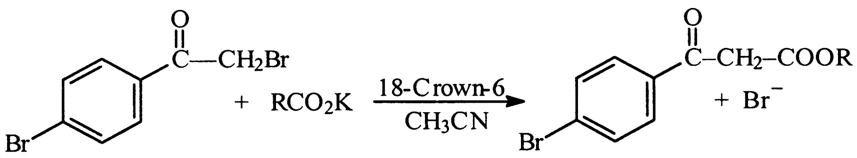
Scheme 27. Noyori synthesis of adipic acid

Crown Ethers

This is a group of cyclic polyethers which are used as phase transfer catalysts. These have been used for esterifications, saponifications, anhydride formation, oxidations, aromatic substitution reactions, elimination reactions, displacement reactions, generation of carbenes, alkylations etc. Some of the examples are as follows:

Esterification

Crown ethers are useful for esterification. Reaction of p-bromophenacyl bromide with potassium salt of a carboxylic acid using 18-crown-6 as the solubilizing agent have been used to prepare4S p-bromophenacyl esters (Scheme 28).

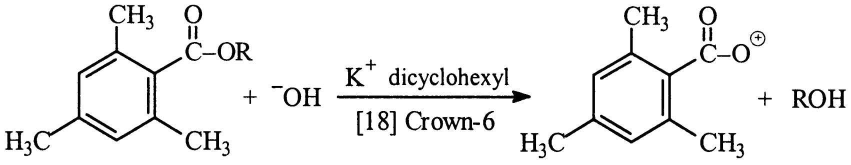


R = H, CH_3, CH_3CH_2, $CH_3CH_2CH_2$, C_6H_5, 2-$CH_3C_6H_4$, 2,4,6-trimethylbenzoyl, 4-t-butyl C_6H_4

Scheme 28

Saponification

The main problem of using potassium hydroxide for saponification is its insolubility in organic solvents like toluene, but this can be solved by using hydrophobic and hydrocarbon soluble macrocyclic derivatives like dicyclohexyl 18-crown-6, it has been shown that potassium hydroxide is soluble in toluene. This special observation46 has been used for the hydrolysis of sterically hindered esters using potassium hydroxide complex in toluene (Scheme 29).

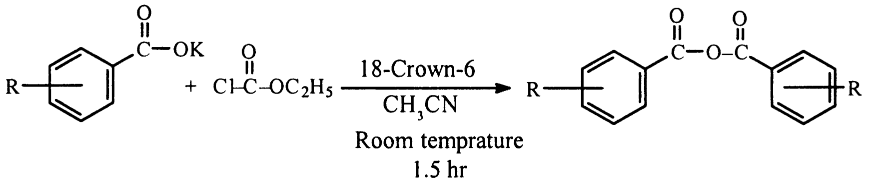


R = CH_3, t-Bu, neopentyl

Scheme 29

Anhydride Formation

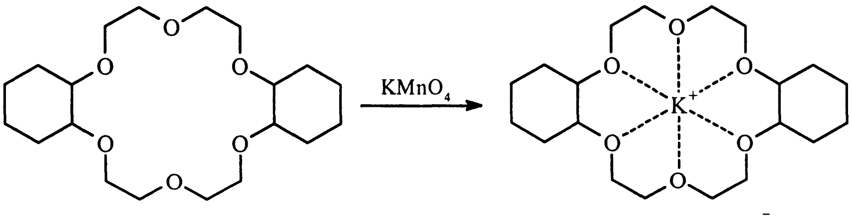
A convenient synthesis of anhydrides has been described47 by the reaction of potassium or sodium salts of carboxylic acids with activating halides (ethyl chloroformate, cyanuric chloride and benzyl chloroformate) in acetonitrile in the presence of 18-crown-6. Using this procedure, cinnamic acid, p-nitrobenzoic acid, benzoic acid, acetic acid and propionic acid are also converted into their anhydrides (Scheme 30).



Scheme 30

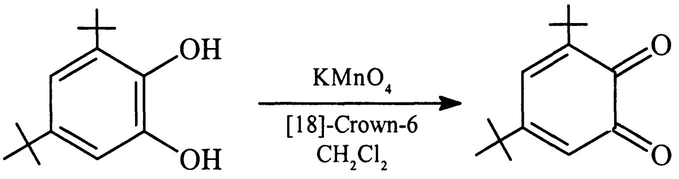
Potassium Permanganate Oxidation

Potassium permanganate is the most widely used reagent for the oxidation of organic compounds. It is usually used in aqueous solution and this restricts its usefulness since many compounds are not sufficiently soluble in water and only a few organic solvents like acetic acid, t-butanol, dry acetone and pyridine are resistant to the oxidising action of the reagent. Alternatively, oxidation in presence of crown ether, dicyclohexano-18-crown-6 forms a permanganate complex. Under these conditions permanganate becomes soluble in benzene and the resulting solutions are excellent reagents for oxidation of a variety of organic substrate in organic solvents (Scheme 31).



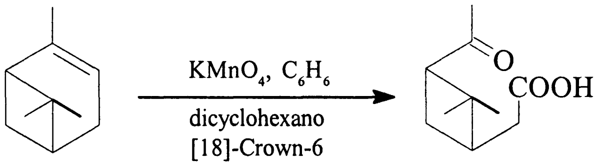
Scheme 31

Applying this technique, substituted catechols are converted into corresponding o-quinones in excellent yields wherein only one equivalent of KMn04 is used (Scheme 32).



Scheme 32

Oxidation of a.-pinene in the presence of crown ethers yield pinonic acid in 90% yield (Scheme 33).



