GREEN CHEMISTRY IN ORGANIC SYNTHESIS

Narinder Kaur¹, R.K.Dhawan¹, Balwinder singh²

Khalsa College of Pharmacy and Technology, Amritsar, Punjab¹
Department of Pharmacy GPCG Jalandhar, Punjab²

Abstract: Green chemistry or sustainable chemistry focuses on designing products and processes that minimize the generation or use of hazardous substances. Green chemistry, though not a new area, has recently gained much importance because of increasing environmental concerns. Industries now focus on adopting processes which are mainly non-hazardous, easier to undertake, lesser energy and time consuming, using re-usable reagents, degeneration of drastic materials, and more economical. These concepts have identified and developed various technologies such as microwave, ultrasonic, UV radiation, electrochemistry, etc., as green technologies. Solvents such as water, has significant importance, being non-hazardous, easily recoverable, and lowering unnecessary wastage of energy. Other recoverable solvents such as acetone, alcohol, methanol, etc., come under green chemicals. Catalysts that promote chemical reactions, without causing hazardous effect and are recoverable are also a part of green chemistry. All the aspects of green chemistry, improving the level of research in chemistry and advance techniques make the experimental work easier to new researchers. This is a positive and harmless growth in the field of chemistry.

Keywords: Green chemistry, principles of green chemistry, Green solvents, organic synthesis.

1. INTRODUCTION

A green signal permits to proceed. That is how ‘green chemistry’ suggests a branch of chemistry that is acceptable and most valuable. Green chemistry is a synthetic process that avoids many technical, environmental problems, hazardous atmosphere, and formation of specific products in high yields, avoids the use of hazardous chemicals, attains more economical status, reduces by-products and creates an environmentally friendly atmosphere.

Green chemistry addresses our future challenges in working with chemical processes and products by inventing novel reactions that can maximize the desired products and minimize by-products, designing new synthetic schemes that can simplify operations in chemical productions, and seeking greener solvents that are inherently environmentally and ecologically benign.

Green chemistry searches for an alternative, environmentally friendly reaction media and at the same time strives to increase reaction rates and lower reaction temperatures 1-5. Green chemistry takes into account the environmental impact and seeks to prevent or lessen that impact through several key principles outlined below.

These principles can be grouped into "Reducing Risk" and "Minimizing the Environmental Footprint 6-10."

• Prevention of waste - better to minimize the formation of waste than to remove it or reduce its toxicity when formed.
• Atom economy - atom wise maximize the incorporation of all reactants used in the process into the final products.
• Less hazardous chemical synthesis - use of chemical reactants and formation of final products with minimized or no toxicity.
• Designing safer chemicals and products - preparation of effective chemicals with reduced toxicity.
• Safer Solvents and Auxiliaries - avoid auxiliary substances such as solvents, separating agents, etc., wherever applicable.

• Design for Energy Efficiency - energy requirements should be recognized for environmental and economic impacts and to be minimized to conduct the synthetic procedure at ambient temperature and pressure.

• Renewable feedstock - a raw material or feedstock should be renewable rather than depleting whenever possible.

• Reduce derivatives - use of derivatives as reactants with protecting groups and temporary modified structures should be avoided whenever possible.

• Catalysis - catalytic reagents are superior to stoichiometric reagents. It can enhance the extent of product formation under reduced temperature and pressure and reduce the waste formation.

• Design for degradation - chemical products should be designed so that at the end of their function, they do not persist in the environment and break down into innocuous degradation products and do not persist in the environment.

• Real-time analysis for pollution prevention - analytical methodology be developed to allow real-time in-process monitoring and control before the formation of hazardous substances.

• Safety - substances should be chosen to minimize the potential for chemical accidents, explosion, fire, etc.

These principles, along with suitable examples of reactions carried out under these mentioned 12 principles

1) Prevention of Waste:

It is better to prevent the formation of waste materials and/or by-products than to process or clean them.

It is better to prevent waste formation that to treat it after it is formed. An example is the manufacture of phenol. It used to be made from benzene using sulfuric acid and sodium hydroxide in a multi-stage process with 78% yield; the reaction can be expressed as:

Sodium sulfite is the by-product, can be used in other processes. However, if it is not in demand, that would mean this may not be the most suitable reaction for manufacturing phenol 12, 13.