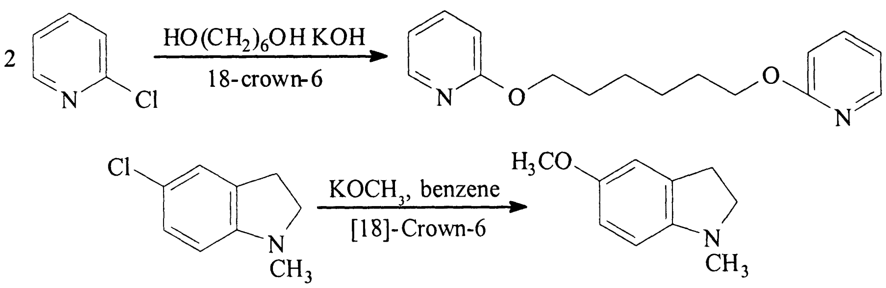
α-Pinene

Pinonic acid

Scheme 33

Aromatic Substitution Reaction

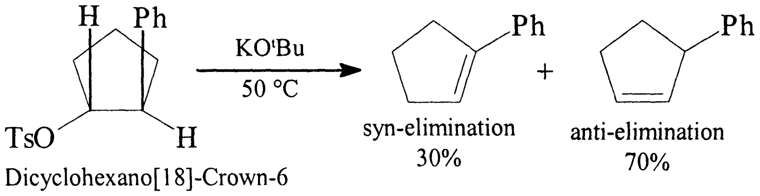
The substitution of 2-chloropyridine by 1,6-dihydroxyhexane in good yield was carried out using 18-crown-6 as a catalyst. Furthermore, the electron rich ring undergoes methoxide substitution in excellent yield using the same catalyst (Scheme 34)



Scheme 34

Elimination Reaction

Crown ethers ability to enhance or alter the reaction is significantly important. This is depicted in (Scheme 35).

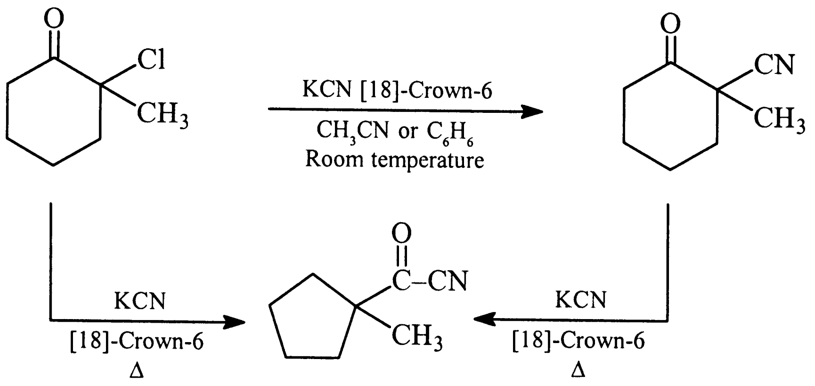


Scheme 35

In the absence of crown ether syn-elimination takes place in 91 % yield along with 9% of anti-elimination.

Displacement Reaction

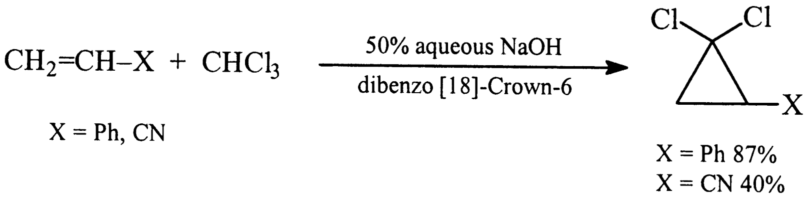
Crown ether has been used for nucleophilic displacement of chloride by cyanide at hindered position. At room temperature the reaction of 2-chloro-2-methyl cyclohexanone with potassium cyanide in acetonitrile in presence of 18-crown- 6 affords the cyanide in excellent yield, but when the reaction is conducted at reflux temperature Favorskii rearrangement occurs to yield five membered compound in high yield (Scheme 36).



Scheme 36

Generation of Carbene

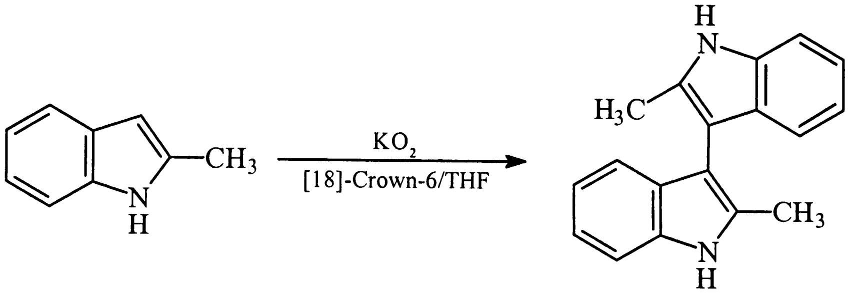
Dicyclohexyl-18-crown-6 has been used50 to convert cyclohexene and trans stilbene to the respective gem dihalocyclopropanes in 30-70% yields by the reaction of sodium hydroxide and chloroform at 40°C. Dibenzo 1S-crown-6 has also been used as liquid-liquid phase transfer catalyst for carbene generation (Scheme 37).



Scheme 37

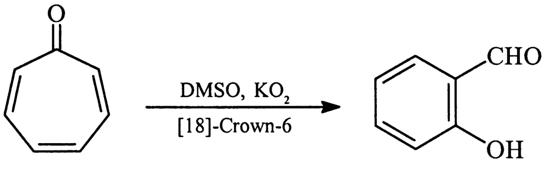
Superoxide Anion Reaction

The most important application of crown ether is in superoxide chemistry. In fact the use of super oxide (K_2O and NaO_2) has been limited due to the solubility problem. Use of crown ether along with a superoxide for the oxidative dimerisation is a typical application. A cheap potassium superoxide (KO_2) is available from commercial source and is a source for the generation of superoxide radical anion readily available for the reaction (Scheme-38).



Scheme 38

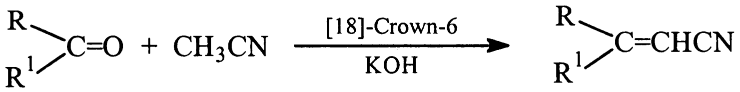
When tropone is treated with KO_2 and 18-crown-6 in DMSO solution salicylaldehyde is obtained. This is an addition induced rearrangement (Scheme 39).



Scheme 39

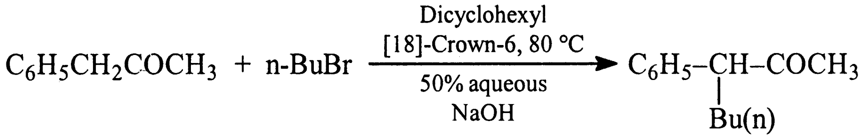
Alkylation

Many aldehydes and ketones condense with acetonitrile in the presence of solid potassium hydroxide using 18-crown-6 as a catalyst (Scheme *40).*



Scheme 40

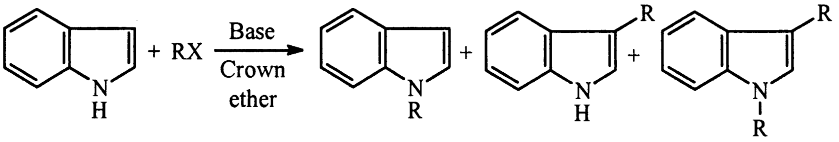
Similarly, phenyl acetone can be aikyiatedS3 with n-butyl bromide in aqueous sodium hydroxide using dicyclohexyl-18-crown-6 as a catalyst (Scheme 41).



$$C_6H_5CH_2COCH_3 + n\text{-}BuBr \xrightarrow[\text{50\% aqueous NaOH}]{\text{Dicyclohexyl [18]-Crown-6, 80 °C}} C_6H_5\text{-}\underset{\displaystyle \text{Bu(n)}}{\underset{|}{CH}}\text{-}COCH_3$$

Scheme 41

N-alkylation of pyrrole is carried out using crown ether. The indolyl anion behaves as an ambidient nucleophile and alkylation occurs at nitrogen and at C-3 (Scheme 42).



Scheme 42

Unit - V

Microwave Assisted Synthesis - A Green Chemistry Approach

Organic synthesis on a large scale involves the use of basic chemical ingredients from the petrochemical sector and catalysts; and after the end of the reaction, separation, purification, storage, packaging, distribution etc. Conventional methods of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/reagents. During these processes there are many problems of health and safety for workers in addition to the environmental problems caused by their use and disposition as waste. Green Chemistry would like to increases the efficiency of synthetic methods, to use less toxic solvents, reduce the stages of the synthetic routes and minimize waste as far as practically possible.

Microwave synthesis gives the chemists more time to expand their creativity, test new theories and develop new processes. Instead of spending hours or even days synthesizing a single compound, chemists can now perform the same reaction in minutes. The problem associated with waste disposal of solvents has been overcome by performing reactions without a solvent under microwave irradiation. Coupling of microwave irradiation with the use of mineral-supported catalysed reactions, under solvent-free conditions, provides clean chemical processes with the advantage of enhanced reaction rates, higher yields, greater selectivity, and greater ease of manipulation. Thus microwave synthesis acts as a potential tool for green chemistry.

Microwave irradiation provides an alternative to the conventional methods, for heating or introducing energy into the system. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Microwave radiations are electromagnetic waves. In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radio waves. Microwaves have wavelength of 1 mm to 1 m corresponding to frequencies between 0.3 and 300 GHz. Telecommunication and microwave radar equipment occupy many of the band frequencies in this region. Microwave dielectric heating; uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions. This technology opens up new opportunities to the synthetic chemist in the form of new reactions that are not possible using conventional heating.

1) Speed: Microwave reactions can be completed in minutes. Some chemical reactions complete in seconds. In many cases, it reduces the reaction time from hours to minutes to seconds.

2) Economy: Microwave reactions utilize no or low volume of solvents.

3) Cost effective: Microwave reactions reduce the cost per microwave reactions mainly through increasing the reaction rate there by yields.

4) Simplicity: The products of microwave reactions can be isolated very easily and requires no purification (recrystallization) in most cases.

5) Consistency: Microwave reactions are reproducible.

6) Rapid optimization: Microwave reactions complete very fast. Hence, the organic reaction optimization can be achieved faster than the conventional synthesis.

7) Energy efficient reaction: Microwave reactions offer enhanced reaction conditions.

8) Higher yield: The rapid-efficient reaction inhibits the byproducts formation and hence offers higher yields of the products.

9) High purity: The rapid-efficient reaction inhibits the byproducts formation and hence offers highly pure compounds.

10) Superheating: It takes the reaction environment to very high temperature (super heating). It is very essential for the several reactions such as substitution and coupling reactions.

11) Versatility: The microwave heating can be utilized for all kinds of organic reactions. It includes substitution, coupling, rearrangement, oxidation and reduction, etc.

Microwave Heating

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

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

Theory of Microwave heating:

- The rotational states of the molecules undergo excitation with electromagnetic radiation. The microwave irradiation, when absorbed by organic molecules induces the rotational changes. The frequency of molecular rotation is similar to the frequency of microwave radiation. The molecule continually attempts to realign itself with the applied electric field and absorbs the energy. This effect is utilized in microwave ovens to heat food materials. Chemists also utilize the microwave irradiation as an energy source for chemical reactions.
- Microwave oven contains microwave generator called as magnetron (inside the string metal box). It receives electricity and converts them into high-energy radio waves.
- Microwave guide (channel) introduces microwave heat energy (radiation) into the heat compartment.
- The microwaves bounce back and forth off the reflective metal walls of the heat compartment.
- The microwaves penetrate the material to be heated (reaction vessel) and vibrate them to cause molecular friction. The rate of vibration decides the heating and initiates the reaction.

Principle

Microwave ovens more efficiently channel heat energy into the molecules. In the microwave heating process energy transfer occurs by three mechanisms namely dipole rotation, ionic conduction and interfacial polarization. Microwave ovens inject the energy directly into the molecules, rather than warming the outside walls of a reaction vessel to spread heat by convection and conduction. High frequency electromagnetic radiations (electric fields) exert a force on charged particles of molecules and that causes molecular friction to generate super heat. Ionic conduction: Ionic conduction is the electrophoretic migration of ions, when an electromagnetic field is applied. The oscillating electromagnetic field generates an oscillation of electrons in a conduction and results electric current.