Another example of green synthesis is the synthesis of ibuprofen. Traditional synthesis of ibuprofen produces 60% waste, as shown below.

SCHEME 1: Conventional method of synthesising Ibuprofen
SCHEME 2: Green Chemistry method of synthesising Ibuprofen

Alternate green chemistry of ibuprofen produces just 1% waste.

II) Atom Economy:

*Synthetic methods should be designed in such a way that all products participating in the reaction process are included in the final product.*

Atom economy is a measure of the amount of atoms from the starting material that is present in the useful products at the end of a chemical process. Side products from reactions that aren’t useful can lead to a lower atom economy and more waste. Therefore, processes that maximize the atom economy are preferred.

Atom economy \( \% = \frac{\text{Relative molecular mass of desired products}}{\text{Relative molecular mass of all reactants}} \times 100 \)

An example of Diel’s Alder Reaction with 100% atom economy is as follows: 14-18

SCHEME 3: Diels Alder reaction

The addition, condensation and rearrangement reactions will generally have higher atom economies than either elimination or substitution.

For example, the addition of chlorine to ethene, to form 1,2-dichloroethane (an important reaction in the manufacture of poly (chloroethene) (PVC)) has an atom economy of 100%:

\[ \text{H}_2\text{C} = \text{CH}_2 + \text{Cl}_2 \rightarrow \text{ClCH}_2\text{CH}_2\text{Cl} \]

However, if the product is hydrolyzed, the atom economy falls:

\[ \text{ClCH}_2\text{CH}_2\text{Cl} + 2\text{H}_2\text{O} \rightarrow \text{HOCH}_2\text{CH}_2\text{OH} + 2\text{HCl} \]

The first is an addition reaction; the latter is a substitution reaction.

III) Less Hazardous Chemical Synthesis:

*Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.*

It is also important that chemicals that are produced are safe for the environment. In all cases, the material should degrade to harmless products. Synthetic methods should where practicable, use or generate materials of low human toxicity and
environmental impact. For example, polycarbonate synthesis is carried out using phosgene (COCl2). To avoid phosgene, the hazardous chemical, solid-state polymerization is undertaken, which also leads to polycarbonate formation under green chemistry 19, 20.

**SCHEME 4: Green chemistry method of synthesising Polycarbonate**

![Scheme 4](image)

**IV) Designing Safer Chemicals:**

The design of products should be safe in terms of human health and the environment.

The design of safer chemical targets requires a knowledge of how chemicals act in our bodies and the environment. In some cases, a degree of toxicity to animals or humans may be unavoidable, but alternatives should be sought. Toxic chemicals used, such as repellent DEET as an insecticide, bisphenol- A, as a plasticizer, , and some acidic catalysts, need their replacement to achieve a safer side. Designing such requirements, safer chemicals is an important part of green chemistry, e.g. solid acid catalysts Zeolite H-FER, as a safer catalyst 21.

**V) Safer Solvents and Auxiliaries:**

The solvent chosen for a given reaction should not pollute the environment or be hazardous to human health.

Many chemical reactions require the use of solvents or other agents to facilitate the reaction. They can also have a number of hazards associated with them, such as flammability and volatility. Solvents might be unavoidable in most processes, but they should be chosen to reduce the energy needed for the reaction, should have minimal toxicity, and should be recycled if possible. Solvents are also the major contributors to the overall toxicity profile and because of that, compose the majority of the materials of concern associated with a process. Water is also capable of accelerating the process even when the diene and the dienophile are associated 22.

**SCHEME 5: Conversion of Diene to Dienophile**

![Scheme 5](image)
On average, they contribute the greatest concern for process safety issues because they are flammable and volatile, or under the right conditions, explosive. They also generally drive workers to don personal protective equipment of one kind or another. The use of auxiliary substances (e.g., solvents or separation agents) should be made unnecessary whenever possible and innocuous when used. Some of the safer auxiliaries (e.g., solvents, separating agents, etc.) are water and carbon dioxide. Water is used as a solvent in catalytic reactions 1, 2, and CO2 is also used as a solvent for chemical reaction and extraction 23.