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

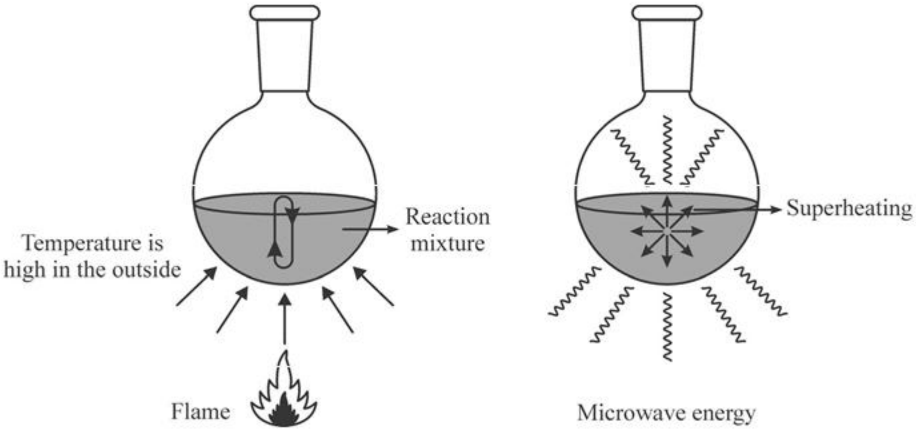
- *Dipole rotation*: It means rearrangement of dipoles with the applied field. Polar molecules are the ideal material for dipolar polarization. Dipole polarization depends on the dipole moment of a molecule. The difference in the electronegativity of the atoms and molecular symmetry is responsible for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

How Microwave Radiations are Irradiated?

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

Superheating: Superheating of liquids is common under microwave irradiation because of molecular friction. In super heating, a liquid attains a temperature much above its conventional reflux boiling point. This super heating, which is not commonly seen in conventional heating may help in increasing the rate of reaction. Microwave irradiation provides super heating. Super heating in closed vessels and under pressure facilitates the organic reactions. Super heating offers highly accelerated reaction rate and enables chemical synthesis in much lesser time with good yields. Super heating of liquids or solutions under microwave irradiation raises the temperature above the conventional boiling point. It reduces several hour conventional reactions into fewer minutes microwave reactions. Water, for example reaches 105 °C (5 °C above actual boiling point) and acetonitrile reaches 120 °C (38 °C higher than normal boiling point).

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



Microwave Instrument Components

1) Magnetron: Microwave oven magnetron converts the shortest microwaves (12 cm; 4.7 inches), which carry higher energy into electromagnetic radiations. A magnetron is a microwave source (thermionic diode) consist an anode and a cathode. Cathode releases electrons upon direct heating. The anode consists even numbered small cavities (tuned circuit). The gap across the end of each cavity behaves as a capacitance. The electrons released from cathode are attracted towards the anode. It causes bending of the path of electrons, when they travel from cathode to anode. These deflected electrons pass through the cavity gaps and induces a small charge in the tuned circuit. This is responsible for oscillation of the cavity and microwave generation.

2) Wave-guide feed: A wave-guide feed is a rectangular channel made from a metal sheet. The reflective walls of wave-guide feed allows the transmission of microwaves from the magnetron to the oven cavity.

3) Oven cavity: It refers to the place in an oven for placing the material to be heated. It is usually made of glass or fiber material of metal with reflective surfaces. Reflective surfaces increase the oven efficiency and to prevent the hazardous leakage. A wire mesh door of the cavities also prevents the microwave leakage. The ovens are equipped with fans to remove hot air and vapors and prevents oven from getting heated upto higher temperatures.

Microwave Solvents

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

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

Table 1 Microwave solvents along with their dielectric constant values

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

Microwave Reaction Vessels

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

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

A sealed reaction vessel (Teflon or Pyrex glass) covered with vermiculite absorb the reaction content in the event of explosion. Open vessel reactions: Borosil beaker, conical flask and Erlenmeyer flask are useful. Glass wares covered with funnel and a watch glass avoids excessive solvent evaporation (incase of domestic microwave ovens). A flask fitted with condenser is available in microwave synthesisers.

Microwave-Assisted Chemical Reactions

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

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

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

Applications

1) Microwave irradiation is very much useful in the following chemical reactions.

- Protection and deprotection reactions: Functional group protection and deprotection strategies are important in carbohydrate chemistry and peptide synthesis. Microwave chemistry is more useful in these reactions.
- Named organic reactions: Gabriel synthesis, Suzuki reaction, Williamson- ether synthesis and Pinacol-Pinacolone rearrangement.
- Oxidation, esterification, O-alkylation and aromatic electrophilic substitution reactions.
- Preparation of medicinal compounds such as sildenafil, phenytoin, benzocaine are attempted successfully.
- Drug intermediates, namely, 1,4-dihydropyridines, chalcones, carvones. Thioflavanoids and γ-carbolines also are synthesised.
- Novel cepahalosporins are synthesised using microwaves.
- Asymmetric reactions were also successfully attempted.

2) In analytical chemistry

Ashing: The ash content determination such as loss on ignition (LOI) and residue on ignition (ROI) is an important quality control procedure. Microwave ashing provides reduced time, cost and reduced exposure to fumes.

Digestion: Microwave digestion assists in dissolving the metals in minutes during elemental analysis. Microwave digestion can oxidize compounds more effectively than conventional methods.

Moisture analysis: The microwave-assisted moisture analysis overcomes the limitations of Karl-Fischer (destructive). Microwave analyzers works on higher dielectric constant (attentuate energy transfer) and offers non-destructive moisture measurement.

3) In natural product extraction and isolation: Extraction and isolation of active principles from plant materials is very critical. The conventional methods requires longer extraction procedures and higher solvent volume. Longer extraction and high volume of solvents pose the thermal degradation issues.

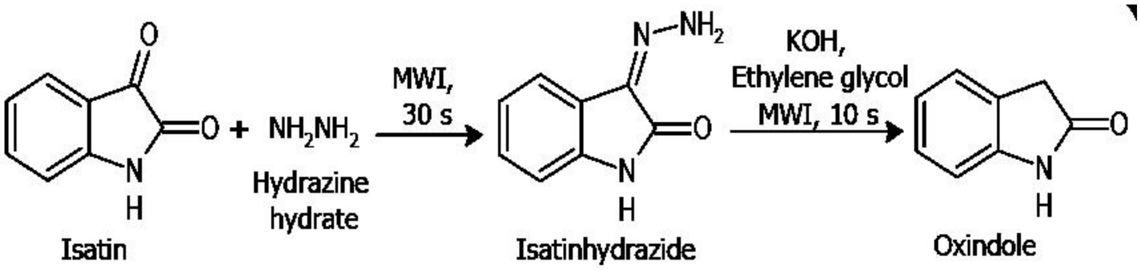
Microwave-assisted extraction (MAE) is useful in the extraction of plant tissues using relatively less volume of solvent with higher extraction power. Thus it helps in overcoming the issues of conventional methods.

4) In food industry: Microwave heating is successfully applied in the food processing such as pasteurization and preservation. Microwave pasteurization is an efficient technique for milk and fruit juice. Microwave blanching is an another important application for the food industry. for freezing, canning and drying processes.

Some important Microwave assisted reactions

1) Microwave-assisted Wolf-Kishner reduction

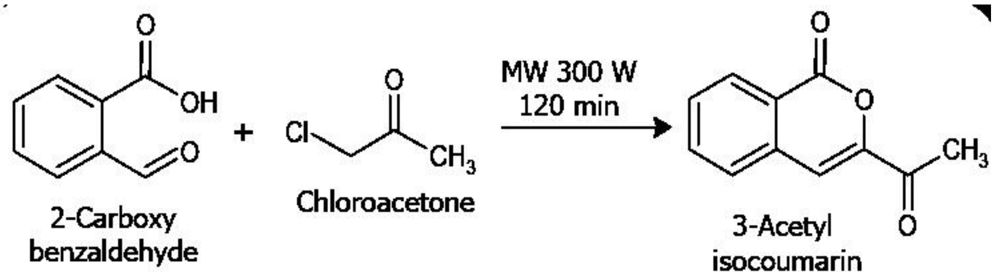
Wolf-Kishner reduction converts a carbonyl compounds (aldehyde or ketone) into an alkane using hydrazine hydrate and potassium hydroxide. The conventional reaction requires elevated temperatures and prolonged heating. Parquet and Lin (1997) reported the microwave assisted conversion of isatin into oxindole.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



Ref: *J Chem Edu, 1997, 74(10), 1225*

Microwave-assisted intermolecular Aldol condensation

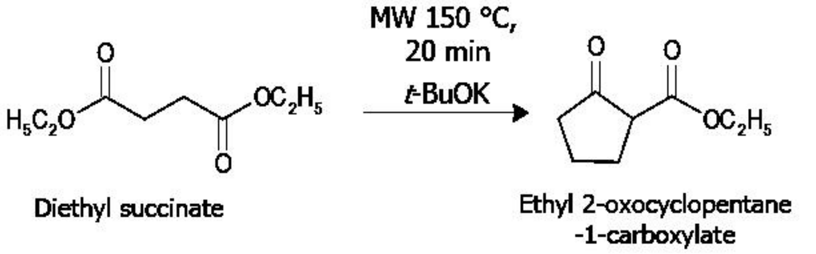
Aldol condensation involves the condensation of enolate ion with a carbonyl compound in the presence of catalyst (acid/base) to generate β-hydroxy aldehyde (or β - hydroxy ketone). The dehydration of the β-hydroxy product forms conjugated enone. Molecules with dicarbonyl functionalities (e.g. 2-carboxybenzaldehyde)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



Ref: *Arabian J Chem, 2018, 11,538-545*

Microwave-assisted Dieckmann condensation

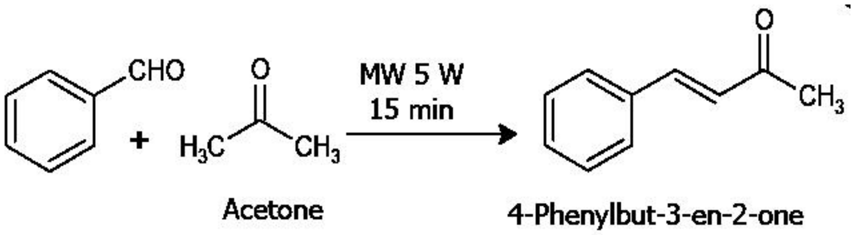
Dieckmann condensation involves the intramolecular condensation of diesters containing carbon length of 6 and 7 in the presence of strong base to generate cyclic ȕ-keto ester. Horta (2011) reported the synthesis ethyl 2-cyclopentane-carboxylate through Dieckmann condensation. The self condensation of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



Ref: *J. Chem. Educ. 2011, 88, 7, 1014–1015*

Microwave-assisted Claisen-Schmidt reaction

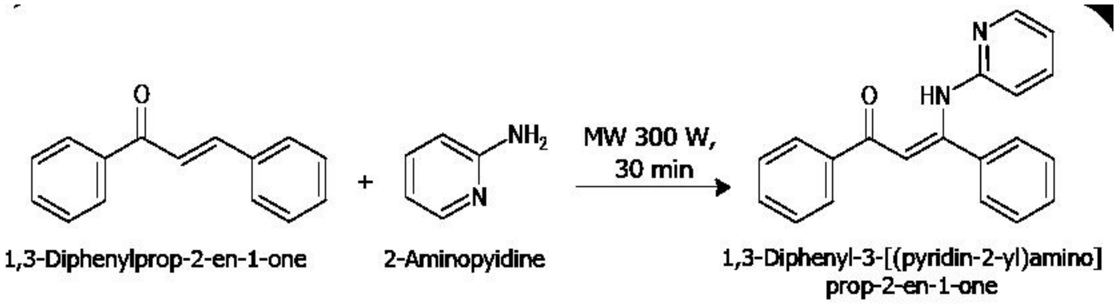
The condensation of aromatic carbonyl compound (lacking Į-hydrogen) with carbonyl compound (aldehyde or ketone) having Į-hydrogen in the presence of base is known as Claisen-Schmidt reaction. This reaction generates Į, ȕ-unsaturated aldehyde or Į, ȕ-unsaturated ketone. Rayar et al (2015) reported the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