Some reactions use water as a solvent, for example, in the manufacture of inorganic compounds such as hydrogen peroxide, phosphoric acid, sodium carbonate, and organic compounds such as ethane-1,2-diol and ethanol. Water is not a harmful solvent, but it is a precious resource, and it is important to ensure that it is not wasted. Supercritical (liquid) carbon dioxide is widely used as a solvent in the extraction of caffeine from coffee beans and in the latest dry cleaning equipment it replaces chlorinated solvents such as perchloroethylene, C2Cl4.

Green Solvents

The organic solvents used in numerous syntheses are quite hazardous to the environment. Volatile organic solvents are released into the environment by evaporation or flow in substantial amounts, since they are used in much higher proportions than the reagents themselves. A new approach to overcome this problem is to carry out the chemical reactions in the absence of such media, i.e., with- out solvents or by the use of non-volatile solvents that are harmless to humans and the environment. The ideal “green” solvent should have a high boiling point and it must be non-toxic, dissolve numerous organic compounds, cheap and, naturally, recyclable. Clearly such requirements strongly limit the choice of substance or class of compound as a green solvent. The substantial efforts of research groups throughout the world have led to the establishment of good alternatives to the common organic solvents, including: supercritical liquids, ionic liquids, low-melting polymers, perfluorinated (fluorous) solvents and water.

Fluorous liquids have quite unusual properties and these include high density, high stability (mainly due to the stability of the C–F bond), low dissolving ability and extremely low solubility in water and organic solvents although they are miscible with the latter at higher temperatures. The low solubility of the perfluorinated solvents can be explained in terms of their low surface tension, the weak intermolecular interactions, high densities and low dielectric constants.

Schematic representation of organic syntheses in fluorous solvents.

Water is the basis and bearer of life. For millions of years, water has been at work to prepare the earth for the evolution of life. Water is the solvent in which numerous biochemical organic reactions (and inorganic reactions) take place. All of these reactions affect living systems and have inevitably occurred in an aqueous medium. On the other hand, modern organic chemistry has been developed almost on the basis that organic reactions often have to be carried out in organic solvents. It is only within the last two decades or so that people have again focused their attention on carrying out organic reactions in water.

Why should we consider using water in organic reactions as a green solvent?

There are many potential advantages:

- **Cost.** Water is the cheapest solvent available on earth; using water as a solvent can make many chemical processes more economical.

- **Safety.** Many organic solvents are flammable, potentially explosive, mutagenic, and/or carcinogenic. Water, on the other hand, has none of these adverse properties.
- Synthetic efficiency. In many organic syntheses it may be possible to eliminate the need for the protection and deprotection of functional groups, thus saving numerous synthetic steps. Water-soluble substrates can be used directly and this would be especially useful in carbohydrate and protein chemistry.

- Simple operation. In large industrial processes, isolation of the organic products can be performed by simple phase-separation. It is also easier to control the reaction temperature, since water has one of the highest heat capacities of all substances.

- Environmental benefits. The use of water may alleviate the problem of pollution by organic solvents since water can be recycled readily and is benign when released into the environment (when harmful residues are not present).

- Potential for new synthetic methodologies. Compared to reactions in organic solvents, the use of water as a reaction medium has been explored to a much lesser extent in organic chemistry. Furthermore, there are many opportunities to develop novel synthetic methodologies that have not been discovered before.

On the basis of the above characteristics water is probably the greenest solvent in view of its price, availability, safety and environmental effects. The drawbacks of using water, however, are that many organic compounds are insoluble or slightly soluble in water, and with some reagents (e.g., organometallic compounds) water is highly reactive. The use of water is often restricted to hydrolysis reactions, but in the early 1980s it was shown that water has unique properties that can lead to surprising results. The use of co-solvents or surfactants helps to increase the solubility of non-polar reagents by disrupting the dense hydrogen bonding network of pure water.