Ref: *SpringerPlus, 2015, 4, 221-225*

Microwave-assisted Michael reaction

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



Ref: *Res Chem Intermed, 2015, 41, 5809-5819*

Sonochemistry – Ultrasound assisted Green synthesis

The word 'ultrasound' has become common knowledge due to the widespread use of ultrasound scanning equipments in medical applications. Ultrasound refers to sound waves having frequencies higher than those to which the human ear can respond (μ, > 16 KHz) (Hz = Hertz = cycles per second). High frequency ultrasound waves are used in medical equipments. The ultrasound frequencies of intrest for chemical reactions (about 20-100 KHz) are much lower than those used for medical applications, but the power used is higher. The ultrasound is generated with the help of an instrument having an ultrasonic transducer, a

device by which electrical or mechanical energy can be converted into sound energy. The most commonly used are the electromechanical transducers which convert energy into sound - they are mostly made of quartz and are commonly based on the piezoelectric effect. When equal and opposite electrical charges are applied to opposite faces of a crystal of quartz, expansion or contraction occurs. Application of rapidly reversing charges sets up a vibration that emits ultrasonic waves called the *piezoelectric effect.* In modern ultrasonic equipments, the piezoelectric transducers are made from ceramic impregnated barium titanate. Such devices
convert over 95% of the electrical energy into ultrasound. In practice, the devices only have an optimum operating frequency.

When a sound wave, propagated by a series of compression and refraction cycles, pass through a liquid medium, it causes the molecules to oscillate around their mean position. During the compression cycle, the average distance between the molecules is reduced and during refraction, the average distance between the molecules is increased. In the refraction cycle, under appropriate conditions, the attractive forces of the molecules of the liquid may be overcome, causing formation of bubbles. In case the internal forces are great enough to ensure collapse of these bubbles, very high local temperature (around 5000°C) and pressure (over 1000 bar) may be created. It is this very high temperature' and pressure that initiate chemical reactions.

The term 'sonochemistry' is used to describe the effect of ultrasound waves on chemical reactivity. A number of reviews on the chemical applications of ultrasound have been published.

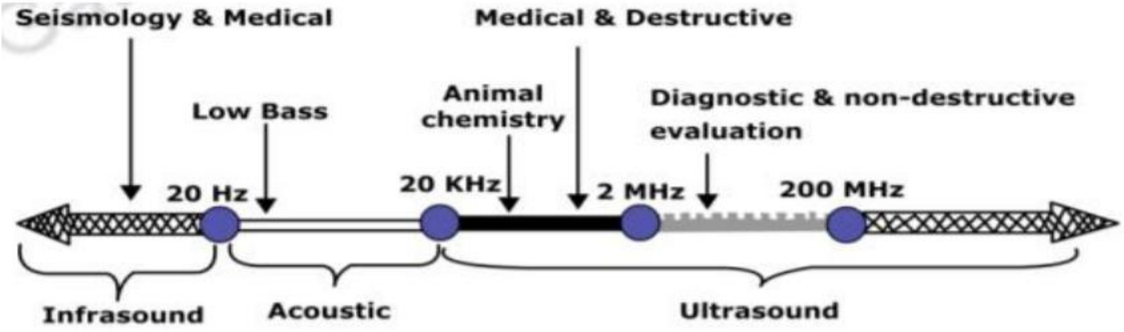


Diagram of ultrasound range

The sonochemical process is usually thought to be localized either inside the cavitation bubble or in the liquid shell surrounding it, or in both simultaneously. A general model developed by Reisse etal. considers the cavitating liquid as heterogeneous: each collapsing bubble, acting as a closed microreactor, presents a physical environment that is quite different from that of the bulk liquid phase. However, its outer boundary is diffuse rather than definite. Sonochemistry in solution has been often rationalized in terms of this theory: solvents that are volatile enough can be vaporized into the bubble where they will undergo pyrolytic cleavage to form radicals or excited chemical species (Figure). These may induce subsequent reactions with less volatile substrates at the bubble shell or, perhaps most frequently, in the bulk medium. It is hardly possible to conceive of a neat heterolytic reaction in the gas-face of the bubble, however, such reactions can take place in the liquid shell. It is important to mention that intense shock waves form upon the collapse of cavitation bubbles, causing various mechanical actions. These are the mainstays of the explanation of sono-chemical effects on heterogeneous processes (enhanced reaction rates and yields), which often do not differ from those obtained by the use of a high-speed stirrer.

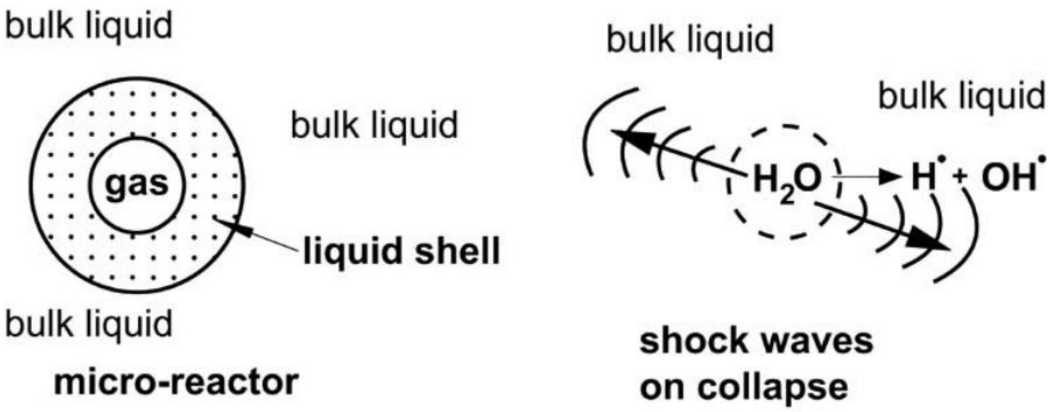
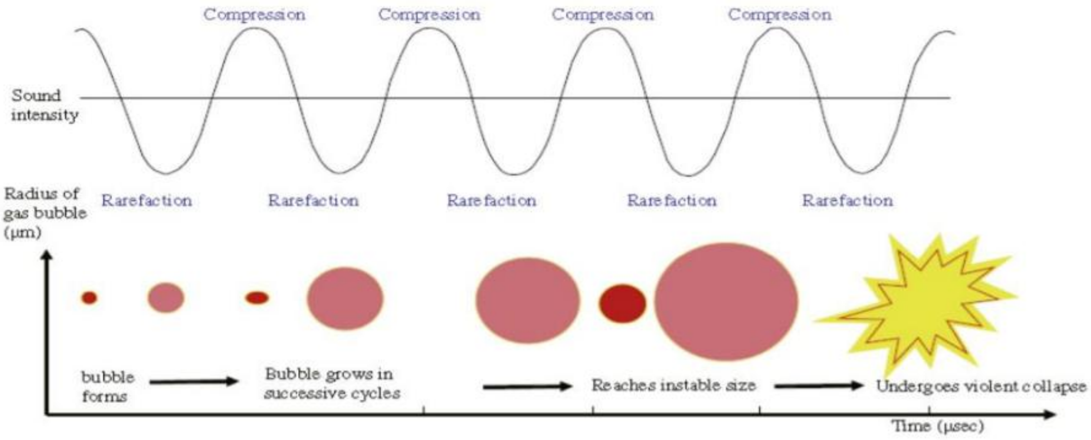


Fig.: Cavitation bubble as a chemical microreactor: cleavage of a water molecule to free radicals that are transferred to the bulk liquid, as well as formation of shock waves on collapse are schematically depicted.

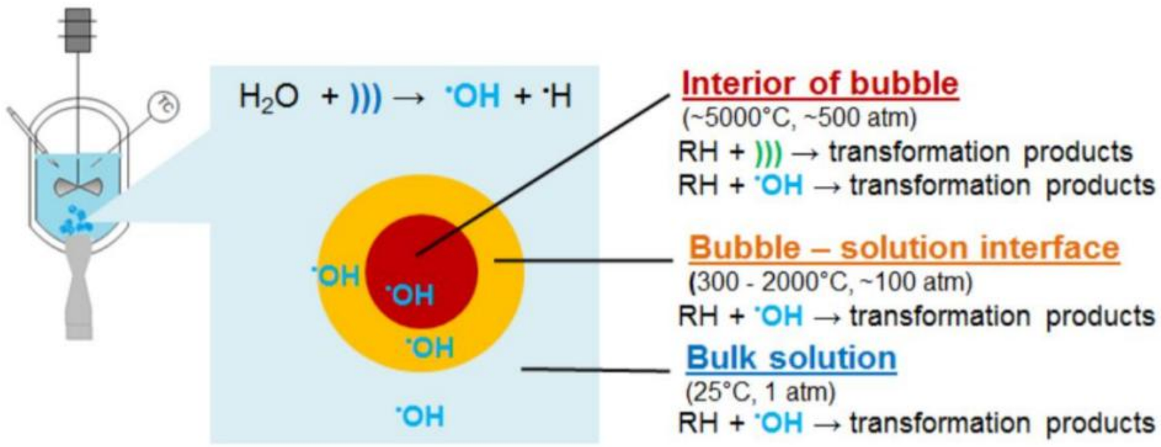
Principle and mechanisms:

Ultrasound process: The development of ultrasound-based technology in water treatment originated from the discovery that ultrasonic waves (at 20 kHz) were able to cause a thinning of cell walls of microbes, attributed to the freeing of the cytoplasm membrane from the cell wall. In recent years, ultrasound has been used for water disinfection, anti-scaling treatment and algae control. Theoretically, ultrasound irradiation (or ultrasonication) alone is capable to generate hydroxyl radicals through water pyrolysis. When water is irradiated with sound waves, it generates compressions and rarefactions, thus micro-bubbles (cavitation bubbles) are formed in the rarefaction regions. These micro-bubbles grow in successive cycles until they reach their resonant diameter and finally collapse violently producing shock waves (temperature of around 5000°C and pressure of 500 atmospheres during a few microseconds). The process of rapid growth and implosive collapse of bubbles is known as cavitation and creates three regions for sonochemical reactions to take place



Typical scheme of acoustic activation

i. The region inside the bubble cavity (gaseous region) where volatile and hydrophobic molecules are degraded via pyrolysis and hydroxyl radical attacks.
ii. The region at the bubble-liquid interface where hydrophobic molecules are degraded via hydroxyl radical attacks.
iii. The liquid bulk region where free radicals formed at the bubble-liquid interface generate secondary sonochemical reactions.



General mechanism of sono-chemical reactions

Organic compound +))) → Transformation products

Transformation products +))) → CO_2 + H2O

H2O +))) → •OH + •H

Where))) refers to the ultrasound irradiation

Sonochemical reaction

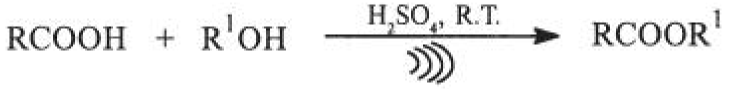
Three classes of Sonochemical reaction

- Type 1 Homogeneous systems which proceed via radical or radical-ion intermediates. This implies that sonication is able to effect reactions proceeding through radicals and further that it is unlikely to effect ionic reactions.
- Type 2 Heterogeneous systems proceeding via ionic intermediates. Here the reaction is influenced primarily through the mechanical effects of cavitation such as surface cleaning, particle size reduction and improved mass transfer. This is what has sometimes been referred to as ‘false sonochemistry’.
- Type 3 Heterogeneous reactions which include a radical pathway or a mixed mechanism i.e. radical and ionic. Radical reactions will be chemically enhanced by sonication but the general mechanical effect referred to above may well still apply. If the radical and ionic mechanisms lead to different products ultrasound should favour the radical pathway and this could lead to a switch in the nature of the reaction products.

Applications

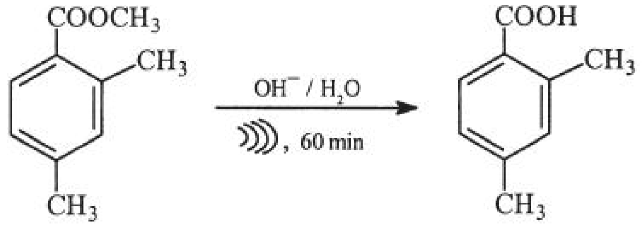
1. Esterification reactions

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.