VI) Design for Energy Efficiency:

**The energy requirements involved in the chemical processes should be accounted for, in view of their influence on the environment and the economic balance, and the energy requirements should be diminished. If possible, the chemical processes should be carried out at room temperature and atmospheric pressure.**

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

**SCHEME 6: Green chemistry method of synthesis less time consumption**

Various Microwave-Assisted Diels-Alder reactions have been carried out for energy effective reaction, as a part of green chemistry. One such example is shown below. Replacement of Br with CN under conventional condition takes place at 100 °C with around 75% conversion in 72 h. Under Micro Wave, 100% conversion in only 10 min is produced at 200 °C. Traditional processes are being overhauled, and more energy efficient ones substituted. Catalysts are being developed so that a process can be run at lower temperatures and pressures (high temperatures and pressures are very energy consuming. Similarly, the development of molecular sieves means that processes such as the purification of ethanol can be carried out at ambient temperatures instead of by distillation 24.

VII) Renewable Feedstock:

**The intermediates and materials should be renewable rather than depleting (which is the case with, e.g., crude oil) whenever this is technically and economically advantageous.**

Renewable biomass feedstock forms the basis of many successful industries such as pulp & paper, and wood product industries. Crops grown for fiber, oils or other materials, provide necessary feedstock to such industries. One renewable resource hydrogen is obtained from biomass such as water, natural gas, crude oils, hydrocarbon, and organic fossil mater-
rials. Recently glycerin has become increasingly available as a by-product of the manufacture of bio-diesel, and this renewable feedstock has improved the production of epichlorohydrin, a largely used chemical for the manufacture of epoxy resins. Some other solvents which can be distilled, purified, and reused such as acetone, methanol, ethanol, acetonitrile, etc. are considered as green solvents.

VIII) Reduce Derivatives:

*Derivatizations, such as protection/deprotection and various other modifications, should be decreased or avoided wherever possible since these stages require additional amounts of reagents and waste products could be formed.*

Unnecessary derivatization (use of blocking groups, protection/ de-protection, and temporary modification of physical/chemical processes) should be minimized or avoided if possible because such steps require additional reagents and can generate waste. An alternative that has been explored in some processes is the use of enzymes. As enzymes are highly specific, they can be used to target particular parts of a molecule’s structure without the need for the use of protecting groups or other derivatives. Enzymes are so specific that they can often react with one site of the molecule and leave the rest of the molecule alone and hence protecting groups are often not required.

A great example of the use of enzymes to avoid protecting groups and clean up processes is the industrial synthesis of semi-synthetic antibiotics such as ampicillin and amoxicillin. In the first industrial synthesis Penicillin G (R=H) is first protected as its silyl ester [R = Si(Me)3] then reacted with phosphorus pentachloride at -40 °C to form the chlorimidate 1 subsequent hydrolysis gives the desired 6-APA from which semi-synthetic penicillins are manufactured.

Covalent bond formation in solid state condition under hv, in high yields, with limited by-products, and with minimal waste has been reported.

**SCHEME 7: Green chemistry method of synthesis less waste**

IX) Catalysis:

*It is well known that catalysts increase substantially the chemical process rates, without their consumption or insertion into the final products.*

A primary goal of green chemistry is the minimization or preferably the elimination of waste in the manufacture of chemicals and allied products. The use of catalysts can enable reactions with higher atom economies. Catalysts themselves aren’t used up by chemical processes, and as such can be recycled many times over, and don’t contribute to waste. They can allow for the utilization of reactions which would not proceed under normal conditions, but which also produce less waste. For example, benzene and propane are converted into cumene in the manufacture of phenol. This reaction needs an acid catalyst, such as aluminum chloride. A solid zeolite with acid groups, such as ZSM-5 is now the favored catalyst.
The zeolite is more environmentally friendly as the effluent is much cleaner and lower temperatures and pressures can be used. Another similar example is in the manufacture of one of the most important polymers used to make fabrics, nylon 6,6. In this process, cyclohexanone is converted into caprolactam via the oxime (produced by the reaction of the ketone with hydroxylamine hydrogensulfate). The oxime is isomerized by sulfuric acid to caprolactam; the released sulfuric acid is converted to ammonium sulfate.

**SCHEME 9: Synthesis of Caprolactum**

However, again, a zeolite catalyst, with acidic sites, is now being used to effect the rearrangement. The zeolite is regenerated and saves the use and subsequent waste of sulfuric acid. Catalytic reagents are better than stoichiometric reagents. It has higher activation energy enhancing the selectivity of a reaction, reduce transformation temperature, enhance the yield of the conversion product, and reduce reagent-based waste.

**SCHEME10: Green chemistry method of synthesis reducing waste and increasing yield**

X) Degradation Design:

*The design of the final chemical products should be such that, after fulfilling their functions, these products should easily degrade to harmless substances that do not cause environmental pollution.*

Chemical products should be designed so that at the end of their function, they break down into innocuous degradation products and do not persist in the environment. Exposure to persistent chemicals can be significant as a result of global dispersion enabled by properties such as volatility or sorption to particles and partitioning into organisms based on properties such as fat solubility. In green chemistry, chemical products should be designed in a way that at the end of their function, it degrades into hazard less substance without persisting environmentally.
XI) Real Time Analysis for the Avoidance of Contamination. Increase in the Role of Analytical Chemistry in Green Technologies:

Analytical methodologies should be developed in such a way that the process can be monitored in real time.

New analytical tools are needed for real-time monitoring of industrial processes and to prevent the formation of toxic materials. The growing field of process analytical chemistry is aimed primarily at obtaining the analytical data close to the production operation. A real-time field measurement capability is desired for continuous environmental monitoring and this would replace the common approach of sample collection and transport to a central laboratory. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring, and control before the formation of hazardous substances. Monitoring a chemical reaction as it is occurring can help prevent the release of hazardous and polluting substances due to accidents or unexpected reactions. With real-time monitoring, warning signs can be spotted, and the reaction can be stopped or managed before such an event occurs. There should be a provision to analyze and estimate the progress of product formation and detect the production of any unwanted by-product creating hazardous environment 32.

XII) Inherently Safer Chemistry for Accident Prevention:

The reagents used to carry out chemical processes should be chosen with caution in order to avoid accidents, such as the release of poisonous substances into the atmosphere, explosions and fires.

Safety can be defined as the control of recognized hazards to achieve an acceptable level of risk. Substances and the form of the substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires. Safer solvents such as water, liquid CO2, or avoiding the use of solvents is a part of green chemistry. Diels-Alder reactions of neat reactive dienes and dienophiles are sometimes very vigorous and are, therefore, limited preparative value. Addition of a limited amount of water in such reaction makes it valuable by lowering its temperature, increasing its rate of formation and creating higher purity product 33.

e.g. The oxidation of isatins to isatoic anhydrides has been achieved using a safe, cheap, stable and green oxidizing agent urea/hydrogen peroxide complex and ultrasound irradiation at room temperature. The oxidant is safer than liquid hydrogen peroxide.

2. CONCLUSIONS

- Green Chemistry is not a new branch of science. It is a new philosophical approach that, through the introduction and expansion of its principles, could lead to a substantial development in chemistry, the chemical industry and environmental protection.

- Future generations of chemists should be trained in the principles of Green Chemistry and should possess knowledge and habits that should be applied in practice.
- At present, one can easily find in the literature quite interesting examples of the use of the rules of Green Chemistry. These principles could be applied not only to the synthesis, but to the processing and use of chemical substances. Numerous new analytical methodologies have been described and these are carried out according to the rules of Green Chemistry. These approaches are particularly important in conducting chemical processes and assessing their impact on the environment.

- In the coming decades Green Chemistry will continue to be attractive and practical. It is expected that this approach will solve numerous ecological problems. The development of waste-free technologies as well as technologies that have a lesser impact on the environment at the research stage does not guarantee their adoption on an industrial scale. The implementation of such technologies in industry can be ensured by more flexible legislation, new programs for the acceleration of the technological transfer between academia and governments and, last but not least, tax advantages for companies for the industrial application of cleaner technologies.

- All of us, by using the comforts of modern civilization, contribute to environmental pollution and are in debt to Mother Nature. The education in Green Chemistry of future generations of chemists will contribute to the solution of numerous ecological problems on the national, regional and global scale and will allow the specialists trained by us to be competitive within the global economy.

- By starting education in Green Chemistry right now we should travel a long way along the path to fulfill our mission and to enjoy the results of our efforts for future generations of chemists and other specialists.

In our opinion this will inevitably happen in the very near future.

**The biggest challenge to Green Chemistry is to put its rules into practice.**

**REFERENCES**


[22] [Freund R: Multifunctional efficiency: Extending the concept of atom economy to functional nanomaterials. ACS Nano 2018; 12(3): 2094-05.