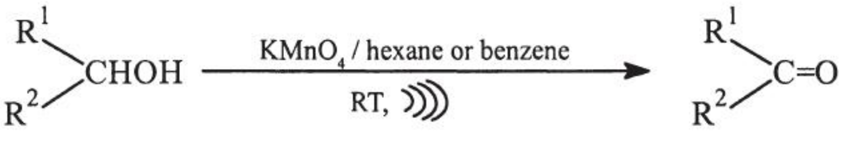
2. **Saponification**

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).



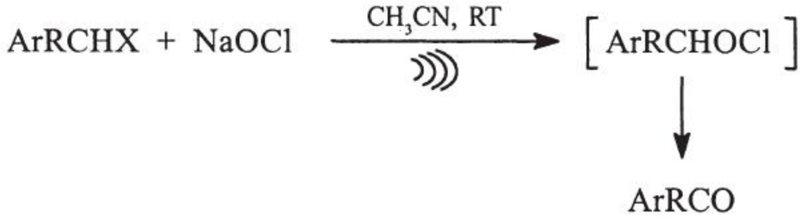
3. **Oxidation**

The oxidation of alcohols by solid potassium permanganate in hexane or benzene is enhanced considerably by sonication.



Using the above method, octan-2-01 gives corresponding ketone in 92.8% yield in 5 hr compared to 2% yield by mechanical stirring. Similarly, cyc1ohexanol gave 53% yield of cyc1ohexanone by oxidation under sonication (5 hr) compared to the 4% yield under usual conditions.

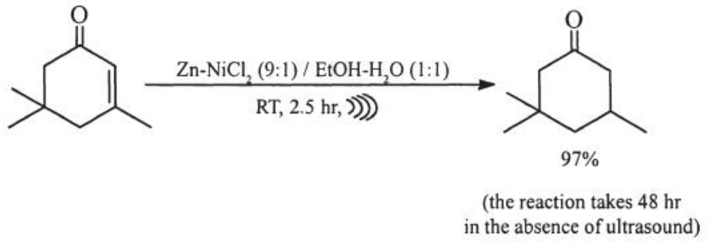
Oxidation of cinnamyl alcohol with manganese dioxide in a suitable solvent (like hexane or octane) gives the corresponding aldehyde on sonication. It is believed that under sonication the low reactive manganese dioxide is activated. Benzylic halides can be oxidised with aqueous sodium hypochlorite at room temperature on sonication. The oxidations are believed to proceed via benzylic hypohalides.

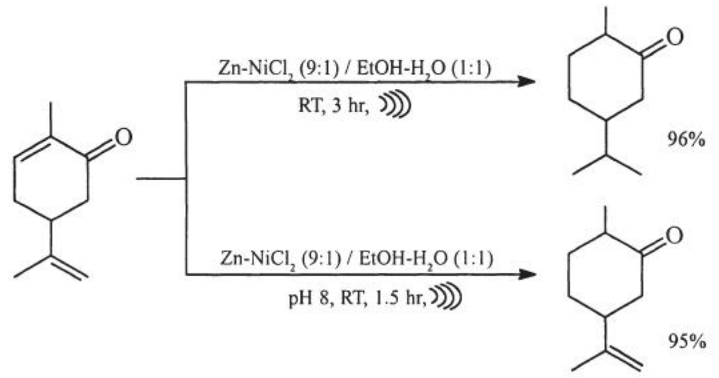


4. Reduction

Sonication increases considerably the reactivity of platinum, palladium and rhodium black in formic acid medium making easier the hydrogenation of a wide range of alkenes at room temperature by sonication. Also, hydrazine-palladium on copper couple is useful for the hydrogenation of alkenes in ethanol at room temperature using an ultrasonic bath. A commercially used example of a sonochemically enhanced catalytic reaction is the ultrasonic hydrogenation of soyabean oil.

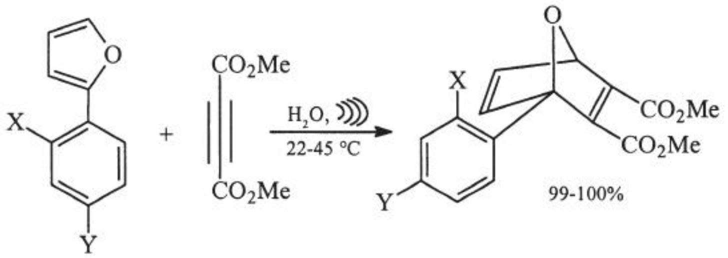
Sonication also increases the activation of nickel powder which is used for the reduction of alkenes. Sonochemical reduction of nickel salts such as chloride with zinc powder gives catalytically active nickel. Under these conditions the excess of metallic zinc also gets activated and reduces the water present in the medium producing hyrdrogen gas. In this way, not only the catalyst but also the reagent is produced *in situ* with maximum efficiency and safety. This process has been used for the reduction of carbon-carbon double bonds in α,β-unsaturated carbonyl compounds; the C-C double bond is reduced much faster than the carbonyl group. The variation in the conditions, especially pH permits the selective reduction of C = C in preference to C = O.





4. Diels Alder Reaction

Sonication facilitates Diels-Alder reaction. Therefore, the addition of dimethyl acetylene dicarboxylate to furan in water at 22-45 °C gives quantitative yield of the adduct. The Diels-Alder cycloaddition of various dienes (mostly belonging to 1-vinyl cyclohexenes) with o-quinone proceeds very well under ultrasound conditions to give the expected adducts in 59% yield compared to 30% under normal reaction conditions. Better results are obtained by soniciation of the neat mixture.



7. Cannizaro reaction

The Cannizarro reaction under heterogenous conditions catalysed by barium hydroxide is considerably accelerated by sonication. The yields are 100% after 10 min, whereas no reaction is observed during this period with the use of ultrasound.

$$C_6H_5CHO \xrightarrow[\text{))), 10 min}]{Ba(OH)_2,\ EtOH} C_6H_5CH_2OH + C_6H_5COOH$$

7. **Synthesis of Chromones**

The condensation of o-hydroxybenzaldehyde with p-nitrostyrene using basic alumina catalyst gives good yield of 3-nitro-2H-chromene on sonication.